Vitamin D, magnesium, calcium, and their interaction in relation to colorectal cancer recurrence and all-cause mortality

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ABSTRACT

Background: Higher concentrations of 25-hydroxyvitamin D3 [25(OH)D3] at diagnosis are associated with a lower mortality risk in colorectal cancer (CRC) patients. However, magnesium and calcium are important in vitamin D metabolism.

Objectives: We aimed to investigate 25(OH)D3, magnesium, or calcium and their interaction among patients with CRC in relation to recurrence and all-cause mortality.

Methods: The study population included 1169 newly diagnosed stage I–III CRC patients from 2 prospective cohorts. Associations between 25(OH)D3 concentrations, magnesium or calcium intake through diet and/or supplements at diagnosis, and recurrence and all-cause mortality were evaluated using multivariable Cox proportional hazard models. The interaction between 25(OH)D3 and magnesium or calcium was assessed by investigating 1) joint compared with separate effects, using a single reference category; and 2) the effect estimates of 1 factor across strata of another.

Results: Serum 25(OH)D3, calcium, and magnesium, alone and their interactions, were not associated with recurrence. Serum 25(OH)D3 concentrations seemed to be associated with all-cause mortality. An inverse association between magnesium intake (HRQ3 vs. Q1: 0.55; 95% CI: 0.32, 0.95 and HRQ4 vs. Q1: 0.65; 95% CI: 0.35, 1.21), but not calcium intake, and all-cause mortality was observed. When investigating the interaction between 25(OH)D3 and magnesium, we observed the lowest risk of all-cause mortality in patients with sufficient vitamin D concentrations (≥50 nmol/L) and a high magnesium intake (median split) (HR: 0.53; 95% CI: 0.31, 0.89) compared with patients who were vitamin D deficient (<50 nmol/L) and had a low magnesium intake. No interactions between calcium and vitamin D in relation to all-cause mortality were observed.

Conclusions: Our findings suggest that the presence of an adequate status of 25(OH)D3 in combination with an adequate magnesium intake is essential in lowering the risk of mortality in CRC patients, yet the underlying mechanism should be studied. In addition, diet and lifestyle intervention studies are needed to confirm our findings. The COLON study was registered at clinicaltrials.gov as NCT03191110.

The EnCoRe study was registered at trialregister.nl as NTR7099.

Keywords: colorectal cancer patients, 25(OH)D3, interactions, magnesium, calcium, recurrence, all-cause mortality

Introduction

Evidence is accumulating that circulating vitamin D concentrations are inversely associated with mortality in colorectal cancer patients. However, magnesium and calcium are important in vitamin D metabolism. Our findings suggest that the presence of an adequate magnesium intake (median split) (HR: 0.53; 95% CI: 0.31, 0.89) with sufficient vitamin D concentrations (≥50 nmol/L) the effect

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Because the data consist of identifying cohort information, some access restrictions apply, and therefore they cannot be made publicly available. Data will be shared with permission, from the acting committee of the COLON Study. Requests for data can be sent to Dr. Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, Netherlands (e-mail: franzel.vanduijnhoven@wur.nl).

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Abbreviations used: COLON, COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life; CRC, colorectal cancer; DCRA, Dutch Colorectal Audit; EnCoRe, Energy for life after ColoRectal cancer; RERI, relative excess risk due to interaction; 25(OH)D3, 25-hydroxyvitamin D3.

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cancer (CRC) patients (1–11). Recently, Maalmei et al. (12) performed a meta-analysis, including 11 original studies with a total of 7718 CRC patients. Pooled effect estimates comparing the highest with the lowest category of circulating 25-hydroxyvitamin D [25(OH)D] showed an HR of 0.68 (95% CI: 0.55, 0.85) for all-cause mortality and 0.67 (95% CI: 0.57, 0.78) for CRC-specific mortality (12). Although recurrence of the disease is a concern for CRC survivors (13) and a contributor to morbidity and mortality in CRC survivors (14), the association between 25(OH)D concentrations and CRC recurrence has hardly been reported so far.

Magnesium plays crucial roles in several biochemical processes involved in the synthesis and metabolism of vitamin D (15). The enzymatic conversion of 25(OH)D3 to 1,25(OH)2D3, the active form of vitamin D, is magnesium dependent (16, 17). Vitamin D–resistant rickets, in which patients do not respond to vitamin D supplementation, could be reversed by magnesium supplementation (18). In addition, a previous cohort study in the general population observed a stronger inverse association between 25(OH)D3 concentrations and all-cause mortality in participants with a high magnesium intake (median >264 mg/d) than in participants with a low magnesium intake (<264 mg/d) (15). When investigating magnesium alone, a borderline statistically significant inverse association between magnesium intake and all-cause mortality was observed in a meta-analysis of 6 prospective cohort studies among the general population (HR_{highest vs. lowest} = 0.88; 95% CI: 0.76, 1.01). Whether magnesium, alone or in interaction with vitamin D, is also beneficial for patients with CRC is unknown.

