Higher Serum Vitamin D Concentrations Are Longitudinally Associated with Better Global Quality of Life and Less Fatigue in Colorectal Cancer Survivors up to 2 Years after Treatment

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ABSTRACT

Background: Vitamin D status may be an important determinant of health-related quality of life of colorectal cancer survivors. The current study investigated longitudinal associations between serum 25-hydroxyvitamin D_3 ($25OHD_3$) concentrations and quality of life in stage I–III colorectal cancer survivors up to 2 years after treatment.

Methods: Patients with colorectal cancer ($n = 261$) were included upon diagnosis. Home visits (including blood sampling) were performed at diagnosis and at 6 weeks, 6 months, 1 year, and 2 years after treatment. Serum $25OHD_3$ concentrations were measured using LC/MS-MS and adjusted for season. Validated questionnaires were used to assess global quality of life and cognitive functioning (EORTC-QLQ-C30), fatigue (EORTC-QLQ-C30 and Checklist Individual Strength, CIS), and depression and anxiety (Hospital Anxiety and Depression Scale). Statistical analyses were performed using linear mixed models and adjusted for sex, age, time since diagnosis, therapy, comorbidities, physical activity, and body mass index.

Results: At diagnosis, 45% of patients were vitamin D deficient (<50 nmol/L). After treatment, $25OHD_3$ concentrations increased on average with 3.1 nmol/L every 6 months. In confounder-adjusted models, 20 nmol/L increments in $25OHD_3$ were longitudinally associated with increased global quality of life [β 2.9; 95% confidence interval (CI), 1.5–4.3] and reduced fatigue (EORTC-QLQ-C30 subscale: β −3.5; 95% CI, −5.3 to −1.8 and CIS: β −2.8; 95% CI, −4.7 to −0.9). Observed associations were present both within and between individuals over time.

Conclusions: Higher concentrations of $25OHD_3$ were longitudinally associated with better global quality of life and less fatigue in colorectal cancer survivors.

Impact: This study suggests that higher $25OHD_3$ concentrations may be beneficial for colorectal cancer survivors. Future intervention studies are needed to corroborate these findings.

Introduction

Colorectal cancer survivors are susceptible to enduring physical and psychologic distress as a result of the tumor and therapy. A growing number of individuals are living with a history of colorectal cancer given the improving 5-year survival rate after colorectal cancer, currently 65% in the Netherlands (1, 2). Previous studies reported complaints of fatigue by more than one third of Dutch colorectal cancer survivors, especially within 5 years after diagnosis (3–5). In addition, colorectal cancer survivors are at increased risk of impaired cognitive functioning and mental health problems such as depression (6–8).

Vitamin D is a potentially important determinant of health-related quality of life (HRQoL) of colorectal cancer survivors given its involvement in many cellular processes related to cognition (9, 10), depression (11, 12), and fatigue (13). Exposure of the skin to ultraviolet B radiation contributes to about two thirds of vitamin D supply, whereas about one third originates from vitamin D intake (14). Vitamin D deficiencies have become a concern of public health (15, 16), and the Dutch Health Council recommends women aged 50 to 70 (10 mcg) and men and women aged >70 (20 mcg) to daily supplement vitamin D (14). No specific guidelines for cancer survivors are available. To maintain adequate vitamin D concentrations, 15 to 30 minutes of daily sunlight exposure from March to November is generally sufficient for the general population (17). Colorectal cancer survivors are at risk of low vitamin D because of the negative impact of the cancer and chemotherapy on circulating concentrations (18–20). Moreover, the association between low vitamin D and increased colorectal cancer risk (21–24) makes colorectal cancer survivors particularly susceptible as low concentrations may be sustained after therapy. Inflammation may be an important confounder in the association between vitamin D and HRQoL. Inflammatory processes and vitamin D interact through 1,25-dihydroxyvitamin D, the biologically active metabolite also known as calcitriol, which is engaged in different intracellular inflammatory reactions (25). In addition, as inflammatory markers have been associated with increased fatigue

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after cancer, a potential observed association between vitamin D and HRQoL may be altered by inflammation (26).

Few studies have investigated associations between vitamin D and HRQoL after colorectal cancer. An observational study among 453 stage II colorectal cancer survivors reported better symptom-related quality of life among participants using vitamin D supplements over 2 years of follow-up (27). Cancer survivors are known to be highly motivated to intentionally alter their lifestyle in order to make health improvements (28). Therefore, lifestyle recommendations that focus on the enhancement of vitamin D concentrations may be an opportunity to prevent or reduce problems of diminished HRQoL after colorectal cancer.

The objective of the present study was to investigate longitudinal associations of serum 25-hydroxyvitamin D3 ($25OHD_3$) concentrations with HRQoL in colorectal cancer survivors from 6 weeks to 2 years after treatment, including global quality of life, fatigue, depression, anxiety, and cognitive functioning.

Materials and Methods

Study design and population

The EnCoRe study (Energy for Life after ColoRectal Cancer) is an ongoing prospective cohort study that was initiated in 2012 (Netherlands Trial Register no. NL6904; refs. 5, 29). The purpose of the EnCoRe study is to evaluate longitudinal associations between lifestyle factors and HRQoL, functioning, and prognosis after colorectal cancer. Patients with stage I–III colorectal cancer ≥18 years of age were recruited at diagnosis. Research dietitians performed home visits at diagnosis (prior to treatment) and at 6 weeks, 6 months, 1 year, and 2 years after the end of treatment. The study was approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University, the Netherlands. All participants signed informed consent. Exclusion criteria were: diagnosis with stage IV colorectal cancer, no home address in the Netherlands, inability to understand the Dutch language, and the presence of comorbidities obstructing successful study participation. Data used in the current analyses were based on the first 4.5 years of follow-up until November 1, 2016. Participants with at least 1 follow-up visit with available data on both $25OHD_3$ and HRQoL were included in the current analyses. The final analyses contained 261 participants at diagnosis, 260 at 6 weeks, 213 at 6 months, 168 at 12 months, and 77 at 24 months after treatment. Response rate for inclusion was 46% and >90% for follow-up visits.

