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Significant 25-Hydroxyvitamin D Deficiency in Child and Adolescent Survivors of Acute Lymphoblastic Leukemia: Treatment with Chemotherapy Compared with Allogeneic Stem Cell Transplant

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Abstract

Background—25-hydroxyvitamin D insufficiency is common in healthy children and adolescents. There have been limited studies of the 25-hydroxyvitamin D status of survivors of pediatric and adolescent acute lymphoblastic leukemia (ALL).

Procedure—In a cohort of 78 ALL survivors (52 chemotherapy-treated and 26 HCT-treated), we determined the prevalence of, and host, treatment and environmental risk factors for 25-hydroxyvitamin D insufficiency and deficiency.

Results—There were no differences in serum 25-hydroxyvitamin D levels between ALL survivors treated with conventional chemotherapy and those treated with HCT (median 26.0 vs 25.5 ng/ ml). Fifty-three percent of pediatric ALL survivors were 25-hydroxyvitamin D insufficient (15-29 ng/ dl), and 12% were deficient (<15 ng/ dl). Younger age, higher reported dietary vitamin D intake, use of vitamin D supplementation, and increased ambient ultraviolet light were associated with higher serum 25-hydroxyvitamin D levels. There was not enough evidence to suggest treatment type, gender, race, years since diagnosis or BMI were associated with serum 25-hydroxyvitamin D levels. Only 27% of conventional chemotherapy-treated ALL survivors and 8% of HCT-treated ALL survivors met RDA for dietary vitamin D intake.

Conclusions—The prevalence of vitamin D deficiency and insufficiency in ALL survivors is similar to that of the general pediatric population in the United States, and there is no difference in serum 25-hydroxyvitamin D status between chemotherapy-treated and HCT-treated ALL survivors. ALL survivors rarely meet the RDA requirements for vitamin D. Further studies are needed to determine whether dietary and behavioral interventions can improve the vitamin D status of ALL survivors.

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Keywords

vitamin D deficiency; acute lymphoblastic leukemia; cancer survivorship; late effects; vitamin D insufficiency

Introduction

Cure from childhood acute lymphoblastic leukemia (ALL) exceeds 80% (1) and survivors of ALL, in particular those treated with hematopoietic cell transplantation (HCT), are at increased risk for a variety of adverse long-term health-related outcomes. Treatment-related risk factors for such outcomes include cytotoxic chemotherapy, cranial radiotherapy, and for transplant recipients, total body irradiation as well as immunosuppressive therapy for prevention and/or treatment of graft versus host disease (GVHD)(2,3). A well-described adverse effect is decreased bone mineral density (BMD), which occurs in patients who received conventional chemotherapy (4) as well as those who also received HCT (5,6). Bone mineral density has been shown to recover after treatment in some (4,7), but not all studies (8,9). ALL survivors as a group may achieve lower peak bone mass compared with a healthy adult population(10,11). The etiologies of low BMD are not entirely clear, but are likely caused at least in part by physical inactivity, prolonged glucocorticoid treatment, increased pro-inflammatory cytokines, and vitamin D deficiency/ insufficiency (12).

Vitamin D insufficiency is very common in the United States, with 70% of children and adolescents deficient or insufficient (13). Decreased exposure to ambient ultraviolet (UV) light contributes to this as is evidenced by worsened vitamin D deficiency during the winter months (14). This is of particular significance in childhood cancer survivors, and in particular, HCT patients, who are often counseled to avoid ultraviolet sunlight due to the increased risk of nonmelanoma skin cancer (15) as well as potential activation of chronic GVHD (16). However, avoidance of sun exposure may exacerbate low vitamin D levels.

We therefore examined Vitamin D levels in ALL survivors treated with conventional chemotherapy or HCT. We hypothesized that vitamin D deficiency would be more common in ALL survivors, compared with the general population, and that children and adolescents who received HCT would have lower serum 25-hydroxyvitamin D levels than those who underwent conventional chemotherapy.

