

Suboptimal Vitamin D levels among adult survivors of childhood cancers

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Abstract

Purpose: Vitamin D plays an important role in many bodily systems, with increasing evidence suggesting its importance for the prevention of chronic diseases and cancer. The identification of vitamin D levels in childhood cancer survivors becomes, therefore, particularly relevant, given that optimizing levels may contribute to the prevention of secondary malignancies and chronic diseases.

Methods: A cross-sectional analysis of serum 25-hydroxyvitamin D levels among adult survivors of childhood cancers living in New York State and surrounding areas (n = 139) was performed. Independent variables included gender, race/ethnicity, cancer site, year of diagnosis, past medical and surgical history, prior radiation therapy; prior chemotherapy, age at diagnosis, age at last clinic visit, year of last clinic visit, height, weight, body mass index, and vitamin D supplementation. **Results:** Overall, 34% of survivors were vitamin D deficient (< 20 ng/ml), 39% were classified as insufficient (20 - 29 ng/ml) and 27% (≥ 30 ng/ml) were classified as having sufficient levels. Despite vitamin D supplementation among 41 patients, 68.3% continued to have insufficient or deficient levels. Participants with a BMI > 25 demonstrated lower levels of vitamin D (p < 0.05). Vitamin D levels did not vary by age group, race, ethnicity, diagnosis, or years since diagnosis. **Conclusion:** Given the growing awareness of the role of vitamin D and the documented late effects of treatment for childhood cancers, the high prevalence of vitamin D deficiency within the childhood cancer survivor population is of concern. Vitamin D represents an important target for surveillance and intervention to help improve long-term outcomes of childhood cancer survivors.

Keywords: Vitamin D deficiency, Cancer survivor, Pediatrics, Preventive care, Quality of care

1. Introduction

The success in treating childhood and adolescent cancers is evident by the dramatic reduction in mortality rates over the past several decades, with more than 80% of current patients now surviving for five years.^{1,2} This achievement, however, has led to a growing number of long-term survivors with new complications from their previous therapies. An extended follow-up by Mertens *et al.*², for example, found excess overall mortality of 8.4 fold when compared to age-, sex- and year-matched

US population controls. Excess mortality was due primarily to secondary malignancies, followed by cardiac and pulmonary causes.² As a result, late effects of therapy and quality of life among adult survivors of childhood cancers have become areas of intense investigation.^{3,4}

Given the critical need for structured follow-up of survivors of childhood cancer, evaluations should

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include assessment of important health-related factors such as levels of Vitamin D, a fat soluble vitamin which is involved in many physiologic pathways. Emerging evidence suggests that Vitamin D levels should be greater than 30 ng/ml to achieve the desired health effects.⁵ A data brief issued by the National Center for Health Statistics (NCHS) provides Vitamin D levels as assessed in the National Health and Nutrition Examination Surveys (NHANES). Findings from this survey indicate that approximately one-third of the general population were at risk of Vitamin D deficiency with levels < 20 ng/ml.⁶ In a study by Forrest et al, Vitamin D status was examined using the NHANES data. Overall prevalence of Vitamin D deficiency (≤ 20 ng/mL) was found to be 41.6%; with African Americans presenting with the highest rate of Vitamin D deficiency at 82.1% and Caucasians at 30.9%. Furthermore, a significant link was found between those participants that were Vitamin D deficient and had less than a college education, poor health status, hypertension, low high-density lipoprotein cholesterol levels, and those not consuming milk.⁷ A comprehensive review conducted by Holick along with other research has found a significant increase in long term cancer risk among individuals with deficient vitamin D levels.⁸⁻¹² As is clear from these findings, deficiency states are of great concern given the evidence suggesting that adequate Vitamin D levels may be important for prevention and management of type 1 and type 2 Diabetes mellitus, hypertension, and cancer.¹³⁻¹⁶ However, research on the clinical impact of screening and treatment of Vitamin D remains inadequate. Several studies in Acute Lymphocytic Leukemia survivors have shown that patients with exposure to corticosteroids have increased bone demineralization and poor mineral homeostasis.¹⁷⁻¹⁹ This suggests that childhood cancer survivors may be at an increased risk of Vitamin D deficiency.