Measurement of $25OHD_3$

At diagnosis, blood samples were drawn either during the first home visit or at the hospital, and were mostly nonfasting. At follow-up, fasting blood samples were drawn during home visits. Samples were collected in 8.5 mL serum tubes (BD Vacutainer SST II Advance) and pipetted into aliquots after centrifugation. Aliquots were stored at −80°C within 4 hours after blood draw until analysis. Serum $25OHD_3$ concentrations were measured using LC/MS-MS at the Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands (30). Interassay coefficients of variation were 5.3%, 3.1%, and 2.9% at $25OHD_3$ concentrations of 39.0, 92.5, and 127.0 nmol/L, respectively. $25OHD_3$ concentrations are a robust indicator and the most commonly used marker of vitamin D status (31).

Health-related quality of life

HRQoL was assessed during posttreatment time points. Global quality of life, cognitive functioning, and fatigue were assessed by the Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30, version 3.0; refs. 32, 33). Higher scores reflect better global quality of life, better cognitive functioning, and more fatigue (range, 0–100). Fatigue was also measured by the Checklist Individual Strength (CIS), a validated 20-item questionnaire that has been used in colorectal cancer survivors before (34, 35). Higher scores indicate more fatigue (range, 20–140). Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS; refs. 36, 37). The HADS includes separate depression and anxiety scales, and higher scores indicate more depression and anxiety (range, 0–42).

Sociodemographic, lifestyle, and clinical data

Sociodemographic information was collected based on self-report. Cancer stage, type of therapy, and other clinical information were obtained from medical records. Information on comorbidities at diagnosis was retrieved from medical records by the Charlson Comorbidity Index (38) and during follow-up from the Self-Administered Comorbidity Questionnaire, which included heart condition; stroke; high blood pressure; asthma, chronic bronchitis, or chronic obstructive pulmonary disease; diabetes; stomach ulcer; kidney disease; liver disease; anemia or other disease of the blood; thyroid gland disease; depression; osteoarthritis; back pain; and rheumatoid arthritis (39).

Information on dietary supplement use, including vitamin D supplements, was collected during home visits. Information on (brand) name, dosage, frequency, duration, and ingredients was listed on standardized forms. Vitamin D intake from supplements was calculated in micrograms per day by multiplying daily frequency and dosage. At diagnosis, participants completed a semiquantitative 253-item food frequency questionnaire to retrospectively assess dietary vitamin D intake during the preceding year (40). Participants completed a 7-day dietary record as part of each posttreatment follow-up visit. Vitamin D levels in food products for both methods were obtained from the 2011 Dutch Food Composition Database (41). Methods were described in more detail previously (5, 42).

Measurements of height and weight were performed during home visits to determine body mass index (BMI). Physical activity was self-reported using the Short QUestionnaire to ASsess Health enhancing physical activity (SQUASH). Time spent in moderate-to-vigorous physical activity (MVPA; ≥3 metabolic equivalents of task) was calculated in hours/week (43). Sun exposure was self-reported at each time point by the number of days per week that participants had spent at least 15 minutes outside (in daylight), on average over the preceding month. The variable was dichotomized for the analyses in order to reflect adherence to the Dutch recommendations regarding sun exposure (spent 15 minutes outside on 7 or <7 days/week).

Plasma concentrations of inflammation markers IL6, IL8, IL10, and TNFα were measured for all time points. The selection of this set of inflammation markers was based on a review that evaluated inflammation markers that interact with vitamin D and that are specifically relevant in relation to colorectal cancer (25). Samples were collected in 6.0 mL EDTA plasma tubes (BD Vacutainer K2E) and pipetted into aliquots after centrifugation. Aliquots were stored at −80°C within 4 hours after blood draw until analysis. Measurements were performed using a custom-made multiplex assay and electrochemiluminescence (Meso Scale Diagnostics) at Wageningen University and Research, the Netherlands. Assay plates were analyzed on a QuickPlex SQ 120 plate reader (Meso Scale Diagnostics).

Statistical analyses

Descriptive analyses were performed to calculate means and SD for normally distributed variables and medians and interquartile ranges

Table 1. Sociodemographic and clinical characteristics of study participants at time of inclusion (colorectal cancer diagnosis), included in the EnCoRe study.

	Total population ($n = 261$)[a]	Vitamin D deficiency (<50 nmol/L)[b]	
		Yes ($n = 111$)	No ($n = 136$)
Age, mean (SD)	67 (9)	67 (9)	66 (9)
Sex, *n* (%)			
Men	179 (69)	78 (70)	91 (67)
Women	82 (31)	33 (30)	45 (33)
Education level, *n* (%)			
Low	66 (25)	26 (23)	35 (26)
Medium	105 (40)	48 (43)	53 (39)
High	89 (34)	37 (33)	47 (35)
Cancer type, *n* (%)			
Colon	159 (61)	72 (65)	79 (58)
Rectum	102 (39)	39 (35)	57 (42)
Cancer stage[c], *n* (%)			
I	77 (30)	32 (30)	43 (34)
II	60 (23)	26 (24)	27 (21)
III	113 (43)	50 (46)	58 (45)
Treatment, *n* (%)			
Neither chemotherapy nor radiotherapy	143 (55)	60 (54)	77 (57)
Chemotherapy only	46 (18)	25 (23)	18 (13)
Radiotherapy only	20 (8)	6 (5)	10 (7)
Both chemotherapy and radiotherapy	52 (20)	20 (18)	31 (23)
Inflammatory markers, median (IQR)			
IL6 in pg/mL	1.1 (0.7–1.7)	1.2 (0.8–1.8)	1.0 (0.6–1.6)
IL8 in pg/mL	5.5 (4.4–8.0)	5.7 (4.4–8.0)	5.5 (4.5–7.9)
IL10 in pg/mL	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.3 (0.2–0.4)
TNFα in pg/mL	2.2 (1.8–2.8)	2.2 (1.9–2.7)	2.2 (1.7–2.8)
Summary z-score	−0.1 (−1.4 to 1.1)	−0.1 (−1.0 to 1.2)	−0.1 (−1.6 to 1.1)
Sun exposure[d], *n* (%)			
<7 days	87 (33)	41 (37)	41 (30)
7 days	173 (67)	70 (63)	94 (70)
Number of comorbidities, *n* (%)			
None	49 (19)	18 (16)	29 (21)
1	57 (22)	21 (19)	36 (26)
≥2	155 (59)	72 (65)	71 (52)
BMI in kg/m^2, mean (SD)	28.4 (4.5)	29.2 (5.0)	27.6 (4.1)
Physical activity, median (IQR)			
LPA (hours/week)	11 (4–23)	11 (4–21)	12 (4–30)
MVPA (hours/week)	11 (5–20)	11 (4–19)	12 (6–21)
Current smoking, *n* (%)			
Yes	33 (13)	15 (14)	16 (12)
No	227 (87)	96 (86)	119 (88)