Besides magnesium, calcium is also involved in vitamin D metabolism. A low calcium intake causes a high turnover of vitamin D metabolites, resulting in vitamin D deficiency, whereas a high calcium intake is vitamin D sparing (19). Previously, a high postdiagnostic calcium intake was associated with a lower risk of all-cause mortality in CRC patients (20, 21). Moreover, 3 previous randomized controlled trials in patients with colorectal adenomas showed a reduced adenoma recurrence with high-dose calcium supplementation (pooled RR: 0.80; 95% CI: 0.68, 0.93) (22). On the contrary, another large randomized controlled trial observed no associations between high-dose calcium and/or vitamin D supplementation and the risk of recurrent adenomas and even a higher risk of sessile serrated adenomas (23, 24). Until now, however, it is unknown whether calcium intake is associated with CRC recurrence, especially in interaction with vitamin D concentrations.

The aim of our study was to investigate our hypothesis that higher vitamin D concentrations, magnesium intake, and calcium intake, at diagnosis, are associated with a lower risk of recurrence and all-cause mortality in CRC patients. Beyond that, given the importance of magnesium and calcium in vitamin D metabolism, the interaction between vitamin D concentrations and magnesium intake or calcium intake in relation to CRC recurrence and all-cause mortality was investigated.

Methods

Study design

The designs of the COLON (COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life) study (25) (NCT03191110) and the EnCoRe (Energy for life after ColoRectal cancer) study (26) (NTR7099) have been described elsewhere. Briefly, newly diagnosed CRC patients were recruited directly after diagnosis in 14 hospitals and were followed during and after treatment from 2010 (COLON) or 2012 (EnCoRe) onwards. Men and women >18 y of age were eligible. In the COLON study, patients with stage I–IV CRC were eligible. In the EnCoRe study, patients with stage IV disease were not recruited. Non–Dutch speaking patients, and those with (partial) bowel resection, chronic inflammatory bowel disease, hereditary CRC syndromes (e.g., Lynch syndrome, Familial Adenomatous Polyposis, Peutz-Jegher), dementia, or another mental condition obstructing participation were excluded in both studies. The COLON study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, Netherlands (2009-349). The EnCoRe study was approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University, Netherlands (METC 11-3-075). All patients provided signed informed consent.

Blood samples were available for 1169 patients, 71% of all recruited participants. Patients with stage IV disease (n = 90) or with unknown stage (n = 37) were excluded from the analyses (Figure 1).

Blood collection and measurement of 25(OH)D3 concentrations

For the COLON study, blood samples were obtained in the hospital at diagnosis. In 93% of the patients included in these analyses, blood was collected before the start of treatment. For the EnCoRe study, blood samples at diagnosis were obtained in the hospital or by a research assistant during a home visit before the start of treatment. For both studies, blood samples were collected in a serum tube, centrifuged (at 1300 × g at 4 °C for 15 minutes in the COLON study and at 1800 × g at 20 °C for 10 minutes in the EnCoRe study), and aliquots were immediately stored at −80 °C until further analysis.

For both cohorts, serum 25(OH)D3 concentrations were measured by isotope-dilution LC–tandem MS in Canisius Wilhelmina Hospital, Nijmegen, Netherlands (27). The interassay CVs were 7.4%, 4.0%, and 3.1% at 25(OH)D3 concentrations of 36.0, 88, and 124 nmol/L, respectively. Serum 25(OH)D3 is the main circulating form of vitamin D and generally considered the most reliable measurement of an individual’s vitamin D status (28).

Data collection

Habitual dietary intake in the month (COLON study) or year (EnCoRe study) preceding diagnosis was assessed using an extended semiquantitative FFQ. The validated FFQ used in the COLON study consists of 204 items. The FFQ used in the EnCoRe study consists of 253 items and was recently validated for macro- and micronutrients (29). Dietary intake of vitamin D, magnesium, and calcium was calculated for each food item based on frequency of intake, number of portions, and portion size, as well as the type of product (e.g., whole grain or brown bread). Mean daily vitamin D (μg/d), magnesium
Vitamin D, magnesium, calcium, and CRC outcomes

Total patients recruited between August 2010 and October 2015
n = 1340

Baseline blood samples available
n = 1014

Included in study population
n = 903

Total population included in analyses regarding vitamin D concentrations
n = 1164 for all cause mortality
n = 1155 for recurrence

COLON

No blood samples available
n = 326

Excluded
Missing stage n = 21
Stage IV n = 90

Baseline blood samples available
n = 1014

Included in study population
n = 903

Total population included in analyses regarding magnesium and calcium intake
n = 1125 for all cause mortality
n = 1121 for recurrence

EnCoRe

No blood samples available
n = 17

Excluded
Missing stage n = 16

Baseline blood samples available
n = 282

Included in study population
n = 266

Missing date of blood collection n = 4

Total population included in analyses regarding magnesium and calcium intake
n = 1125 for all cause mortality
n = 1121 for recurrence

Study endpoints

Information on recurrence was collected from medical records by the Dutch Cancer Registration. Recurrence is defined as a loco-regional recurrence or distant metastasis. Information on all-cause 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 until the date of recurrence or until the date recurrence status was updated (February 2018 for the COLON study and March 2018 for the EnCoRe study) or until the...
date of end of follow-up, whichever came first. Follow-up time for all-cause mortality was defined starting from the date of blood collection until the date of death, the last date vital status was updated (25 June, 2019 for the COLON study and 20 May, 2019 for the EnCoRe study), or the date of end of follow-up, whichever came first.

