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Nutritional Intake of Long Term Survivors of Childhood Acute Lymphoblastic Leukemia: Evidence for Bone Health Interventional Opportunities

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Abstract

Background—Survivors of childhood acute lymphoblastic leukemia (ALL) are vulnerable to exaggeration of the aging process including decreased bone mineral density (BMD). As little is known about their dietary or nutrient intake that may affect their long-term bone health, we examined nutrient intake in long-term survivors of childhood ALL.

Procedure—Survivors (n=164) of childhood ALL who had completed treatment for at least 5 years and were in continuous remission, completed a 110-item food questionnaire that reflected dietary intake over the previous year. The analyzed cohort comprised 34 females and 38 males younger than 19 years and 45 females and 47 males at least 19 years. Reported nutrient intake and food selection were compared with age-specific Recommended Dietary Allowance and USDA Pyramid Food Guide. Body mass index was compared to the general US population, adjusted for age, gender, Tanner stage and race.

Results—Less than 30% of participants met recommended dietary intakes for vitamin D, calcium, potassium or magnesium regardless of age. Mean daily caloric intake was 2204 Kcal

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(51% from carbohydrates) for younger and 2160 Kcal (49% from carbohydrates) for older participants. Energy intake from sweets was 70% higher than recommended. Participants <19 years were less likely to have a healthy weight (Odds Ratio 0.48, 95% CI 0.30-0.79); < 19 years more likely to be overweight (Odds Ratio 1.95, 95% CI 1.11-3.32, $p < 0.002$)

Conclusions—Survivors of childhood ALL need careful dietary intervention to optimize long-term health.

Keywords

body mass index; dietary intake; acute lymphoblastic leukemia; pediatric leukemia; childhood cancer survivors

Introduction

With contemporary treatments, 80% to 90% of children with acute lymphoblastic leukemia (ALL) become long-term survivors[1] and represent a rapidly growing population of young adults who are vulnerable to exaggeration of the aging process[2]. Possible late effects include not only decreased bone mineral density (BMD)[3,4] and obesity[5-8] but also an increased risk of secondary cancers and chronic illnesses[9,10]. Whether these maladies are due to poor health practices or are long-term consequences from cancer or its treatment remain in question[2]. Some studies suggest that long term survivors of childhood ALL are more likely to be overweight or obese than the healthy population[11]; others show that the increased rate of being overweight or obese in the survivors reflects the trend seen in the general population[11,12]. Despite this uncertainty, poor nutritional practices may predispose individuals to chronic disease or increase the likelihood of developing another cancer [13]. Because little is known about the nutritional habits of long-term survivors of childhood ALL, we studied their nutritional practices, particularly as they relate to BMD, and evaluated opportunities for interventions to promote healthy food choices integral to bone health.

Participants and Methods

Participants for this study represent long-term survivors of ALL. These individuals were treated and followed under Institutional Review Board (IRB)-approved treatment protocols (1984 to 1997): Total Therapy Studies XI, XII, XIII A and XIII B [14-17]. All participants were approached by a research study nurse in person or via phone and provided informed consent or assent for those < 18 years and had parents or legal guardians consent to participate in a nutritional interventional trial whose goal was to improve BMD[18]. Briefly, those targeted for recruitment and enrolled in the nutritional intervention trial had to be in complete remission and at least 5 years since completion of therapy. The focus of the intervention was on increasing calcium and vitamin D intake through foods and/or supplements. Thus, participants were ineligible if they had active disease, were pregnant or lactating, had anemia, were unable to take pills, or had prior bone marrow transplantation. Individuals reported taking calcium and vitamin D supplements were asked to abstain from their use for 3 months prior to study enrollment. All data were managed according to the Health Insurance Portability and Accountability Act (HIPAA) of 1996. This report includes those individuals who enrolled in the nutrition intervention trial and completed the baseline nutrition evaluation.

Dietary Intake Measures

A self-administered food frequency questionnaire (FFQ)[19] was completed by participants or with help by caregiver at the baseline visit of the nutrition intervention trial. This 110

food item questionnaire (Block 1998 [19]), developed from NHANES III dietary recall data, was designed to estimate usual intake of macro and micro nutrients. The nutrient database was developed from the USDA Nutrient Database for Standard Reference. Individual portion size was asked for each food; pictures were provided to enhance quantification accuracy. The completed questionnaires were processed to yield nutrient and food intake according to the USDA pyramid food guide [www.mypyramid.gov] for the previous 12 months. Initially, study participants (n=261) were permitted to complete their questionnaire independent of the study coordinator and return the completed form by mail. The percentage of returned questionnaires was suboptimal and of those returned, many with incomplete responses were deemed unacceptable for processing. Thus, we modified the administration process such that all questionnaires were reviewed by a registered nutritionist for completeness during a clinic visit and submitted prior to participant departure. The study participants in this report comprise only those who completed the questionnaire after process modification (n=174).

