Nutrition of Children With Cancer in Brazil: A Systematic Review

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PURPOSE The objective of this systematic review was to describe nutrition-related publications on children and adolescents diagnosed with cancer in Brazil.

METHODS The methodology followed that of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Medline, LILACS (the Latin American & Caribbean Health Sciences Literature), and Embase were searched in April 2019, and data extraction and rating of methodologic study quality (according to the National Institutes of Health quality score assessment) were performed independently by reviewers.

RESULTS Twenty-seven studies met the inclusion criteria, reporting on 3,509 patients from 1994 to 2018. Most of the studies (74%) were of poor quality in methodology and reporting. Different cancer diagnoses were included in 52% of studies, whereas acute leukemia was the exclusive focus in 41%. The majority of the articles (70%) were from institutions in the Southeast Region of Brazil, mainly the state of São Paulo (74%); no publications were from the North Region of the country. Twelve studies addressed nutritional status and body composition, reporting an abundance of malnourished patients in the Brazilian population of children and adolescents with cancer. Six studies on micronutrients pointed to possible deficiencies in this population, with a yet unclear but promising role for supplementation during treatment.

CONCLUSION Evidence indicates that there is great interest in the impact of nutrition on childhood cancer treatment and clinical outcomes in Brazil. However, there is a need to focus on high-quality research, particularly with multicentric/national studies. This will help establish research priorities and better planned clinical interventions, adapted to each region of the country.

INTRODUCTION

Of the estimated 400,000 annual incident cases of cancer in children 0 to 14 years of age worldwide,[1] more than 80% of those diagnosed live in low- and middle-income countries (LMICs).[2] In Brazil, an upper-middle-income country, there are approximately 12,500 new patients each year among 1- to 19-year-olds, and cancer currently represents the leading cause of death by disease in this age group.[3] With an increasing pediatric population undergoing treatment for cancer, the need for timely supportive care, including nutritional interventions, is of considerable importance.

The impact of poor nutritional status, both undernutrition and overnutrition, on clinical outcomes (including survival) is well recognized. Such conditions can increase treatment-related morbidities and mortality, as well as health care costs and abandonment of therapy.[4-9] Moreover, studies in children with acute lymphoblastic leukemia (ALL) have demonstrated that the remediation of compromised nutritional status during treatment can improve survival, which supports the hypothesis that nutritional status is a modifiable risk factor for adverse outcomes.[10,11] However, there is a significant gap in the literature regarding high-quality research on the relationship between nutrition and cancer in children in LMICs, including in Brazil, which creates obstacles to determining the optimal standards of nutritional care for this patient population and remains a barrier to setting educational and research priorities, thereby preventing the field from advancing. The purpose of this review was to describe published nutrition-related data in children and adolescents diagnosed with cancer in Brazil.

METHODS

The systematic review methodology was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12] The electronic databases of Medline, LILACS (the Latin American & Caribbean

CONTEXT

Key Objective

To describe nutrition-related publications in children and adolescents diagnosed with cancer in Brazil.

Knowledge Generated

Seventy-four percent of included studies were of poor quality. The majority of articles were from institutions in the Southeast Region of Brazil, with no publications from the North Region of the country.

Relevance

There is a need to focus on high-quality research, particularly with multicentric studies representative of all regions of the country, in order to establish research priorities and better planned clinical interventions.

Health Sciences Literature), and Embase were searched systematically from inception through April 2019. The inclusion criteria were (1) children ages 0 to 18 years with a cancer diagnosis, (2) nutrition-related investigations, and (3) studies conducted in Brazil. There was no language restriction. Publications that were not indexed, case reports or reviews were excluded. Search strategies are outlined in Appendix Table A1.

Titles and abstracts of references were reviewed by two authors (K.V. and R.D.B.) independently. Lack of consensus was resolved by consultation with a third author (E.J.L.). Potentially relevant publications were retrieved for full-text review.

Data were extracted by two authors (K.V. and L.A.) and verified independently by one author (E.J.L.). Attempts were made to contact authors for additional information when appropriate. Extracted data comprised state of origin, year, study design, sample size, diagnoses, treatment consortium and regimen, definition and categorization of anthropometric data, treatment-related toxicity, and survival data. Because of heterogeneity of the data and the small number of clinical trials evaluating a single diagnosis, statistical analysis was not feasible.

RESULTS

Figure 1 is a flow diagram of the search strategy results on the basis of the PRISMA template. After removal of duplicates, 794 articles met initial search criteria. A full-text review was conducted on 40 articles, 27 of which met eligibility criteria and were included in the analysis. Included studies reported on a total of 3,509 patients between 1994 and 2018. Study characteristics are detailed in Tables 1 and 2.
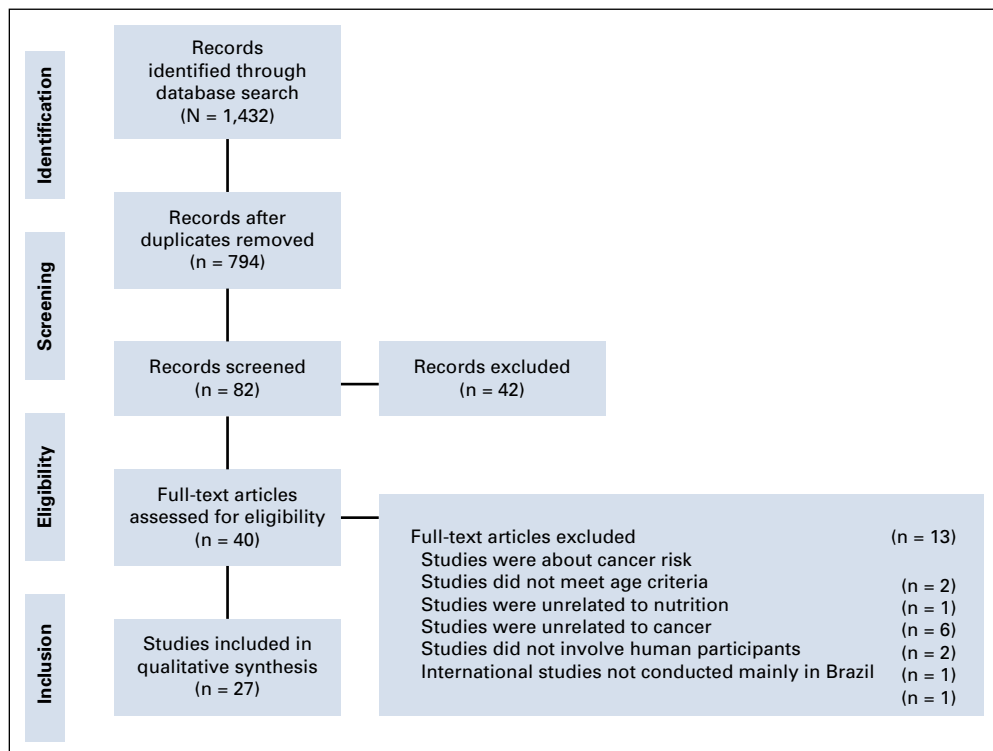