Given the growing awareness of the role of Vitamin D and the documented late effects associated with treatment of childhood cancer, the issue of Vitamin D levels in the childhood cancer survivor population is of great relevance. Childhood cancer survivors are an ideal group to study Vitamin D levels, since optimizing levels may help to contribute to the prevention of secondary malignancies and chronic diseases. Childhood cancer survivors experience an increased risk of developing secondary malignancies and other chronic illnesses as a result of prior therapies. This study examines the prevalence of Vitamin D deficiency among adult survivors of childhood cancers.

2. Methods and Materials

Roswell Park Cancer Institute operates a Long-Term Follow - Up (LTFU) Center as part of the Department of Pediatrics which provides specialized surveillance, medical care, and counseling to former childhood cancer

patients. Patients who are more than 5 years from their cancer diagnosis are seen in this outpatient center.

A cross - sectional medical chart review was utilized to abstract selected variables from patients seen in the LTFU center between 2009 and 2014. Two hundred and three patients were seen at 383 separate office visits over the period of 5 years. Sixty-four patients (31.5%) were excluded due to a lack of data on vitamin D levels leaving 139 patients (68.5%) with at least one measurement of Vitamin D who were included in the analytic data set. Among these 139 patients, 70 patients (50.4%) had Vitamin D levels available for at least 2 visits.

The main dependent variable was serum 25 - hydroxyvitamin D. The first Vitamin D level during the observation period was used for the analysis. Vitamin D sufficiency was defined as a serum 25 - hydroxy vitamin D level ≥ 30 ng/ml, insufficiency as a level from 20 ng/ml to 29.9 ng/ml, and deficiency as ≤ 20 ng/ml.

Independent variables included gender, race/ethnicity (non-Hispanic white versus all other), cancer site (leukemia, lymphoma, sarcoma, Central Nervous System (CNS), other), year of cancer diagnosis, past medical history, past surgical history, prior radiation therapy; prior chemotherapy, zip code of residence, age at diagnosis, age at last clinic visit, calendar year of last clinic visit, height, weight, body mass index (BMI, normal BMI < 25, overweight BMI 25 - 29.9, and obese BMI ≥ 30), and self - reported Vitamin D supplementation / use of multivitamins. Seasons were categorized as Winter (December 1 - February 28), Spring (March 1 - May 31), Summer (June 1 - August 31), and Fall (September 1 - November 30).

SPSS Version 21 (© IBM, Cary, NC) was used to facilitate data analyses, which included descriptive summaries and a comparison of Vitamin D status by demographic characteristics and supplementation status using chi-square tests. Vitamin D levels by supplementation status were analyzed using the Mann Whitney - U test. Analysis of variance was used to examine the relationship between mean vitamin D levels and BMI. In addition, a logistic model was constructed to examine factors associated with Vitamin D deficiency. The protocol for this research project was approved by the Roswell Park Cancer Institute Institutional Review Board.

3. Results

As reported above, one hundred thirty-nine patients with at least one Vitamin D assessment were identified for analysis. Clinical characteristics of childhood cancer survivors are presented in Table 1. The mean serum 25 - hydroxyvitamin D level for all patients was 26.6 ng/ml (median 25.2, range: 5.0 - 96.6). Overall, 34% of

survivors were Vitamin D deficient, 39% were classified as insufficient and 27% were classified as having sufficient Vitamin D levels. Chi - square testing revealed no significant difference in categorical Vitamin D status by gender, age group, race, cancer diagnosis, and years since diagnosis.

3.1. The distribution of Vitamin D levels based on supplementation status is shown in Figure

Median vitamin D levels among those supplemented (26.8 ng/ml) was greater than those not reporting supplementation (21.2 ng/ml, $p = 0.0016$, Mann - Whitney U test); however these median levels remain within the "insufficiency" range. Among the 41 patients who reported taking supplemental Vitamin D, 68.3% continued with insufficient or deficient Vitamin D levels at the subsequent draw despite supplementation.