Methods

Subjects

Details of our study population have been published previously (17). Eligible subjects for this prospective cross-sectional study were diagnosed with ALL at age <22 years, treated at either Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, or Vanderbilt Children's Hospital from 1990-2008, and currently age 8-21 years. Two patient cohorts were recruited, one consisting of individuals in first complete remission after treatment with conventional chemotherapy, and the other consisting of individuals treated with HCT, currently in remission, and off any immunosuppression for GVHD. All subjects had to be at least one year off-therapy or from date of HCT. Subjects were recruited in Seattle, Washington, from July 2007 to June 2009, and in Nashville, Tennessee, from April 2009 to June 2009. Subjects and/ or parents who were unable to speak, read, and write English also were excluded. All participants, or their parents if less than 18 years of age, provided written, informed consent. All study protocols were approved by the corresponding institutional human subjects review boards.

Anthropometric Evaluation

Height and weight were obtained, and body mass index was calculated based on the following formula: weight (kg) / height $(m)^2$. Weight, height, and BMI z-scores were calculated using age and gender-standardized growth population norms (based on the Centers for Disease Control and Prevention's Year 2000 Growth Charts).

Laboratory Evaluation

Survivors provided a blood sample for serum 25-hydroxyvitamin D, which is the standard indicator of vitamin D status, and levels were measured via liquid chromatography/tandem mass spectrometry (Mayo Medical Laboratories, Rochester MN). The total 25-OHD concentrations were calculated by summing the measured values of $25OHD_2$ and $25OHD_3$. Intra- and inter-assay coefficients of variation have previously been reported to be <7% (18). The criteria used to determine vitamin D sufficiency, insufficiency, and deficiency were 25-hydroxyvitamin D levels ≥ 30 ng/ mL, from 15-29 ng/ mL, and <15 ng/ mL, respectively (13). Serum insulin and glucose levels were obtained following an 8-hour overnight fast. Glucose was measured using an automated hexokinase method (Roche Diagnostics, Indianapolis, IN) while insulin was measured using an automated immuno-enzymometric assay (Tosoh Bioscience Inc., San Francisco, CA). As a measure of insulin resistance, we calculated the homeostasis model assessment (HOMA) from fasting glucose and insulin values, based on the formula: glucose (mmol/ L) × insulin (mU/L) / 22.5 (19).

Dietary Evaluation

Participants completed a 10-page self-administered food frequency questionnaire that has been validated for use in adults and adolescents (20). This questionnaire provides estimates of the average daily dietary intake of nutrient categories such as vitamin D and calcium over the previous month.

UV Exposure

Ambient UV exposure was summarized using recorded UV index for the locations of the study centers. Records of the UV index issued for Nashville, TN and Seattle, WA from 2007, 2008, and 2009 were obtained from the National Oceanic and Atmospheric Administration website (ftp://ftp.cpc.ncep.noaa.gov/long/uv/cities) (21). Reported UV indices issued for the 30 days preceding serum vitamin D measurement were averaged. This UV summary is referred to as UV30.

Chart Review

Chart reviews were performed to ascertain age, race, gender, treatment history (chemotherapy and radiotherapy doses, transplant type and conditioning regimen), history of chronic GVHD, hypothyroidism, growth hormone deficiency, and medications (including any vitamin supplements) taken during the 6 months prior to the study visit. Cumulative doses of glucorticoids given as part of chemotherapy (e.g., prednisone, dexamethasone) were summed with prednisone equivalent glucocorticoid dosing calculated by multiplying the dose/ m^2 of dexamethasone by 6.67 (22,23,24). Cumulative doses of glucorticoids given as part of post-HCT immunosuppression were not available.

Statistics

Demographic, anthropometric and treatment variables were summarized and tested across treatment group and vitamin D category with the Wilcoxon rank-sum, Kruskall-Wallis, or Pearson chi-squared test depending upon the type of variable and number of categories. Prevalence of vitamin D insufficiency/ deficiency was estimated and compared with the prevalence reported in NHANES with a Pearson chi-squared test.

