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Sufficient 25-Hydroxyvitamin D Levels 2 Years after Colorectal Cancer Diagnosis are Associated with a Lower Risk of All-cause Mortality

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ABSTRACT

Background: Whether changes in 25 hydroxy vitamin D_3 (25$(OH)D_3$) levels after colorectal cancer diagnosis influence clinical outcomes is unclear. We investigated the association of trajectories of 25$(OH)D_3$ levels with recurrence and all-cause mortality.

Methods: In total, 679 patients were included in our data analyses. Trajectories of 25$(OH)D_3$ levels were defined on the basis of vitamin D status at diagnosis, at 6 months, and 2 years after diagnosis. Observed trajectories of 25$(OH)D_3$ levels were consistent deficient levels (20%), consistent sufficient levels (39%), increasing levels (20%), and a temporary drop in levels (13%). Associations of trajectories of 25$(OH)D_3$ with recurrence and all-cause mortality were assessed using multivariable Cox proportional hazards regression models.

Results: During a follow-up time of 2.2 years for recurrence and 3.5 years for all-cause mortality, 31 and 65 events occurred, respectively. No statistically significant associations were observed for vitamin D trajectories and the risk of recurrence. Patients who were consistently sufficient compared with patients who were consistently deficient had a lower risk of all-cause mortality [HR 0.39; 95% confidence interval (CI), 0.21–0.73]. The risk of all-cause mortality seems lower in patients with increasing levels or a temporary drop in levels (HR 0.54; 95% CI, 0.27–1.10 and HR 0.40 95% CI, 0.17–0.93) relative to patients with consistent deficient levels.

Conclusions: Patients with colorectal cancer following a trajectory characterized by sufficient levels of 25$(OH)D_3$ 2 years after diagnosis all appeared to have a lower risk of all-cause mortality compared with patients having consistent deficient levels.

Impact: Further studies should investigate how trajectories of 25$(OH)D_3$ levels are associated with colorectal cancer recurrence.

Introduction

Evidence is accumulating that 25 hydroxy vitamin D_3 (25$(OH)D_3$) levels are inversely associated with all-cause mortality as well as colorectal cancer–specific mortality in patients with colorectal cancer (1–12). Maalmi and colleagues published a meta-analysis, including 11 original studies with a total of 7,718 patients with colorectal cancer (13). Pooled effect estimates comparing the highest versus lowest category of circulating 25$(OH)D_3$ at diagnosis showed a HR of 0.68 [95% confidence interval (CI), 0.55–0.85] for all-cause mortality (13). In addition to mortality, a study including 2,910 patients diagnosed with colorectal cancer observed a 32% higher risk of recurrence in patients with very low plasma 25$(OH)D_3$ concentrations at diagnosis (<11.8 nmol/L) compared with patients with 25$(OH)D_3$ levels > 45.2 nmol/L (10). On the contrary, in our previous work, no association between 25$(OH)D_3$ levels at colorectal cancer diagnosis and colorectal cancer recurrence was observed when comparing severe deficient patients (<30 nmol/L) with patients with sufficient levels (50–75 nmol/L; ref. 14). However, in the aforementioned studies 25$(OH)D_3$ was assessed only once, often at time of diagnosis.

Vitamin D deficiency (<50 nmol/L) is highly prevalent at diagnosis (40%–80%) in patients with colorectal cancer (13, 15). Cancer treatment may further challenge achievement and maintenance of sufficient (>50 nmol/L) 25$(OH)D_3$ levels for patients with colorectal cancer (15, 16). As the main source of vitamin D is sunlight, other factors such as spending less time outdoors due to being bed-bound or experiencing fatigue may also play a role in a decrease of 25$(OH)D_3$ levels after diagnosis (15, 16). On the other hand, 25$(OH)D_3$ levels can be improved by an increased exposure to sunlight and by taking vitamin D supplementation (15, 16).

However, research focusing on changes in 25$(OH)D_3$ levels after diagnosis and associations with colorectal cancer outcomes remains scarce. One previous study combining data of in total 3,535 patients with colorectal cancer observed a postoperative fall in 25$(OH)D_3$ levels followed by a recovery (12). In this study, preoperative 25$(OH)D_3$ levels were available for 486 patients, while postoperative 25$(OH)D_3$ levels were assessed in 3,049 other patients (12). Higher versus lower preoperative as well as higher versus lower postoperative 25$(OH)D_3$ levels were associated with a lower risk of all-cause mortality (HR 0.30; 95% CI, 0.12–0.71; HR 0.65; 95% CI, 0.51–0.81, respectively; ref. 12). Although timing of 25$(OH)D_3$ levels (preoperative vs. postoperative)

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Trial registration: clinical trials.gov, NCT03191110 (The COLON study); trialregister.nl, NL6904 (The EnCoRe study)

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was investigated in this study, one measurement per patients was taken, while 25(OH)D_3 levels are likely to change over time. Those changes over time, for example a steep decrease during cancer treatment or delayed recovery of 25(OH)D_3 levels after treatment, could also affect health outcomes in patients with colorectal cancer. Hence, investigating trajectories of 25(OH)D_3 levels over time is of importance. Therefore, the aim of this study was to investigate our hypothesis that trajectories of 25(OH)D_3 levels over time are associated with colorectal cancer recurrence and all-cause mortality.

