

REGULAR ARTICLE

Prevalence of and factors influencing vitamin D deficiency in paediatric patients diagnosed with cancer at northern latitudes

Natalja Jackmann¹  | Jan Gustafsson¹  | Arja Harila-Saari¹ | Gustaf Ljungman¹ |
Dzeneta Nezirevic Dernroth² | Per Frisk¹ | Outi Mäkitie³

¹Department of Women's and Children's Health, University Children's Hospital, Uppsala, Sweden

²Department of Clinical Chemistry and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

³Department of Molecular Medicine and Surgery, Karolinska Institute, and Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden

Correspondence

Natalja Jackmann, Department of Women's and Children's Health, University Children's Hospital, 75185 Uppsala, Sweden.
Email: natalja.jackmann@kbh.uu.se

Funding information

This work was supported by the Swedish Childhood Cancer Foundation (PR2018-0101, ST2013-0008, and TJ2014-0007) and the Mary Béves Foundation.

Abstract

Aim: To investigate the prevalence of vitamin D deficiency among children with non-haematological malignancies and to explore possible causes of low vitamin D levels among these patients.

Methods: We performed a cross-sectional study of 458 children diagnosed with solid tumours, brain tumours, non-Hodgkin lymphoma or Hodgkin disease at the University Children's Hospital, Uppsala, Sweden. Serum 25-hydroxyvitamin D and parathyroid hormone levels were measured in samples taken at the time of cancer diagnosis and related to clinical data. Vitamin D deficiency was defined as a 25-hydroxyvitamin D level below 50 nmol/L.

Results: The prevalence rate of vitamin D deficiency among children with non-haematological malignancies was 41%. There was no association between sex or diagnosis and vitamin D status. Vitamin D deficiency was more common among school children than preschool children (51% vs. 24%). Older age, season outside summer, and a more recent calendar year were significant predictors of lower 25-hydroxyvitamin D. There was a significant, albeit weak, negative correlation between 25-hydroxyvitamin D and parathyroid hormone.

Conclusion: Vitamin D deficiency is common among children diagnosed with cancer, particularly among school-aged children diagnosed outside summer. The prevalence appears to be increasing, underlining the need for adequate replacement of vitamin D in these patients.

KEYWORDS

25-hydroxyvitamin D, solid tumour, brain tumour, non-Hodgkin lymphoma, Hodgkin disease

Key Notes

- This study found that the prevalence of vitamin D deficiency (defined as 25-hydroxyvitamin D below 50 nmol/L) among children diagnosed with cancer was 41%.
- Vitamin D deficiency was more common among school children than preschool children.

Abbreviations: B, Unstandardised estimate; Beta, Standardised estimate; HD, Hodgkin disease; MDS, Myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma; PTH, Parathyroid hormone; R², Coefficient of determination; SD, Standard deviation; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Acta Paediatrica* published by John Wiley & Sons Ltd on behalf of Foundation Acta Paediatrica

- Lower 25-hydroxyvitamin D level was associated with older age, season outside summer and time of sampling (a more recent calendar year), but not with sex or diagnosis.

1 | INTRODUCTION

Today, more than 80% of all children with cancer survive for at least 5 years after their initial diagnosis.¹ Therefore, an increasing number of cancer patients survive until adulthood, and attention is shifting towards the reduction of adverse effects and evaluation of long-term health consequences. Adults treated for cancer during childhood are at risk of chronic health conditions, with 95% developing any chronic health condition and 80% experiencing at least one severe, life-threatening, or disabling condition by the age of 45 years. Adverse skeletal effects account for 10% of chronic health conditions.²

The bone mass increases throughout childhood and adolescence and reaches a peak between the ages of 20 and 30 years.³ Therefore, disturbances in bone mass accretion during this time may lead to skeletal problems later in adult life.⁴ Skeletal development in children with cancer may be adversely affected by the primary disease itself, and by chemotherapy and radiation therapy, which may influence bone metabolism either directly or through impairment of endocrine functions. Further, nutritional deficiencies, limited exposure to sunlight, and reduced physical activity may affect the skeleton adversely.^{4,5}

