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Prevalence of Vitamin D Insufficiency in Survivors of Childhood Cancer

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Background. Data on 25-hydroxyvitamin D (25-OH D) status among survivors of childhood cancer are limited. Our aim was to determine the prevalence of and risk factors for 25-OH D insufficiency in a large, diverse population of cancer survivors being followed in a childhood cancer survivor clinic. ***Procedure.*** Retrospective chart review in survivors seen for routine long-term follow-up, who underwent routine screening blood studies including 25-OH D levels. Vitamin D insufficiency was defined as 25-OH D <20 ng/ml. ***Results.*** Four hundred eighty-four subjects (234 males) were evaluable for this analysis. Median age at 25-OH D testing was 12.3 years (2.05–36.4) and median age at cancer diagnosis was 3.9 years (0–18). Diagnoses included brain tumors (23.6%), neuroblastoma (21%), and leukemia (17.6%). Mean 25-OH D level was 25.2 ng/ml (SD = 10.37); 29% of subjects were 25-OH D insufficient. In univariate analysis, race, pubertal status, and age at cancer diagnosis were associated with 25-OH D insufficiency ($P < 0.05$). In multivariate analysis, a model including race and pubertal status provided a good fit for the data. ***Conclusions.*** The prevalence of 25-OH D insufficiency in these cancer survivors was high but similar to what has been described in the general population. No cancer specific variables were associated with 25-OH D insufficiency. Since cancer survivors are at a higher risk for subsequent malignancies, cardiovascular disease, and low bone mineral density, all of which may be affected by 25-OH D levels, interventions to improve 25-OH D status in this vulnerable population are needed. Pediatr Blood Cancer 2013;60:1237–1239.

Key words: cancer survivors; prevalence; vitamin D

INTRODUCTION

25-Hydroxyvitamin D (25-OH D) insufficiency is common in healthy children and adolescents, with the prevalence being 14–49% in the general population [1–3]. The known risk factors for 25-OH D insufficiency include being overweight or obese, race, and seasonality [4,5].

Survivors of childhood cancer are at increased risk for a variety of adverse medical outcomes, including osteoporosis, cardiovascular disease, and subsequent malignancies compared to the general population, outcomes that might be affected by their 25-OH D status [6–11]. Potential risk factors for impaired 25-OH D status in this population include poor diet, more time spent indoors, use of sunscreen, exposure to chemotherapy, steroids, radiation therapy, and immunosuppressive therapy [12–15]. However, data on 25-OH D status among survivors of childhood cancer are sparse and confined to small series, often limited to one diagnostic group.

The objective of this study was to determine the prevalence of and risk factors for 25-OH D insufficiency in a large, diverse population of cancer survivors being followed in a Survivorship Clinic.

METHODS

Subjects

This is a retrospective chart review approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (MSKCC). The inclusion criteria included: all consecutive patients seen in the Long-Term Follow-Up (LTFU) Clinic at MSKCC, who had a serum 25-OH D level measured as a part of routine screening during the time period January 2008 to January 2011. Subjects were excluded if: (1) they had no treatment data available; (2) had a non-cancer diagnosis and had not undergone a stem cell transplant; (3) if they were being treated with Calcitriol. We did include individuals (n = 58) without a cancer diagnosis but who had undergone an allogeneic stem cell transplant. The non-cancer diagnoses included bone marrow failure syndromes (n = 35), immunodeficiency syndromes (n = 17), sickle cell anemia (n = 5), and Wolman syndrome (n = 1). A total of 484 survivors met the inclusion criteria and are the subjects of this analysis.

Chart Review

Electronic medical records, paper charts, and the LTFU database were used to obtain demographics and treatment related data for each subject. Race/Ethnicity was based on self-reported records and was classified as White, Black, Asian, or Hispanic. Data on serum 25-OH D levels, age at testing of serum 25-OH D in relation to the cancer diagnosis, gender, and season of testing were collected. Seasons were designated as *summer* if the subject had 25-OH D testing from April to September and *winter* if the testing was done from October to March. Puberty was classified according to the standard Tanner staging system [16,17]. Individuals diagnosed with primary hypothyroidism, hyperthyroidism, isolated or multiple pituitary hormone deficits, insulin resistance, lipid abnormalities, diabetes insipidus, and diabetes mellitus were designated as having an *endocrinopathy.*

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Height and BMI z scores and percentile were calculated using age and gender-standardized population norms (Centers for Disease Control and Prevention's Year 2000 Growth Charts) [18]. Obesity was defined as a BMI ≥ 95th percentile for age and sex for those <18 years and a BMI ≥ 30 for those ≥18 years of age. Overweight was defined as a BMI ≥ 85 to <95 percentile for age and gender in those <18 years of age and a BMI 25 to <30 in those >18 years.