Data analyses

Patient characteristics at diagnosis were described as numbers with percentages or medians with IQRs for the total study population and stratified by vitamin D status [deficiency = serum 25(OH)D$_3$ < 50 nmol/L and sufficiency = serum 25(OH)D$_3$ ≥ 50 nmol/L] (33). Patients with missing data in the main exposure variables (n = 343 for vitamin D concentrations and n = 44 for dietary intake) were excluded from analyses (Figure 1). Descriptive statistics were used to assess differences in characteristics between patients with missing exposure data and those without missing exposure data. Correlations between magnesium, calcium, and vitamin D intake and concentrations were assessed using Pearson correlation coefficients.

The associations between serum 25(OH)D$_3$ concentrations and CRC recurrence as well as all-cause mortality were assessed using multivariable Cox proportional hazard models. Serum 25(OH)D$_3$ concentrations were entered in the model continuously per 10 nmol/L, and based on clinically defined cutoffs (33) [severely deficient: <30 nmol/L; deficient: 30–49 nmol/L; sufficient: 50–74 nmol/L (reference); optimal: ≥75 nmol/L]. The association between magnesium and calcium intake and CRC recurrence and all-cause mortality was also assessed using multivariable Cox proportional hazard models. Serum 25(OH)D$_3$ concentrations were entered in the model continuously per 10 nmol/L, and based on clinically defined cutoffs (33) [severely deficient: <30 nmol/L; deficient: 30–49 nmol/L; sufficient: 50–74 nmol/L (reference); optimal: ≥75 nmol/L].

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TABLE 1  Baseline characteristics of stage I–III colorectal cancer patients, overall and stratified by vitamin D status

|                          | Total population \( (n = 1169) \) | Deficient \([25(OH)D < 50 \text{ nmol/L}] (n = 500) \) | Sufficient \([25(OH)D \geq 50 \text{ nmol/L}] (n = 669) \) |
|--------------------------|------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Serum 25(OH)D\(_3\) concentrations, nmol/L** | 54.5 [39.8–70.2] | 37.3 [28.4–43.9] | 67.4 [58.9–79.6] |
| **Season of blood collection\(^2\)** | | | |
| Spring                   | 295 (25) | 162 (33) | 133 (20) |
| Summer                   | 327 (28) | 69 (14)  | 258 (39) |
| Autumn                   | 268 (23) | 103 (21) | 165 (25) |
| Winter                   | 274 (24) | 164 (33) | 110 (17) |
| Unknown, \( n \)         | 5                   | 3                  | 3                   |
| **Age, y**               | 67.0 [61.7–72.9] | 67.0 [60.9–74.4] | 66.9 [62.3–72.4] |
| **Gender, female**       | 418 (36) | 164 (33) | 254 (38) |
| **BMI, kg/m\(^2\)**      | 26.3 [24.1–29.3] | 26.8 [24.2–29.8] | 26.1 [24.1–29.0] |
| **Education\(^3\)**     | | | |
| Low                      | 542 (49) | 225 (48) | 317 (49) |
| Medium                   | 260 (23) | 105 (22) | 155 (24) |
| High                     | 314 (28) | 142 (30) | 172 (27) |
| Unknown, \( n \)         | 53                  | 28                | 25                  |
| **Smoking habits**       | | | |
| Current                  | 141 (12) | 58 (12)  | 83 (13)  |
| Former                   | 665 (59) | 278 (57) | 387 (59) |
| Never                    | 329 (29) | 148 (31) | 181 (28) |
| Unknown, \( n \)         | 34                  | 16                | 18                  |
| **Physical activity,\(^4\) h/wk** | 10.5 [5.0–19.5] | 8.7 [4.0–17.5] | 12.0 [5.9–20.5] |
| Unknown, \( n \)         | 36                  | 16                | 20                  |
| **Dietary intake**       | | | |
| Vitamin D, \( \mu g/d \) | 3.1 [2.2–4.2] | 3.1 [2.2–4.0] | 3.2 [2.3–4.3] |
| Calcium, mg/d            | 861 [639–1094] | 862 [630–1109] | 859 [648–1087] |
| Magnesium, mg/d          | 318 [257–384] | 316 [252–381] | 321 [259–387] |
| Alcohol, g/d             | 8.1 [0.8–20.5] | 6.1 [0.4–19.4] | 8.9 [1.3–20.7] |
| Unknown, \( n \)         | 44                  | 20                | 24                  |
| **Supplement use, yes**  | | | |
| Vitamin D                | 289 (25) | 76 (16)  | 213 (33) |
| Calcium                  | 238 (21) | 80 (16)  | 158 (24) |
| Magnesium                | 226 (19) | 81 (16)  | 145 (22) |
| **Type of cancer**       | | | |
| Colon                    | 768 (66) | 320 (64) | 448 (67) |
| Rectum                   | 401 (34) | 180 (36) | 221 (33) |
| **Tumor stage**          | | | |
| I                        | 312 (27) | 115 (23) | 197 (29) |
| II                       | 346 (30) | 148 (30) | 198 (30) |
| III                      | 511 (44) | 237 (47) | 274 (41) |
| **Comorbidities**        | | | |
| Yes                      | 285 (71) | 361 (72) | 464 (70) |
| Unknown, \( n \)         | 8                   | 1                  | 7                   |