Adequate intake of calcium and vitamin D is necessary for normal bone growth.^{6,7} Low levels of vitamin D may be a risk factor for both skeletal and extra-skeletal diseases, including cardiovascular diseases and immune-related diseases (e.g. type 1 diabetes mellitus and asthma).^{8,9}

A recent meta-analysis showed that vitamin D deficiency is common in children and adolescents with cancer, particularly in Europe. The prevalence rates of vitamin D levels below 50 nmol/L were 41% (range 21%–61.5%) in Europe, 24% (range 24%–25%) in the Middle East and 15% (range 0%–16%) in North America.¹⁰ The differences may be attributed to differences in food fortification policies, vitamin D supplementation guidelines and geographic factors, as well as ethnic (e.g. skin pigmentation¹¹) and cultural (e.g. covering clothing¹²) differences among countries. Therefore, the prevalence of vitamin D deficiency has to be determined in each country separately to formulate national supplementation guidelines.

We have previously reported that one-third of paediatric patients with leukaemia treated at our hospital had vitamin D levels below 50 nmol/L at the time of diagnosis. Older age, season outside summer, acute myeloid leukaemia and more recent calendar year were associated with lower 25-hydroxyvitamin D (25(OH)D) levels.¹³ Data on the vitamin D statuses of children living in Sweden with other cancer diagnoses are unavailable.

The aim of the present study was to establish the prevalence of vitamin D deficiency at the time of diagnosis among children with a solid tumour, brain tumour, non-Hodgkin lymphoma (NHL), and Hodgkin disease (HD), hereafter referred to as non-haematological

malignancies, and to explore possible predictors of low vitamin D levels in this patient population. Previously published data on the vitamin D statuses of children with leukaemia were used to allow comparison among children with various types of cancers.

2 | METHODS

2.1 | Patients and study design

The present cross-sectional study assessed children diagnosed with different types of cancer at the University Children's Hospital, Uppsala, Sweden, between June 1990 and August 2016.

The main study cohort included 458 children with non-haematological malignancies. In addition, we used our recently reported data of 295 children with leukaemia,¹³ complemented with data on 3 children with myelodysplastic syndrome (MDS; all males, aged 3.1, 14.1 and 14.2 years) to enable comparisons among different diagnostic categories. Samples were obtained routinely at the time of diagnosis, before the initiation of cancer treatment, stored at -75°C , and assayed with reagents from the same batch in January 2018. Clinical data were collected from the Swedish Childhood Cancer Registry.

The study protocol was approved by the Regional Ethical Review Board of Uppsala (approval number: 2014/511). The study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki.

2.2 | Serum 25(OH)D and parathyroid hormone level measurements

We assessed the levels of serum 25(OH)D and parathyroid hormone (PTH) at the accredited Clinical Chemistry Laboratory of Linköping University Hospital, Linköping, Sweden. Serum 25(OH)D levels were measured via the direct competitive immunochemiluminescent assay (LIAISON 25-OH Vitamin D TOTAL Assay; CLIA DiaSorin, Stillwater, Minnesota, USA). The levels of intact PTH were measured using a two-site chemiluminescent assay on the Roche Cobas e601 platform (Roche Diagnostics, Penzberg, Germany). Details of the measurements have been reported elsewhere.¹³

Vitamin D status was defined according to the recommendation of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition: all values below 50 nmol/L were considered deficient, a concentration below 25 nmol/L indicated severe deficiency. Values at or above 50 nmol/L were considered normal and indicative of vitamin D sufficiency.¹⁴ We also separately analysed the proportion of subjects with 25(OH)D values above 75 nmol/L, which has

been suggested as threshold for optimal vitamin D status in adults.¹⁵ Values above 250 nmol/L were regarded excessive. A reference interval of 1.6–6.9 pmol/L was used for PTH at the laboratory.