Materials and Methods

Study design

Data from two prospective cohort studies were used, the COLON study and the EnCoRe study. The original aim of the COLON study was to assess associations of diet and other lifestyle factors, with colorectal cancer recurrence, survival, and quality of life. The original aim of the EnCoRe study was to assess associations of diet and other lifestyle factors with quality of life in patients with colorectal cancer. The designs of the COLON study (ref. 17; ClinicalTrials.gov identifier: NCT03191110) and the EnCoRe study (ref. 18; trialregister.nl identifier: NL6904) have been described previously. In short, in both studies, newly diagnosed patients with colorectal cancer were recruited directly after diagnosis in 14 hospitals and were followed during and after treatment. Men and women above the age of 18 were eligible. In the COLON study, patients with a first primary stage I–IV colorectal cancer were eligible. In the EnCoRe study, patients with primary stage I–III colorectal cancer were eligible. The COLON and EnCoRe studies were was approved by regional Medical Ethics Committees (NL30446.091.09 and NL38786.068.11, respectively). All patients signed informed consent.

Blood collection and vitamin D levels

For the COLON study, blood samples were obtained in the hospital shortly after diagnosis, 6 months, and 2 years after diagnosis. For the EnCoRe study, blood samples shortly after diagnosis were obtained in the hospital or by a research assistant during a home visit before start of treatment and at 6 weeks, 6 months, 1 year, and 2 years after the end of treatment. To harmonize the data of both cohorts, we selected the timepoint in the EnCoRe cohort closest to either 6 months [median 5.8; interquartile range (IQR), 5.4–6.5 months] or 2 years (median 23.9; IQR, 23.4–24.7 months) after diagnosis as the second and third timepoints for these analyses. For both studies, blood samples were obtained in a serum tube, centrifuged, and serum was aliquoted and stored in a freezer at −80°C until further analysis.

For both cohorts, serum 25(OH)D_3 levels, the most reliable measurement of an individual's vitamin D status (19), were measured by isotope dilution LC/MS-MS in the Canisius Wilhelmina Hospital, Nijmegen, the Netherlands (20). The interassay coefficients of variation were 5.3%, 3.1%, and 2.9% at 25(OH)D_3 levels of 39.0, 92.5, and 127.0 nmol/L, respectively.

To correct for the influence of season on vitamin D levels, 25(OH)D_3 levels were adjusted for week of blood collection using the locally weighted polynomial regression (LOESS) method (21, 22). To obtain interpretable 25(OH)D_3 level values, we added the mean 25(OH)D_3 level to the residuals of the LOESS method.

Vitamin D trajectories

Vitamin D deficiency was defined as 25(OH)D_3 levels lower than 50 nmol/L, while vitamin D sufficiency was defined as 25(OH)D_3 levels of 50 nmol/L or higher (23). On the basis of the season-adjusted vitamin D status (deficient/sufficient) measured at the three timepoints, four main vitamin D trajectories were observed in the data. Patients who were deficient at all three timepoints were categorized into trajectory 1 (consistent deficient levels). Patients who were sufficient at all three timepoints were categorized into trajectory 2 (consistent sufficient levels). Patients who were deficient at diagnosis, but sufficient after 2 years were categorized into trajectory 3 (increasing levels). Patients who were sufficient at diagnosis, deficient after 6 months and again sufficient after 2 years were categorized into trajectory 4 (temporary drop in levels). Categorization into trajectories was done based on crude season-adjusted 25(OH)D_3 levels.

Data collection

Habitual dietary intake in the month (COLON study) or year (EnCoRe study) preceding diagnosis was assessed using a semiquantitative food frequency questionnaire (FFQ). At the other timepoints, that is, 6 months and 2 years after diagnosis, habitual dietary intake was assessed with a semiquantitative FFQ in the COLON study and a 7-day food diary in the EnCoRe study. The FFQ used in the COLON study consist of 204 items. The FFQ used in the EnCoRe study consists of 253 items and is recently validated for macronutrients and micronutrients. Relative to the dietary record, the validity of the FFQ was moderate to good for most nutrients including magnesium ($r = 0.61$) and vitamin D ($r = 0.67$; ref. 24). Dietary intake of vitamin D, magnesium, calcium, alcohol, and fibre was calculated for each food item based on frequency of intake, number of portions and portion size, as well as the type of product. Mean daily intakes were calculated by adding all items containing the respective nutrient using data from the 2011 Dutch food composition table (25). For the COLON study, supplement use was assessed by a dietary supplement questionnaire (17). The dietary supplement questionnaire contains questions on use of single or multivitamin/minerals supplements and on the dosage and frequency of intake. In the EnCoRe study, supplement use was assessed by a research dietician during a home visit, by collecting information on dosage, frequency, duration, and ingredients from supplement packages on standardized forms. Supplement use was in both cohorts defined as using supplements at least once a week for at least 1 month in the last year or since the previous measurement timepoint. In addition, vitamins or minerals that were used once a month, but contained a high dose to cover the intake for a longer period of time (e.g., D-CURE 25.000 IE Cholecalciferol supplementation), were also classified as supplement use. Total intake of magnesium, calcium and vitamin D was calculated by summing intake from diet and intake from dietary supplements.

Information on demographics and lifestyle was obtained using self-administered questionnaires at the same time as the blood samples were collected in both cohorts. Information on height and weight was collected using self-administered questionnaires in the COLON study. In the EnCoRe study, these measurements were performed by research dieticians during home visits. Physical activity in the past 2 months was assessed using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) in both cohorts (26).

Clinical data, such as stage of disease, tumor location (colon/rectum), date of start of treatment, type of treatment (surgery, neoadjuvant/adjuvant chemotherapy, radiotherapy) and presence of comorbidities at diagnosis for both cohorts were derived from the Dutch ColoRectal Audit (27).