Of the 174 participants, eight were excluded from analysis as their daily kilocalorie intake fell either less than 500 or greater than 5,000 kcal per day. Two additional participants were excluded due to incomplete data. Thus, 164 participants were evaluable for this study. Our exclusion criterion was based on a widely used approach in nutritional epidemiology to identify those with implausible reports [20]. The quality of each participant's diet was coded according to the Healthy Eating Index[21] [corrected ref 21] [<http://www.cnpp.usda.gov/healthyeatingindex.htm>] which measures nutritional dietary quality. An average score was calculated according to the age group (<19 years or ≥19 years). Foods considered as sweets were those to which sugars or syrups were added during preparations or processing as grouped in the USDA pyramid food guide[19]. A low Healthy Eating Index score indicates a possible low intake of nutrients important in bone health.

Anthropometric Measurements

Participant's height was measured without shoes using a wall-mounted stadiometer. Two measurements were taken and a third if the difference between the two measurements exceeded 1 cm. The average of the two closest measurements was used as the participant's height. Body weight, recorded to the nearest 0.1 kilogram, was measured using a calibrated digital scale. Participants wore light clothing. Body Mass Index (BMI) was calculated as weight divided by height squared. Body weight status was divided into four groups. For those 19 years of age and younger, Center for Disease Control Growth Charts for age and gender were used as a reference for underweight (BMI below 5th percentile), healthy weight (BMI 5th and <85th percentile); at risk overweight (BMI 85th and <95th percentile); and overweight (BMI ≥95th percentile) [22,23]. For those 20 years of age and older, BMI was used to classify underweight (< 18.5 kg/m²), healthy weight (18.5-24.9 kg/m²); overweight (24.9-29.9 kg/m²); and obese (≥30 kg/m²) [24].

Statistical Analysis

Statistical analyses were performed using SAS statistical software[25] and Proc StatXact released by the Cytel Software Corporation[26]. Descriptive measures of selected characteristics were compared between survivors who did or did not complete the FFQ at baseline entry into the larger clinical trial. We used Wilcoxon-Mann-Whitney test to compare measures as the data was not normally distributed. The significance level was set at p = 0.05. Nutrition information was compared according to gender, race (non-Hispanic white, non-Hispanic black and others), age group (< 19 years and ≥19 years), and BMI group (underweight, healthy, overweight, and obese). The age groups were selected to match the age ranges established for Dietary Reference Intakes (DRI)[27-31]. The percent of each age group meeting the DRI was calculated as the sum of all individuals whose intake

met the DRI for each nutrient. The percent of participants meeting the acceptable macronutrient distribution ranges (AMDR) for percent kilocalories from fat fell within the following ranges (age < 19 years: 25-35% of kcal from fat, ages 19 years: 20-35 % kcal from fat). If the participant's fat intake fell outside of these ranges (either too high or too low), it was considered as not meeting the recommended amount. The same algorithm was used for determining the AMDR for protein (age < 19 years: 10-30%; ages 19 years: 10-35 %) and carbohydrate (age < 19 years: 45-65%; ages 19 years: 45-65 %). To compare the proportion of study participants that were classified as at risk for overweight, overweight or obese compared to the US population[32,33], odds ratio's and 95% exact confidence limits were computed for each weight category for each age group with an algorithm based on Thomas[34]. Fisher's exact test[35] was applied to determine if there were differences using one-sided p-values.

Results

Patient Demographics

The 164 evaluable patients included 34 females and 38 males 18 years of age or younger and 45 females and 47 males 19 years of age or older. Study participants were characterized by 84% Non-Hispanic White (NHW), 15% Non-Hispanic Black (NHB), and 1% other race.

Comparison of participants who did or did not complete the FFQ

Survivors who did or did not complete the FFQ (Table I) were comparable with respect to gender, race, BMI distribution, Tanner stage, years since treatment, and use of multiple vitamin supplements. The only exception was age: survivors who completed the FFQ were older than those who did not (19.6 years vs. 16.6 years; $p < 0.0001$, respectively).

Nutrient Intake

Nutritional intake amongst study participants is presented in Tables II and III. Study participants under-consumed dairy products, fruits, vegetables and whole grain groups when compared to nutrient intake recommended by the USDA Pyramid Guide [www.mypyramid.gov]. Energy intake from sweets was 70% higher than the recommended level. The average Healthy Eating Index Score was 58.9 out of 100 for the younger age group (<19 years) and 56.9 for those 19 years and older. While 100% of the participants met the protein intake, the carbohydrate intake was primarily from low fiber containing foods that were highly processed. Sixty percent of our sample consumed a higher percent of fat than was recommended by the DRI's. Consuming a multivitamin supplement was reported by 13.8% of participants younger than and 30.4% of those older than 19 years.

Less than 30% of participants met the recommended level of intake for vitamin D, calcium, potassium or magnesium. Only 47% of those below 19 years met the recommended levels for phosphorus, compared to 84% of those over 19 years. Other nutrients that were most limited in the diet regardless of age included folate (< 52% met the DRI), vitamin E (<23 %), and fiber (<6%). Nutrient intake meeting the DRI comprised (% by age < 19, 19): vitamins A (73.6%, 27.2%), B₆, (83.3%, 52.2%) B₁₂ (76.4%, 65.2%), and C (84.7%, 63.0%); thiamin (89.9%, 65.2%), and riboflavin (90.3%, 77.2).