2.3 | Statistical analyses

Values of 25(OH)D were normally distributed, but not values of PTH. We used descriptive statistics to evaluate 25(OH)D and PTH values and simple (unadjusted) and multiple (adjusted) linear regression to explore the effects of sex, age, diagnosis, season, and time of sampling (calendar year) on 25(OH)D levels. The four seasons were defined as summer (June–August), fall (September–November), winter (December–February) and spring (March–May). We used bivariate Spearman correlation analysis and Mann-Whitney test to explore the association between 25(OH)D and PTH levels. We performed statistical analyses for the entire cohort and then separately for preschool children (aged ≤6 years) and school children (aged >6 years). This was done since previous data demonstrated considerable differences in vitamin D status between preschool and school children.^{13,16,17} Statistical analyses were performed using SPSS version 26 (IBM Corporation, New York, USA). Analysis items with $p < 0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The study population consisted of 458 patients (52.6% males). The mean age at diagnosis was 8.9 years (range, 0.0–18.9). Of these, 245 patients (53.5%) had solid tumours (soft tissue sarcoma (54), kidney tumour (51), neuroblastoma (35), germ cell tumour (32), osteosarcoma (27), ewing sarcoma (14), liver tumour (9), other (23)), 103 (22.5%) had brain tumours (astrocytoma (38), medulloblastoma (19), glioma (13), ependymoma (12), germ cell tumour (7), craniopharyngoma (5), other (9)), 66 (14.4%) had NHL and 44 (9.6%) had HD. The patients' characteristics are presented in Table 1.

Groups	N	Age (years) mean ± SD	Season of diagnosis (%)			
			Summer	Fall	Winter	Spring
All patients	458	8.9 ± 5.6	20.5	26.9	25.8	26.9
Sex						
Male	241	8.9 ± 5.5	22.0	26.6	24.1	27.4
Female	217	8.8 ± 5.8	18.9	27.2	27.6	26.3
Diagnosis						
Solid tumour	245	7.5 ± 5.8	21.6	26.1	25.7	26.5
Brain tumour	103	8.9 ± 5.0	20.4	30.1	25.2	24.3
NHL	66	10.0 ± 4.9	18.2	25.8	24.2	31.8
HD	44	14.3 ± 3.3	18.2	25.0	29.5	27.2

Note: Abbreviations: HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; SD, standard deviation.

3.2 | Descriptive statistics, correlation between 25(OH)D and PTH

Serum 25(OH)D level measurements were available for all 458 patients. One sample had a value below the detection limit of 10 nmol/L and was recorded as 5 nmol/L. In the entire cohort, vitamin D deficiency was found in 40.9% of the children (5.5% had severe vitamin D deficiency). Vitamin D deficiency was more than twice as common among school children as among preschool children (51.4% versus 23.6%) (Table 2).

Serum PTH measurements were available for 451 patients. Seven patients had sample volumes too small for PTH measurement. PTH levels were subnormal in 23.5%, within the reference range in 75.4%, and supranormal in 1.1% of the patients. There was an inverse correlation between PTH levels and 25(OH)D in the entire population (correlation coefficient = 0.250, $p < 0.001$) (Supplemental Figure S1), among school children (correlation coefficient = 0.313, $p < 0.001$), and among preschool children (correlation coefficient = 0.154, $p = 0.04$). We observed that PTH values were higher in children with 25(OH)D level <25 nmol/L as compared with those with 25(OH)D level ≥25 nmol/L and in children with 25(OH)D level <50 nmol/L as compared with those with 25(OH)D level ≥50 nmol/L (Mann-Whitney test, $p = 0.02$, $p < 0.001$, respectively).

3.3 | Factors influencing 25(OH)D level

We assessed whether sex, age, diagnosis, season or calendar year had an impact on 25(OH)D levels. For the entire cohort, using unadjusted linear regression, higher age ($p < 0.001$), diagnosis (brain tumour, $p = 0.016$ and HD, $p = 0.002$, compared with solid tumour), season (fall, $p < 0.001$; winter, $p < 0.001$; and spring, $p < 0.001$ compared with summer) and more recent calendar year ($p < 0.001$), but not sex, were significant predictors of lower 25(OH)D levels. After adjusting for all significant factors, age ($p < 0.001$), season (fall, winter and spring compared with summer, for all $p < 0.001$), and more recent calendar year ($p < 0.001$), but not diagnosis, remained significant predictors of lower 25(OH)D levels (Table 3).