Colorectal cancer outcomes

Information on recurrence, defined as a local regional recurrence or distant metastases, was collected from medical records by the Dutch

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Cancer Registration. Information on mortality was gathered from linkage with the Municipal Personal Record Database.

Follow-up time for recurrence was calculated starting from the date of blood collection at the 2-year timepoint until date of recurrence or until the date recurrence status was updated (COLON: February 2018; EnCoRe: March 2018) or until the date of end of follow-up, whichever came first. Follow-up time for all-cause mortality was defined starting from date of blood collection at the 2-year timepoint until date of death, or until the last date vital status was updated (COLON: December 2019; EnCoRe: May 2019), or until the date of end of follow-up, whichever came first.

Study population for analyses

In total, 1,681 patients were included (COLON: $n = 1433$ and EnCoRe: $n = 248$) between August 2010 and October 2015. Patients with no blood samples available ($n = 440$) and patients with stage IV disease ($n = 90$) or with unknown stage ($n = 34$) were excluded from these analyses. Of all stage I–III patients with colorectal cancer, 1,117 patients donated a blood sample at diagnosis, whereas 679 (61%) patients donated blood at diagnosis and at 6 months as well as 2 years after diagnosis (**Fig. 1**). The main reason for not donating blood or filling out questionnaires for follow-up timepoints was: "too much effort to participate." Another reason for the smaller number of patients for the 2-year timepoint is that not all EnCoRe patients had already reached the 2-year follow-up timepoint in the study at the moment $25(OH)D_3$ levels were measured in December 2017. Of all stage I–III patients who donated blood at diagnosis ($n = 1,117$), 68 (6%) died within 2 years. Of all stage I–III patients who donated blood at diagnosis 95 (9%) got a recurrence within 2 years, 34 (36%) of them continued in the study and completed the 2 years measurement. Those 34 patients were excluded from the analyses, because the outcome would precede the exposure.

We checked whether there were differences in characteristics between patients who donated blood at all three timepoints ($n = 679$), patients who only donated blood at diagnosis and after 6 months ($n = 270$) and those who only donated blood at diagnosis ($n = 185$) using descriptive statistics. A few differences were observed between patients with complete data and patients with only blood available at diagnosis. Patients with complete data were slightly older, were less often smokers and had less often comorbidities. Besides, a lower percentages of deaths, was observed for patients with complete data (10%) compared with those with incomplete data (23% and 36%). Patients with complete data also had a lower rate of recurrences within 2 years (Supplementary Table S1).

Statistical analyses

Patient characteristics at diagnosis were described as medians with IQR for the total study population and by trajectories of vitamin D levels. To visualize changes in vitamin D levels over time in the different trajectories, generalized linear mixed models were used. Serum $25(OH)D_3$ as the dependent variable was entered as a continuous variable. Patients, time, and time*time were treated as random effect variables. Baseline (diagnosis) was entered as the reference timepoint. The coefficient for time represents average linear change and the coefficient for time*time captures additional quadratic change in $25(OH)D_3$ levels in nmol/L. The analysis was adjusted for age, sex, stage, cohort, and magnesium intake. Total magnesium intake was entered as time-varying variables. The variables, sex, stage, and cohort were entered as fixed factors.

Cox proportional hazards regression analysis was used to assess the association between vitamin D trajectories and recurrence and all-cause mortality in patients with colorectal cancer. Models were adjusted for age, sex, stage of disease, and cohort. In addition, other potential confounders were tested and included in the model when the

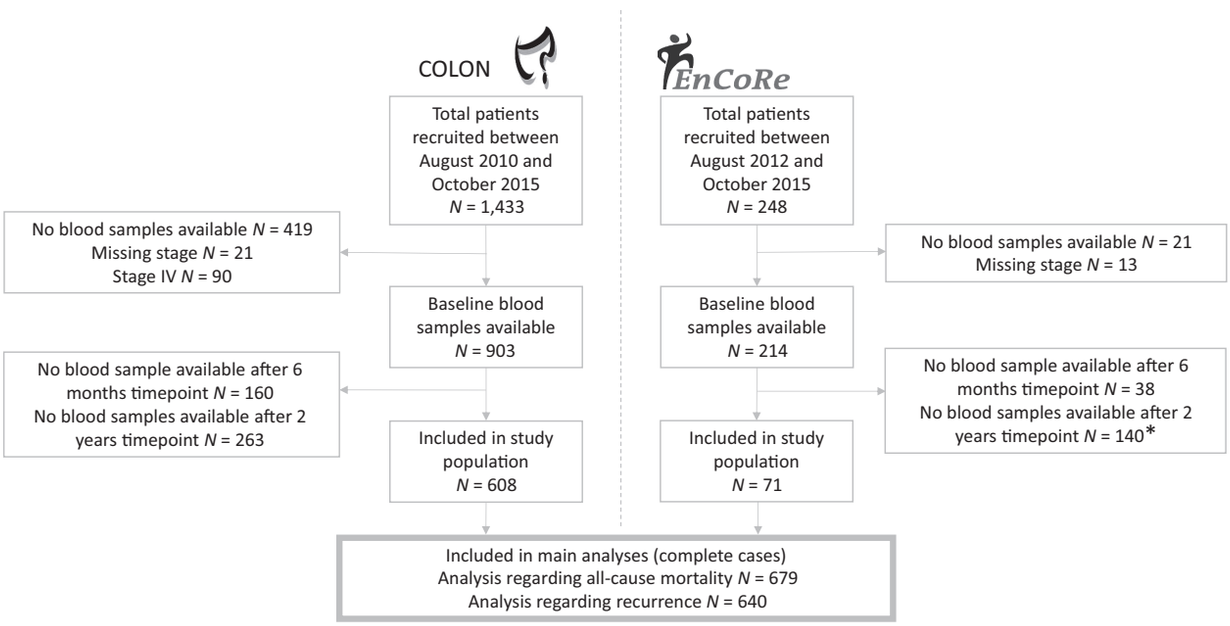

Figure 1.