FIG 1. Results of the search strategy.

TABLE 1. Characteristics of Studies on Nutritional Status and Body Composition Included in the Systematic Review

Study, State	Tumor Type (No. of participants)	Primary Objective	Timing of Assessment	Anthropometric Data Category Definition	Incidence of Nutritional Status, %	Main Findings	Quality Score
Maciel Barbosa et al, 2012,[14] Pernambuco	Solid tumors (N = 71)	To analyze the nutritional status of patients receiving EN and assess the adequacy of this form of nutrition	Beginning and end of EN therapy	BMI (WHO)	Stunted: 32.4 Underweight: 23.9 Well nourished: 47.9 Overweight: 28.2	49.3% reached caloric and 76.1% reached protein requirements; The median duration of EN was 7 days; Malnourished children improved W/A and BMI/A z scores with the use of EN ($P < .05$)	5
Barreto et al, 2013,[15] Federal district	Several cancer diagnoses (N = 29)	To evaluate the nutritional status of pediatric patients with cancer	Any time during treatment	BMI (WHO)	Stunted: 17 Underweight: 35 Well nourished: 44 Overweight: 18 Obese 12	7% had weight loss > 10% in 6 months; 38% used oral supplements	3
Caram et al, 2012,[16] São Paulo	ALL (N = 42)	To identify the nutritional status, type of prescribed diet, use of supplements, GI symptoms, and cancer treatment	Up to 6 months after diagnosis	BMI (WHO)	Stunted: 42.9 Underweight: 52.4 Overweight: 7.2	The predominant GI symptoms were vomiting (71.4%), stomatitis (47.6%), diarrhea (45.2%), nausea (42.9%), oral herpes (14.3%), and constipation (9.5%); 8.7% used oral supplements	3
Cararro et al, 2012,[17] Rio Grande do Sul	Several cancer diagnoses (N = 19)	To compare nutritional status based on anthropometric measurements and BIA	After at least 1 chemotherapy cycle	BMI (WHO) MUAC, TSF (Frisancho[55])	BMI Underweight: 10.5 Well nourished: 52.6 Overweight: 36.8	Mean lean mass, 79.8%; fat mass, 19.6%; Overweight patients had lower mean lean mass percentage (67.9%); Correlations: TSF × BMI r = 0.8, TSF × FM (BIA) r = 0.74, TSF × FFM (BIA) r = −0.76	4

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TABLE 1. Characteristics of Studies on Nutritional Status and Body Composition Included in the Systematic Review (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Timing of Assessment	Anthropometric Data Category Definition	Incidence of Nutritional Status, %	Main Findings	Quality Score
Garófolo et al, 2005,[18] São Paulo	Several cancer diagnoses (N = 127)	To evaluate differences between 2 anthropometric methods and compare deficits	Within the first month of treatment	Children: W/H adolescents: BMI (WHO) MUAC, TSF (Frisancho[56])	Malnutrition BMI: 18.9 TSF: 40.2 MUAC: 35.4	Patients with nonhematologic tumors had higher malnutrition prevalence compared with patients with hematologic diseases ($P < .05$). Comparison of malnutrition prevalence: BMI × TSF ($P < .05$), BMI × MUAC ($P < .05$), TSF and MUAC detected more patients with malnutrition than BMI or W/H z scores	5
Gelelete et al, 2011,[19] Rio de Janeiro	ALL (N = 181)	To investigate the prognostic impact of overweight/obesity in 5-year EFS	Diagnosis	BMI (WHO)	Overweight: 35.9	5-year EFS of overweight/obese patients was lower (67% v 81%, $P = .03$), mainly in intermediate- and high-risk groups (58.8% v 76.7%, $P = .02$). Overweight/obesity HR, 1.92 (95% CI 1.42 to 2.60, $P = .031$)	7
Lemos et al, 2014,[20] São Paulo	Several cancer diagnoses (N = 1,154)	To assess the nutritional status at diagnosis	Diagnosis	BMI (WHO) MUAC, TSF, AMC (Frisancho[57])	BMI Underweight: 10.85 Well nourished: 69.15 Overweight: 15.43; MUAC Underweight: 24.74 Well nourished: 71.15 Overweight: 4.09	Nutritional status did not differ according to the different anthropometric parameters ($P > .05$). The mean weight loss adjusted to 7 days was −2.82% in the hematologic group and −2.9% in the solid tumor group ($P = .11$)	4