\(^1\)Values are median [IQR] or \( n \) (%) unless otherwise indicated. \(25(OH)D_3\), 25-hydroxyvitamin D3.

\(^2\)Spring: March–May; summer: June–August; autumn: September–November; winter: December–February.

\(^3\)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.

\(^4\)Activities with a Metabolic Equivalent score \( \geq 3 \) were defined as moderate-to-vigorous physical activity.

No differences were observed between patients who donated blood and patients who did not. Patients for whom no dietary data were available seemed to be slightly older and more often had advanced disease and comorbidities (data not shown). Magnesium intake and calcium intake were moderately correlated \((r = 0.6)\). A moderate correlation between vitamin D intake and magnesium or calcium intake was observed \((r = 0.4)\). Vitamin D concentrations were not linearly correlated with magnesium or calcium intake \((r = 0.1)\).

During a median follow-up of 3.5 [IQR: 2.5–4.7] y for recurrence and 4.7 [IQR: 4.0–6.2] y for all-cause mortality, 155 recurrences and 191 deaths occurred. Almost half \((42\%\) of the patients died after a recurrence. The total follow-up time was 4084 y for recurrence and 5769 y for all-cause mortality.

Circulating concentrations of 25(OH)D\(_3\) and CRC recurrence and all-cause mortality

No association between 25(OH)D\(_3\) concentrations at diagnosis and CRC recurrence was observed (Table 2). Severe vitamin D deficiency \((<30 \text{ nmol/L})\) compared with sufficient concentrations \((50–74 \text{ nmol/L})\) tended to be associated with a higher risk of all-cause mortality (HR: 1.46; 95% CI: 0.92, 2.32; \(P\)-trend = 0.08).
HQR4 vs. Q1: 0.65; 95% CI: 0.35, 1.21; 25(OH)D3 concentrations and calcium intake, this association was attenuated (HQR3 vs. Q1: 0.55; 95% CI: 0.32, 0.95 and HR Q4 vs. Q1: 0.58; 95% CI: 0.34, 0.40, 1.21; P-trend = 0.08) interactions were observed.

When analyzing the association for magnesium across strata of vitamin D status, the association between magnesium and all-cause mortality was statistically significant in patients who had deficient vitamin D concentrations (HR: 0.43; 95% CI: 0.25, 0.76), whereas no association was observed in patients who had deficient 25(OH)D3 concentrations (HR: 0.94; 95% CI: 0.52, 1.69). When analyzing the association for vitamin D across strata of magnesium intake, the association between vitamin D concentrations and all-cause mortality was stronger in patients with a high magnesium intake (HR: 0.69; 95% CI: 0.42, 1.18) than in patients with a low magnesium intake (HR: 0.98; 95% CI: 0.65, 1.49), but observed associations were not statistically significant.

Vitamin D and calcium.

No interactions between calcium and vitamin D with respect to CRC recurrence and all-cause mortality were observed (Table 6). Similar results were observed when excluding patients who donated blood after the start of treatment (data not shown).

Discussion

No associations between serum 25(OH)D3 concentrations and magnesium or calcium intake and CRC recurrence were observed in the current study. Lower vitamin D concentrations appear to be associated with a higher risk of all-cause mortality.

### TABLE 2

Association of serum 25-hydroxyvitamin D3 concentrations at diagnosis with CRC recurrence and all-cause mortality in CRC patients.