Flowchart of patients included in this study. Patients with complete data (data about serum vitamin D levels available at all timepoints) were included in the main analyses. *The mean reason for unavailable data of vitamin D levels at the 2-year timepoint in the EnCoRe study was that patients had not reached this timepoint when lab measurements of vitamin D were done.

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HR changed by more than 10%, which only held true for total magnesium intake (cohort-specific quartiles). Smoking, education level, having comorbidities at diagnosis (yes/no), colorectal cancer treatment (surgery, chemotherapy, radiotherapy, chemoradiation), mean body mass index (BMI), mean physical activity level (hours of moderate to vigorous physical activity per week), mean total calcium intake (cohort-specific quartiles), alcohol intake (cohort-specific quartiles), mean fibre intake (cohort-specific quartiles), and energy intake (cohort-specific quartiles) over the 2 years did not influence the HR by more than 10% and were thus not included in the models. Log-transformed curves were used for visual inspection of the assumption for the Cox proportional hazards model. No strong evidence of nonparallelism of the log-log curves was observed.

Statistical analyses were performed in SAS 9.4 (SAS Institute). P values <0.05 were considered statistically significant.

Data availability

Because the data consist of identifying cohort information, some access restrictions apply, and therefore they cannot be made publicly available. Requests for data of the COLON study can be sent to Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands (e-mail: franzel.vanduijnhoven@wur.nl). Requests for data of the EnCoRe study can be sent to Martijn Bours, Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands (e-mail: m.bours@maastrichtuniversity.nl).

Results

The median age of the included patients was 67 (IQR, 61–72) years (**Table 1**). Thirty-five percent of the study population was female. Stage III of disease was most prevalent (41%). During a median follow-up of 2.2 years for recurrence and 3.5 years for all-cause mortality, 31 and 65 events occurred, respectively. In the total population, a slightly lower 25(OH)D_3 level was observed after 6 months, as compared with diagnosis, and these levels recovered to levels above baseline values after 2 years (**Fig. 2**; **Table 2**). When patients were categorized based on their vitamin D trajectories over time, 136 (20%) had consistent deficient 25(OH)D_3 levels, 264 (39%) had consistent sufficient levels, 133 (20%) had increasing levels over time, 90 (13%) had a temporary drop over time, and 56 (8%) could not be categorized in one of the trajectories, in these patients vitamin D levels were either decreasing over time ($n = 34$) or were higher at 6 months compared with levels at diagnosis and at 2 years ($n = 22$). Patients who were consistently deficient had the lowest level of physical activity, the highest BMI, were more often in stage III of disease and consequently received chemotherapy and/or radiotherapy most frequently. The percentages of female patients and supplement users were highest in patients who were consistently sufficient. The percentages of smokers and patients with colon cancer or comorbidities were highest in those patients who followed the trajectory with a temporary drop in levels (**Table 1**).

Vitamin D trajectories in relation to colorectal cancer recurrence and all-cause mortality

Patients who were consistently vitamin D sufficient tended to have a lower risk of recurrence compared with patients who were consistently deficient (HR 0.40; 95% CI, 0.14–1.19; **Table 3**). Increasing levels and a temporary drop in levels compared with consistent deficient levels were not associated with the risk of recurrences.

For all-cause mortality, patients who were vitamin D sufficient over time had a 61% lower risk of all-cause mortality compared with consistently deficient patients (HR 0.39; 95% CI, 0.21–0.73). A lower risk of all-cause mortality was also observed in patients with a temporary drop in levels (HR 0.41; 95% CI, 0.17–0.94) as compared with patients with consistent deficient levels. Patients with increasing levels also tended to have a lower risk of all-cause mortality compared with consistent deficient levels (HR 0.55; 95% CI, 0.27–1.10).

Discussion

In the total population, from the moment of colorectal cancer diagnosis, a small decrease at 6 months followed by an increase in 25(OH)D_3 levels at 2 years was observed. Four main trajectories of 25(OH)D_3 levels over time were observed (i) consistent deficient levels, (ii) consistent sufficient levels, (iii) increasing levels, and (iv) a temporary drop in levels. Patients who had consistent sufficient levels at all timepoints appeared to have a lower risk of recurrence and had a lower risk of all-cause mortality as compared with those with consistent deficient levels. Also patients with increasing levels or with a temporary drop in 25(OH)D_3 levels at 6 months after diagnosis appeared to have a lower risk of all-cause mortality compared with patients who had consistent deficient levels.

The small decrease followed by an increase in 25(OH)D_3 levels observed in the total population, is in line with the results of a previous study, where also a postoperative fall in 25(OH)D_3 levels followed by a recovery was observed in two cohorts combining data of 3,535 patients with colorectal cancer in total (12).