Body Weight Status

Study participants between the ages 8 and 19 years had a lower prevalence of healthy weight (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.30-0.79; $p=0.002$) and higher prevalence of overweight (OR, 1.95; 95% CI, 1.11-3.32; $p=0.010$) than described by NHANES[32] (Figure 1). Though not attaining statistical significance, survivors older than 19 years tended to have low prevalence of healthy weight (OR 0.74; 95% CI, 0.45-1.18) and

high prevalence of at risk of overweight (OR, 1.12; 95% CI, 0.68-1.83) and of overweight (OR, 1.25; 95% CI, 0.76-2.02). The prevalence of being underweight was 4.3% in the younger group and 2.3 % in the older group. Patients who had received cranial irradiation were significantly more likely to be overweight or obese compared to the other survivors ($p = 0.0466$, OR=2.124, CI= (1.011,4.461).

Discussion

Dietary intake affects all metabolic processes with the net effect on metabolism being dependent on the stage of the life cycle, physical activity and hormonal milieu. The trial in which participants were ultimately randomized focused on improving BMD. However, important information was obtained prior to any intervention and provides insight into dietary habits contributing to overall health with specific focus on BMD in survivors of childhood ALL.

The AMDR provides a range of intake of carbohydrate, fat and protein that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients[31]. While reported protein intake fell within the AMDR in more than 90% of the cohort, reported carbohydrate and fat intake exceeded recommendation in 38% and 47% of the participants, respectively. Since fiber intake was low, the majority of the carbohydrates consumed might have come from refined sources. This suggests that the high intake of carbohydrates and fat was at the expense of foods high in nutrients important to bone health. Therefore, dietary interventions should focus on the quantity and quality of dietary fats and carbohydrates as well as assuring adequate intake of vitamin D, calcium, potassium, magnesium and folate. We also found that the majority of the study participants failed to meet the DRI for vitamin D, calcium, potassium, magnesium and folate – all important nutrients for skeletal development.

Selection of food sources

The prudent diet that includes fruits, vegetables, whole grains, low-fat dairy products, fish and poultry is promoted to prevent chronic diseases such as heart disease, hypertension, diabetes mellitus, cancer, obesity and perhaps osteoporosis. Nutrition interventions usually emphasize changes in food habits, which translate into changes in nutrients consumed. Cornerstones of most dietary interventions include increasing consumption of fruits and vegetables while minimizing intake of foods high in fat and refined carbohydrates. The fact that only 1% of our participants met the AI for fiber implies that whole grains, fruits and vegetables had a limited presence in their diet. Intake of fruits and vegetables is typically low in the US population with one study reporting only 35.1% being compliant with recommendations[36]. Like the majority of the US population, our study participants fall short of consuming 5 to 9 servings of fruits and vegetables and 3 or more servings of dairy products daily[37]. Our findings contrast with one study that showed ALL survivors consume higher quantities of fruits, vegetables and dairy products[38]. Fruits and vegetables are excellent sources of potassium but also provide bicarbonate, essential oils and monoterpenes[39-41] that may be beneficial for bone metabolism.

Weight status

Based on weight status as an indicator of long term energy balance, the majority of long-term survivors consumed more energy than they expended, contributing to risk for overweight or obesity. Thirty-seven to 51% of study survivors met their energy requirements. However, 49% younger than 19 years and 63% of older survivors are at risk for overweight, overweight or obese. Our current estimate and that of a recent report from our institution [12], show 11-57% of children are at risk for overweight or fell well within

that range [42-44]. Being overweight as a child or adolescent is a strong risk factor for overweight or obesity as an adult[12]. The increase in overweight or obesity in ALL survivors has been linked to decreased physical activity and increased energy intake from treatment with corticosteroids[43]. The finding of association between obesity and treatment with cranial irradiation in this study has been previously reported [45]. Reported associations between increased BMI and hypertension, dyslipidemia, cardiovascular disease, type II diabetes, osteoarthritis and some cancers, has prompted concern for long-term health of ALL survivors[46]. Although excess body weight has been considered a protective factor for osteoporosis[47], body weight does not account for differences in the rates of bone loss and fracture risk in adults aged 70 to 79 years of age with type II diabetes[48,49]. Thus, concern for bone health in persons who are overweight or obese may depend on the long-term sequelae associated with treatment combined with genetic predisposition to diabetes[43].

Weight control is universally important for overall health making weight reduction for overweight or obese survivors a logical target for intervention. However, weight loss and preservation of BMD must be balanced as intentional weight loss has been purported as a possible detriment to bone mass [50-52]. It is estimated that a 1-2% decline in BMD is associated with a 10% weight loss. Research suggests that energy deficiency of 500 kilocalories has little or no effect on bone metabolism [53]. Thus, interventions targeting excess weight in adult survivors of pediatric ALL should focus on obtaining a healthy body weight while minimizing mineral loss. Since weight loss effects on bone mass in children are unknown, the focus should optimize growth while minimizing the adverse effect on bone acquisition and promoting healthy regimes consistent with the prevention of other chronic diseases.