Abbreviations: BMI, body mass index; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity.
[a]The number of participants may slightly vary for the different variables given a small percentage of missing data.
[b]Fourteen participants had unknown $25OHD_3$ status at time of inclusion.
[c]Eleven participants had missing stage I, II, or III colorectal cancer.
[d]Number of days per week spent at least 15 minutes outside (in daylight), on average over the preceding 4 weeks.

(IQR) for skewed variables. $25OHD_3$ concentrations at each time point were adjusted for season using the week (1–52) of blood collection. Locally weighted regression analyses (LOWESS) were performed in order to account for the variation caused by seasonal differences (44, 45). For posttreatment time points, longitudinal associations between $25OHD_3$ concentrations and HRQoL were investigated using linear mixed-model analyses. Each model contained a random intercept for subject. The addition of a random slope for vitamin D was evaluated in each model according to the change in log-restricted likelihood values. A separate model was used to disentangle inter- and intraindividual associations (46). Interindividual associations were estimated by the centered person-mean value, indicating the difference between participants' mean $25OHD_3$ concentrations over time. Intraindividual associations were estimated by the individual deviations from the person-mean, indicating individual changes in vitamin D concentration over time. Vitamin D was modeled as a continuous variable in units of 20 nmol/L and as a dichotomous variable (vitamin D concentration <50 nmol/L; yes/no; ref. 20). In addition, scoring on the outcomes was compared for $25OHD_3$ concentrations of <30 nmol/L, 30–50 nmol/L, and >50 nmol/L. Vitamin D supplement use (yes/no), total vitamin D intake from diet and supplements (μg/day), and vitamin D intake only from supplements (μg/day) were

Table 2. Descriptive statistics of $25OHD_3$ concentrations, vitamin D supplement use and dietary intake, HRQoL outcomes, and other important characteristics of patients with colorectal cancer from the EnCoRe study, from inclusion (colorectal cancer diagnosis) to 24 months after treatment.

		Posttreatment follow-up measurements			
	At diagnosis ***n*** **= 261[a]**	**6 weeks after treatment** ***n*** **= 260**	**6 months after treatment** ***n*** **= 213**	**12 months after treatment** ***n*** **= 168**	**24 months after treatment** ***n*** **= 77**
$25OHD_3$ concentration in nmol/L, median (IQR)	53.1 (40.6–67.6)	48.0 (35.2–66.1)	53.4 (41.8–69.4)	57.0 (42.5–70.5)	62.9 (46.5–82.4)
Vitamin D deficiency, *n* (%)					
Yes (<50 nmol/L)	111 (45)	133 (53)	87 (42)	60 (36)	22 (30)
No (≥50 nmol/L)	136 (55)	120 (47)	120 (58)	106 (64)	52 (70)
Vitamin D supplement use, *n* (%)					
Yes	62 (24)	49 (19)	44 (21)	38 (23)	17 (22)
No	194 (76)	207 (81)	163 (79)	129 (77)	60 (78)
Vitamin D intake from supplements in μg/d, median (IQR)	5 (5–10)	5 (5–10)	6 (5–15)	7 (5–20)	10 (5–20)
Dietary vitamin D intake[b] in μg/d, median (IQR)	3.5 (2.5–4.7)	4.1 (2.9–5.6)	3.7 (2.8–4.7)	3.8 (2.9–5.0)	3.7 (2.6–4.6)
EORTC QLQ-C30[c]					
Global quality of life, mean (SD)		74.1 (18.3)	76.9 (19.0)	77.8 (18.0)	79.6 (18.5)
Range (min–max)		16.7–100	0–100	0–100	33.3–100
Cognitive functioning, mean (SD)		86.3 (20.8)	85.9 (19.1)	87.6 (19.4)	87.7 (15.1)
Range (min–max)		0–100	16.7–100	16.7–100	33.3–100
Fatigue, mean (SD)		29.1 (23.0)	23.6 (21.6)	21.6 (23.0)	19.3 (21.5)
Range (min–max)		0–100	0–100	0–100	0–88.9
CIS (incl. 4 subscales)[d]					
Total fatigue, mean (SD)		62.9 (26.4)	59.3 (27.4)	54.0 (25.9)	51.5 (25.2)
Range (min–max)		20–127	20–132	20–134	20–101
Subjective fatigue, mean (SD)		27.2 (13.3)	24.9 (12.8)	22.6 (12.3)	21.3 (12.8)
Range (min–max)		8–56	8–56	8–56	8–54
Reduced motivation, mean (SD)		12.3 (6.1)	12.0 (6.2)	10.9 (6.1)	10.5 (5.9)
Range (min–max)		4–28	4–27	4–28	4–27
Reduced physical activity, mean (SD)		10.6 (5.1)	9.6 (5.1)	8.6 (5.0)	8.1 (4.8)
Range (min–max)		3–21	3–21	3–21	3–21
Concentration problems, mean (SD)		12.9 (7.3)	12.8 (7.3)	11.9 (6.7)	11.6 (6.5)
Range (min–max)		5–34	5–33	5–31	5–28
HADS (incl. 2 subscales)[e]					
Total depression and anxiety, mean (SD)		7.4 (6.4)	7.4 (6.7)	6.8 (6.2)	5.6 (5.5)
Range (min–max)		0–30	0–32	0–33	0–28
Depression, mean (SD)		3.8 (3.6)	3.9 (3.9)	3.4 (3.4)	2.7 (3.1)
Range (min–max)		0–15	0–19	0–17	0–14
Anxiety, mean (SD)		3.6 (3.4)	3.5 (3.4)	3.4 (3.5)	2.9 (3.1)
Range (min–max)		0–16	0–15	0–16	0–16
Inflammatory markers, median (IQR)					
IL6 in pg/mL	1.1 (0.7–1.7)	1.5 (0.8–2.2)	1.2 (0.8–2.0)	0.9 (0.6–1.4)	0.9 (0.5–1.5)
IL8 in pg/mL	5.5 (4.4–8.0)	5.6 (4.4–7.3)	5.2 (4.4–7.0)	3.9 (3.1–4.8)	4.8 (3.8–6.2)
IL10 in pg/mL	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.4 (0.2–0.5)	0.2 (0.2–0.4)	0.2 (0.1–0.3)
TNFα in pg/mL	2.2 (1.8–2.8)	2.9 (2.4–3.8)	2.8 (2.3–3.6)	2.0 (1.6–2.5)	2.0 (1.6–2.9)
Summary z-score	−0.1 (−1.4 to 1.1)	−0.1 (−1.5 to 1.1)	−0.2 (−1.1 to 1.1)	−0.3 (−1.4 to 1.0)	0.1 (−1.5 to 1.3)
Sun exposure[f], *n* (%)					
<7 days	87 (33)	119 (46)	87 (41)	65 (39)	32 (44)
7 days	173 (67)	141 (54)	124 (59)	102 (61)	40 (56)
Number of comorbidities, *n* (%)					
None	49 (19)	55 (21)	49 (21)	41 (24)	16 (21)
1	57 (22)	64 (25)	51 (24)	39 (23)	17 (22)
≥2	155 (59)	141 (54)	113 (53)	87 (52)	43 (57)
BMI in kg/m^2, mean (SD)	28.4 (4.5)	27.7 (4.4)	28.2 (4.4)	28.5 (4.5)	28.5 (5.0)
Physical activity, median (IQR)					
LPA (hours/week)	11 (4–23)	8 (2–16)	11 (4–21)	11 (3–22)	11 (5–24)
MVPA (hours/week)	11 (5–20)	7 (3–14)	9 (4–15)	9 (4–18)	8 (3–18)
Current smoking, *n* (%)					
Yes	33 (13)	24 (9)	17 (8)	17 (10)	6 (8)
No	227 (87)	235 (91)	194 (92)	150 (90)	66 (92)