| Serum 25(OH)D3 concentration | Continuous per 10 nmol/L | Severe deficient (<30 nmol/L) | Deficient (30–49 nmol/L) | Sufficient (50–74 nmol/L) | Optimal (≥75 nmol/L) | P-trend |
|------------------------------|--------------------------|-------------------------------|--------------------------|---------------------------|----------------------|---------|
| Events/1000 person-years     | 37                       | 43                            | 39                       | 38                        | 37                   | 1.00    |
| Model 1 HR (95% CI)          | 0.97 (0.91, 1.05)         | 1.10 (0.67, 1.81)             | 0.99 (0.68, 1.44)        | 1.0 (ref)                 | 0.88 (0.56, 1.39)    | 0.50    |
| Model 2 HR (95% CI)          | 0.98 (0.90, 1.07)         | 1.18 (0.68, 2.04)             | 1.09 (0.72, 1.63)        | 1.0 (ref)                 | 1.07 (0.66, 1.73)    | 0.69    |
| Model 3 HR (95% CI)          | 0.98 (0.90, 1.07)         | 1.19 (0.69, 2.06)             | 1.10 (0.73, 1.65)        | 1.0 (ref)                 | 1.04 (0.64, 1.69)    | 0.62    |

1Model 1: crude Cox proportional hazard model. Model 2: adjusted for age, sex, stage, BMI, physical activity (moderate to vigorous; h/wk), tumor location, season of blood collection, cohort, and total energy intake. Model 3: as model 2 and further adjusted for total magnesium and calcium intake. CRC, colorectal cancer.

2P-trend values were calculated by including categories of vitamin D status (severely deficient, deficient, sufficient, optimal) as a continuous variable in the model.
TABLE 3  Association of dietary and total magnesium intakes at diagnosis with recurrence and all-cause mortality in CRC patients

| Dietary magnesium intake | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P-trend |
|--------------------------|-----------|-----------|-----------|-----------|---------|
| **CRC recurrence** | | | | | |
| n/Events                | 280/34    | 281/36    | 280/35    | 280/40    |         |
| Events/1000 person-years| 35        | 35        | 35        | 43        |         |
| Model 1                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 1.02 (0.64, 1.63) | 1.01 (0.63, 1.61) | 1.20 (0.76, 1.89) | 0.47    |
| Model 2                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 1.19 (0.72, 1.97) | 1.10 (0.61, 2.01) | 1.38 (0.66, 2.87) | 0.70    |
| Model 3                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 1.25 (0.74, 2.08) | 1.20 (0.64, 2.26) | 1.56 (0.71, 3.46) | 0.40    |
| **All-cause mortality** | | | | | |
| n/Events                | 280/56    | 282/42    | 282/34    | 281/42    |         |
| Events/1000 person-years| 41        | 29        | 24        | 31        |         |
| Model 1                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.71 (0.48, 1.06) | 0.59 (0.38, 0.90) | 0.76 (0.51, 1.13) | 0.10    |
| Model 2                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.65 (0.42, 1.00) | 0.46 (0.26, 0.79) | 0.51 (0.26, 0.98) | 0.04    |
| Model 3                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.69 (0.44, 1.09) | 0.52 (0.29, 0.93) | 0.59 (0.29, 1.20) | 0.15    |
| **Total magnesium intake (diet and supplements)** | | | | | |
| **CRC recurrence** | | | | | |
| n/Events                | 280/34    | 281/34    | 280/37    | 280/40    |         |
| Events/1000 person-years| 35        | 33        | 38        | 42        |         |
| Model 1                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.96 (0.60, 1.55) | 1.07 (0.67, 1.70) | 1.18 (0.75, 1.86) | 0.42    |
| Model 2                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 1.15 (0.69, 1.90) | 1.20 (0.69, 2.11) | 1.39 (0.77, 2.53) | 0.24    |
| Model 3                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 1.19 (0.72, 1.99) | 1.32 (0.74, 2.36) | 1.57 (0.84, 2.92) | 0.13    |
| **All-cause mortality** | | | | | |
| n/Events                | 280/55    | 282/46    | 282/36    | 281/37    |         |
| Events/1000 person-years| 41        | 33        | 26        | 27        |         |
| Model 1                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.80 (0.54, 1.18) | 0.63 (0.41, 0.95) | 0.66 (0.40, 1.00) | 0.02    |
| Model 2                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.77 (0.50, 1.19) | 0.48 (0.29, 0.82) | 0.55 (0.31, 0.98) | 0.02    |
| Model 3                 | | | | | |
| HR (95% CI)             | 1.0 (ref) | 0.83 (0.53, 1.28) | 0.55 (0.32, 0.95) | 0.65 (0.35, 1.21) | 0.11    |

1Quartiles of intake were cohort-specific. Dietary intake of magnesium: COLON quartile 1: <246 mg/d; quartile 2: 246–305 mg/d; quartile 3: 306–371 mg/d; quartile 4: >371 mg/d; EnCoRe quartile 1: <300 mg/d; quartile 2: 300–364 mg/d; quartile 3: 364–429 mg/d; quartile 4: >429 mg/d. Total intake of magnesium: COLON quartile 1: <258 mg/d; quartile 2: 258–322 mg/d; quartile 3: 323–398 mg/d; quartile 4: >398 mg/d; EnCoRe quartile 1: <315 mg/d; quartile 2: 315–383 mg/d; quartile 3: 384–463 mg/d; quartile 4: >464 mg/d. Model 1: crude Cox proportional hazard model. Model 2: adjusted for age, sex, stage, BMI, physical activity (moderate to vigorous; h/wk), tumor location, cohort, and total energy intake. Model 3: as model 2 and further adjusted for dietary calcium and vitamin D concentrations for the dietary intake models and total calcium and vitamin D concentrations for the total intake (diet and supplements) models. P values for trend were calculated by including the quartiles as a continuous variable in the model. COLON, COlorectal cancer; Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life; CRC, colorectal cancer; EnCoRe, Energy for life after ColoRectal cancer.