Intake of minerals

Diet-related bone research promotes a positive calcium balance during childhood and adolescence and a net calcium balance of zero during adulthood. More recent investigations characterize potassium, sodium and magnesium as modulators of bone metabolism [54-57]. Both childhood and adult survivors of ALL studied, reported suboptimal intake of most minerals. However, the average intake reported for these nutrients by our participants are similar to those reported from the Nutrition Health and Examination Survey 1999-2000[58]. Suboptimal intake of minerals combined with insults to bone metabolism from ALL therapy[59] and possible coexisting endocrinopathies[60] may predispose survivors to a higher risk of osteoporosis and other chronic diseases at a younger age than would be expected.

Vitamin intake

Vitamins directly or indirectly affect bone metabolism through the endocrine and/or paracrine system by modulating calcium homeostasis. While our cohort reported low vitamin D intake, we did not consistently measure their serum 25 hydroxy-vitamin D level, a marker of vitamin D adequacy that integrates both diet and ultraviolet exposure. Some B vitamins, have been implicated in affecting bone metabolism either by acting directly on BMD by impaired cross link formation[61] or via homocysteine in adults[62,63]. Vitamins A, C, E and K have been linked to bone metabolism via collagen synthesis or bone turnover, and to BMD and fractures in adults [64-67]. The importance of these nutrients is only now being examined in children [68,69].

Study limitations and strengths

The limitations of our report include a modest sample size, making it difficult to examine relationships between individual nutrients, body weight status and BMD. We were able to

identify significant dietary differences between younger and older survivors. Such information is important for developing interventional programs directed at improving overall nutrition and long-term health. The cross-sectional nature of investigation reflects a single point in time. Our findings nevertheless demonstrate a need for nutritional intervention programs over a broad spectrum of ages ranging from teens to young adults and indicate dietary intake characteristics that could be targeted relative to patient age. We also acknowledge that the dietary intake of the predominately white American population, most of whom reside in the midsouth, may have limited generalizability. As in other studies[38], the FFQ does not measure salt or sugar added during food preparation. Despite this limitation, the FFQ is fairly easy to complete and provides a cost- and effort-efficient means to assess dietary intake in a large patient population. While the FFQ is used to rank individuals, it has been deemed adequate for reporting intakes of groups. The intake by our childhood survivors is similar to that reported by other researchers using a FFQ[38,70]. The intake of the adults is similar to that reported by NHANES suggesting that our population of ALL survivors is similar to the general US population.

Strengths of this study include the quality control measures used to collect, process and evaluate nutrient and food intake and the large patient cohort evaluated.

In summary, long-term survivors of ALL are similar to the general US population with regard to consuming less minerals and vitamins than are considered essential for optimal health. The low consumption of dairy foods, fruits and vegetables provides a target for interventions. When coupled with behavioral interventions that increase nutrient density of the diet while normalizing body weight, the amelioration or prevention of complications and development of osteoporosis and other chronic diseases may ensue.

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References

1. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med.* 2006; 354(2):166–178. [PubMed: 16407512]
2. Aziz NM. Cancer survivorship research: challenge and opportunity. *J Nutr.* 2002; 132(11 Suppl): 3494S–3503S. [PubMed: 12421876]
3. Eakin EG, Youlden DR, Baade PD, et al. Health status of long-term cancer survivors: results from an Australian population-based sample. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(10):1969–1976. [PubMed: 17035407]
4. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia.* 2001; 15(5):728–734. [PubMed: 11368432]
5. Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2003; 21(7):1359–1365.
6. Kaste SC, Rodriguez-Galindo C, Furman WL, et al. Imaging aspects of neurologic emergencies in children treated for non-CNS malignancies. *Pediatr Radiol.* 2000; 30(8):558–565. [PubMed: 10993541]
7. Didi M, Didcock E, Davies HA, et al. High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. *J Pediatr.* 1995; 127(1):63–67. [PubMed: 7608813]