Abbreviations: BMI, body mass index; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity.

[a]Participants with at least 1 follow-up measurement with available data on both vitamin D and quality of life were included in the analyses. The numbers of included participants decrease during follow-up because data collected until November 1, 2016, were used and participants had not yet reached their follow-up measurement at that time. The number of participants may slightly vary for the different variables given a small percentage of missing data.

[b]Dietary intake of vitamin D was measured by a semiquantitative 253-item food frequency questionnaire at diagnosis, and by a 7-day dietary record at each follow-up measurement.

[c]Ranges EORTC QLQ-C30 subscales: 0–100.

[d]Ranges CIS: total score, 20–140; subjective fatigue, 8–56; reduced motivation, 4–28; reduced physical activity, 3–21; concentration problems, 5–35.

[e]Ranges HADS: total score, 0–42; depression, 0–21; anxiety, 0–21.

[f]Number of days per week spent at least 15 minutes outside (in daylight), on average over the preceding 4 weeks.

modeled separately as the independent variable in multivariable adjusted models to obtain more insight into the role of vitamin D supplement use.

A summary score for the inflammatory markers was calculated by summing z-scores of natural-log transformed concentrations of IL6, IL8, and TNFα, and subtracting IL10, for each time point (47). Higher scores are indicative of higher inflammation.

Relevant confounders were preselected according to the literature and included sex, age at diagnosis, time since diagnosis (units of 6 months), cancer treatment (neither chemotherapy nor radiotherapy, chemotherapy only, radiotherapy only, or both), number of comorbidities (0, 1, or ≥2), MVPA (h/wk), and BMI (kg/m^2). All time-dependent variables, including confounders, were included in the model as the repeated measurements. Other potential covariates that did not change the beta-coefficients for the relationship of main exposures with outcomes, and therefore not included in the models, were: inflammatory markers (z-score), 25OHD$_3$ at diagnosis, season, vitamin D intake from supplements (μg/d), and sun exposure (dichotomous: spent 15 minutes outside on 7 or <7 days/week). Subgroup analyses were performed for sex (men/women), age at diagnosis (<70 and ≥70 years), vitamin D supplement use (users/nonusers), and (neo-)adjuvant chemotherapy (yes/no).

Statistical analyses were performed using Stata15 (StataCorp.). *P* values <0.05 (two-sided) were considered as statistically significant.

Results

Participant characteristics

The 261 participants who enrolled in the study (31% women) had a mean ± SD age of 67 ± 9 years (**Table 1**). Median 25OHD$_3$ concentrations decreased after diagnosis and subsequently increased during follow-up (**Table 2**, **Fig. 1**). Almost half (45%) of participants were vitamin D deficient (<50 nmol/L) at diagnosis. Regarding the subgroups advised to use extra vitamin D, 24% of men and women aged ≥70 years (n = 98) were vitamin D supplement users at diagnosis. In addition, 33% of women aged 50–70 years (n = 39) used vitamin D supplements at diagnosis. Users of vitamin D supplements had higher serum concentrations compared with nonusers (**Fig. 1B**). Participants who received chemotherapy had consistently lower concentrations compared with the group who did not receive chemotherapy (**Fig. 1C**).