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TABLE 1. Characteristics of Studies on Nutritional Status and Body Composition Included in the Systematic Review (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Timing of Assessment	Anthropometric Data Category Definition	Incidence of Nutritional Status, %	Main Findings	Quality Score
Paes et al, 2003,[21] Minas Gerais	ALL (N = 186)	To determine the relative frequency of different ALL immunologic subtypes and investigate the association between nutritional condition and socioeconomic status	Diagnosis	H/A, W/A (CDC)	Stunted: 7.5 Underweight: 11.4	Unable to demonstrate any association between the nutritional variables and immunophenotypes Low monthly per capita income was associated with the T phenotype ($P = .024$)	5
Pedrosa et al, 2000,[22] Pernambuco	Acute leukemias and solid tumors (N = 443)	To investigate the relationship between survival and malnutrition at diagnosis among children treated for cancer in 2 developing countries (Brazil and El Salvador)	Diagnosis	W/A, W/H, H/A (CDC)	Stunted: 22.8 (Brazil: 18.5) Malnutrition W/H: 15.7 (Brazil: 14.9) W/A: 23.5 (Brazil: 20.9)	No relationship between nutritional status at diagnosis and survival (H/A $P = .229$, W/A $P = .996$, W/H $P = .887$), even when patients with solid tumors and leukemia were analyzed separately (solid tumors: H/A $P = .687$, W/A $P = .160$, W/H $P = .722$; leukemia: H/A $P = .151$, W/H $P = .407$, W/H $P = .709$)	4
Tosta-Hernandez et al, 2018,[23] São Paulo	Craniopharyngioma (N = 57)	To describe the main clinical characteristics of patients with childhood craniopharyngioma	Diagnosis and at study assessment (post-treatment)	BMI (WHO)	Obesity 21 (diagnosis) 57.9 (post-treatment) 68.4 increased WC	44% had metabolic syndrome BMI at diagnosis positively determined; BMI at study assessment ($P = .005$) Obesity at diagnosis determined the presence of metabolic syndrome (OR, 6.1; $P = .031$)	7

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TABLE 1. Characteristics of Studies on Nutritional Status and Body Composition Included in the Systematic Review (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Timing of Assessment	Anthropometric Data Category Definition	Incidence of Nutritional Status, %	Main Findings	Quality Score
Viana et al, 1994,[24] Minas Gerais	ALL (N = 128)	To determine the influence of nutritional status on the probability of OS and duration of first complete remission	Diagnosis	H/A, W/A (CDC)	Stunted: 17.4 Underweight: 21.2	45% of children not stunted with complete remission for 2.5 years v no stunted patients (P = 0.00001)	9
						The adjusted risk of relapse for children who were stunted was > 8.2% (95% CI, 3.1-21.9)	
						W/A was also an unfavorable prognostic variable (P = .0005)	
Viana et al, 1998,[25] Minas Gerais	ALL (N = 167)	To investigate the impact of malnutrition and socioeconomic status on outcomes	Diagnosis	H/A, W/A (CDC)	Stunted: 8.9 Underweight: 15.1	H/A and socioeconomic status were predictive risk factors for relapse and seem to be highly associated (P = .00001)	10
						50% 8-year disease-free survival for children with H/A z score > −1.28 v 0% for H/A z score < −1.28 (P = .000003)	
						The adjusted risk of relapse for children who were stunted was > 2.2% (95% CI, 1.2 to 4.1; P = .015)	
						W/A was also an unfavorable prognostic variable (P = .0005)	
Vilela and Viana, 2007,[26] Minas Gerais	ALL (N = 129)	To analyze longitudinal growth of patients who received cranial irradiation	Diagnosis, after 1 year of treatment, at end of treatment, 1 year after end of treatment, last visit to clinic, and when final height achieved	BMI (CDC)	Underweight: 6 Well nourished: 75 Overweight: 13 Obese: 6	Height deficit at the end of the treatment (P < .0001)	9
						Catch-up occurred 1 year after treatment (P = .016)	
						Growth impairment was more severe in children < 4 years at diagnosis (P = .05)	

Abbreviations: ALL, acute lymphoblastic leukemia; AMC, arm muscle area; BIA, bioelectric impedance analysis; BMI, body mass index; BMI/A, body mass index for age; CDC, Centers for Disease Control and Prevention; EFS, event-free survival; EN, enteral nutrition; FFM, fat-free mass; FM, fat mass; H/A, height-for-age; HR, hazard ratio; MUAC, mid–upper arm circumference; OR, odds ratio; OS, overall survival; TSF, triceps skinfold; W/A, weight-for-age; WC, waist circumference; W/H, weight-for-height.

TABLE 2. Characteristics of Studies on Energy Needs and Clinical Intervention, Micronutrients, Survivors, and Risk Factors

Study, State	Tumor Type (No. of participants)	Primary Objective	Study Design	Timing of Assessment	Main Findings	Quality Score
Energy needs and clinical intervention						
Galati et al, 2011,[27] São Paulo	Several cancer diagnoses (N = 16)	To describe the nutritional status, energy expenditure, and substrate use of children and adolescents with cancer compared with healthy children	Cross-sectional	Unclear	No evidence of increased energy expenditure or change in lipid and carbohydrate metabolism in children with cancer compared with the healthy control group ($P > .05$)	3
					The control group had a higher protein intake ($P = .027$)	
Garófolo et al, 2007,[28] São Paulo	Several cancer diagnoses (N = 41)	To evaluate parenteral nutrition efficiency in supplying energy	Cross-sectional	During use of parenteral nutrition	Energy supply did not meet the demands in a high percentage of the patients (82%)	5
Garófolo, 2012,[29] São Paulo	Several cancer diagnoses (N = 142)	To evaluate the use of EN in patients with autologous and allogeneic HSCT	Prospective cohort	At admission and discharge for HSCT	47.2% of patients undergoing HSCT presented with an indication for EN via feeding tube	8
					The main contraindications for EN were severe GI toxicities and sinusitis	
					Minor complications from tube feeding were more prevalent in patients with allogenic HSCT	
					No major complications were observed	
Maia et al, 2010,[30] São Paulo	Several cancer diagnoses (N = 116)	To evaluate the impact of nutritional supplementation on the nutritional status and on the compliance with the nutritional therapy	Randomized clinical trial	3, 8, and 12 weeks after receiving supplements	TSF improvement from week 0 to week 12 ($P < .02$)	6