8. Moyer-Mileur LJ, Ransdell L, Bruggers CS. Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy: response to a home-based exercise and nutrition program. *J Pediatr Hematol Oncol.* 2009; 31(4):259–266. [PubMed: 19346877]
9. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA.* 2003; 290(12):1583–1592. [PubMed: 14506117]
10. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol.* 2009; 27(14):2339–2355. [PubMed: 19364955]
11. Asner S, Ammann RA, Ozsahin H, et al. Obesity in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2008; 51(1):118–122. [PubMed: 18338394]
12. Razzouk BI, Rose SR, Hongeng S, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. *J Clin Oncol.* 2007; 25(10):1183–1189. [PubMed: 17401007]
13. Sagar SM, Lawenda BD. The role of integrative oncology in a tertiary prevention survivorship program. *Prev Med.* 2009; 49(2-3):93–98. [PubMed: 19523482]
14. Evans WE, Relling MV, Rodman JH, et al. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med.* 1998; 338(8):499–505. [PubMed: 9468466]
15. Pui CH, Mahmoud HH, Rivera GK, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. *Blood.* 1998; 92(2):411–415. [PubMed: 9657739]
16. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIII B at St Jude Children's Research Hospital. *Blood.* 2004; 104(9):2690–2696. [PubMed: 15251979]
17. Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute lymphoblastic leukaemia with reinforced early treatment and rotational combination chemotherapy. *Lancet.* 1991; 337(8733):61–66. [PubMed: 1670723]
18. Rai SN, Hudson MM, McCammon E, et al. Implementing an intervention to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia: BONEII, a prospective placebo-controlled double-blind randomized interventional longitudinal study design. *ContempClinTrials.* 2008; 29(5):711–719.
19. Block Food Frequency Questionnaire. *Nutrition-Quest.* 1998. <http://www.nutritionquest.com/products/questionnaires_screens.htm> Accessed
20. Willet, W. *Nutritional Epidemiology.* 2nd. New York: Oxford University Press; 1998. p. 322
21. Guenther PM, Reedy J, Krebs-Smith SM, et al. Evaluation of the Healthy Eating Index-2005. *J Am Diet Assoc.* 2008; 108(11):1854–1864. [PubMed: 18954575]
22. CDC. 2000 CDC Growth Charts: United States. 2009. <<http://www.cdc.gov/growthcharts/>> Accessed
23. CDC CfDC. About BMI for Children and Teens. U.S. Department of Health & Human Services; 2009. <http://www.cdc.gov/NCCDPHP/DNPA/healthyweight/assessing/bmi/childrens_BMI/about_childrens_BMI.htm> Accessed
24. About BMI for Adults. U.S. Department of Health & Human Services; 2009. <http://www.cdc.gov/nccdp/hnpa/healthyweight/assessing/bmi/adult_BMI/about_adult_BMI.htm> Accessed
25. *The SAS System V9.* Cary, NC: SAS Institute Inc; 2003.
26. *Proc-StatXact 5.* Cambridge, MA.: CYTEL Software Corporation; 2002.
27. Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D and fluoride: standing committee on the scientific evaluation of dietary reference intakes. Washington, D.C.: Food and Nutrition Board, Institute of Medicine; 1997. p. 430Report
28. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc: a report of the panel on micronutrient, subcommittees on upper reference levels of nutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary

- reference intakes. Washington, D.C.: Food and Nutrition Board, Institute of Medicine; 2001. p. 113Report
29. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids: a report of the panel on micronutrient, subcommittees on upper reference levels of nutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes. Washington, D.C.: Food and Nutrition Board, Institute of Medicine; 2000. p. 139Report
 30. Dietary reference intakes for water, potassium, sodium, chloride and sulfate: a report of the panel on micronutrient, subcommittees on upper reference levels of nutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes. Washington D.C.: Food and Nutrition Board, Institute of Medicine; 2005. p. 71-145.Report
 31. Dietary reference intakes for: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids: a report of the panel on macronutrients: subcommittees on upper reference levels of nutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes. Washington, D.C.: Food and Nutrition Board, Institute of Medicine; 2002. p. 936Report
 32. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006; 295(13):1549-1555. [PubMed: 16595758]
 33. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003-2006. *JAMA*. 2008; 299(20):2401-2405. [PubMed: 18505949]
 34. Thomas D. Exact Confidence Limits for the Odds Ratio in a Two by Two Table. *Applied Statistics*. 1971; 20:36.
 35. Agresti, A. *Categorical data analysis*. New York: Wiley; 2002.
 36. Berrigan D, Dodd K, Troiano RP, et al. Patterns of health behavior in U.S. adults. *Prev Med*. 2003; 36(5):615-623. [PubMed: 12689807]
 37. Fruit and Vegetable Consumption Among Adults --- United States, 2005. *Morbidity and Mortality Weekly Report*. 2007; 56:213-217.
 38. Robien K, Ness KK, Klesges LM, et al. Poor adherence to dietary guidelines among adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2008; 30(11):815-822. [PubMed: 18989158]
 39. Muhlbauer RC, Lozano A, Reinli A. Onion and a mixture of vegetables, salads, and herbs affect bone resorption in the rat by a mechanism independent of their base excess. *J Bone Miner Res*. 2002; 17(7):1230-1236. [PubMed: 12096836]
 40. Muhlbauer RC, Lozano A, Reinli A, et al. Various selected vegetables, fruits, mushrooms and red wine residue inhibit bone resorption in rats. *J Nutr*. 2003; 133(11):3592-3597. [PubMed: 14608079]
 41. Muhlbauer RC, Lozano A, Palacio S, et al. Common herbs, essential oils, and monoterpenes potently modulate bone metabolism. *Bone*. 2003; 32(4):372-380. [PubMed: 12689680]
 42. Chow EJ, Pihoker C, Hunt K, et al. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. *Cancer*. 2007; 110(10):2313-2320. [PubMed: 17896787]
 43. Nathan PC, Jovcevska V, Ness KK, et al. The prevalence of overweight and obesity in pediatric survivors of cancer. *J Pediatr*. 2006; 149(4):518-525. [PubMed: 17011325]
 44. Rogers PC, Meacham LR, Oeffinger KC, et al. Obesity in pediatric oncology. *Pediatr Blood Cancer*. 2005; 45(7):881-891. [PubMed: 16035086]
 45. Garmey EG, Liu Q, Sklar CA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2008; 26(28):4639-4645. [PubMed: 18824710]
 46. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci*. 2003; 58(1):82-91. [PubMed: 12560417]
 47. Shapses SA, Riedt CS. Bone, body weight, and weight reduction: what are the concerns? *J Nutr*. 2006; 136(6):1453-1456. [PubMed: 16702302]
 48. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health,