25-OH D was measured by a Chemiluminescent (Diasorin) assay. 25-OH D insufficiency was defined as a level <20 ng/ml as per the recent guidelines proposed by the Institute of Medicine (IOM)[19].

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Biostatistics

A logistic regression model was developed to determine the set of factors that independently predicted Vitamin D insufficiency. The Hosmer and Lemeshow goodness-of-fit test was used to evaluate the final fit of the model. The statistical packages SAS (9.2) was used to generate the test statistics and build the regression model. All data are reported as median (range) unless specified otherwise.

RESULTS

Patient characteristics are summarized in Table I. A total of 484 subjects (234 males) were evaluable. The median age at cancer diagnosis was 3.9 years (0–18), median interval from cancer diagnosis to 25-OH D testing was 6.3 (0–22.7), and median age at 25-OH D testing was 12.3 years (2.05–36.4).

The most common diagnoses were brain tumors (23.5%), neuroblastoma (20.9%), and leukemia (17.6%). Four hundred and thirty-three (89.4%) of the subjects received chemotherapy, 234 (48.4%) received radiation, and 73 (15.1%) received glucocorticoid medications. Endocrine complications as a result of either the diagnosis or treatment were seen in 225 (46.5%) of the subjects. Two hundred and eighty-one of the subjects (58.1%) had their 25-OH D testing during the summer time. Twenty-nine percent of subjects were 25-OH D insufficient.

In univariate analysis (Table II), race, pubertal status, and age at diagnosis were associated with 25-OH D insufficiency ($P < 0.05$ for all factors). Borderline associations were seen between 25-OH D insufficiency and seasonality ($P = 0.2$) and exposure to total body irradiation (TBI) ($P = 0.061$). There were no associations between 25-OH D insufficiency and BMI, gender, cancer diagnoses, presence of an endocrinopathy, exposure to radiation, or glucocorticoid medications.

In the multivariate analysis (Table III), a model including race and pubertal status provided a good fit for the data. Subjects who were non-Hispanic Black, Asian, or Hispanic and who were Tanner stage 3–5 were more likely to be 25-OH D insufficient. In addition, there was some evidence of a seasonality effect on 25-OH D.

TABLE I. Demographic and Treatment Characteristics of Study Subjects

Characteristics	n = 484
Age at cancer diagnosis (years)	
Median	3.90
Range	0–18
Age at testing (years)	
Median	12.26
Range	2.05–36.4
Gender, n (%)	
Male	234 (48.3%)
Female	250 (51.7%)
Anthropometry (Mean ± SD)	
Height Z score	−0.78 ± 1.71
BMI Z score	0.27 ± 1.34
Race, n (%)	
White	381 (78.7%)
Black	59 (12.2%)
Hispanic	3 (0.6%)
Asian	41 (8.5%)
Puberty, n (%)	
Tanner 1–2	259 (53.5%)
Tanner 3–5	225 (46.5%)
Diagnosis, n (%)	
Brain tumor	114 (23.5%)
Neuroblastoma	101 (20.9%)
Leukemia	85 (17.6%)
Non-malignant post SCT	58 (11.9%)
Soft tissue Sarcoma	44 (9.1%)
Bone tumors	29 (6%)
Thyroid cancer	28 (5.8%)
Miscellaneous	15 (3.1%)
Hodgkins/non-Hodgkins Lymphoma	10 (2.1%)
Treatment, n (%)	
Chemotherapy	433 (89.4%)
Glucocorticoid	73 (15.1%)
Radiation	234 (48.3%)
Cranial Irradiation	165 (34%)
Total body Irradiation	69 (14%)
Endocrinopathy, n (%)	225 (46.5%)

BMI, body mass index; SCT, stem cell transplant.

DISCUSSION

In this large and diverse cohort of survivors of childhood cancer followed in our childhood cancer survivor clinic, we observed a high prevalence of 25-OH D insufficiency of 29%. This is similar to the prevalence of 25-OH D insufficiency that has been described in large population based studies in children and adolescents in the general population [1–3]. The risk factors for