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TABLE 2. Characteristics of Studies on Energy Needs and Clinical Intervention, Micronutrients, Survivors, and Risk Factors (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Study Design	Timing of Assessment	Main Findings	Quality Score
Micronutrients						
Lima de Araújo et al, 2012,[31] Pernambuco	Several cancer diagnoses (N = 30)	To assess the nutritional status and frequency of inadequate vitamin C levels and determine associated factors	Cross-sectional	Within 48 hours of admission	70% had vitamin C deficiency	3
					According to H/A, W/A, and BMI/A, there was a low prevalence of weight and height deficit	
					The body composition measures revealed greater frequencies of inadequacy, with a greater depletion of fat reserves on diagnosis	
					60% of patients had experienced weight loss, but only 20% of the parents/guardians reported this sign at the time of diagnosis	
Campos et al, 2014,[32] Parana	Several cancer diagnoses (N = 66)	To assess serum 25-hydroxyvitamin D levels of children and adolescents undergoing allogeneic hematopoietic stem cell transplantation	Cross-sectional	Before hospitalization for HSCT, at 30 and 180 days after HSCT	Low levels of 25-hydroxyvitamin D were detected before HSCT and were significantly lower at 180 days after HSCT ($P = .01$)	11
					The prevalence of vitamin D deficiency was higher in patients compared with controls (32% v 8%, $P = .01$)	
					There were no significant differences in serum 25(OH)D levels between patients with or without GVHD	
					No correlation was found between 25-hydroxyvitamin D levels and vitamin D intake, GVHD, corticoid use, or survival rates	
Consolo et al, 2013,[33] Mato Grosso do Sul	ALL and AML (N =38)	To evaluate the effects of oral zinc supplementation on weight gain and infectious episodes	Randomized, double-blind, placebo-controlled clinical trial	At the beginning of supplementation, 30 and 60 days later	Plasma zinc concentrations did not increase significantly with the addition of the micronutrient ($P = .217$)	9
					Supplementary zinc promoted positive weight gain ($P = .032$)	
					The number of infection episodes was significantly reduced ($P = .02$)	
					Supplementation of zinc did not affect presence of xerostomia, taste dysfunction, nausea, and vomiting ($P = .812$), or mucositis ($P = 0.923$)	

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TABLE 2. Characteristics of Studies on Energy Needs and Clinical Intervention, Micronutrients, Survivors, and Risk Factors (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Study Design	Timing of Assessment	Main Findings	Quality Score
Rocha et al, 2016,[34] São Paulo	Several cancer diagnoses (N = 36)	To evaluate the effects of daily supplementation of Se on the hematologic cellularity and the immunoglobulin synthesis	Double-blind, placebo-controlled, crossover study	NR	Supplementation with Se reduced neutropenia in patients with LL and ST during chemotherapy	10
					IgA and IgG levels in patients with ST were higher than in patients with LL after Se supplementation ($P = .0051$ and $P = .0055$, respectively)	
					Increase in IgA production after Se supplementation in the ST group compared with the LL group ($P = .0011$)	
Sgarbieri et al, 1999,[35] São Paulo	ALL (N = 23)	To describe the protein-energy nutritional status and serum zinc and copper levels	Cross-sectional	Within 24 hours of admission and before start of chemotherapy	30% of children were malnourished at admission	3
					Reduced energy intake was seen only in patients from the upper age range (6 to 10 years)	
					Zinc and copper intakes were below the recommended values	
					Serum zinc levels were significantly lower, and serum copper levels were significantly higher in the leukemia group compared with controls ($P < .05$)	
Sgarbieri et al, 2006,[36] São Paulo	ALL (N = 45)	To follow anthropometric parameters and serum levels of zinc and copper during treatment	Prospective cohort	Diagnosis, induction, re-induction, and maintenance therapy	6.7% underweight, 4.4% stunted at diagnosis	5
					Reduced calorie intake in 76% of the children	
					During the initial phase of treatment, there was an increase in energy intake accompanied by weight gain	
					During the later phases of treatment, there was a reduction in energy intake with accompanying weight loss	
					Decreased growth rate during treatment was more pronounced in children with high-risk ALL	
					Serum zinc levels remained unaltered during treatment, whereas copper levels decreased with the beginning of treatment	

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TABLE 2. Characteristics of Studies on Energy Needs and Clinical Intervention, Micronutrients, Survivors, and Risk Factors (Continued)