Table 1: Selected demographics and clinical characteristics of study subjects by gender, n = 139

	Male		Female		p-value*
	n	(%)	n	(%)	
Age (in years)					0.73
18-39	51	(76.1)	53	(73.6)	
40+	16	(23.9)	19	(26.4)	
					0.2
Race/Ethnicity					
Non-Hispanic White	60	(89.6)	59	(81.9)	
Other	7	(10.4)	13	(18.1)	
					0.39
Cancer Type					
Leukemia	28	(41.8)	24	(33.3)	
Lymphoma	20	(29.9)	18	(25.0)	
Sarcoma	5	(7.5)	13	(18.1)	
CNS	7	(10.4)	9	(12.5)	
Other	7	(10.4)	8	(11.1)	
					0.91
Years Since Diagnosis					
0-9	6	(9.0)	8	(11.1)	
10-19	18	(26.9)	21	(29.2)	
20-29	24	(35.8)	22	(30.6)	
30+	19	(28.4)	21	(29.2)	
					0.89
Body Mass Index					
<25 (normal)	24	(35.8)	27	(37.5)	
25-29.9 (overweight)	24	(35.8)	23	(31.9)	
≥30 (obese)	19	(28.4)	22	(30.6)	
					0.28
Vitamin D Level (ng/mL)					
Median	22.2		26.2		
Range	5.0-96.6		7.8-77.6		
-deficient	24	(36)	23	(32)	
-insufficient	27	(40)	27	(38)	
-adequate	16	(24)	22	(31)	

* p-values calculated using Chi-Square test.

Table 2: Vitamin D status by gender and supplementation status.

	Male				Female			
	Supplement		No Supplement		Supplement		No supplement	
Deficient	6.7%	(n=1)	45.1%	(n=23)	11.5%	(n=3)	45.5%	(n=20)
Insufficient	53.3%	(n=8)	37.3%	(n=19)	61.5%	(n=16)	22.7%	(n=10)
Adequate	40%	(n=6)	17.6%	(n=9)	26.9%	(n=7)	31.8%	(n=14)