Serum vitamin D levels were compared among children and adolescents who received HCT and those who underwent conventional chemotherapy (non-HCT) in a multivariable linear model which simultaneously accounted for age, race, gender, BMI z-score, years from diagnosis, dietary vitamin D intake, vitamin D supplement use, and 30-day UV levels. As some patients (n=5) lived in sunnier locations outside the vicinity of their study centers, a sensitivity analysis was performed to evaluate the effect that higher UV30 for those patients would have on our reported estimates (Supplemental Appendix). The analysis suggested that our reported results are in fact conservative and that UV30 effects may be slightly underestimated. Summary statistics, graphics, and linear models were generated using R version 2.9 statistical software (25).

Results

Patient Characteristics

We enrolled 52 subjects (30 from Seattle) in the chemotherapy group, and 26 subjects (21 from Seattle) in the HCT group. Age, gender, race/ ethnicity, or years since diagnosis did not differ between the two treatment groups (Table I). Only 12% of the non-HCT group received cranial radiotherapy (CRT, all 1,800 cGy), compared with the HCT group, where 39% received some form of CRT, either as upfront therapy or as salvage therapy for recurrence (median 1,000 cGy, range 600-2,400 cGy). All subjects in the HCT group were conditioned with myeloablative doses of cyclophosphamide and TBI (median dose 1,320 cGy, range 1,200-1,575). Subjects in the non-HCT group received a mean of 8,132 ± 1851 mg/ m^2 prednisone equivalents during treatment. Seventeen HCT survivors had a history of chronic GVHD. One non-HCT and 13 HCT survivors were diagnosed with growth hormone deficiency, and nine survivors were currently receiving growth hormone supplementation. Three non-HCT and six HCT survivors were receiving thyroid hormone replacement for hypothyroidism. Median HOMA calculations were 1.4 (0.9-2) in the non-HCT group and 2.6 (1.5-3.7) in the HCT group, p=0.01. No patients had diabetes mellitus.

Height z-scores were higher in the non-HCT group compared with the HCT group (median 0.15 and -0.44, respectively, p=0.02). There were no other differences in anthropometric measurements between the 2 groups. Non-HCT survivors had higher ambient UV 30 index than survivors who received HCT (median 5.4 vs 3.9, p= 0.02). Non-HCT survivors reported higher dietary vitamin D intake / day (not including supplements) than those treated with HCT (283 IU vs 177 IU/ day, p=0.05). Only 27% of the non-HCT group and 8% of the HCT group met current RDA guidelines for vitamin D intake/ day (400 IU/ day) (26) (p=0.08). There were no differences in reported dietary calcium intake between groups. Nineteen percent of non-HCT survivors reported some supplementation with vitamin D, with almost 35% of HCT survivors reporting some use of vitamin D supplementation.

Serum Vitamin D

There were no differences between non-HCT and HCT-treated survivors in serum 25-hydroxyvitamin D levels (median 26.0 compared with 25.5 ng/ ml, p=0.95; Table II). Of those who received HCT, 11.5% were 25-hydroxyvitamin D deficient, and 53.8% were insufficient, with 34.6% sufficient. This was not different from those who received only chemotherapy (11.5% deficient, 51.9% insufficient, with 36.5% sufficient, p=0.99). There were no differences in serum 25-hydroxyvitamin D levels between those who received HCT who had a history of cGVHD (median 26 ng/ ml (17-35)) and those without a history of cGVHD (26 ng/ ml (22-28), p=0.87).