Study, State	Tumor Type (No. of participants)	Primary Objective	Study Design	Timing of Assessment	Main Findings	Quality Score
Survivors and risk factors						
Molinari et al, 2017,[37] São Paulo	ALL survivors (N = 101)	To evaluate the impact of therapy on bone mineral density and body composition in survivors of ALL	Cross-sectional	At first complete clinical remission	22.8% overweight and 15.8% obese	6
					No correlation between being obese or overweight and previous exposure to radiation ($P = .28$)	
					23.4% had vitamin D insufficiency	
					The group that presented femoral BMD osteopenia was older than the group with normal BMD ($P = .001$)	
Papadia et al, 2007,[38] Federal District	ALL survivors (N = 27)	To assess biochemical parameters possibly related to intermediate metabolism and body composition	Cross-sectional	After 2 years of complete remission	Higher serum leptin levels than controls living in the same environmental conditions ($P < .05$)	3
					Leptin levels presented significant positive correlation with the insulin level in the control group, but not in the ALL group ($P = .08$)	
					ALL group had larger WC than the control group ($P < .05$), whereas hip circumference, waist/hip ratio, and BMI z score were similar ($P > .05$)	
Siviero-Miachon et al, 2011,[39] São Paulo	Medulloblastoma survivors (N = 16)	To analyze traits of metabolic syndrome in medulloblastoma survivors	Cross-sectional	After 2 years off therapy	Adolescent and young adult survivors of medulloblastoma showed centripetal fat deposition and decreased insulin sensitivity, associated with GH status	5
					Medulloblastoma survivors had increased WC ($P = .024$), waist-to-hip ratio ($P = .001$), and waist-to-height ratio ($P = .018$) compared with controls	
Teixeira et al, 2018,[40] São Paulo	Survivors, several cancer diagnoses (N = 79)	To evaluate the characteristics of dietary intake among child cancer survivors	Cross-sectional	First evaluation at the survivors' outpatient clinic, at least 2 years after treatment	25.5% of subjects were overweight and 2.5% were underweight	4
					All age groups showed sufficient carbohydrate and protein consumption	
					Survivors showed low consumption levels of polyunsaturated and monounsaturated fats, whereas the consumption level of saturated fats was close to the upper limit	
					Fiber intake was below the recommended level in all patient categories	
					The average daily intake of some vitamins and minerals was below the recommended intake levels, with values < 50% of adequacy	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMD, bone mineral density; BMI, body mass index; BMI/A, body mass index for age; EN, enteral nutrition; GH, growth hormone; GVHD, graft-versus-host disease; H/A, height-for-age; HSCT, hematopoietic stem cell transplantation; IgA, immunoglobulin A; IgG, immunoglobulin G; LL, leukemia/lymphoma; NR, not reported; Se, selenium; ST, solid tumors; TSF, triceps skinfold; W/A, weight-for-age; WC, waist circumference.

Study Quality

National Institutes of Health quality score assessment[13] for all included studies was calculated independently by two authors (K.V. and L.A.) and presented in Appendix Table A2. There were 15 initial disagreements, narrowed down to 12. After discussing with 2 more authors (E.J.L. and R.D.B.), all disagreements were resolved. Most studies (74%) were of poor quality (scoring < 8/14) in design and reporting, whereas the others were of fair and good quality.[8,13]

Study Characteristics

The majority of studies (52%) included patients with different cancer diagnoses, followed by studies focused on patients with acute leukemia (41%). Five articles (19%) were published in Brazilian Portuguese, whereas the rest were in the English language. Most studies were cross-sectional (70%), mainly retrospective chart reviews, and there were three clinical trials. The majority of the articles (63%) were published in the last decade and represented institutions located in the Southeast Region of Brazil (70%), mainly the state of São Paulo (74%), whereas no publications were from the North Region.

Results by Primary Outcome

Nutritional status and body composition. Thirteen studies addressed nutritional status and body composition (Table 1).[14-26] Overall, the prevalence of underweight patients at diagnosis varied from 6% to 25% and during treatment from 10.5% to 52.4%. In patients with ALL, the most studied diagnosis, the prevalence of underweight varied from 6% to 21.2% at diagnosis,[19,24-26] increasing to 52.6% in one study that assessed patients after at least one chemotherapy cycle.[16] Stunting prevalence ranged from 8.9% to 42.9%,[14-16,22,24,25] and one good-quality study reported growth deficit during and several years after treatment, with a negative impact on the final height, particularly in children younger than 4 years of age and in those who received cranial irradiation.[26] Overweight and obesity, however, had a reported prevalence of 4.1%-35% at diagnosis,[19,20,23,26] and 7.2%-57.9% during or after treatment.[14-17,23] In one study of patients with craniopharyngioma, 68.4% reported increased waist circumference, with a 44% prevalence of metabolic syndrome. This study also found that obesity at diagnosis was predictive of metabolic syndrome (OR, 6.1; P = .031).[23] Another study found overweight patients to have lower lean mass percentage on average (67.9%) than well-nourished (87.3%) or undernourished (84.1%) patients.[17]

Three studies compared different anthropometric measurements to assess nutritional status in patients with several cancer diagnoses. One found strong to moderate correlations between triceps skinfold thickness (TSFT) and body mass index (BMI; r = 0.8), as well as fat mass (r = 0.74) and fat-free mass (r = 0.76) measured by bioelectric impedance analysis.[17] Another study concluded that TSFT and mid–upper arm circumference (MUAC) detected more patients with malnutrition than BMI or weight-for-height (W/H) z scores (P < .05).[18] The third study found no differences in nutritional status according to BMI, MUAC, and TSFT (P > .05).[20]

Regarding the impact of undernutrition on outcomes, Pedrosa et al[22] found no relationship between nutritional status at diagnosis and survival (height-for-age [H/A] P = .229; weight-for-age [W/A] P = .996; W/H P = .887), whereas good-quality studies from Viana et al[24,25] found W/A at diagnosis to be unfavorable for prognosis (P = .0005). Moreover, stunting at diagnosis increased the risk of relapse 8.2-fold (95% CI, 3.1 to 21.9-fold) in one study[24] and 2.2-fold (95% CI, 1.2 to 4.1-fold; P = .015) in another.[25] Additionally, children with H/A z score above −1.28 at diagnosis had a 50% 8-year disease-free survival, compared with 0% for those with a z score lower then -1.28 (P = .000).[25] In contrast, Gelelete et al[19] found 5-year event-free survival of patients who were overweight/obese at diagnosis to be lower (67% v 81%; P = .03) than in nonoverweight/nonobese patients, reporting an overweight/obesity hazard ratio of 1.92 (95% CI, 1.42 to 2.60, P = .031). Last, one study investigated different ALL immunologic subtypes and was unable to demonstrate an association with W/A or H/A z score at diagnosis.[21]

The interpretation of these findings is challenging because of the heterogeneity of methodologies, as well as the classification of nutritional status. However, it seems clear that malnourished patients, both undernourished and overnourished, are widely prevalent in the Brazilian population of children and adolescents with cancer.