TABLE 1 Characteristics of 458 children with non-haematological malignancies. Distribution of children who were diagnosed with tumours during different seasons.

TABLE 2 Distributions of serum 25(OH)D levels among 458 children with non-haematological malignancies according to sex, age, diagnosis, and season

Groups	N	Mean (SD) nmol/L	<25 nmol/L (%)	25 < 50 nmol/L (%)	50 < 75 nmol/L (%)	≥75 nmol/L (%)
All patients	458	57.9 (24.0)	5.5	35.4	35.6	23.6
Sex						
Male	241	58.1 (23.9)	6.6	34.0	36.1	23.2
Female	217	57.7 (24.2)	4.1	36.9	35.0	24.0
Age (years)						
≤6	174	67.9 (24.8)	2.9	20.7	38.5	37.9
>6	284	51.8 (21.3)	7.0	44.4	33.8	14.8
Diagnosis						
Solid tumour	245	60.9 (25.2)	4.5	32.2	35.1	28.2
Brain tumour	103	54.2 (19.5)	3.9	40.8	41.7	13.6
NHL	66	58.6 (25.4)	6.1	31.8	33.3	28.8
HD	44	48.2 (21.4)	13.6	45.5	27.3	13.6
Season						
Summer	94	71.3 (22.6)	2.1	16.0	36.2	45.7
Fall	123	58.7 (22.2)	6.5	30.9	39.0	23.6
Winter	118	53.2 (22.8)	5.9	40.7	39.0	14.4
Spring	123	51.3 (24.0)	6.5	49.6	28.5	15.4

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; other, see Table 1.

TABLE 3 Factors influencing the levels of 25(OH)D among 458 children with non-haematological malignancies

Linear regression	Unadjusted			Adjusted		
	B	p	R ²	B	p	Beta
All patients (458)						
Sex (male reference)	-0.35	0.8	0.000			
Age (years)	-1.35	<0.001*	0.102	-1.29	<0.001*	-0.306
Diagnosis			0.028			
Solid tumour	Ref.					
Brain tumour	-6.74	0.016*		-3.18	0.2	-0.05
NHL	-2.25	0.4		0.27	0.9	0.00
HD	-12.02	0.002*		-2.34	0.5	-0.02
Season			0.095			
Summer	Ref.					
Fall	-12.60	<0.001*		-13.45	<0.001*	-0.249
Winter	-18.09	<0.001*		-18.90	<0.001*	-0.344
Spring	-20.08	<0.001*		-19.61	<0.001*	-0.362
Calendar year	-0.69	<0.001*	0.038	-0.603	<0.001*	-0.169
R ²	0.26			0.23		

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; B, unstandardised estimate; Beta, standardised estimate; other, see Table 1 R², coefficient of determination.

*p < 0.05.

When we analysed the data of preschool and school children separately, season (winter [$p = 0.003$] for preschool children and fall, winter, and spring [all $p < 0.001$] for school children) and calendar year ($p < 0.001$ for preschool children and $p = 0.038$ for school children), but not sex, age, or diagnosis, were independent predictors of

lower 25(OH)D levels. Seasonal variations were more pronounced among school children than preschool children and accounted for 19% and 4%, respectively of the variation in vitamin D status. Calendar year accounted for 7% of the variation in vitamin D status among preschool children, and for 2% among school children.

To enable a comparison of 25(OH)D levels across all paediatric cancer diagnoses, we also included our previous cohort of 295 children with haematological malignancies in the analyses,¹³ as well as the data of 3 children with MDS. We then performed a multiple regression analysis using the data of these 756 children. The results showed a consistent pattern: older age, season outside summer, and a more recent calendar year, but not sex or diagnosis were associated with lower 25(OH)D levels (Supplemental Table S1). In this entire cohort of children with cancer, 37.8% had vitamin D deficiency.

Figure 1 shows the distribution of 25(OH)D levels among preschool and school children with different cancer diagnoses. Figure 2 shows the distribution of 25(OH)D deficiency and normal levels according to age and season.