chi-square, $p = 0.018$ in males; $p = 0.002$ in females

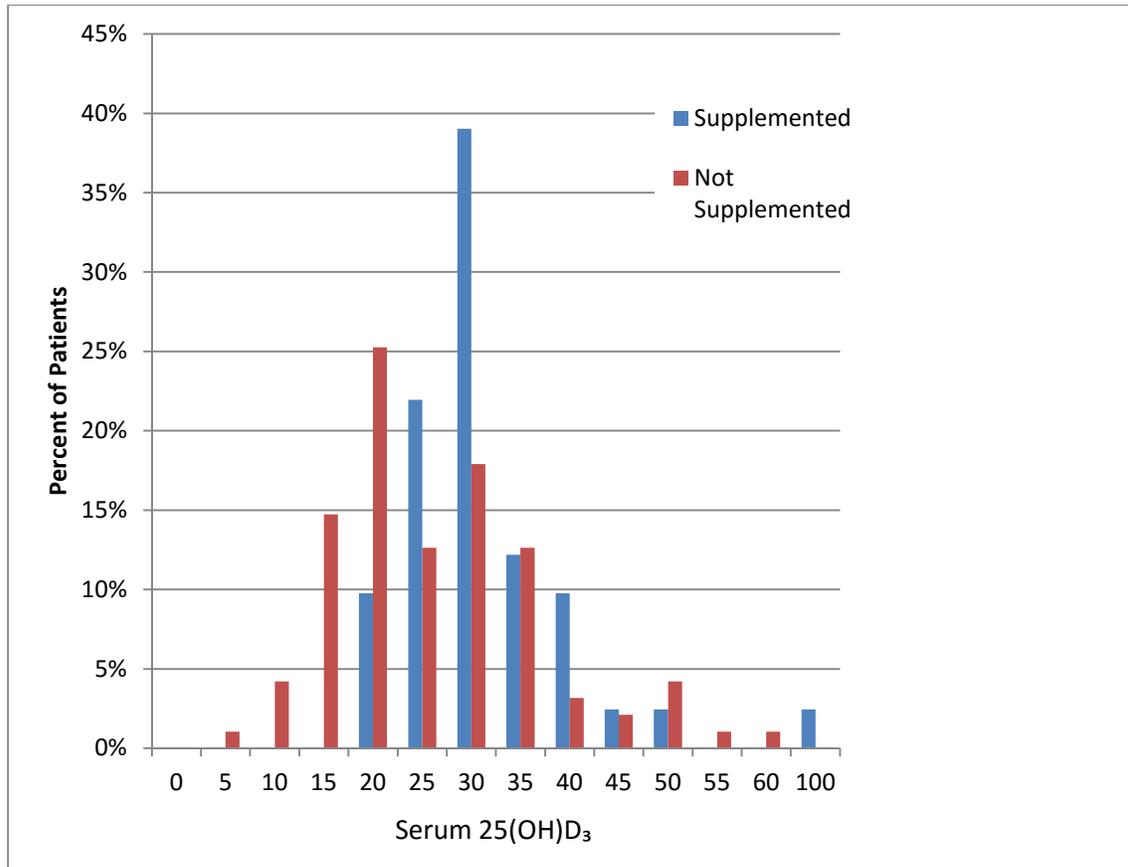


Figure 1: Distribution of Vitamin D levels, by supplementation status. Patients taking supplements had significantly higher levels of vitamin D than patients not taking supplements (Mann - Whitney U, $p = 0.0016$)

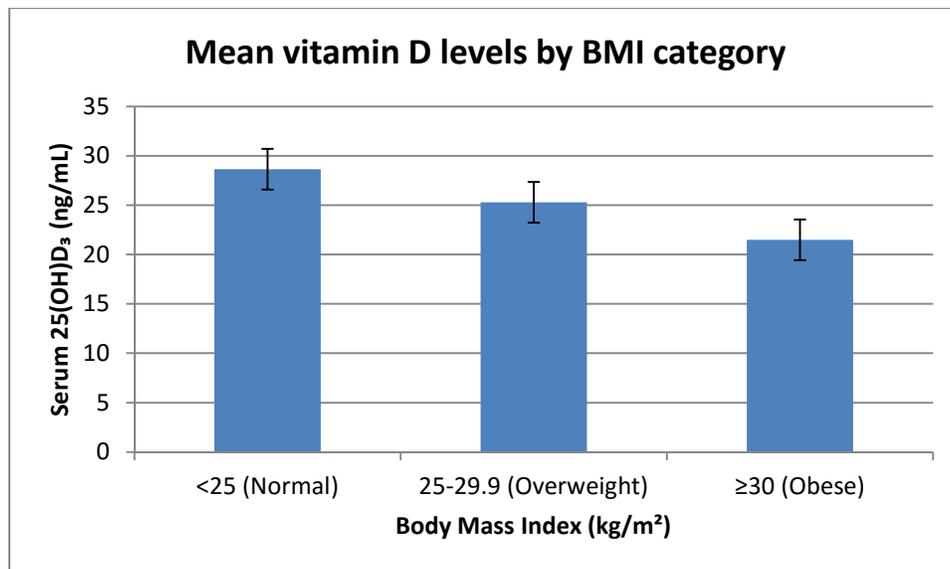


Figure 2: Mean Vitamin D levels by BMI category. Inverse relationship with lowest Vitamin D levels observed among those with highest BMIs (F - test, $p = 0.003$).

As seen in Table 2, among males taking supplements, only 6.7% had deficient Vitamin D levels compared to 45.1% of males not taking supplementation. Furthermore, 40% of supplemented males had adequate Vitamin D levels compared to only 17.6% of non-supplemented males (chi - square, $p = 0.018$). Among females taking supplements, only 11.5% had deficient Vitamin D levels compared to 45.5% of non-supplemented females. While the proportion of females with sufficient Vitamin D levels was similar in those taking versus not taking supplements, 26.9% and 31.8%, respectively, a significant difference in categorical vitamin D levels was observed in females that were supplemented compared to those not supplemented ($p = 0.002$).