Consistent sufficient 25(OH)D_3 levels compared with consistent deficient 25(OH)D_3 levels were associated with a 60% lower risk of recurrence, although not statistically significantly. It is suggested that higher vitamin D levels decreases the risk of colorectal cancer and potentially also colorectal cancer recurrence due to its effects on cell differentiation, proliferation, and apoptosis (28, 29), as well as due to anti-inflammatory effects (29–31). In our previous work, in participants of this same pooled COLON and EnCoRe cohort, higher levels of vitamin D were associated with lower levels of IL6 (32). IL6 plays an important role in chronic inflammation (33) and is also suggested to stimulate cancer progression (34–36). We hypothesized that the risk of recurrences would also be lower in patients with increasing levels of 25(OH)D_3. However, no trend was observed for the group of patients with increasing levels nor for those with a temporary drop in levels. This could be due to the low number of events which resulted in a very low power to detect associations (power = 70% with a HR of 0.4). Observational cohort studies with a longer follow-up and/or more events are needed to unravel the association between trajectories of vitamin D levels and recurrence.

All three trajectories characterized by sufficient vitamin D levels at 2 years after diagnosis seemed to be associated with a lower risk of all-cause mortality compared with the consistent deficient trajectory. A temporary drop in levels was associated with a 61% lower mortality risk compared with consistent deficient levels. In fact, the risk of all-cause mortality was comparable in the group with consistent sufficient levels (60% lower risk), indicating that a temporary drop, probably due to cancer treatment in particular chemotherapy (2, 15, 16), may not be associated with a higher risk of all-cause mortality, as long as levels restore afterward. In addition, increasing levels over time compared with consistent deficient levels appeared to be associated with a lower risk of all-cause mortality. This all together indicates that restoring vitamin D levels may improve all-cause mortality, which stresses the

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Table 1. Characteristics of patients with colorectal cancer at diagnosis, overall and stratified by vitamin D trajectory.[a]

	Total population ($n = 679$)	Consistently deficient levels ($n = 136$)	Consistently sufficient levels ($n = 264$)	Increasing levels ($n = 133$)	Temporary drop in levels ($n = 90$)
Season adjusted 25(OH)D_3 levels[b]	54.3 (42.1–69.1)	36.7 (29.2–42.5)	71.8 (62.4–82.9)	42.7 (36.6–46.0)	60.0 (51.2–66.8)
Season of blood collection[c], *N* (%)					
Spring	177 (26)	39 (29)	60 (23)	45 (34)	15 (17)
Summer	185 (27)	29 (21)	79 (30)	26 (20)	37 (41)
Autumn	154 (23)	31 (23)	55 (21)	36 (27)	20 (22)
Winter	163 (24)	37 (27)	70 (27)	26 (20)	18 (20)
Age (years)	66.8 (61.3–72.0)	68.0 (60.7–75.2)	66.7 (61.6–71.1)	66.6 (61.3–72.8)	67.0 (62.2–70.3)
Sex (female)	239 (35)	46 (34)	107 (41)	39 (29)	28 (31)
BMI[d] (kg/m^2)	26.2 (24.1–29.1)	27.7 (24.3–30.5)	25.8 (23.9–28.2)	26.2 (24.1–29.4)	25.7 (23.9–28.4)
Education[e]					
Low	305 (45)	66 (49)	120 (46)	51 (39)	44 (49)
Medium	164 (24)	33 (25)	65 (25)	32 (24)	20 (22)
High	204 (30)	35 (26)	78 (30)	49 (37)	25 (28)
Unknown	6	2	1	1	1
Smoking habits					
Current	67 (10)	15 (11)	19 (7)	14 (11)	14 (16)
Former	407 (60)	76 (56)	162 (61)	86 (65)	50 (56)
Never	204 (30)	45 (33)	83 (31)	32 (24)	26 (29)
Unknown	1	0	0	1	0
Physical activity[f] (hours/week)	10.7 (5.0–19.5)	7.5 (3.0–16.3)	12.0 (5.9–21.3)	11.0 (5.0–17.4)	13.2 (5.0–25.0)
Unknown	1	0	0	1	0
Dietary intake					
Vitamin D (μg/day)	3.0 (2.1–4.0)	3.0 (2.2–3.9)	2.9 (2.1–4.0)	3.0 (2.2–4.2)	3.4 (2.5–4.0)
Calcium (mg/day)	860 (648–1089)	854 (625–1122)	871 (677–1088)	920 (688–1128)	892 (650–1049)
Magnesium (mg/day)	313 (254–374)	288 (234–356)	319 (260–378)	325 (256–383)	313 (256–388)
Alcohol (g/day)	8.3 (1.0–20.5)	5.2 (0.10–19.3)	8.0 (1.5–19.1)	9.7 (1.9–21.3)	10.3 (1.0–21.3)
Fibre (g/day)	20.3 (16.3–24.6)	19.0 (15.7–25.1)	21.0 (16.8–24.9)	20.1 (16.3–24.7)	20.3 (16.1–24.4)
Total energy (kcal/day)	1816 (1516–2202)	1811 (1477–2214)	1809 (1548–2173)	1927 (1563–2271)	1875 (1571–2191)
Unknown	2	0	0	1	1
Supplement use					
Vitamin D	179 (26)	24 (18)	103 (39)	20 (15)	15 (17)
Calcium	143 (21)	26 (19)	71 (27)	17 (13)	14 (15)
Magnesium	148 (22)	26 (19)	73 (28)	19 (14)	15 (17)
Unknown	1	0	1	0	0
Type of cancer					
Colon	450 (66)	82 (60)	174 (66)	90 (68)	64 (71)
Rectum	229 (34)	54 (40)	90 (34)	43 (32)	26 (29)
Type of treatment					
Only surgery	358 (53)	57 (43)	159 (60)	71 (53)	42 (47)
Surgery + chemo	142 (21)	34 (26)	41 (16)	24 (18)	28 (31)
Surgery + radio	121 (18)	32 (24)	43 (16)	24 (18)	13 (14)
Surgery + chemo + radio	51 (8)	9 (7)	20 (8)	14 (11)	6 (7)
Unknown	5	3	1	0	0
Tumor stage					
Stage I	185 (27)	25 (18)	86 (33)	38 (29)	21 (23)
Stage II	220 (32)	43 (32)	90 (34)	42 (32)	29 (32)
Stage III	274 (41)	68 (50)	88 (33)	53 (40)	40 (44)
Comorbidities					
Yes	457 (68)	95 (70)	173 (66)	97 (73)	53 (60)
Unknown	2	0	1	0	1
Cohort					
COLON	608 (90)	117 (86)	237 (90)	127 (95)	81 (90)
EnCoRe	71 (10)	19 (14)	27 (10)	6 (5)	9 (10)