4 | DISCUSSION

Our results demonstrate that vitamin D deficiency is common among paediatric patients with non-haematological malignancies at the time of diagnosis. This is illustrated by the fact that 41% had 25(OH)D levels below 50 nmol/L and 5% had values below 25 nmol/L. Only 24% of the subjects had 25(OH)D levels ≥ 75 nmol/L. Among school children, vitamin D deficiency was more than twice as common as among preschool children (51% vs. 24%).

Only limited data are available on vitamin D status in healthy children in Sweden. Moreover, it is difficult to compare data from different studies due to differences in patient characteristics and study conditions known to influence vitamin D status. In

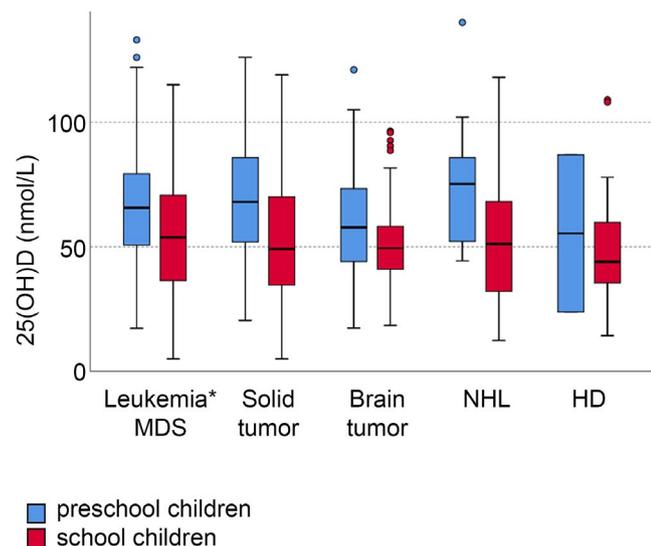


FIGURE 1 Distributions of 25(OH)D levels among 756 preschool and school children according to the various cancer diagnoses. Adjusted linear regression indicated that the age, season and calendar year, but not the diagnosis were significant predictors of lower 25(OH)D levels. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; other, see Table 1. *The data on 295 patients with leukaemia were previously published elsewhere¹³

keeping with our results, Andersson et al. reported that among 2048 Swedish Caucasian children referred for evaluation of statural growth, 34% had 25(OH)D levels below 50 nmol/L and 3% had levels below 25 nmol/L.¹⁸ Furthermore, Öhlund et al. reported that among 4–6 years old children living in northern Sweden, the prevalence rates of vitamin D deficiency were 25% in the late summer and 40% during the winter months. The corresponding proportions with 25(OH)D levels ≥ 75 nmol/L were 15% and 10%, respectively.¹⁹ Unfortunately, these results do not allow more detailed comparisons of vitamin D statuses between children with cancer and healthy children.

As far as children with cancer are concerned, our results indicate a negative trend in vitamin D status over the years. Since all samples were analysed simultaneously, using the same method, the negative trend cannot be attributed to methodological differences. Our data are in agreement with those of a meta-analysis performed by Revuelta et al., who reported that most studies