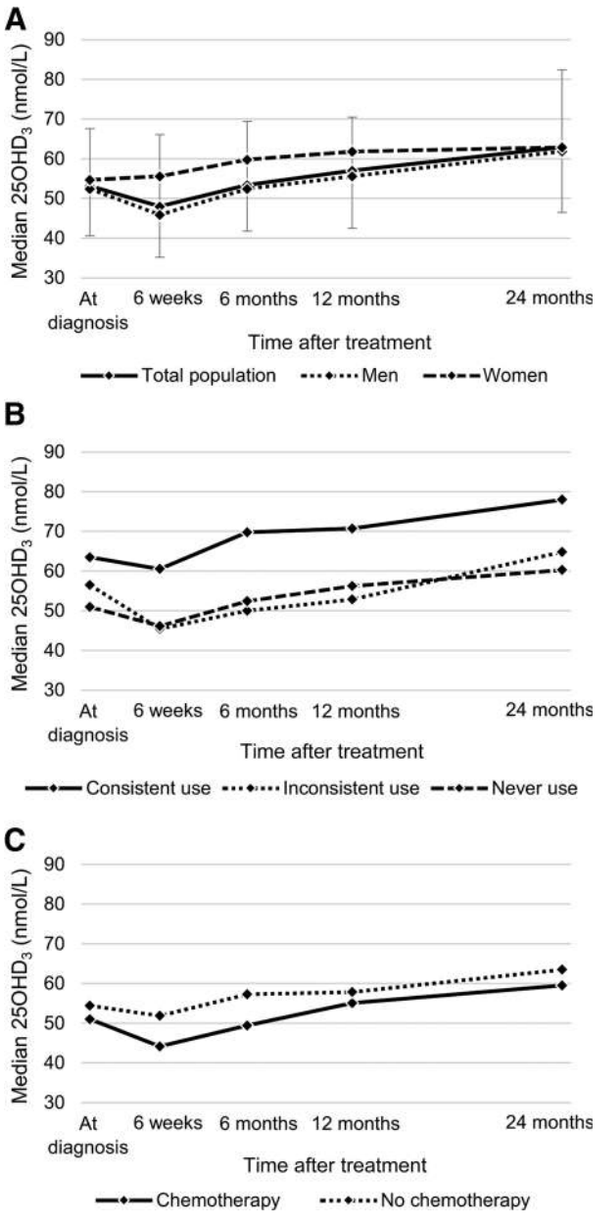

Figure 1.

Median concentrations of 25OHD$_3$ over time from colorectal cancer diagnosis (study inclusion) to 24 months after treatment for patients with colorectal cancer included in the EnCoRe study, in the total population (with IQR) and stratified by sex (**A**), stratified by vitamin D supplement user type (**B**), and stratified by chemotherapy (**C**). The actual time between the measurement at diagnosis and the measurement 6 weeks after treatment can vary between individual patients due to differences in treatment duration.

Vitamin D and HRQoL

With every 6 months, global quality of life scores improved on average by 1.3 points [95% confidence interval (CI), 0.4–2.1], and fatigue levels decreased by 2.8 points (95% CI, −3.8 to −1.8; EORTC) and 3.3 points (95% CI, −4.3 to −2.2; CIS; **Table 3**, Supplementary Fig. S1).

25OHD$_3$ was longitudinally associated with better global quality of life (β 2.9; 95% CI, 1.5–4.3) and reduced fatigue (EORTC: β −3.5; 95% CI, −5.3 to −1.8 and CIS: β −2.8; 95% CI, −4.7 to −0.9). An increase of 20 nmol/L 25OHD$_3$ within an individual over time was associated with an average 3.7 point (95% CI, 1.7–5.6) higher global quality of life score. In addition, a 20 nmol/L higher mean 25OHD$_3$ concentration between individuals over time was associated with an average 2.1 point (95% CI, 0.2–4.1) higher global quality of life score. Intra- and interindividual associations of 25OHD$_3$ with fatigue were of similar degree when measured by the CIS (β's −2.5 and −3.2, respectively), whereas for fatigue as measured by the EORTC, the association for intraindividual changes was stronger compared with interindividual differences (β's −4.4 and −2.6, respectively). Not being vitamin D deficient was longitudinally associated with better global quality of life (β 4.4; 95% CI, 1.6–7.2) and less fatigue (EORTC: β −5.2; 95% CI, −8.6 to −1.8 and CIS: β −5.4; 95% CI, −9.0 to −1.8), both within and between individuals (**Table 3**). Dose–response relations were observed for the outcomes global quality of life and fatigue when comparing the scoring of participants having severely deficient (<30 nmol/L) and

Table 3. Results of mixed-model analyses on changes of HRQoL outcomes over time and longitudinal associations of vitamin D with HRQoL outcomes in patients with colorectal cancer from the EnCoRe study followed up from diagnosis to 2 years after treatment.