The prevalence of 25-hydroxyvitamin D deficiency and insufficiency in ALL survivors was 11.5% and 52.6%, respectively, similar to the prevalence recently reported in NHANES

(p=0.31; Table II). There were no differences in gender, race, exposure to therapeutic radiation, coexistant growth hormone deficiency or hypothyroidism, HOMA, or anthropometrics between those subjects who were vitamin D deficient, insufficient, or sufficient, although there were differences in age at the time of study visit (median 17.6 years 25-hydroxyvitamin D deficient, 15.2 years insufficient, and 14.2 years sufficient, p=0.01; Table III). There was a trend toward less reported dietary vitamin D intake between subjects who were vitamin D deficient, insufficient, and sufficient (median 148 vs 292 vs 274 IU, p=0.07), but no differences between groups in calcium intake. There was a trend toward more reported vitamin D supplementation with higher serum 25-hydroxyvitamin D (deficient 11%, insufficient 17%, sufficient 39%, p=0.08). There was a trend toward lower UV30 in vitamin D-deficient subjects compared with vitamin D insufficient and sufficient subjects (median 2.4, 4.5, 5.4, p=0.08).

After adjusting for age, years from diagnosis, gender, race, BMI z-score, UV30, dietary vitamin D intake and vitamin D supplementation, serum vitamin D levels were not different among treatment groups (p=0.77; Table IV). Factors found to be associated with increased serum 25-hydroxyvitamin D levels were younger age, increased self-reported dietary intake, vitamin D supplementation, and increased UV30 exposure. A one year increase in age was associated with a decrease in serum 25-hydroxyvitamin D of 0.75 ng/mL (95% CI: -1.37 to -0.14). An increase in UV30 of one unit was associated with an increase of 1.04 ng/mL of serum 25-hydroxyvitamin D (95% CI: 0.26 to 1.82). An increase of 100 IU in dietary vitamin D intake was associated with a 0.90 ng/mL increase in serum 25-hydroxyvitamin D (95% CI: 0.01 to 1.78). Report of vitamin D supplementation was associated with a 5.33 mg/mL increase in serum 25-hydroxyvitamin D (95% CI: 0.89 to 9.76). Years from diagnosis, gender, race, and BMI z-scores were not associated with differences in serum 25-hydroxyvitamin D levels. Results were unchanged if pre-HCT exposure to cranial radiation was adjusted for (Supplemental Table V).

Discussion

There have been minimal studies evaluating vitamin D status in childhood and adolescent survivors of ALL (27,28), and no studies to our knowledge have compared the vitamin D status of childhood and adolescent ALL survivors treated with chemotherapy alone versus those who also received HCT. Peak bone mass is almost fully attained by late adolescence, and suboptimal vitamin D status has been demonstrated to have an adverse effect on the accretion of bone mass in adolescent girls (29). Vitamin D deficiency/ insufficiency can lead to secondary hyperparathyroidism (30,31), which causes increased osteoclast activity, thereby activating bone resorption.

The prevalence of 25-hydroxyvitamin D deficiency and vitamin D insufficiency in the healthy US adolescent population has been estimated to be 9% and 61%, respectively (13). The current study demonstrates a similar prevalence of vitamin D deficiency and insufficiency in adolescent ALL survivors (11.5% and 52.6%, respectively), which does not appear to be influenced by treatment with HCT. This is important for several reasons. First, patients who have received total body irradiation with HCT are counseled to avoid UV exposure unless they have adequate skin protection, due to the risk of secondary skin malignancies (15) and possible activation of chronic GVHD (16). The UV 30 index was lower in the HCT group, due to a higher percentage of subjects from Seattle compared with the percent from Nashville in this group. With strict adherence to the recommendations to avoid UV light, serum 25-hydroxyvitamin D levels should be lower in the HCT group, particularly considering that reported dietary vitamin D intake was lower in the HCT group. However, more HCT survivors reported supplementation with vitamin D, and this likely explains the lack of differences between groups.