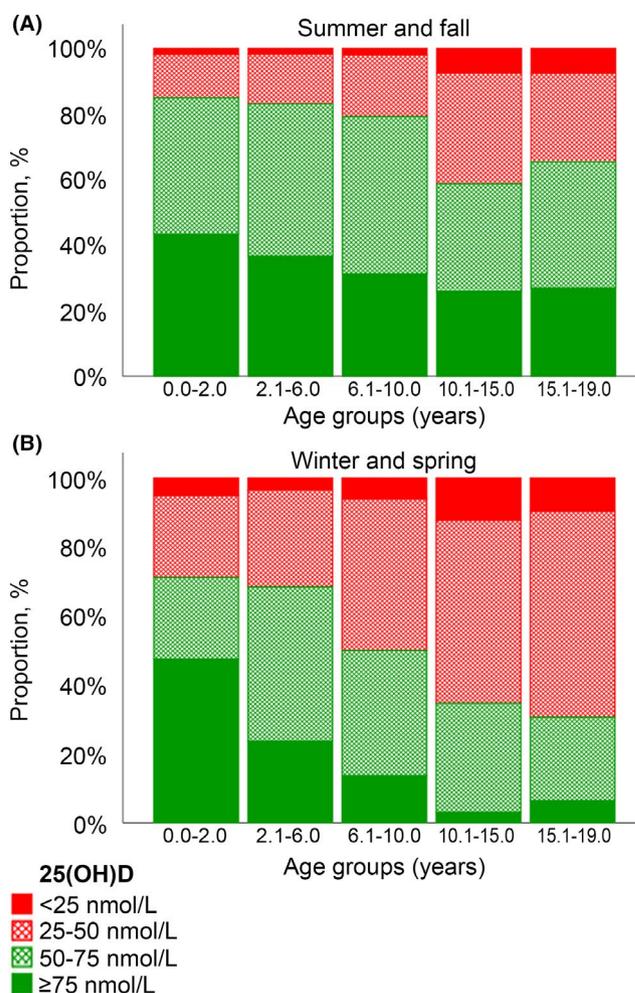


FIGURE 2 Distributions of vitamin D status among 756 children with haematological and non-haematological malignancies during the (A) summer and fall and (B) winter and spring. Adjusted linear regression indicated that the age, season, and calendar year were significant predictors of lower 25(OH)D levels. The data on 295 patients with leukaemia were previously published elsewhere¹³

emanating from Europe and North America, published after the year 2000, found higher prevalence of vitamin D deficiency among children with cancer than those published in the 1980s and the 1990s.¹⁰ In line with our results, studies have indicated an increased prevalence of vitamin D deficiency and rickets in the general paediatric population in Northern Europe^{20,21} and recognised this as a rising health issue. Possible causes for this trend could be (a) changes in lifestyle, such as less time spent playing outdoors and use of more sun protection due to an increased awareness of the risk of skin cancer,²² (b) an increasing proportion of children with obesity,²³ (c) changes in the ethnic composition of the Swedish population with an increase in the number of children with dark skin, and (d) changes in Swedish guidelines for vitamin D supplementation.²⁴

In agreement with the most previous reports,^{16,25,26} we found no association between sex and 25(OH)D.

In line with other studies on healthy children and children with cancer and chronic illnesses,^{10,16-18,25-28} our results demonstrate that older age is a factor that contributes significantly to lower 25(OH)D levels. Although it is not possible to draw any conclusion about causality, it could be speculated that older children spend less time outdoors and have more unhealthy nutritional habits than younger children. They also have higher absolute fat mass, which impacts the tissue distribution of this fat-soluble vitamin. Furthermore, it is known that 1,25-dihydroxyvitamin D (1,25(OH)₂D) levels are increased during puberty, this, to meet the higher physiological demand for calcium by increased intestinal absorption during the pubertal growth spurt. The decrease in 25(OH)D levels may occur secondarily, due to increased metabolism of 25(OH)D to 1,25(OH)₂D.²⁹

In contrast to studies emanating from Scotland (Edinburg),²⁶ Hungary (Budapest),³⁰ and the USA (San Diego and Richmond),^{16,28} but in agreement with reports from Finland (Helsinki),¹⁷ Turkey (Istanbul),²⁵ and the UK (Newcastle upon Tyne),²⁷ vitamin D status in our study varied with season. Part of the explanation behind this difference may lie in the fact that the number of sunny days per year varies among countries. In addition, there are marked differences in the definitions of seasons. Thus, some investigators used a two-season model,^{16,28,30} whereas, others used a four-season model.¹⁷ According to our results, seasonal variations were more pronounced among school children than preschool children and accounted for 19% and 4%, respectively of the variation in vitamin D status. This could be explained by the assumption that younger children are more likely to receive vitamin D supplementation or consume foods that naturally contain or are fortified with vitamin D.