An inverse association between magnesium intake, but not calcium intake, and all-cause mortality was observed. All-cause mortality was lowest in patients with sufficient vitamin D concentrations in combination with a high magnesium intake.

Severe vitamin D deficiency compared with sufficient vitamin D concentrations was statistically nonsignificantly associated with a higher risk of all-cause mortality in our study. A recent meta-analysis including 11 studies among 7718 CRC patients observed a similar, but statistically significant, association between 25(OH)D concentrations and all-cause mortality (12). However, previous studies did not take magnesium intake into account, whereas we found an attenuated association after correction for magnesium intake. Magnesium is essential in the conversion of 25(OH)D3 to the active form of vitamin D, 1,25(OH)D3 (15), and could potentially strengthen the association between vitamin D and outcomes.

In the present study, we observed a statistically significant lower risk of all-cause mortality for quartile 3 of magnesium intake (∼300–400 mg/d), but not for quartile 4 (∼>400 mg/d), than for quartile 1 (∼<250 mg/d). As far as we know, this association has not been reported before in CRC patients. In the general population, a dose-response meta-analysis showed an inverse nonlinear association between dietary magnesium...
TABLE 4  Association of dietary and total calcium intakes at diagnosis with recurrence and all-cause mortality in CRC patients

|                           | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P-trend |
|---------------------------|------------|------------|------------|------------|---------|
| **Dietary calcium intake** |            |            |            |            |         |
| CRC recurrence             |            |            |            |            |         |
| n/Events                  | 280/36     | 281/42     | 280/32     | 280/35     |         |
| Events/1000 person-years  | 38         | 43         | 33         | 34         |         |
| Model 1 HR (95% CI)        | 1.0 (ref)  | 1.16 (0.74, 1.81) | 0.87 (0.54, 1.40) | 0.92 (0.57, 1.46) | 0.46    |
| Model 2 HR (95% CI)        | 1.0 (ref)  | 1.20 (0.76, 1.90) | 0.93 (0.56, 1.55) | 0.95 (0.55, 1.65) | 0.66    |
| Model 3 HR (95% CI)        | 1.0 (ref)  | 1.17 (0.74, 1.86) | 0.87 (0.52, 1.48) | 0.86 (0.48, 1.54) | 0.39    |
| **All-cause mortality**    |            |            |            |            |         |
| n/Events                  | 280/47     | 282/46     | 282/44     | 281/37     |         |
| Events/1000 person-years  | 34         | 33         | 31         | 26         |         |
| Model 1 HR (95% CI)        | 1.0 (ref)  | 0.97 (0.65, 1.45) | 0.93 (0.61, 1.40) | 0.74 (0.48, 1.14) | 0.17    |
| Model 2 HR (95% CI)        | 1.0 (ref)  | 0.97 (0.64, 1.48) | 0.86 (0.55, 1.35) | 0.66 (0.40, 1.11) | 0.31    |
| Model 3 HR (95% CI)        | 1.0 (ref)  | 1.02 (0.67, 1.57) | 0.97 (0.61, 1.54) | 0.76 (0.44, 1.32) | 0.52    |
| **Total calcium intake (diet and supplements)** |            |            |            |            |         |
| CRC recurrence             |            |            |            |            |         |
| n/Events                  | 280/38     | 281/39     | 280/36     | 280/32     |         |
| Events/1000 person-years  | 41         | 40         | 37         | 31         |         |
| Model 1 HR (95% CI)        | 1.0 (ref)  | 0.99 (0.63, 1.44) | 0.91 (0.58, 1.44) | 0.78 (0.49, 1.25) | 0.28    |
| Model 2 HR (95% CI)        | 1.0 (ref)  | 0.99 (0.62, 1.56) | 0.95 (0.58, 1.55) | 0.79 (0.46, 1.38) | 0.44    |
| Model 3 HR (95% CI)        | 1.0 (ref)  | 0.95 (0.60, 1.50) | 0.88 (0.53, 1.46) | 0.71 (0.40, 1.27) | 0.25    |
| **All-cause mortality**    |            |            |            |            |         |
| n/Events                  | 280/47     | 282/46     | 282/44     | 281/37     |         |
| Events/1000 person-years  | 36         | 31         | 36         | 23         |         |
| Model 1 HR (95% CI)        | 1.0 (ref)  | 0.86 (0.57, 1.30) | 0.99 (0.66, 1.47) | 0.63 (0.40, 0.98) | 0.09    |
| Model 2 HR (95% CI)        | 1.0 (ref)  | 0.86 (0.57, 1.32) | 0.88 (0.57, 1.36) | 0.58 (0.34, 0.98) | 0.07    |
| Model 3 HR (95% CI)        | 1.0 (ref)  | 0.97 (0.63, 1.49) | 1.06 (0.66, 1.67) | 0.70 (0.40, 1.21) | 0.27    |