These data indicate that adolescent ALL survivors appear to be similar to the average adolescent in the US in terms of 25-hydroxyvitamin D status. Unfortunately, only 21% of our study population met RDA requirements for dietary vitamin D (400 IU per day) (26) and 39% met requirements for calcium intake (800 mg / day for children 4-8 years, 1300 mg/ day for children 9-18 years, and 1000 mg/ day for adults 19-50 years). Recent data from NHANES 2001-2004 demonstrated that only 4% of children and adolescents take the currently recommended 400 IU vitamin D supplementation (13). Previous data from NHANES III (1988-1994) demonstrated that 53-63% of all US children consume at least 200 IU of vitamin D (200 IU per day) from diet and/ or supplementation. 200 IU was reported in this paper because it was considered adequate intake for vitamin D at that time (32).

To ameliorate the deleterious effects of ALL and its treatment on bone mineral density, vitamin D and calcium supplementation is commonly advised. Repletion of vitamin D has been demonstrated to have multiple positive health effects, as patients in the general population who have had adequate replacement of vitamin D have been shown to have a decrease in fractures (33), falls (34), total mortality (35), and all-cause cancer risk (36). However, supplementation at standard doses does not completely assuage the adverse effects on BMD in chemotherapy-treated ALL patients (37) or in HCT survivors (38). In HCT survivors, this may be due at least in part to poor gastrointestinal absorption of the supplements, particularly in patients with gut GVHD. Decreased ultraviolet sunlight exposure may also contribute to suboptimal vitamin D levels.

Only 33% of ALL survivors in our study have sufficient serum vitamin 25-hydroxyvitamin D levels, and vitamin D deficiency was more common among older survivors, with a median age of 17.5 years in those vitamin D deficient compared with a median age of approximately 14 in those insufficient or sufficient. This difference in age seems to be minor, but has been reported in other populations (13,39). The reasons for a higher prevalence of vitamin D deficiency in older adolescents are unclear, and have previously been attributed in a healthy population to age-related decreases in physical activity (40), leading to decreased outdoor activities and sun exposure (41). Age-related decreased dietary vitamin D intake has previously been excluded as an etiology of age-related decreased serum 25-hydroxyvitamin D (42). We did not find gender or racial differences in 25-hydroxyvitamin D levels, which differs from some previous reports which have demonstrated lower serum 25-hydroxyvitamin D levels in females and non-Caucasians (13). This is likely due to our small sample size, as we had a relatively small percentage of non-Caucasian subjects. However, some larger studies have not found gender differences in vitamin D levels (41). We also did not find overweight status to be a predictor of low vitamin D levels, as BMI z-scores were not significant predictors of vitamin D. This is in agreement with some studies (41), but not others (13).

Limitations of this study include an inability to accurately determine each subject's actual UV light exposure. UV exposure was obtained based on an average of the ambient UV light 30 days prior to his/ her serum 25-hydroxyvitamin D level. Some of the subjects did not live in the city of the study center, but instead travelled from their home to the study center for treatment. As those who lived furthest from the study centers lived in sunnier areas, we may have underestimated the UV effect (Supplemental Appendix). Food frequency questionnaires were used to determine vitamin D and calcium intake, which could introduce possible recall and other biases (43). However, we would not expect ALL survivors treated with HCT versus those treated without HCT to complete our questionnaires differently and any biases should be non-differential. Small sample size may also have led us to a Type II error, as there was a trend towards statistical significance of several variables which might have been significant with a larger sample size. Due to limitations of our questionnaire and

the medical record, we were unable to quantify more precisely the amount of vitamin D and calcium taken in the form of dietary supplements. Additionally, we did not evaluate bone mineral density at the time of study visit. Possible correlations between serum vitamin D levels and bone mineral density findings will be important to evaluate in future studies.