- Aging, and Body Composition Study. *J Bone Miner Res.* 2004; 19(7):1084–1091. [PubMed: 15176990]
49. Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. *J Bone Miner Res.* 2005; 20(4):596–603. [PubMed: 15765178]
 50. Jensen L, Quadde F, Sorensen O. Bone loss accompanying voluntary weight loss in obese humans. *J Bone Miner Res.* 1994; 9:459–463. [PubMed: 8030433]
 51. Macdonald HM, New SA, Campbell MK, et al. Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. *Osteoporos Int.* 2005; 16(2): 163–171. [PubMed: 15185065]
 52. Ensrud KE, Fullman RL, Barrett-Connor E, et al. Voluntary weight reduction in older men increases hip bone loss: the osteoporotic fractures in men study. *J Clin Endocrinol Metab.* 2005; 90(4):1998–2004. [PubMed: 15671096]
 53. Ihle R, Loucks AB. Dose-response relationships between energy availability and bone turnover in young exercising women. *J Bone Miner Res.* 2004; 19(8):1231–1240. [PubMed: 15231009]
 54. Rafferty K, Davies KM, Heaney RP. Potassium intake and the calcium economy. *J Am Coll Nutr.* 2005; 24(2):99–106. [PubMed: 15798076]
 55. Macdonald HM, New SA, Fraser WD, et al. Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in premenopausal women and increased markers of bone resorption in postmenopausal women. *Am J Clin Nutr.* 2005; 81(4):923–933. [PubMed: 15817873]
 56. Ryder KM, Shorr RI, Bush AJ, et al. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. *J Am Geriatr Soc.* 2005; 53(11):1875–1880. [PubMed: 16274367]
 57. Palacios C, Wigertz K, Martin BR, et al. Sodium retention in black and white female adolescents in response to salt intake. *J Clin Endocrinol Metab.* 2004; 89(4):1858–1863. [PubMed: 15070956]
 58. Wright J, Wang C, Kennedy-Stephenson M, et al. Dietary Intake of ten key nutrients for Public Health, United States: 1999–2000. 2003 Apr 17. 2003 Report.
 59. Atkinson SA, Halton JM, Bradley C, et al. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. *Int J Cancer Suppl.* 1998; 11:35–39. [PubMed: 9876475]
 60. Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. *Acta Paediatr Suppl.* 1999; 88(433):1–4. [PubMed: 10626537]
 61. Levasseur R. Bone tissue and hyperhomocysteinemia. *Joint Bone Spine.* 2009; 76(3):234–240. [PubMed: 19217816]
 62. Rejnmark L, Vestergaard P, Hermann AP, et al. Dietary Intake of Folate, but not Vitamin B(2) or B (12), Is Associated with Increased Bone Mineral Density 5 Years after the Menopause: Results from a 10-Year Follow-Up Study in Early Postmenopausal Women. *Calcif Tissue Int.* 2008; 82(1): 1–11. [PubMed: 18175033]
 63. Yazdanpanah N, Zillikens MC, Rivadeneira F, et al. Effect of dietary B vitamins on BMD and risk of fracture in elderly men and women: the Rotterdam study. *Bone.* 2007; 41(6):987–994. [PubMed: 17936100]
 64. Cheung AM, Tile L, Lee Y, et al. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med.* 2008; 5(10):e196. [PubMed: 18922041]
 65. Jackson HA, Sheehan AH. Effect of vitamin A on fracture risk. *Ann Pharmacother.* 2005; 39(12): 2086–2090. [PubMed: 16249271]
 66. Martinez-Ramirez MJ, Palma Perez S, Delgado-Martinez AD, et al. Vitamin C, vitamin B12, folate and the risk of osteoporotic fractures. A case-control study. *Int J Vitam Nutr Res.* 2007; 77(6): 359–368. [PubMed: 18622945]
 67. Zhang J, Munger RG, West NA, et al. Antioxidant intake and risk of osteoporotic hip fracture in Utah: an effect modified by smoking status. *Am J Epidemiol.* 2006; 163(1):9–17. [PubMed: 16306312]
 68. Kalkwarf HJ, Khoury JC, Bean J, et al. Vitamin K, bone turnover, and bone mass in girls. *Am J Clin Nutr.* 2004; 80(4):1075–1080. [PubMed: 15447922]