		Longitudinal associations of $25OHD_3$ concentrations (per 20 nmol/L)				Longitudinal associations of vitamin D deficiency (yes/no)			
			Adjusted model II[c]				Adjusted model II[c]		
	Change in quality of life outcome over time[a] β (95% CI)	Adjusted model I[b] β (95% CI)	Overall β (95% CI)	Intraindividual β (95% CI)	Interindividual β (95% CI)	Adjusted model I[b] β (95% CI)	Overall β (95% CI)	Intraindividual β (95% CI)	Interindividual β (95% CI)
EORTC QLQ-C30[d]									
Global quality of life	**1.3 (0.4–2.1)**	**3.6 (2.2–5.0)**	**2.9 (1.5–4.3)**	**3.7 (1.7–5.6)**	**2.1 (0.2–4.1)**	**5.7 (3.0–8.4)**	**4.4 (1.6–7.2)**	**4.4 (0.9–7.9)**	4.4 (−0.03 to 8.9)
Cognitive function	−0.1 (−0.9 to 0.7)	0.3 (−1.1, 1.7)	0.3 (−1.1 to 1.8)	0.1 (−1.9 to 2.0)	0.8 (−1.6 to 3.1)	0.9 (−1.9 to 3.6)	1.1 (−1.7 to 3.9)	0.2 (−3.2 to 3.5)	3.2 (−2.0 to 8.5)
Fatigue	**−2.8 (−3.8** to **−1.8)**	**−4.8 (−6.5** to **−3.1)**	**−3.5 (−5.3** to **−1.8)**	**−4.4 (−6.9** to **−2.0)**	**−2.6 (−5.1** to **−0.2)**	**−7.4 (−10.8** to **−4.1)**	**−5.2 (−8.6** to **−1.8)**	**−5.0 (−9.3** to **−0.7)**	**−5.7 (−11.2** to **−0.1)**
CIS (incl. 4 subscales)[e]									
Total fatigue	**−3.3 (−4.3** to **−2.2)**	**−4.5 (−6.4** to **−2.7)**	**−2.8 (−4.7** to **−0.9)**	**−2.5 (−4.9** to **−0.1)**	**−3.2 (−6.1** to **−0.2)**	**−8.1 (−11.7** to **−4.5)**	**−5.4 (−9.0** to **−1.8)**	**−4.3 (−8.6** to **−0.1)**	**−7.9 (−14.6** to **−1.3)**
Subjective fatigue	**−1.7 (−2.2** to **−1.2)**	**−2.5 (−3.4** to **−1.5)**	**−1.5 (−2.4** to **−0.6)**	**−1.7 (−2.9** to **−0.4)**	−1.3 (−2.8 to 0.2)	**−4.4 (−6.3** to **−2.6)**	**−2.9 (−4.7** to **−1.2)**	**−2.8 (−4.9** to **−0.7)**	**−3.3 (−6.5** to **−0.03)**
Reduced motivation	**−0.6 (−0.8** to **−0.3)**	**−0.5 (−0.9** to **−0.1)**	−0.2 (−0.6 to 0.3)	0.0 (−0.6 to 0.6)	−0.4 (−1.0 to 0.3)	**−1.5 (−2.3** to **−0.6)**	**−1.0 (−1.9** to **−0.1)**	−0.8 (−1.9 to 0.3)	−1.4 (−2.9 to 0.1)
Reduced physical activity	**−0.8 (−1.0** to **−0.5)**	**−0.9 (−1.3** to **−0.5)**	**−0.5 (−0.9** to **−0.1)**	−0.4 (−0.9 to 0.2)	**−0.6 (−1.2** to **−0.1)**	**−1.6 (−2.4** to **−0.8)**	**−0.9 (−1.7** to **−0.2)**	−0.7 (−1.6 to 0.3)	**−1.4 (−2.6** to **−0.2)**
Concentration problems	−0.3 (−0.6 to 0.1)	**−0.7 (−1.2** to **−0.1)**	**−0.6 (−1.2** to **−0.1)**	−0.5 (−1.2 to 0.3)	**−0.8 (−1.7** to **−0.1)**	−0.8 (−1.8 to 0.2)	−0.7 (−1.7 to 0.4)	−0.1 (−1.4 to 1.2)	**−1.9 (−3.7** to **−0.1)**
HADS (incl. 2 subscales)[f]									
Total anxiety/depression	−0.2 (−0.4 to 0.1)	−0.1 (−0.5 to 0.4)	−0.0 (−0.5 to 0.4)	0.1 (−0.5 to 0.6)	−0.2 (−1.0 to 0.5)	−0.1 (−0.9 to 0.7)	−0.1 (−0.9 to 0.7)	−0.1 (−0.9 to 1.0)	−0.6 (−2.3 to 1.1)
Depression	**−0.1 (−0.3** to **−0.0)**	−0.1 (−0.4 to 0.1)	−0.1 (−0.3 to 0.2)	0.0 (−0.3 to 0.3)	−0.2 (−0.6 to 0.2)	−0.2 (−0.7 to 0.3)	−0.1 (−0.6 to 0.4)	−0.04 (−0.6 to 0.5)	−0.4 (−1.3 to 0.7)
Anxiety	−0.1 (−0.2 to 0.1)	0.1 (−0.2 to 0.3)	0.1 (−0.2 to 0.3)	0.1 (−0.2 to 0.4)	0.0 (−0.4 to 0.4)	0.05 (−0.4 to 0.5)	0.03 (−0.4 to 0.5)	0.1 (−0.4 to 0.7)	−0.2 (−1.1 to 0.7)

Note: Bold content indicates statistically significant associations.

Abbreviation: β, beta-coefficient.

[a]Changes in quality of life scores over time were measured from 6 weeks to 24 months after treatment, in units of 6 months.

[b]Model I: adjusted for sex, age at diagnosis.

[c]Model II: adjusted for sex, age at diagnosis, time since diagnosis, cancer treatment (neither chemotherapy nor radiotherapy, chemotherapy only, radiotherapy only, and both chemotherapy and radiotherapy), number of comorbidities (0, 1, and ≥2), MVPA (hours/week), BMI (kg/m^2).

[d]Ranges EORTC QLQ-C30 subscales: 0–100.

[e]Ranges CIS: total score, 20–140; subjective fatigue, 8–56; reduced motivation, 4–28; reduced physical activity, 3–21; concentration problems, 5–35.

[f]Ranges HADS: total score, 0–42; depression, 0–21; anxiety, 0–21.