Energy needs and clinical intervention. Four studies addressed energy needs or tested clinical interventions (Table 2).[27-30] One article reported no evidence of increased energy expenditure or change in lipid and carbohydrate metabolism in children with cancer compared with a healthy control group.[27] Another study evaluated the use of parenteral nutrition (PN), reporting that most patients (82%) did not meet the recommended energy requirements despite receiving PN.[28] In contrast, in a good-quality study evaluating the use of enteral nutrition via feeding tube in patients undergoing hematopoietic stem cell transplantation (HSCT), 47.2% met an indication for this intervention, and no major complications were observed.[29] A fourth study evaluated the impact of oral supplementation on nutritional status and found improvement in TSFT from week 0 to week 12 of the intervention (P < .02).[30] The available studies are difficult to interpret because of the heterogeneity of objectives and designs, and reinforce the need to further understand nutritional therapy and its impact on Brazilian children with cancer.

Micronutrients. Six studies explored micronutrient status among children with cancer (Table 2).[31-36] One reported

that 70% of children were classified with vitamin C deficiency.[31] A study of good quality examined vitamin D (25-hydroxyvitamin D) and found that 32% were deficient before HSCT and became more deficient after HSCT ($P = .01$).[32] Another good-quality study supplemented participants with selenium (27 to 100 μg/day, according to age), which led to higher levels of immunoglobulin (Ig) A and IgG in patients with solid tumors ($P = .0051$ and $P = .0055$) and fewer neutropenia episodes during chemotherapy in patients with leukemia/lymphoma and solid tumors.[34] Three studies focused on zinc in patients with acute leukemia; the first reported lower serum levels than in controls ($P < .05$) and dietary intakes below the recommended values.[35] The second observed that serum zinc levels remained unaltered during treatment,[36] whereas the third was a good-quality study that observed no increase in plasma zinc concentrations ($P = .217$) with supplementation (2 mg/kg/day; maximum, 60 mg/day). Supplementation was associated with weight gain ($P = .032$) and reduction in the number of episodes of infection ($P = .02$).[33] Two studies reported on copper. One study found higher serum levels in patients with ALL compared with controls ($P < .05$) and intake below recommended values,[35] whereas another observed that copper levels decreased at the beginning of treatment.[36] Taken together, these studies seem to point to possible micronutrient deficiencies in children with cancer in Brazil, with an unclear but promising role for supplementation during treatment.

Survivors. Four studies examined the impact of treatment on the nutrition of survivors (Table 2).[21,25,37-40] Two studies examined ALL survivors, the first reporting higher serum leptin levels ($P < .05$) and larger waist circumference ($P < .05$) in cases compared with controls, with no differences in hip circumference, waist-to-hip ratio, and BMI-for-age z score ($P > .05$).[38] The second study reported 23.4% prevalence of vitamin D insufficiency, 22.8% prevalence of overweight, and 15.8% prevalence of obesity. There was no correlation between nutritional status and exposure to radiation ($P = .28$). The authors also found that patients at risk for low bone mineral density had lower values of lean body mass measured by dual-energy x-ray absorptiometry ($P = .03$).[37] Another study analyzed medulloblastoma survivors and showed increased waist circumference ($P = .024$), waist-to-hip ratio ($P = .001$), and waist-to-height ratio ($P = .018$) compared with controls.[39] By comparison, a study that evaluated the dietary intake of survivors of several types of cancer reported that 25.5% were overweight/obese and had low consumption of fiber, polyunsaturated and monounsaturated fats, and some micronutrients, such as vitamin E, calcium, and selenium.[40] Overall, these studies indicate that survivors might be at a higher risk for metabolic disease because of elevated anthropometric indicators and that there is an evident need for nutritional education on healthy eating habits.

DISCUSSION

To the authors' knowledge, this is the first systematic review of nutrition in children with cancer in an LMIC setting, applying rigorous criteria. A small number of Brazilian studies were identified, approximately 1.1 indexed publications per year, increasing to approximately 1.7 per year in the last decade. This is an insufficient amount in such an essential and growing field of research. Moreover, some of those publications were in the Brazilian Portuguese language, inaccessible to most of the global research community.

Most studies were of poor methodologic quality, based on retrospective chart reviews, thereby limiting our conclusions. Additionally, many studies included patients with different tumor types, with resulting difficulty in comparisons deriving from different disease burdens and treatments. Of the studies that focused on specific diagnoses, the majority were hematologic tumors, highlighting the need to also study patients with CNS and solid tumors.

A great discrepancy was noted in the number of publications among different states and regions of Brazil, with the majority of them from the Southeast Region, especially São Paulo. This reinforces the requirement for more representative data from the country, especially from regions such as the north, which has the highest prevalence of stunting in children younger than 9 years old, and the northeast, with the highest prevalence of underweight children and adolescents.[41] Furthermore, although not surprisingly, these under-represented regions are the ones with the greatest prevalence of food insecurity in Brazil.[42] The authors also observed the nonexistence of national or even multicentric studies on nutrition in pediatric oncology, studies that could bridge the gap in representation of the population of a vast and economically diverse country.

The variations in the prevalences found in nutritional status studies reflect a global lack of standardization on methods to clearly define undernutrition and overnutrition, diversity in the studied populations (different ages and diagnoses), and the country's socioeconomic inequality. The reported prevalence of underweight patients at diagnosis was approximately 1.5 to 7 times higher than that of the Brazilian population data for children (4.1%) and adolescents (3.4%),[41] and 4.5 to 19 times higher than data representative of South America (1.3%).[43] The prevalence of stunting was 1.2 to 6 times higher than the national and South American reported prevalences (7.1%).[43] Conversely, the prevalence of overweight or obese patients at diagnosis was compatible with Brazilian population data (overweight, 20.5%-33.5%; obese, 4.9%-14.3%); however, our study suggests a higher prevalence during and after treatment (1.7 times the national prevalence).[41,43] Endemic rates of stunting were found in either older publications when measured at diagnosis or in studies that assessed patients during treatment. In the first case, this

might be a reflection of the progressive reduction of height deficit prevalence over the decades in Brazil, which has been associated with the increase of family income, partly attributed to social welfare programs, such as Bolsa Família.[41,44] In the latter, treatment may be accountable for such results, because stagnant growth during cancer treatment has been previously reported for children with ALL in both LMICs and high-income countries.[26,45]