69. O'Connor E, Molgaard C, Michaelsen KF, et al. Serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, and its relationship to bone health indices in Danish girls. *Br J Nutr.* 2007; 97(4):661–666. [PubMed: 17349078]
70. Rockett HR, Breitenbach M, Frazier AL, et al. Validation of a youth/adolescent food frequency questionnaire. *Prev Med.* 1997; 26(6):808–816. [PubMed: 9388792]

Abbreviations

ALL	acute lymphoblastic leukemia
QCT	quantitative computed tomography
BMD	bone mineral density
NHW	Non Hispanic White
NHB	Non-Hispanic Black
SD	standard deviation
DRI	Dietary Reference Intake
RDA	Recommended Dietary Allowance
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
USDA	United States Department of Agriculture
BMI	Body mass index
FFQ	Food frequency questionnaire

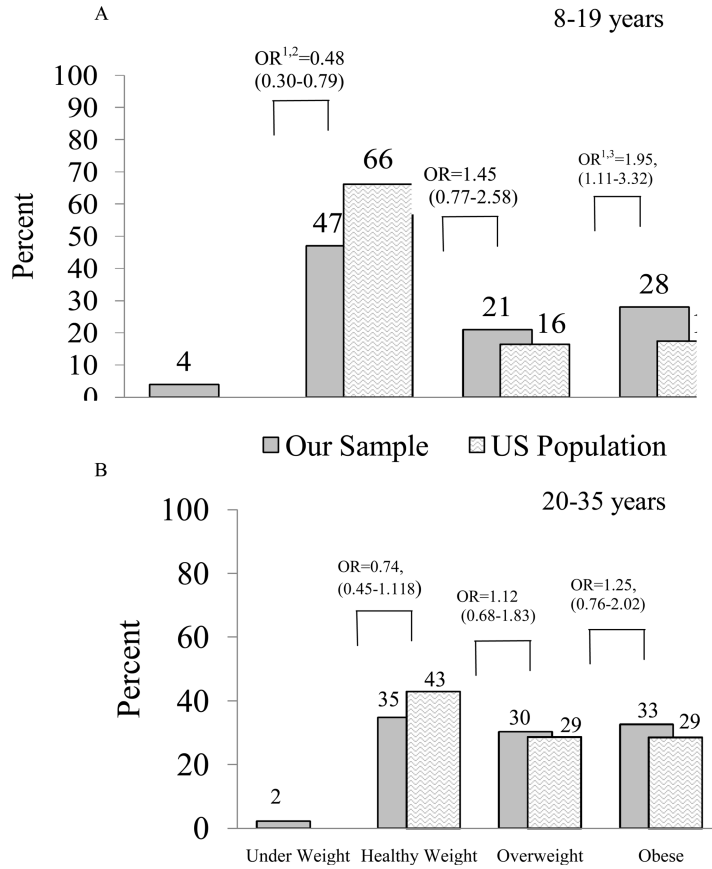


Figure 1. Weight Status of Participants according to Age and sex groups (%) as defined by Center for Disease Control Growth Charts[24]. **(A)** Depicts the distribution of reported pediatric participants and **(B)** the distribution of reported adult participants (dark gray) compared to the general population (light gray). ¹Odds ratio (95% Confidence Interval); ²p=0.004; ³p=0.016 distribution different than US population for 8-19 y; percent in the US population ages 8-19[33]; percent in the US population ages 20-35[32]. Underweight values for US population not available.

Table 1
Distribution of Selected Patient Characteristics: Age, Height, Weight, Years Since Treatment and Years on Multi-Vitamin Supplements

	Completed FFQ	N	Mean	SD ¹	Median	Min	Max	p-values ²
Age (year)	No	260	16.6	5.4	16	8	36	<0.0001
	Yes	164	19.6	7.0	20.5	9	35	
Height (cm)	No	260	162.2	12.6	162.6	130.8	190.6	0.5233
	Yes	164	162.9	14.2	163.2	124.6	192.6	
Weight (kg)	No	260	67.5	22.8	62.4	30.3	172.6	0.4998
	Yes	164	68.9	23.4	65.6	28.7	155.3	
Years Since Treatment	No	260	9.3	3.4	8.8	4.5	18.6	0.4397
	Yes	164	9.7	4.7	7.0	4.9	19.1	
Years Multivitamin	No	4	3	1.8	3	1	5	0.8019
	Yes	47	2.9	1.27	3	1	6	

¹SD=Standard Deviation;

²Significance level comparing those who did and did not complete the FFQ at baseline, Wilcoxon-Mann-Whitney test

Table II
Patients meeting Dietary Acceptable Macronutrient Distribution Range

Nutrient category	Dietary Level*	Number of patients (percentage)			Recommended level
		Female	Male	Total	
Percentage of Fat	Low	4(2.4)	3(1.8)	7 (4.2)	25-35%
	Normal	31(18.9)	28(17.1)	59 (36.0)	
	High	44(26.8)	54(32.9)	98 (59.7)	
Percentage of Protein	Normal	79(48.2)	85(51.8)	164 (100.0)	10-30%
Percentage of Carbohydrate	Normal	72(43.9)	79(48.2)	151 (92.1)	45-60%
	High	7(4.3)	6(3.6)	13 (7.9)	