There are few studies that compare vitamin D statuses among children with various types of cancer at the baseline. According to these studies, and in keeping with our results, 32%–64% of children have low vitamin D levels; however, there was no association between type of cancer and 25(OH)D level.^{25,26,28}

Our data further demonstrate a negative association between serum 25(OH)D and PTH levels. This is in line with data reported by Juhász et al., who studied children with cancer before the start

of treatment,³⁰ but is in contrast with some other studies, which included children undergoing cancer treatment or those with a history of malignancy.^{26,27} One could speculate that the fact that cancer treatment has an impact on calcium levels, bone health and consequently on PTH levels, both in the short and long term, may explain the differing results. Further studies are needed to investigate the interactions between vitamin D and PTH levels in children with cancer, and to define the role played by PTH on the vitamin D dependent effects.

Our concern is that vitamin D status will deteriorate during cancer treatment. This is because cancer patients are often encouraged to avoid sun exposure, are likely to spend more time indoors, are at risk of nutritional problems, and may undergo treatments that impair vitamin D bioavailability and metabolism. Therefore, these patients may develop negative health consequences due to the low vitamin D level.

4.1 | Study limitations and strengths

The main limitations of the study are the use of a retrospective cross-sectional study design and the lack of a control population. Furthermore, we had no data regarding the ethnic background, skin type, pubertal status and body mass index of the patients, which limited our ability to recognise all risk factors for vitamin D deficiency.

Our study also has several strengths. It provides the largest analysis of vitamin D status among children with various cancer diagnoses at the time of cancer diagnosis and prior to cancer therapy. Furthermore, we were able to minimise methodological differences, since all samples were analysed simultaneously, at the same laboratory, and using the same batch of reagents.

5 | CONCLUSION

We found that vitamin D deficiency is common among children with cancer, particularly after early childhood. Lower 25(OH)D level was associated with older age, season outside summer and a more recent calendar year, but not with sex or diagnosis. Since a normal vitamin D level is needed for skeletal and cardiovascular health and normal immunologic function, adequate replacement of vitamin D has to be ensured in patients. Further research is warranted, including prospective longitudinal studies and studies on vitamin D supplementation in children with cancer.

ACKNOWLEDGEMENTS

The authors would like to thank senior statistician Jonas Selling at Statistikakademin, Uppsala, for providing statistical advice; Birgitta Högberg, the manager of Uppsala Clinical Research Center Laboratory; Mikaela Magnusson, the customer manager of Uppsala Biobank, for providing support in the preparation and biobanking of blood samples and Editage (www.editage.com) for English language editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Natalja Jackmann  <https://orcid.org/0000-0003-2817-3299>