Note: Values presented are median (quartile 1–quartile 3) or number (percentage).

[a]Trajectories were predefined on the basis of season-adjusted vitamin D status (<50 nmol/L = deficient; ≥ 50 nmol/L = sufficient) at the moment of measuring (at diagnosis, 6 months after diagnosis, and 2 years after diagnosis). Patients who were deficient at all three timepoints were categorized into trajectory 1 (consistently deficient). Patients who were sufficient at all three timepoints were categorized into trajectory 2 (consistently sufficient). Patients who were deficient at diagnosis, but sufficient after 2 years were categorized into trajectory 3 (increasing levels). Patients who were sufficient at diagnosis, deficient after 6 months, and again sufficient after 2 years were categorized into trajectory 4 (temporary drop in levels). Remaining patients ($n = 56$) could not be categorized in one of the trajectories. In those patients, vitamin D levels were either decreasing over time ($n = 34$) or higher levels at 6 months compared with at diagnosis and at 2 years ($n = 22$).

[b]Using the LOESS method.

[c]Spring: March–May; Summer: June–August; Autumn: September–November; Winter: December–February.

[d]BMI: body mass index. Normal <25 kg/m^2, overweight 25–29.9 kg/m^2, obese >30 kg/m^2.

[e]Low education was defined as primary school and lower general secondary education; medium as lower vocational training and higher general secondary education; high as high vocational training and university.

[f]Activities with a metabolic equivalent score (MET score) ≥ 3 were defined as moderate to vigorous physical activity.

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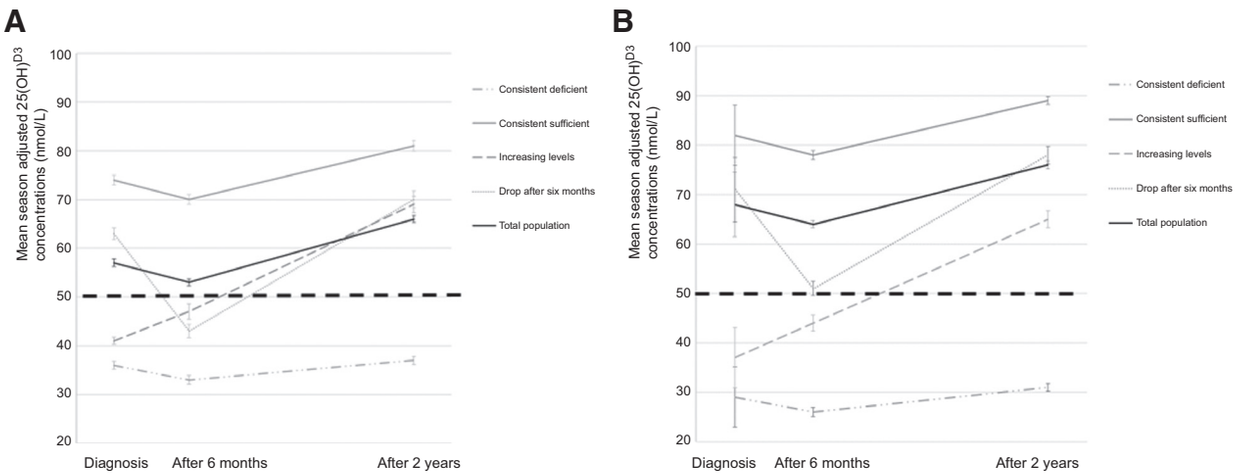

Figure 2.

Mean season-adjusted 25(OH)D_3 levels in patients with colorectal cancer stratified by trajectory of vitamin D status. **A,** The unadjusted trajectories are depicted. **B,** Trajectories adjusted for age, sex, stage, cohort, and total magnesium intake (cohort-specific quartiles) are depicted. Trajectories were predefined on the basis of season-adjusted vitamin D status (<50 nmol/L = deficient; ≥ 50 nmol/L = sufficient) at the moment of measuring (at diagnosis, after 6 months, and after 2 years). Patients who were deficient at all three timepoints were categorized into trajectory 1 (consistently deficient; $n = 136$). Patients who were sufficient at all three timepoints were categorized into trajectory 2 (consistently sufficient; $n = 264$). Patients who were deficient at diagnosis, but sufficient after 2 years were categorized into trajectory 3 (increasing levels; $n = 133$). Patients who were sufficient at diagnosis, deficient after 6 months, and again sufficient after 2 years were categorized into trajectory 4 (temporary drop in levels; $n = 90$). Remaining patients were categorized in the "other" trajectory. Because of the low number of patients in the "other" trajectory, it was not possible to adjust this trajectory for potential confounders.

importance of monitoring vitamin D levels over time and optimize levels where needed. On the other hand, it is not clear whether actively improving 25(OH)D_3 levels will also improve survival, because low 25(OH)D_3 could also be a marker instead of a cause for impaired survival (37). However, similar trends were observed when patients who died in the first year after the last measurement were excluded (Supplementary Table S2). This implies that vitamin D is on the causal pathway rather than just a marker of reduced survival.