In conclusion, the prevalence of vitamin D insufficiency and deficiency was similar between pediatric ALL survivors and healthy US adolescents, and there were no differences between ALL survivors treated with HCT compared with those treated without HCT. A significant percentage of ALL survivors did not attain the RDA via diet for vitamin D or calcium, and those who had HCT generally consumed less dietary vitamin D than those treated with conventional chemotherapy. Dietary vitamin D intake has been demonstrated in the current study and others (41) to be an important predictor of serum 25-hydroxyvitamin D levels. As increased vitamin D intake is thought to be safe, it seems prudent that future studies focus on ways to increase oral vitamin D intake to improve 25-hydroxyvitamin D status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

ALL	Acute Lymphoblastic Leukemia
GVHD	graft versus host disease
BMD	bone mineral density
HCT	hematopoietic stem cell transplant
BMI	body mass index
RDA	Recommended Daily Allowance
UV	ultraviolet
cGVHD	chronic graft versus host disease

Table I

Patient Characteristics by Treatment Group. Data presented as median (25^{th} – 75^{th} percentile).

	n	Non-HCT n= 52	HCT n= 26	p-value*
Age (years) at study visit	78	14.5 (11.6 – 16.7)	15.6 (12.5 – 17.2)	0.47
Gender (% male)	78	48% (25)	62% (16)	0.38
Race (% Caucasian)	78	81% (42)	69% (18)	0.39
Years since Diagnosis	78	10.0 (6.8 – 11.2)	10.5 (6.2 – 12.0)	0.88
Received CRT	**78**	**12% (6)**	**39 % (10)**	**0.01**
Received TBI	78	0% (0)	100% (26)	NA
Diagnosis of growth hormone deficiency	27	4% (2)	50% (13)	0.78
Hypothyroidism	27	6% (3)	23% (6)	0.38
HOMA	**77**	**1.4 (0.9 – 2.0)**	**2.6 (1.5 – 3.7)**	**0.01**
Height z-score	**70**	**0.15 (-0.53 – 1.10)**	**-0.44 (-1.28 – 0.02)**	**0.02**
Weight z-score	70	0.77 (0.12 – 1.45)	0.68 (-0.50 – 1.56)	0.47
BMI z-score	74	0.70 (0.14 – 1.43)	0.83 (-0.24 – 1.62)	0.94
UV 30 **	**78**	**5.4 (2.5 – 6.9)**	**3.9 (1.4 – 4.9)**	**0.02**
Dietary vitamin D intake/ day (IU) ***	**76**	**283 (171 – 409)**	**177 (108 – 321)**	**0.05**
% meeting RDA for vitamin D intake	76	27% (14)	8% (2)	0.08
Calcium intake/ day (mg) **	76	1145 (809 – 1698)	948 (622 – 1336)	0.11
% meeting RDA for calcium intake	76	42% (22)	31% (8)	0.38
% receiving vitamin D supplements	76	19% (10)	35% (9)	0.20

* For continuous variables the Wilcoxon rank sum test, for categorical variables the Pearson chi-squared test;

** UV30: a measurement of the average amount of UV light in the patient's geographic location during the 30 days prior to the serum vitamin D evaluation;

*** Reported dietary intake, not including supplement use

Table II

Serum 25-hydroxyvitamin D status: ALL survivors requiring chemotherapy compared with those requiring hematopoietic stem cell transplant and ALL survivors compared to child and adolescent healthy population from NHANES

	Non-HCT n= 52	HCT n= 26	p-value	NHANES[1]	ALL Survivors n= 78	CI	p-value
Serum 25 hydroxy-vitamin D(ng/ ml)[2]	26.0 (21.0-33.2)	25.5 (21.0-33.2)	0.95[3]				
Deficient (<15 ng/mL)	11.5%	11.5%	0.99[4]	9%	11.5%	4.5% to 18.5%	0.31[4]
Insufficient (15-29 ng/mL)	51.9%	53.8%		61%	52.6%	41.6% to 63.5%	
Normal (≥ 30 ng/mL)	36.5%	34.6%		30%	35.9%	25.4% to 46.4%	

[1] Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and Associations of 25-Hydroxyvitamin D Deficiency in US Children: NHANES 2001-2004. Pediatrics 2009;

[2] presented as the median and (25^{th} – 75^{th} percentile);

[3] Wilcoxon rank sum test;

[4] Chi-squared test

Table III

Univariate Analysis of Patient Characteristics by 25-hydroxyvitamin D category. Data presented as median (25^{th} – 75^{th} percentile).