Jan Gustafsson  <https://orcid.org/0000-0002-7540-438X>

REFERENCES

- Erdmann F, Frederiksen LE, Bonaventure A, et al. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol*. 2020;71(Pt B):101733.
- Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371-2381.
- Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R. Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. *J Clin Endocrinol Metab*. 1999;84(12):4702-4712.
- Wilson CL, Ness KK. Bone mineral density deficits and fractures in survivors of childhood cancer. *Current Osteoporosis Rep*. 2013;11(4):329-337.
- El-Hajj Fuleihan G, Muwakkit S, Arabi A, et al. Predictors of bone loss in childhood hematologic malignancies: a prospective study. *Osteoporos Int*. 2012;23(2):665-674.
- Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81(3):353-373.
- Pekkinen M, Viljakainen H, Saarnio E, Lamberg-Allardt C, Makitie O. Vitamin D is a major determinant of bone mineral density at school age. *PLoS One*. 2012;7(7):e40090.
- Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79(3):362-371.
- Christakos S, DeLuca HF. Minireview: Vitamin D: is there a role in extraskeletal health? *Endocrinology*. 2011;152(8):2930-2936.
- Revuelta Iniesta R, Rush R, Paciarotti I, et al. Systematic review and meta-analysis: Prevalence and possible causes of vitamin D deficiency and insufficiency in pediatric cancer patients. *Clin Nutr (Edinburgh, Scotland)*. 2016;35(1):95-108.
- Åkeson PK, Lind T, Hernell O, Silfverdal SA, Öhlund I. Serum Vitamin D depends less on latitude than on skin color and dietary intake during early winter in Northern Europe. *J Pediatr Gastroenterol Nutr*. 2016;62(4):643-649.
- El-Hajj Fuleihan G, Nabulsi M, Choucair M, et al. Hypovitaminosis D in healthy schoolchildren. *Pediatrics*. 2001;107(4):e53.
- Jackmann N, Makitie O, Harila-Saari A, Gustafsson J, Nezirevic Dernroth D, Frisk P. Vitamin D status in children with leukemia, its predictors, and association with outcome. *Pediatr Blood Cancer*. 2020;67(4):e28163.
- Braegger C, Campoy C, Colomb V, et al. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr*. 2013;56(6):692-701.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
- Helou M, Ning Y, Yang S, et al. Vitamin D deficiency in children with cancer. *J Pediatr Hematol Oncol*. 2014;36(3):212-217.
- Holmlund-Suila E, Koskivirta P, Metso T, Andersson S, Makitie O, Viljakainen HT. Vitamin D deficiency in children with a chronic illness-seasonal and age-related variations in serum 25-hydroxy Vitamin D concentrations. *PLoS One*. 2013;8(4):e60856.
- Andersson B, Swolin-Eide D, Magnusson P, Albertsson-Wikland K. Vitamin D status in children over three decades - Do children get enough vitamin D? *Bone reports*. 2016;5:150-152.
- Öhlund I, Silfverdal SA, Hernell O, Lind T. Serum 25-hydroxyvitamin D levels in preschool-age children in northern Sweden are inadequate after summer and diminish further during winter. *J Pediatr Gastroenterol Nutr*. 2013;56(5):551-555.
- Ahmed SF, Franey C, McDevitt H, et al. Recent trends and clinical features of childhood vitamin D deficiency presenting to a children's hospital in Glasgow. *Arch Dis Child*. 2011;96(7):694-696.
- Högberg U, Winbo J, Fellman V. Population-based register study of children born in Sweden from 1997 to 2014 showed an increase in rickets during infancy. *Acta Paediatr*. 2019;108(11):2034-2040.
- Rodvall Y, Wahlgren CF, Wiklund K. Future reduction of cutaneous malignant melanoma due to improved sun protection habits and decreased common melanocytic nevi density among Swedish children?: A follow-up from 2002 to 2012. *Eur J Cancer*. 2019;118:149-155.
- Flodmark CE. Prevention models of childhood obesity in Sweden. *Obesity facts*. 2018;11(3):257-262.
- Livsmedelverket [Internet]. <https://www.livsmedelverket.se/livsmedel-och-innehall/naringsamne/vitaminer-och-antioxidanter/d-vitamin>. Accessed October 15, 2020.
- Genc DB, Vural S, Yagar G. The incidence of and factors associated with vitamin D deficiency in newly diagnosed children with cancer. *Nutr Cancer*. 2016;68(5):756-761.
- Iniesta RR, Paciarotti I, Davidson I, et al. 5-Hydroxyvitamin D concentration in paediatric cancer patients from Scotland: a prospective cohort study. *Br J Nutr*. 2016;116(11):1926-1934.
- Sinha A, Avery P, Turner S, Bailey S, Cheetham T. Vitamin D status in paediatric patients with cancer. *Pediatr Blood Cancer*. 2011;57(4):594-598.
- Aristizabal P, Sherer M, Perdomo BP, et al. Sociodemographic and clinical characteristics associated with vitamin D status in newly diagnosed pediatric cancer patients. *Pediatr Hematol Oncol*. 2020;37(4):314-325.
- Kimball S, Fuleihan Gel H, Vieth R. Vitamin D: a growing perspective. *Crit Rev Clin Lab Sci*. 2008;45(4):339-414.
- Juhász O, Jakab Z, Szabó A, Garami M. Examining the vitamin D status of children with solid tumors. *J Am Coll Nutr*. 2020;39(2):128-134.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Jackmann N, Gustafsson J, Harila-Saari A, et al. Prevalence of and factors influencing vitamin D deficiency in paediatric patients diagnosed with cancer at northern latitudes. *Acta Paediatr*. 2021;110:2252-2258. <https://doi.org/10.1111/apa.15788>