* Low: Lower than lower bound of recommended range; High: Higher than upper bound of the recommended range; Normal: fall in the recommended range[31]

Table III

Distribution of dietary intake by age groups

Nutrient category	Age group	Dietary level*	# of patients (percentage)			Recommended Level [†]	
			Female	Male	Total	Female	Male
Fiber (g/d)	9-13 years	Not Met	15 (9.2)	24 (14.6)	39 (23.8)	26	31
		Met	0 (0.0)	1 (0.6)	1 (0.6)		
	14-18 years	Not Met	19 (11.6)	13 (7.9)	32 (19.5)	26	38
		Met	0 (0.0)	0 (0.0)	0 (0.0)		
	19-30 years	Not Met	33 (20.1)	41 (25.0)	74 (45.1)	25	38
		Met	5 (3.1)	0 (0.0)	5 (3.1)		
	>31years	Not Met	7 (4.3)	6 (3.7)	13 (8.0)	25	38
		Met	0 (0.0)	0 (0.0)	0 (0.0)		
Vitamin D (IU)	9-13 years	Not Met	11 (6.7)	15 (9.1)	26 (15.8)	200	200
		Met	4 (2.4)	10 (6.1)	14 (8.5)		
	14-18 years	Not Met	16 (9.8)	9 (5.5)	25 (15.3)	200	200
		Met	3 (1.8)	4 (2.4)	7 (4.2)		
	19-30 years	Not Met	25 (15.2)	31 (18.9)	56 (34.1)	200	200
		Met	13 (7.9)	10 (6.1)	23 (14.0)		
	>31years	Not Met	5 (3.0)	3 (1.8)	8 (4.8)	200	200
		Met	2 (1.2)	3 (1.8)	5 (3.0)		
Calcium (mg)	9-13 years	Not Met	11 (6.7)	16 (9.8)	27 (16.5)	1300	1300
		Met	4 (2.4)	9 (5.5)	13 (7.9)		
	14-18 years	Not Met	16 (9.8)	10 (6.1)	26 (15.8)	1300	1300
		Met	3 (1.8)	3 (1.8)	6 (3.6)		
	19-30 years	Not Met	26 (15.9)	32 (19.5)	58 (35.4)	1000	1000
		Met	12 (7.3)	9 (5.5)	21 (12.8)		
	>31years	Not Met	4 (2.4)	5 (3.1)	9 (5.5)	1000	1000
		Met	3 (1.8)	1 (0.6)	4 (2.4)		
9-13 years	Not Met	10 (6.1)	8 (4.9)	18 (11.0)	1250	1250	
	Met	5 (3.1)	17 (10.4)	22 (13.5)			

Nutrient category	Age group	Dietary level*	# of patients (percentage)			Recommended Level [†]	
			Female	Male	Total	Female	Male
Potassium (mg)	14-18 years	Not Met	13 (7.9)	7 (4.3)	20 (12.2)	1250	1250
		Met	6 (3.7)	6 (3.7)	12 (7.4)		
	19-30 years	Not Met	10 (6.1)	5 (3.1)	15 (9.2)	700	700
		Met	28 (17.1)	36 (21.9)	64 (39.0)		
	>31 years	Not Met	0 (0.0)	0 (0.0)	0 (0.0)	700	700
		Met	7 (4.3)	6 (3.7)	13 (8.0)		
	9-13 years	Not Met	14 (8.5)	22 (13.4)	36 (21.9)	5400	4700
		Met	1 (0.6)	3 (1.8)	4 (2.4)		
	14-18 years	Not Met	19 (11.6)	12 (7.3)	31 (18.9)	4500	4700
		Met	0 (0.0)	1 (0.6)	1 (0.6)		
	19-30 years	Not Met	34 (20.7)	37 (22.6)	71 (43.3)	4500	4700
		Met	4 (2.4)	4 (2.4)	8 (4.8)		
>31 years	Not Met	7 (4.3)	6 (3.7)	13 (8.0)	4500	4700	
	Met	0 (0.0)	0 (0.0)	0 (0.0)			
9-13 years	Not Met	7 (4.3)	18 (11.0)	25 (15.3)	240	360	
	Met	8 (4.9)	7 (4.3)	15 (9.2)			
14-18 years	Not Met	10 (6.1)	12 (7.3)	22 (13.4)	240	410	
	Met	9 (5.5)	1 (0.6)	10 (6.1)			
19-30 year	Not Met	26 (15.9)	34 (20.7)	60 (36.6)	310	400	
	Met	12 (7.3)	7 (4.3)	19 (11.6)			
>31 years	Not Met	6 (3.7)	6 (3.7)	12 (7.4)	320	420	
	Met	1 (0.6)	0 (0.0)	1 (0.6)			

* Not Met: Lower than recommended level for certain age and gender group.

† Met: Equal to or higher than recommended level for age and gender group [27-31]