	n	25-hydroxyvitamin D deficient (serum <15 ng/ml) n=9	25-hydroxyvitamin D insufficient (serum 15-30 ng/ml) n=41	25-hydroxyvitamin D sufficient (serum > 30 ng/ml) n=28	p-value*
Age (years) at study visit	**78**	**17.6 (17.3 – 20.3)**	**15.2 (11.8 – 16.4)**	**14.2 (10.3 – 16.5)**	**0.01**
Gender (% male)	78	44% (4)	46% (19)	64% (18)	0.30
Race (% Caucasian)	78	56% (5)	73% (30)	89% (25)	0.08
Years from Diagnosis	78	10.0 (6.0 – 12.0)	10.0 (6.0 – 12.0)	10.0 (7.0 – 12.0)	0.98
CRT	78	33% (3)	20% (8)	18% (5)	0.59
TBI	78	33% (3)	34% (14)	32% (9)	0.99
Diagnosis of growth hormone deficiency	27	11% (1)	22% (9)	18% (5)	0.27
Hypothyroidism	27	11% (1)	7% (3)	18% (5)	0.37
HOMA	77	1.9 (1.0 – 3.7)	1.6 (1.0 – 2.8)	1.3 (0.8 – 2.5)	0.46
Height z-score	70	-0.44 (-0.64 – -0.02)	-0.32 (-0.96 – 0.90)	0.02 (-0.48 – 0.75)	0.59
Weight z-score	70	1.13 (0.74 – 1.43)	0.86 (-0.29 – 1.58)	0.51 (-0.13 – 0.93)	0.35
BMI z-score	74	0.82 (0.43 – 1.68)	0.82 (0.16 – 1.77)	0.66 (0.12 – 1.24)	0.52
UV 30 **	78	2.4 (1.3 – 4.3)	4.5 (1.5 – 6.7)	5.4 (3.8 – 6.8)	0.08
Vitamin D intake/ day (IU) ***	76	148 (121 – 182)	292 (148 – 370)	274 (175 – 427)	0.07
% meeting RDA for vitamin D intake	76	0% (0)	20% (8)	29% (8)	0.19
Calcium intake/ day (mg) **	76	835 (610 – 951)	1148 (719 – 1688)	1098 (827 – 1695)	0.11
% meeting RDA for calcium intake	76	11% (1)	39% (16)	46% (13)	0.16
% receiving vitamin D supplements	76	11% (1)	17.1% (7)	39.3% (11)	0.08

* For continuous variables Kruskal-Wallis test, for categorical variables the Pearson chi-square test;

** UV30: a measurement of the average amount of UV light in the patient's geographic location during the 30 days prior to the serum vitamin D evaluation;

*** Reported dietary intake, not including supplement use

Table IV
Multivariable Analysis of Serum Vitamin D with Vitamin D Supplementation

	Effect (ng/ml 25-hydroxyvitamin D)	CI	p-value
Reference *	17.28	9.23 to 25.63	
Categorical variables			
HCT vs. conventional chemotherapy	0.61	-3.44 to 4.65	0.77
Male vs. female	2.45	-1.39 to 6.30	0.21
Not Caucasian vs. Caucasian	-1.82	-6.36 to 2.71	0.42
Oral Vitamin D supplementation vs. none	5.33	0.89 to 9.76	0.02
Continuous variables			
Age older than 8 years (1 yr increase)	-0.75	-1.37 to -0.14	0.02
Years from diagnosis	0.55	-0.01 to 1.11	0.05
BMI z-score	-0.39	-2.38 to 1.60	0.70
UV30	1.04	0.26 to 1.82	0.01
100 IU Vitamin D Intake	0.90	0.01 to 1.78	0.05

* patient who received chemotherapy, female, Caucasian, age=8 years, years from diagnosis=1, BMI z-score=0, UV30=0, vitamin D intake=0, no vitamin D supplements; Adjusted R^2=0.253