TABLE II. Univariate Analysis

Characteristics	ORs	95% CI	*P*-values
BMI			0.871
Non-obese	1.00		
Overweight	1.08	0.64–1.83	
Obese	0.89	0.49–1.61	
Race			<0.001
White	1.00		
Black	3.11	1.78–5.46	
Others (Hispanic & Asian)	2.08	1.09–3.97	
Puberty			<0.001
Tanner 1–2	1.00		
Tanner 3–5	2.29	1.53–3.41	
Age at diagnosis	1.36	1.10–1.70	<0.01
Interval from diagnosis to Testing	1.03	0.98–1.08	0.142
Seasonality			0.200
Summer	1.00		
Winter	1.28	0.86–1.89	
Gender			0.410
Male	1.00		
Female	1.18	0.8–1.74	
Cancer specific risk factors			
TBI (yes vs. no)	1.66	0.98–2.81	0.061
Steroids (yes vs. no)	0.96	0.55–1.66	0.875
Chemotherapy (yes vs. no)	1.12	0.59–2.15	0.729
Cranial radiation (yes vs. no)	1.10	0.73–1.66	0.636
Endocrinopathy (yes vs. no)	1.06	0.72–1.57	0.761

BMI, body mass index; TBI, total body irradiation.

TABLE III. Multivariate Analysis

Characteristics	ORs	95% CI	*P*-values
Race			<0.001
White	1.00		
Black	3.25	1.83–5.78	
Others (Hispanic and Asian)	2.14	1.11–4.13	
Puberty			<0.001
Tanner 1–2	1.00		
Tanner 3–5	2.22	1.55–3.54	
Seasonality			0.08
Summer	1.00		
Winter	1.44	0.95–2.17	

25-OH D insufficiency in our population (race, pubertal status, and seasonality), have all been identified as risk factors for 25-OH D insufficiency in the general population [4,5]. In contrast to most previous studies, we did not find any association between BMI and 25-OH D insufficiency, perhaps due to the small percentage of survivors in our study who fell into the obese range (10%). Cancer specific variables, such as exposure to chemotherapy, glucocorticoid therapy, cranial radiation, TBI, and cancer diagnosis, were included in the analysis but were not associated with risk of 25-OH D insufficiency.

There are limited reports looking at the prevalence of 25-OH D status in cancer survivors [12–14]. A prospective cross-sectional study done in the United Kingdom comparing 61 cancer survivors ages 1–18 years with 60 controls, found a higher prevalence of 25-OH D deficiency (<10 ng/ml) among survivors compared to controls, (21.3% in the cancer survivors vs. 3.3% in the controls). The risk factors which predicted 25-OH D deficiency included seasonality, ethnicity, older age, and a cancer diagnosis [12]. Another study that included 78 leukemia survivors, who had received either chemotherapy or hematopoietic stem cell transplant described a prevalence of 25-OH D deficiency (<15 ng/ml) of 35%. The risk factors described were older age, lack of 25-OH D supplementation and decreased exposure to ultraviolet light [13]. Finally, a study done in Minnesota looked at 95 cancer survivors ages 2.7–72 years with a diagnosis of leukemia or lymphoma, status post hematopoietic stem cell transplant. In the latter study, the prevalence of 25-OH D deficiency (<20 ng/ml) was 10%. Risk factors for 25-OH D deficiency included lack of 25-OH D supplementation and use of steroids [14]. These studies differ from the current study in several important ways, including smaller sample size, less diverse population of cancer survivors, and differing definitions of 25-OH D insufficiency.

As noted above, different cut-offs have been proposed for optimal levels of 25-OH D by different expert groups and panels. The IOM recently concluded that 25-OH D levels of ≥20 ng/ml cover the requirements of at least 97.5% of the population. Moreover, they concluded that serum concentrations of 25-OH D above 30 ng/ml "are not consistently associated with increased benefit" [19]. In addition, another report suggests that a 25-OH D threshold of 20 ng/ml is sufficient for parathyroid hormone suppression and prevention of secondary hyperparathyroidism in individuals with normal renal function [20]. For these reasons, we have used a cut-off of <20 ng/ml to define 25-OH D insufficiency in our study.

Our study has a few limitations. Given the retrospective nature of the study, some important variables such as dietary habits and use of vitamin D supplementation were not available in all subjects and could not be used in the analyses. The distribution of cancer diagnoses in our study population may not be representative of the general pediatric cancer survivor population due to institutional referral biases; hence our data may not be generalizable to other pediatric cancer survivor populations.

The prevalence of 25-OH D insufficiency in cancer survivors was high but similar to what has been described in the general population. We were unable to identify any cancer specific variables that were associated with 25-OH D insufficiency in this population. Cancer survivors are at greater risk for subsequent malignancies, low bone mineral density, cardiovascular risk factors, and cardiovascular disease [6–10,21], all of which might be affected by their 25-OH D status. Moreover, the risk for these adverse outcomes increases as survivors age. Thus, the health implications of a suboptimal level of 25-OH D may be of greater consequence in this population, particularly as they reach adulthood. Targeted interventions to improve 25-OH D status in cancer survivors appear warranted.

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