Patients with a normal BMI had a mean Vitamin D level of 28.7 ng/ml compared to mean Vitamin D levels of 25.0 ng/ml for overweight and 21.5 ng/ml for obese BMI categories ($F(2,133) = 5.7, p = 0.004$); with higher BMI associated with lower mean Vitamin D levels as seen in Figure 2. An analysis of variance showed significant seasonal mean vitamin D variation ($F(3,132) = 4.04, p = 0.009$). Post Hoc testing found that mean Vitamin D levels were significantly lower in the winter ($M = 21.9, SD = 8.8$) and Spring months ($M = 22.4, SD = 10.5$) than during Summer ($M = 29.1, SD = 10.8$). Further, while 53.6% of the sample was found to be Vitamin D deficient during winter months, this percentage dropped to 23.3% during summer.

Predictors of insufficient or deficient vitamin D levels based on multivariate logistic regression modeling included age category (30 + years old, adjusted odds ratio [OR] = 0.39, 95% confidence interval 0.18 - 0.84) and overweight/obese (BMI 25 +, adjusted OR = 2.45, 95% confidence interval 1.08 - 5.52).

4. Discussion

Examination and characterization of critical health related information in the childhood cancer survivor population is fundamental to the provision of comprehensive follow - up care. It is important to note, therefore, that the findings of the current investigation indicate that the median levels of Vitamin D (25.2 ng/ml in our sample of adult childhood cancers survivor is just above the deficiency threshold of 20 ng/ml) and well below suggested adequate levels of > 30 ng/ml. When applying thresholds for Vitamin D categories and matching age groups, patterns noted in the current study were comparable to those observed in the general population as reported in the NHANES data.⁶ Specifically, NHANES revealed that 32.6% of males and 37.3% of females ages 19 - 70 had Vitamin D levels < 20 ng/ml. Our study showed similar outcomes; with 36% of males and 32% of females in a matched age group reporting levels < 20 ng/ml. Comparing results for only white patients ages 18 - 59 years reveals greater levels

of Vitamin D deficiency in our survivor population (32.8%) compared to NHANES (21.8%).²⁰ Childhood cancer survivors remain an important population requiring careful follow - up and intervention due to their high risk of chronic health conditions as a result of the late effects from their prior cancer therapies. Furthermore, emerging evidence suggests that Vitamin D levels should be greater than 30 ng/ml to achieve the desired health effects.^{5,21}

Among survivors who reported that they were taking vitamin D containing supplements, a majority (53.3% of males and 61.5% of females) remained insufficient and 6.7% of males and 11.5% of females continued to have deficient vitamin D levels. It is not clear whether this reflects inadequate levels of supplementation or poor adherence or a combination of these factors. To date, only a limited number of studies have examined Vitamin D deficiency and insufficiency among childhood cancer survivors. In a study by Esbenschade *et al*²², for example, Vitamin D abnormalities were studied in patients aged less than 23 years in Nashville, Tennessee who had received > 28 days of corticosteroid therapy. Vitamin D deficiency and insufficiency rates in the Esbenschade study were found to be 15.8% and 34.5%, respectively. Significant associations were also found between deficiency and BMI > 85th percentile, older age, non - Caucasian or Hispanic, and winter versus summer season.²² A study by Rosen *et al.* found levels of Vitamin D deficiency (14.4%) and insufficiency (39.3%) among patients with a mean age of 12.5 years living in Phoenix, Arizona;²³ proportions similar to those found by Esbenschade *et al.*²² As expected those studies done in areas with warmer, sunnier climates did find a lower percentage of vitamin D deficiency.