1Quartiles of intake were cohort specific. Dietary intake of calcium: COLON quartile 1: <642 g/d; quartile 2: 642–855 g/d; quartile 3: 856–1088 g/d; quartile 4: >1088 g/d; EnCoRe quartile 1: <656 g/d; quartile 2: 656–875 g/d; quartile 3: 876–1144 g/d; quartile 4: >1144 g/d. Total intake of calcium: COLON quartile 1: <669 g/d; quartile 2: 669–888 g/d; quartile 3: 889–1137 g/d; quartile 4: >1137 g/d; EnCoRe quartile 1: <673 g/d; quartile 2: 673–930 g/d; quartile 3: 930–1230 g/d; quartile 4: >1230 g/d. Model 1: crude Cox proportional hazard model. Model 2: adjusted for age, sex, stage, BMI, physical activity (moderate to vigorous; h/wk), tumor location, cohort, and total energy intake. Model 3: as model 2 and further adjusted for dietary magnesium and 25(OH)D3 concentrations for the dietary intake models and total magnesium and 25(OH)D3 concentrations for the total intake (diet and supplements) models. P values for trend were calculated by including the quartiles as a continuous variable in the model. COLON, COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life; CRC, colorectal cancer; EnCoRe, Energy for life after ColoRectal cancer; 25(OH)D3, 25-hydroxyvitamin D3.

intake and the risk of all-cause mortality (36). However, in this meta-analysis results were not adjusted for vitamin D concentrations, whereas the results of our study showed that this is important. Furthermore, a possible explanation for the observation that we found a lower risk of all-cause mortality for quartile 3 of magnesium intake, but not for quartile 4, is the interaction between magnesium and vitamin D. Findings of a recent randomized controlled trial with magnesium supplementation indicate that excessive magnesium intake >400 mg/d may actually reduce 25(OH)D3 concentrations (37). Although increasing dietary magnesium intake until an optimum of ~400 mg/d appears to reduce all-cause mortality, the HRs for the association between magnesium intake and recurrence were > 1. However, the CIs were wide and no trend over quartiles of intake was observed. Thus, although a high magnesium intake seems beneficial in relation to all-cause mortality, this may not be true with respect to recurrence.

A high calcium intake at diagnosis was inversely associated with all-cause mortality in CRC patients; however, after correcting for magnesium the HR for the association between calcium and all-cause mortality attenuated from 0.58 to 0.70. Results of previous studies (20, 21) suggest an inverse association between high postdiagnostic calcium intake and all-cause mortality in CRC survivors. However, these previous studies did not correct...
and low intakes of magnesium were determined based on the median. For total magnesium intake the median was 322 mg/d (COLON) and 383 mg/d (ECORe). CRC, colorectal cancer; RERI, relative excess risk due to interaction; 25(OH)D3, 25-hydroxyvitamin D3.

Considering the importance of magnesium for the enzymatic conversion of vitamin D into its active form (15, 37), magnesium deficiency is crucial in maintaining a sufficient vitamin D status (15, 16, 37). The active form of vitamin D is hypothesized to have beneficial effects on cancer prognosis (38). There are also indications that vitamin D influences CRC mortality by modulation of immune and inflammatory responses (39). In addition, magnesium deficiency is associated with chronic low-grade inflammation (40). Because vitamin D and magnesium are both suggested to influence systemic inflammation (39, 40), it is tempting to speculate that vitamin D and magnesium contribute to a lowered inflammatory status via shared mechanisms, possibly resulting in better survival rates.

In our study among stage I–III patients, no associations between 25(OH)D3, magnesium, or calcium and CRC recurrence were observed. One previous study investigating the association between 25(OH)D3 concentrations and CRC recurrence reported a strong inverse association (HR: 0.37; 95% CI: 0.18, 0.84) (8). However, this study population consisted of CRC patients with liver metastasis (stage IV), which is a very specific population at high risk of recurrences. Although we did not observe an association between 25(OH)D3 concentrations, magnesium intake, as well as vitamin D status × magnesium to the model, adjusted for the aforementioned confounders.

To investigate interaction on an additive scale the RERI was calculated, adjusted for the aforementioned confounders. For example, the RERI for joint effects of vitamin D status and magnesium was calculated as $HR_{vitD \times Mg}=HR_{vitD}+HR_{Mg}−HR_{vitD \times Mg}+1$.