One of the possible underlying mechanisms for the association between vitamin D and all-cause mortality is inflammation (38). Inflammation plays an important role in cancer progression (39–41) and the active form of vitamin D (1,25-dihydroxycholecalciferol), showed anti-inflammatory properties (29). Inflammation is also suggested to play a role in the onset of comorbidities such as cardiovascular diseases (42, 43), from which many cancer survivors suffer (44). We observed no statistical significant associations between trajectories

Table 2. Changes in serum 25(OH)D_3 levels over time for the total study population and per trajectory[a].

Trajectories of vitamin D	*N*	Baseline levels (ref) Estimated mean (95%CI)	Changes Beta (95% CI) After 6 months	Changes Beta (95% CI) After 2 years
Total population				
Crude	679	56.6 (55.1–58.2)	−3.6 (−5.0 to −2.2)	8.6 (7.2–10.1)
Adjusted	677	67.8 (55.8–79.8)	−3.4 (−4.8 to −2.0)	8.9 (7.4–10.4)
Consistently deficient levels				
Crude	136	35.6 (34.1–37.2)	−2.7 (−4.4 to −0.9)	1.9 (0.4–3.5)
Adjusted	136	28.4 (17.3–39.5)	−2.9 (−4.6 to −1.1)	1.7 (0.1–3.3)
Consistently sufficient levels				
Crude	264	74.0 (72.0–76.0)	−3.9 (−5.9 to −1.9)	7.4 (5.3–9.5)
Adjusted	264	81.2 (67.2–95.1)	−4.0 (−6.1 to −1.9)	7.4 (5.2–9.5)
Increasing levels over time				
Crude	133	40.6 (39.2–41.9)	6.8 (3.7–9.9)	27.4 (24.0–30.7)
Adjusted	133	36.9 (25.7–48.3)	7.2 (4.1–10.3)	27.7 (24.3–31.1)
Temporary drop in levels				
Crude	90	62.7 (60.4–65.1)	−20.4 (−23.2 to −17.7)	7.0 (3.6–10.3)
Adjusted	89	69.2 (57.3–81.0)	−20.4 (−23.2 to −17.6)	7.1 (3.6–10.6)

Note: Linear mixed models were adjusted for age, sex, stage of disease, magnesium intake (cohort-specific quartiles), and cohort.

[a]Trajectories were predefined on the basis of season-adjusted vitamin D status (<50 nmol/L = deficient; ≥ 50 nmol/L = sufficient) at the moment of measuring (at diagnosis, 6 months after diagnosis, and 2 years after diagnosis). Patients who were deficient at all three timepoints were categorized into trajectory 1 (consistently deficient levels). Patients who were sufficient at all three timepoints were categorized into trajectory 2 (consistently sufficient levels). Patients who were deficient at diagnosis, but sufficient after 2 years were categorized into trajectory 3 (increasing levels). Patients who were sufficient at diagnosis, deficient after 6 months, and again sufficient after 2 years were categorized into trajectory 4 (temporary drop in levels). Trajectories were based on crude data.

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Table 3. Association between trajectories of vitamin D over time[a] and recurrence and all-cause mortality.

	Consistently deficient (<50 nmol/L)	Consistently sufficient (>50 nmol/L)	Increasing levels	Temporary drop in levels
Risk of CRC recurrence after 2 years				
No./events	119/8	245/6	129/9	80/6
No. of events/1,000 person years	16	6	18	16
Crude HR (95% CI)	1.0 (Ref)	0.36 (0.12–1.03)	0.98 (0.37–2.61)	0.82 (0.27–2.49)
Adjusted HR[b] (95% CI)	1.0 (Ref)	0.40 (0.14–1.19)	1.02 (0.37–2.82)	0.82 (0.26–2.56)
Risk of all-cause mortality after 2 years				
No./events	136/26	264/17	133/12	90/7
No. of events/1,000 person years	36	12	17	13
Crude HR (95% CI)	1.0 (Ref)	0.32 (0.17–0.58)	0.47 (0.24–0.93)	0.36 (0.16–0.83)
Adjusted HR[b] (95% CI)	1.0 (Ref)	0.39 (0.21–0.73)	0.54 (0.27–1.09)	0.40 (0.17–0.93)

[a]Trajectories were predefined on the basis of vitamin D status (<50 nmol/L = deficient; ≥ 50 nmol/L = sufficient) at the moment of measuring (at diagnosis, 6 months after diagnosis, and 2 years after diagnosis). Patients who were deficient at all three timepoints were categorized into trajectory 1 (consistently deficient). Patients who were sufficient at all three timepoints were categorized into trajectory 2 (consistently sufficient). Patients who were deficient at diagnosis, but sufficient after 2 years were categorized into trajectory 3 (increasing levels). Patients who were sufficient at diagnosis, deficient after 6 months, and again sufficient after 2 years were categorized into trajectory 4 (temporary drop in levels).