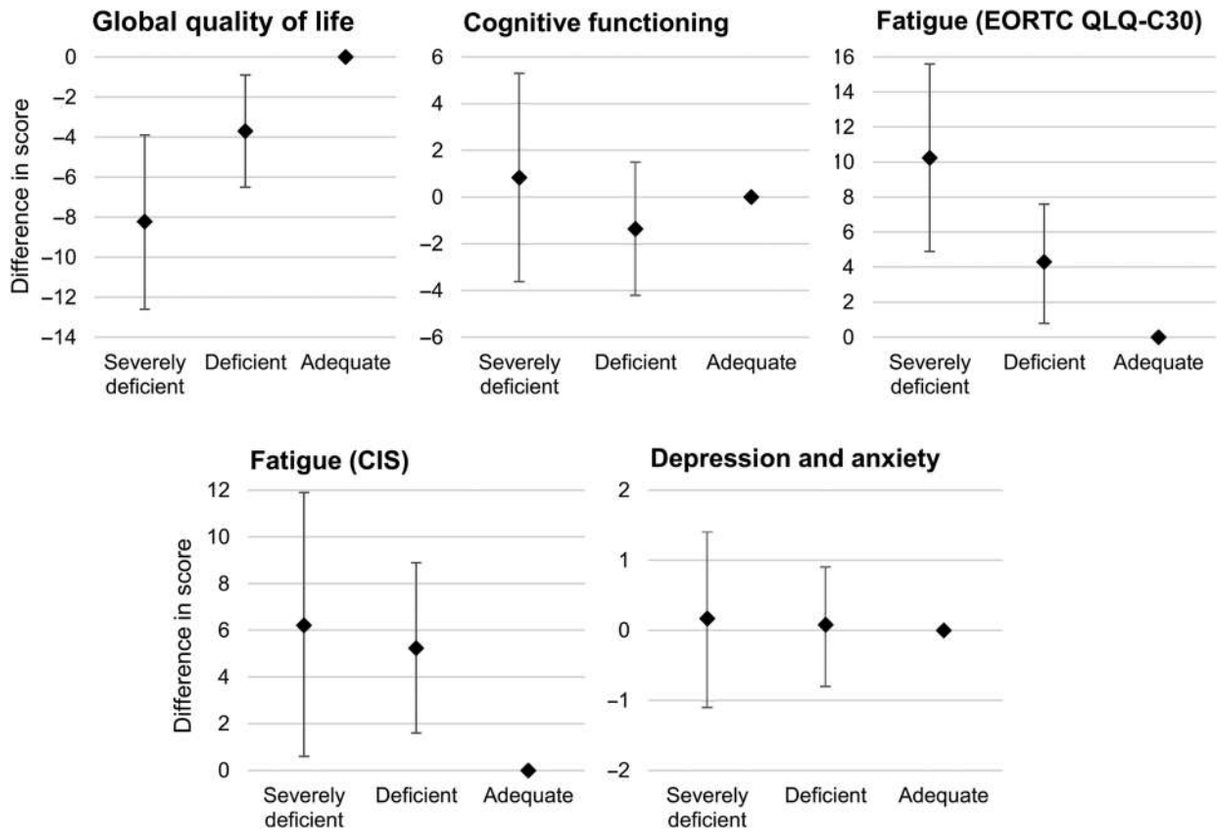

Figure 2.

Comparison of scoring on quality of life outcomes over time for participants having severely deficient (<30 nmol/L) and deficient (30–50 nmol/L) $25OHD_3$ concentrations, with participants having adequate concentrations (>50 nmol/L), from 6 weeks to 24 months after treatment in patients with colorectal cancer from the EnCoRe study.

deficient (30–50 nmol/L) $25OHD_3$ concentrations, with participants having adequate concentrations (>50 nmol/L; **Fig. 2**).

Although not statistically significant, better global quality of life and less fatigue (EORTC QLQ-C30) were observed for individuals who changed from being nonuser to user of vitamin D supplements over time, whereas interindividual differences suggested lower global quality of life and more fatigue for supplement users compared with nonusers (**Table 4**). No longitudinal associations were found between the sum of dietary and supplemental vitamin D intake with global quality of life and fatigue, and between vitamin D intake from supplements only and these outcomes.

In subgroup analyses, longitudinal associations of $25OHD_3$ concentrations with global quality of life and fatigue were only present in men (Supplementary Table S1).

Discussion

To our knowledge, the current study is the first to investigate longitudinal associations between serum $25OHD_3$ concentrations and HRQoL outcomes in colorectal cancer survivors. Higher concentrations of $25OHD_3$ were longitudinally associated with better global quality of life and less fatigue from 6 weeks up to 2 years after colorectal cancer treatment, both within and between individuals. In addition, having a vitamin D deficiency was associated with lower global quality of life and more fatigue. Intraindividual associations suggested better global quality of life and less fatigue for individuals who started using vitamin D supplements during follow-up.

The prevalence of vitamin D deficiency increased from 45% at diagnosis to 53% 6 weeks after treatment (cutoff 50 nmol/L). The latter is slightly higher compared with the general Dutch population aged 60+ with prevalences of 34% to 51% (48). A study among 2,910 patients with stage I–IV colorectal cancer from Germany observed deficiencies in 84% of participants, yet samples were assessed approximately 3 weeks after diagnosis (49). Another study among 1,598 Scottish patients with stage I–III colorectal cancer found concentrations <25 nmol/L among 50% of participants approximately 15 weeks after treatment (50). This compares with only 10% of participants when using the cutoff point of 25 nmol/L in our population. Differences may be due to vitamin D supplement use, latitude, and time of sampling as concentrations in our study steadily increased after treatment. Nevertheless, the important health concern of vitamin D deficiency among this group of patients is indisputable.

Previous studies examining the potential relation between vitamin D and aspects of HRQoL are still inconclusive and scarce among population subgroups such as cancer survivors. A systematic literature review concluded a moderate positive effect of short-term vitamin D supplementation on HRQoL in clinical populations, not including cancer survivors (51). Despite the large heterogeneity between studies included in this review, results correspond to the observed associations

Table 4. Longitudinal associations of vitamin D supplement use, vitamin D intake from diet and supplements, and vitamin D intake from supplements only, with HRQoL outcomes in patients with colorectal cancer from the EnCoRe study followed up from diagnosis to 2 years after treatment.

	Vitamin D supplement use (no/yes)[a]			Sum vitamin D intake from diet and supplements (μg/d)[b]			Vitamin D intake from supplements (μg/d)[c]		
	Overall β (95% CI)	Intraindividual β (95% CI)	Interindividual β (95% CI)	Overall β (95% CI)	Intraindividual β (95% CI)	Interindividual β (95% CI)	Overall β (95% CI)	Intraindividual β (95% CI)	Interindividual β (95% CI)
EORTC QLQ-C30									
Global quality of life	−1.5 (−6.2 to 3.2)	2.7 (−3.5 to 8.8)	−5.2 (−11.0 to 0.7)	−0. 1 (−0.4 to 0.1)	0.2 (−0.1 to 0.6)	**−0.4 (−0.7 to −0.1)**	−0.05 (−0.4 to 0.3)	0.2 (−0.2 to 0.7)	−0.3 (−0.7 to 0.1)
Fatigue	0.3 (−5.5 to 6.0)	−5.6 (−12.9 to 1.8)	5.9 (−1.4 to 13.1)	0.1 (−0.2 to 0.4)	−0.2 (−0.6 to 0.2)	0.3 (−0.1 to 0.7)	−0.01 (−0.4 to 0.3)	−0.3 (−0.8 to 0.2)	0.2 (−0.3 to 0.7)
CIS									
Total fatigue	5.3 (−1.0 to 11.6)	4.2 (−3.2 to 11.7)	6.8 (−1.8 to 15.5)	0.2 (−0.1 to 0.5)	0.2 (−0.3 to 0.6)	0.3 (−0.2 to 0.7)	0.4 (−0.0 to 0.8)	**0.5 (0.01 to 1.0)**	0.2 (−0.4 to 0.8)

Note: Bold content indicates statistically significant associations.