The prevalence of vitamin D deficiency reported by Campos et al[32] is lower than previously stated in the literature for children with cancer,[46,47] but aligned with national data.[48] Patients were from different regions of Brazil, with varying incidences of solar radiation in latitudes between −30° to −5°, which might explain this observation. The remaining studies that evaluated micronutrient levels were limited because of their reliance on serum micronutrient values reflecting recent dietary intake rather than nutrient deficiencies. Therefore, the results should be interpreted with caution for the studies reporting on selenium, vitamin C, and zinc.

In comparison with published studies from the United States, the results of our review found the same or lower prevalences of overweight and obesity among survivors of childhood cancer.[37,38,49,50] Concurring with a meta-analysis by Zhang et al,[49] our review confirmed no correlation of overweight/obesity with previous exposure to cranial radiation. One study reported on the diet of childhood cancer survivors[40] and found low consumption of fiber, vitamin E, and calcium, as was found also by studies on ALL survivors,[51,52] studies during treatment of ALL (calcium, fiber, zinc, and vitamins D and E),[53] and studies in childhood cancer survivors in general (calcium).[52] The results suggest similar suboptimal dietary intakes among Brazilian children with cancer compared with children in the United States; however, variations in nutrient databases limit direct study comparisons.

In this review we were unable to stratify nutritional outcomes according to the advance in access to medical cancer care in Brazil. The Brazilian Society of Pediatric Oncology was established in 1981, enabling treatment protocols for all cancer diagnoses and improving care, as well as access to care all over the country, with an increasing number of registered treatment centers, resulting in a positive impact on survival. Figure 2 reflects the improvement of outcomes in a single major Brazilian institution. However, many patients in Brazil are treated per protocol, not in a clinical trial, reflecting a deficit in trial enrollments.

Other limitations of this systematic review include a publication bias, because we only included indexed journals, and there may have been some Brazilian studies published in this field in nonindexed periodicals. Furthermore, the heterogeneity of themes led to the impossibility of statistical analysis of the data. Despite these limitations,
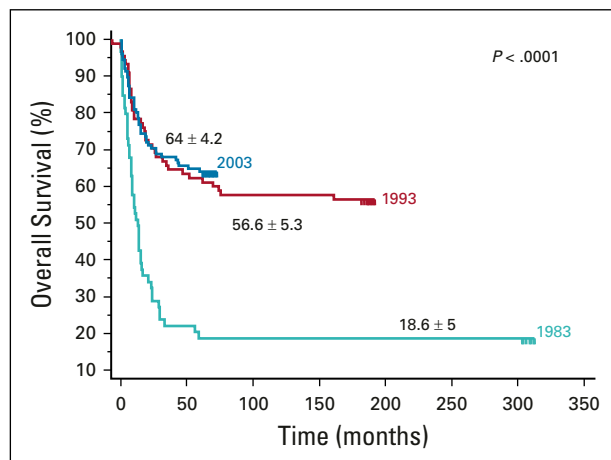

FIG 2. Long-term survival of children and adolescents with cancer.

the data suggest that there is great interest in the role of nutritional status and micronutrients in childhood cancer treatment and clinical outcomes in Brazil. Nutritional intervention studies and publications focused on survivors are scarce.

In conclusion, the authors identified a requirement in Brazil to focus on and invest in high-quality research in the field of nutrition in pediatric oncology. There is a particular need to engage in multicentric/national studies that will help establish research priorities and better planned clinical interventions, as well as educational strategies, tailored and adapted to each region of the country. In 2017, a partnership was established between the Brazilian Society of Pediatric Oncology and International Society of Paediatric Oncology through a nutrition task force, aiming to bridge that gap.[54] The support from such organizations is pivotal in improving nutrition research in pediatric oncology in Brazil, as well as implementing nutritional evaluations nationally at systematic time points. Some suggestions for specific research that could be undertaken are:

1. Prospective cohorts of patients with a single diagnosis or diagnoses that make clinical sense to group, especially solid tumors, to better understand how nutritional variables behave during treatment;
2. Prospective national diet quality and nutrient intake study, representative of different states and cultures;
3. Longitudinal multicentric trial on early nutrition therapy intervention in patients with selected diagnoses, such as medulloblastoma and osteosarcoma; and
4. Clinical trials focusing on specific nutrition interventions, such as protein intake, and their impact on body composition and outcomes.

Overall, it is critical to increase the representation from the under-represented regions in the literature. This may be the way to advance studies of nutrition in children with cancer, not only in Brazil but also in other LMICs.