A limited number of studies have examined vitamin D levels among adult survivors of childhood cancer. Choudhary *et al.* noted 29% insufficiency (< 20 ng/ml) among a population of pediatric cancer survivors, was comparable to that observed in the general population.²⁴ Neville *et al.* found that when adjusted for gender, adult survivors of childhood cancer ages 18 - 39 had a higher proportion of Vitamin D deficiency (42.4%) when compared to community - based controls (20.8%).²⁵

Multiple studies have shown decreases in fracture incidence, decreases in cancer incidence, improved glucose homeostasis, lower risk of hypertension, and a decrease in nursing home admissions in subjects with vitamin D levels greater than 30 ng/ml.^{5,26-28} However, the Food and Nutrition Board has recommended avoiding vitamin D levels above 50 - 60 ng / ml due to several studies showing adverse health effects. In a nested case control study, researchers found a 3 - fold greater risk of pancreatic cancer with vitamin D levels that were greater than 26.2 ng/ml.²⁹ Durup *et al.*²⁹⁻³¹ found a reversed J - shaped relationship between vitamin D level and all - cause mortality and for

mortality due to cardiovascular disease, stroke, or myocardial infarction with the lowest mortality rates at vitamin D levels of approximately 30 ng/ml.²⁹⁻³¹ While the US Preventative Services Task Force (USPSTF) has noted that testing of Vitamin D levels has increased by at least 50% from 2009 to 2010, taken together, results to date suggest the need for further research to more conclusively determine optimal vitamin D levels.³²

Adult survivors of childhood cancers are at an increased risk of developing chronic health conditions.³³⁻³⁵ Oeffinger, *et al.*³⁶ reported that 62.3% of childhood cancer survivors had at least one chronic condition with 27.5% having a severe or life - threatening condition (grade 3 or 4); most commonly seen were secondary malignant cancers, cardiovascular disease, renal dysfunction, severe musculoskeletal problems, and endocrinopathies.³⁶ In addition, childhood cancer survivors are known to have early mortality from secondary malignant neoplasms and cardiopulmonary events when compared to age and gender matched general population controls.³⁷⁻⁴⁰ We are unaware of longitudinal studies evaluating the effect of Vitamin D levels on long term complications among childhood cancer survivors. However, Vitamin D may play an important role in prevention and health maintenance for childhood cancer survivors. Future research might prospectively assess clinical outcomes and Quality of Life (QOL) among cancer survivors by category of Vitamin D levels as well as intervention studies to determine if supplementation with Vitamin D for childhood cancer survivors with insufficient/deficient levels decreases morbidity and mortality.

The current Institute of Medicine recommendations for vitamin D daily intake is 200 IU daily from birth to age 50 years, 400 IU daily for those aged 51 - 70 years, and 600 IU daily for those aged > 70 years. However, given the controversy regarding optimal vitamin D levels, as well as individual and geographic variations, the supplement dose needed to achieve sufficient levels is also difficult to ascertain, and long - term studies need to be performed to assess the safety and efficacy of long term Vitamin D supplementation.

Limitations of the study include self-reported Vitamin D supplement use and dosage among participants. All patients, however, are questioned about their use of prescribed medications and supplements as part of the standardized clinical evaluation. For future research, improved documentation of the dose and frequency of Vitamin D supplements will be important to do a more granular analysis of the impact of Vitamin D levels in childhood cancer survivor populations. While we potentially included all patients seen for surveillance, not all patients had vitamin D levels assessed resulting in a modest sample size.

Despite the noted limitations, the present study is important in providing further evidence regarding the high prevalence of vitamin D deficiency/insufficiency among adult survivors of childhood cancers, and includes a substantial subset of persons > 40 years of age who are generally underrepresented in childhood cancer survivor cohorts.

5. Conclusion

We noted a strikingly low median level of serum vitamin D among this cohort of adult survivors of childhood cancers and high proportions of survivors with insufficient and deficient vitamin D levels. Given the documented late effects associated with therapies for childhood cancer, the issue of suboptimal Vitamin D levels among childhood cancer survivors is of substantial clinical relevance.

Conflict of interest

Dr. Rokitka has received research support from Hyundai Hope on Wheels and the Roswell Park Cancer Institute Alliance Foundation related to survivorship research among pediatric cancer patients. Drs. Rokitka, Mahoney and Zevon declares that they have no conflict of interest related to the content of this manuscript. Mr. Lisac and Ms. Heffler declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and / or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This research was approved by the RPCI IRB.

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