[b]Cox proportional hazards model adjusted for age (at diagnosis), sex, stage of disease, cohort, and mean magnesium intake over the 2 years (cohort-specific quartiles). In the adjusted models, 3 patients with missing data for magnesium intake were excluded (2 in the increasing levels trajectory and 1 in the temporary drop in levels trajectory). The numbers of events were similar for both the crude and adjusted cox proportional hazards models.

of vitamin D and colorectal cancer recurrence. Therefore, it is possible that the observed association of vitamin D with all-cause mortality is not cancer specific but related to the presence of one or more comorbid conditions. Unfortunately, because we had no data available about the cause of death, due to new strict privacy regulations in the Netherlands, we could not distinguish between cancer-specific mortality and mortality from other causes.

Many studies observed a lower risk of all-cause mortality with higher vitamin D levels at and after diagnosis (12, 13). Results of our study also showed beneficial effects of sufficient vitamin D levels over time. Therefore, optimizing vitamin D levels in patients with colorectal cancer is potentially beneficial. The Health Council of the Netherlands recommends an additional intake of vitamin D by means of supplementation of 10 μg/day for women between 50 and 69 years of age and of 20 μg/day for all individuals above the age of 70 in the general population (45, 46). However, the compliance is low in our study population, 34% of the female participants and 23% of the male participants followed the recommendations for vitamin D supplementation. In the Dutch population as a whole, this was 48% for females and 20% for males in 2012–2014 (47). As a first step to improve vitamin D levels on the population level and especially in patients with cancer, the already available recommendations should be emphasized by health care professionals.

An important strength of our study relates to the repeated measures of 25(OH)D_3 levels. By measuring 25(OH)D_3 levels over time in patients with colorectal cancer, we were able to assess trajectories over time. This study provides important insight into characteristics of patients with specific trajectories of 25(OH)D_3 levels and the associations of those trajectories with cancer outcomes. The main limitation of this study is that only 61% of all patients included in the COLON and EnCoRe studies completed the 2-year timepoint. This limited our power. In addition, we decided to exclude patients who had a recurrence in the first 2 years after diagnosis, because for those patients the outcome does precede the exposure. This may mean that a population with a better survival prognosis is included in our data analyses. Indeed, patients with complete data were slightly younger, less often smoker and had less often comorbidities. On the other hand, in our previous work, we observed no association between 25 (OH)D_3 levels at diagnosis and recurrence and a borderline significant association with all-cause mortality ($HR_{per10nmol/L}$ 0.98; 95% CI, 0.90–1.07; $HR_{per10nmol/L}$ 0.94; 95% CI, 0.87–1.01, respectively; ref. 14). When repeating these analyses within this specific study population, slightly stronger associations were observed ($HR_{per10nmol/L}$ 0.86; 95% CI, 0.71–1.05 for recurrence and $HR_{per10nmol/L}$ 0.89; 95% CI, 0.78–1.01 for all-cause mortality). The comparable results indicate that our study population is not a selected population; however, our population for analyses seems to have a greater chance of survival compared with patients with colorectal cancer in general. Therefore, results of this study can only be generalized to stage I–III patients with colorectal cancer with a relatively good prognosis. Another limitation, is that we did not have enough power to stratify our analyses based on magnesium intake, while we observed an interaction between vitamin D levels and magnesium intake in relation to colorectal cancer outcomes in our previous study (14). Besides, due to the observational nature of our study, we cannot prove that high 25(OH)D_3 levels over time are the cause of the observed lower risk of all-cause mortality. High vitamin D levels could also be a marker of better health (37) and therefore be associated with a lower risk of all-cause mortality. However, similar trends were observed when patients who died shortly after the end of follow-up were excluded. Furthermore, although corrected for in the analyses, patients who had consistent sufficient 25(OH)D_3 levels were more often diagnosed with stage I disease, and had as such a better prognosis. On the other hand, also a lower risk of all-cause mortality was observed in patients in the temporary drop in levels trajectory, while these patients were relatively often diagnosed with stage III disease. Thus, the association between 25(OH)D_3 levels and all-cause mortality cannot be explained by stage of disease.

In conclusion, all three trajectories with sufficient vitamin D levels after 2 years appeared to be associated with a lower risk of all-cause mortality compared with the consistent deficient trajectory. Observational studies with a longer follow-up and/or events, and consequently more power, are needed to investigate whether trajectories of 25(OH)D_3 levels are also associated with a lower risk of long-term cancer recurrence.

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Authors' Contributions

E. Wesselink: Conceptualization, resources, data curation, formal analysis, writing–original draft, writing–review and editing. **D.E. Kok:** Conceptualization, writing–review and editing. **J.H.W. de Wilt:** Conceptualization, writing–review and editing. **M.J.L. Bours:** Conceptualization, writing–review and editing. **M. van Zutphen:** Resources, data curation, writing–review and editing. **E.T.P. Keulen:** Resources, writing–review and editing. **F.M. Kruyt:** Resources, writing–review and editing. **S.O. Breukink:** Resources, writing–review and editing. **E.A. Kouwenhoven:** Resources, writing–review and editing. **J. van den Ouweland:** Resources, writing–review and editing. **M.P. Weijenberg:** Conceptualization, funding acquisition, writing–review and editing. **E. Kampman:** Conceptualization, funding acquisition, writing–review and editing. **F.J.B. van Duijnhoven:** Conceptualization, formal analysis, funding acquisition, writing–review and editing.

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Sufficient 25-Hydroxyvitamin D Levels 2 Years after Colorectal Cancer Diagnosis are Associated with a Lower Risk of All-cause Mortality

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