AFFILIATIONS

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APPENDIX

TABLE A1. Search Strategies

Database	Search Terms
Medline	(((cancer) OR malignancy) OR oncology) AND (((((child) OR children) OR childhood) OR pediatric) OR pediatric) AND (((((((((((((((((((((obesity) OR overweight) OR weight) OR malnutrition) OR undernutrition) OR malnourished) OR fat) OR arm) OR diet) OR micronutrients) OR vitamins) OR dietary intake) OR body mass index) OR thinness) OR body composition) OR body size) OR growth) OR nutrition) OR nutritional status) OR enteral nutrition) OR parenteral nutrition) OR supplement) AND (Brazil)
Embase	(((cancer) OR malignancy) OR oncology) AND (((((child) OR children) OR childhood) OR pediatric) OR pediatric) AND (((((((((((((((((((((obesity) OR overweight) OR weight) OR malnutrition) OR undernutrition) OR malnourished) OR fat) OR arm) OR diet) OR micronutrients) OR vitamins) OR dietary intake) OR body mass index) OR thinness) OR body composition) OR body size) OR growth) OR nutrition) OR nutritional status) OR enteral nutrition) OR parenteral nutrition) OR supplement) AND (Brazil)
LILACS	((tw:(cancer)) OR (tw:(malignancy)) OR (tw:(oncology))) AND ((tw:(child)) OR (tw:(children)) OR (tw:(childhood)) OR (tw:(pediatric)) OR (tw:(pediatric))) AND ((tw:(obesity)) OR (tw:(body mass index)) OR (tw:(nutritional status)) OR (tw:(malnutrition)) OR (tw:(fat)) OR (tw:(weight)) OR (tw:(overweight)) OR (tw:(thinness)) OR (tw:(body composition)) OR (tw:(growth)) OR (tw:(body size)) OR (tw:(underweight)) OR (tw:(undernutrition)) OR (tw:(malnourished)) OR (tw:(dietary intake)) OR (tw:(diet)) OR (tw:(micronutrients)) OR (tw:(vitamins)) OR (tw:(enteral nutrition)) OR (tw:(nutrition)) OR (tw:(parenteral nutrition)) OR (tw:(supplement))) AND (tw:(Brazil))

Abbreviation: Latin American & Caribbean Health Sciences Literature.

TABLE A2. Quality Criteria for Assessment

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Lima de Araújo et al, 2012[31]	Yes	Yes	NR	No[a]	No	NA[b]	NA[b]	NA[b]	No[c]	No	NA[b]	NA[b]	NA[b]	NA[b]	3
Maciel Barbosa et al, 2012[14]	Yes	Yes	NA[d]	No[e]	No	Yes	No[f]	No	Yes	Yes	No	NA[d]	NA[d]	No[g]	5
Barreto et al, 2013[15]	Yes	Yes	NA[d]	No[g]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	3
Campos et al, 2014[32]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	11
Caram et al, 2012[16]	Yes	Yes	NA[d]	No[g]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	3
Carraro et al, 2012[17]	Yes	Yes	NR	No[a]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	4
Consolo et al, 2013[33]	Yes	Yes	NR	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	No[h]	9
Galati et al, 2011[27]	Yes	Yes	NR	No[j]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	3
Garófolo et al, 2005[18]	Yes	Yes	Yes	No[a]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	5
Garófolo et al, 2007[28]	Yes	Yes	NA[d]	No[a,i]	No	NA[i]	NA[i]	NA[i]	Yes	Yes	NA[i]	NA[i]	Yes	NA[i]	5
Garófolo et al, 2012[29]	Yes	Yes	NR	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	8
Gelelete et al, 2011[19]	Yes	Yes	NA[d]	Yes	No	Yes	Yes	No	No[k]	No	Yes	No	NA[d]	Yes	7
Lemos et al, 2014[20]	Yes	Yes	NR	No[a]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	4
Maia et al, 2010[30]	Yes	Yes	NR	No[a]	No	Yes	Yes	No[l]	No[l]	Yes	No[m]	No	No	No[l]	6
Molinari et al, 2017[37]	Yes	Yes	NA[d]	Yes	No	NA[b]	NA[b]	Yes	Yes	NA[b]	Yes	NA[b]	NA[b]	No	6
Paes et al, 2003[21]	Yes	Yes	NA[d]	Yes	No	NA[b]	NA[b]	NA[b]	Yes	NA[b]	NA[b]	NA[b]	NA[b]	Yes	5
Papadia et al, 2007[38]	Yes	Yes	NR	No[n]	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	3
Pedrosa et al, 2000[22]	Yes	Yes	NA[d]	No[n]	Yes	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	4
Rocha et al, 2016[34]	Yes	Yes	NR	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	10
Sgarbieri et al, 1999[35]	Yes	Yes	NR	No[g]	No	NA[i]	NA[i]	NA[i]	Yes	Yes	NA[i]	NA[i]	NR	Yes	3
Sgarbieri et al, 2006[36]	Yes	Yes	NR	No[g]	No	NA[i]	NA[i]	NA[i]	Yes	Yes	NA[i]	NA[i]	NR	Yes	5
Siviero-Miachon et al, 2011[39]	Yes	Yes	Yes	Yes	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	5
Teixeira et al, 2017[40]	Yes	Yes	NR	No	No	NA[b]	NA[b]	NA[b]	Yes	No	NA[b]	NA[b]	NA[b]	NA[b]	4
Tosta-Hernandez et al, 2018[23]	Yes	Yes	NR	No[j]	No	NA[b]	NA[b]	Yes	Yes	Yes	Yes	NA	NA[b]	Yes	7
Viana et al, 1994[24]	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	9

(Continued on following page)

TABLE A2. Quality Criteria for Assessment (Continued)

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Viana et al, 1998[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	10
Vilela and Viana, 2007[26]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	NR	Yes	9

NOTE. Options: Yes, No, cannot determine, NA, and NR: A study was attributed 1 point for each "Yes". Quality criteria: 1. Was the research question or objective in this article clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the patients selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? 5. Were a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this article, was the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure or exposure measured as continuous variable)? 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Abbreviations: NA, not applicable; NR, not reported.

aPopulation: all cancer diagnoses.

bCross-sectional study, observational, no outcome.

cSerum vitamin C levels and food-frequency questionnaire were not referenced; no way to know if validated.

dNo inclusion and exclusion criteria reported.

eOnly 3 to 11 (mean, 7) days of enteral nutrition to measure change in nutritional status.

fDifferent diagnoses and treatment moments, prescribed versus real intake was not reported.

gRetrospective chart review.

hNo control for zinc intake.

iNo exclusion criteria reported.

jNo outcomes measured.

kHow overweight/obesity was measured was NR.

lNo control for the amount of supplement intake.

mImprovement of nutritional status was not clearly defined.

nInclusion and exclusion criteria were not clearly defined.