[a]Adjusted for sex, age at diagnosis, overall supplement use (y/n), time since diagnosis, cancer treatment (neither chemotherapy nor radiotherapy, chemotherapy only, radiotherapy only, or both chemotherapy and radiotherapy), number of comorbidities (0, 1, or ≥2), MVPA (hours/week), and BMI (kg/m^2).

[b]Adjusted for sex, age at diagnosis, overall supplement use (y/n), total energy intake (kcal/d), time since diagnosis, cancer treatment (neither chemotherapy nor radiotherapy, chemotherapy only, radiotherapy only, or both chemotherapy and radiotherapy), number of comorbidities (0, 1, or ≥2), MVPA (hours/week), and BMI (kg/m^2).

[c]Adjusted for sex, age at diagnosis, time since diagnosis, cancer treatment (neither chemotherapy nor radiotherapy, chemotherapy only, radiotherapy only, or both chemotherapy and radiotherapy), number of comorbidities (0, 1, or ≥2), MVPA (hours/week), and BMI (kg/m^2).

of the current study. Regarding fatigue, contradicting results were found in two intervention studies. A randomized placebo-controlled trial among patients with chronic fatigue syndrome found no effect of vitamin D supplementation (52), whereas another trial for treating fatigue among otherwise healthy individuals observed lower fatigue among vitamin D supplement users compared with a placebo group (53). A retrospective study among 100 ambulatory advanced cancer patients, including patients with gastrointestinal cancer, found no association between vitamin D concentrations and symptoms of depression, anxiety, and fatigue (54). Our study neither found associations between serum 25OHD$_3$ concentrations and depression, anxiety, and cognitive functioning, potentially caused by the lack of variation over time in these outcomes. In summary, results from the current study are largely in line with the literature, yet comparing results is difficult given the large differences in methodology and study parameters between studies.

The observed effect sizes for associations with global quality of life and fatigue were small and could raise questions about clinical relevance. Minimally important differences for global quality of life and fatigue (EORTC QLQ-C30) were defined as 10 and 9 points (55, 56), respectively, and for overall fatigue (CIS) as 10 points (57). Increments of 20 nmol/L 25OHD$_3$ were used as clinically relevant contrast as it resembled 1 SD and represented realistic fluctuations in intraindividual 25OHD$_3$ concentrations. Although effect sizes were larger in dichotomous analyses (vitamin D deficiency yes/no), none of the effect sizes reached the level of clinical relevance. Nevertheless, observed beta-coefficients suggest the presence of a longitudinal association between higher 25OHD$_3$ and better HRQoL.

An important strength of the current study was the prospective character with repeated measurements of 25OHD$_3$ and HRQoL outcomes. Further, follow-up response rates were high, and the percentage of missing data was low. Another strength was the use of mixed-model analysis techniques that enabled disentangling of inter- and intraindividual associations, thereby providing additional insights into the nature of the associations. A limitation of the current study concerns the inability to draw conclusions on causality. Observed associations could be due to the fact that colorectal cancer survivors with poorer HRQoL spend more time indoors, resulting in lower 25OHD$_3$ concentrations. However, adjustment for sun exposure did not change the associations. In addition, despite adjustment for important variables such as therapy, residual confounding may have occurred, as observed associations could be caused by unmeasured underlying factors related to the cancer that also influenced biological mechanisms related to 25OHD$_3$ and HRQoL.

The use of vitamin D supplements was low despite the national recommendations that applied to about half of the study population. Although vitamin D supplement users on average had higher serum 25OHD$_3$ concentrations compared with nonusers, no direct beneficial association of vitamin D supplement use with HRQoL was found. In addition, associations of 25OHD$_3$ with global quality of life and fatigue were also present in participants not using vitamin D supplements. In fact, vitamin D supplement use itself seemed associated with poorer HRQoL and more fatigue in interindividual associations. An alternative explanation, also hypothesized by Patterson and colleagues (58), is that supplement use may be a coping strategy rather than actually improving health of cancer survivors. Associations with supplement use should therefore be interpreted with caution, because individuals with poorer HRQoL and more fatigue may begin to use (vitamin D) supplements as a way to alleviate complaints (5). Intraindividual associations

contrarily suggested that individuals who started using supplements during follow-up were generally likely to report better global quality of life and less fatigue. Whether this association is causal needs to be addressed in intervention studies.

Our study does not provide strong enough evidence to formulate recommendations on the necessity of vitamin D supplementation for colorectal cancer survivors. However, higher $25OHD_3$ concentrations seem beneficial, and colorectal cancer survivors are advised to follow the guidelines for the general Dutch population because no specific guidelines on vitamin D for cancer survivors are available. According to the national guidelines, women aged >50 and women and men aged >70 are recommended to use vitamin D supplements (10 and 20 mcg, respectively) to ensure adequate blood concentrations for the prevention of osteoporosis (14). In addition, all colorectal cancer survivors should spend the recommended time outdoors to sufficiently expose their skin to sunlight (17). In practice, however, many colorectal cancer survivors seem unaware of the prevailing recommendations, potentially as a consequence of the lack of proper information provided.

In conclusion, our results suggest that higher $25OHD_3$ concentrations are longitudinally associated with better global quality of life and reduced fatigue in colorectal cancer survivors. It is important for colorectal cancer survivors to become aware of the national guidelines regarding sun exposure and vitamin D supplementation, and individual $25OHD_3$ status should be monitored by medical professionals. Placebo-controlled randomized trials are needed to examine the potential advantage of the use of vitamin D supplements in colorectal cancer survivors for improvement of HRQoL and fatigue to clarify questions on cause and effect and to deepen the understanding of possible underlying mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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