### TABLE 5 Interaction of vitamin D concentrations with total magnesium intake in relation to CRC recurrence and all-cause mortality in CRC patients

| Total magnesium intake | n/Events; Events/1000 person-years | HR (95% CI) |
|------------------------|-----------------------------------|-------------|
| **CRC recurrence**     |                                   |             |
| Low magnesium intake   | 248/36; 42                       | 1.0 (ref)   |
| High magnesium intake  | 230/29; 37                       | 0.99 (0.56, 1.77) |
| HR (95% CI) for magnesium within strata of 25(OH)D3 concentrations | 1.08 (0.56, 2.09) |
| *P* for multiplicative interaction = 0.65 | RERI (95% CI) = −0.01 (−0.20, 0.18) |
| **All-cause mortality**|                                   |             |
| Low magnesium intake   | 249/47; 39                       | 1.0 (ref)   |
| High magnesium intake  | 231/36; 30                       | 0.82 (0.49, 1.38) |
| HR (95% CI) for magnesium within strata of 25(OH)D3 concentrations | 0.94 (0.52, 1.69) |
| *P* for multiplicative interaction = 0.062 | RERI (95% CI) = 0.27 (0.08, 0.61) |

1. Analyzed with a Cox proportional hazard model adjusted for age, sex, BMI, physical activity (moderate to vigorous; h/wk), stage, tumor location, season of blood collection, total calcium intake, total energy intake, and cohort. Vitamin D deficient: <50 nmol/L; vitamin D sufficient: ≥50 nmol/L. High and low intakes of magnesium were determined based on the median. For total magnesium intake the median was 322 mg/d (COLON) and 383 mg/d (EnCoRe). CRC, colorectal cancer; RERI, relative excess risk due to interaction; 25(OH)D3, 25-hydroxyvitamin D3.

2. The *P* for multiplicative interaction was calculated by adding vitamin D status, magnesium intake, as well as vitamin D status × magnesium to the model, adjusted for the aforementioned confounders.

3. To investigate interaction on an additive scale the RERI was calculated, adjusted for the aforementioned confounders. For example, the RERI for joint effects of vitamin D status and magnesium was calculated as $HR_{vitD \times Mg}=HR_{vitD}+HR_{Mg}−HR_{vitD \times Mg}+1$.
of the total body magnesium and calcium is circulating (41, 42), thus measuring magnesium and calcium blood concentrations would not likely have resulted in more information (16). Second, the number of events was relatively low in our study population \((n = 155\text{ for recurrence}; n = 191\text{ for mortality})\), which limits the power to detect statistically significant associations, especially in the interaction analyses. Nonetheless, a significant interaction between magnesium and vitamin D was observed for all-cause mortality. Third, it could be that participants of our study are relatively health conscious, which probably led to an attenuation of the real effect. Furthermore, we had no data available about the cause of death. Therefore, we were not able to perform analyses with disease-specific mortality as an outcome. Finally, results of this study can only be generalized to the Western population. The present study also had some important strengths. First, to the best of our knowledge this study was the first to investigate \(25(\text{OH})_3\text{D}_3\) concentrations and magnesium and calcium intakes, individually and jointly, in relation to CRC recurrence and all-cause mortality. Second, we could investigate the influence of total magnesium and calcium intakes, because we obtained information about dietary as well as supplemental intakes. Finally, because of the availability of detailed data on diet and other clinical and lifestyle factors, we could adjust for the most relevant confounders, although residual confounding can never be fully excluded.

To conclude, we observed that \(25(\text{OH})_3\text{D}_3\) and magnesium may work synergistically in decreasing the risk of all-cause mortality in CRC patients. Although our results should be confirmed in diet and lifestyle intervention studies, our findings could contribute to improving recommendations regarding magnesium and vitamin D intake for newly diagnosed CRC patients.

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### References

1. Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, Fuchs CS. Circulating 25-hydroxyvitamin D levels and survival in patients with colorectal cancer. J Clin Oncol 2008;26(18):2984–91.
2. Mezawa H, Sugita T, Watanabe M, Norizoe C, Takahashi D, Shimojima A, Tamez S, Tsutsumi Y, Yanaga K, Urashima M. Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study. BMC Cancer 2010;10:347.
3. Ng K, Sargent DJ, Goldberg RM, Meyerhardt JA, Green EM, Pitot HC, Hollis BW, Pollak MN, Fuchs CS. Vitamin D status in patients with
stage IV colorectal cancer: findings from Intergroup trial N9741. J Clin Oncol 2011;29(12):1599–606.
4. Fedirko V, Riboli E, Tjonneland A, Ferrari P, Olsen A, Bueno-de-Mesquita HB, van Duijnhoven FJJ, Norat T, Jansen EHM, Dahm CC, et al. Prognostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in Western European populations. Cancer Epidemiol Biomarkers Prev 2012;21(4):582–93.
5. Tretti S, Schwarz GG, Torjesen PA, Robsahm TE. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. Cancer Causes Control 2012;23(3):363–70.
6. Zagala L, Theodoratou E, Farrington SM, Din FV, Ooi LY, Glodzid K, Johnston S, Tenesa A, Campbell H, Dunlop MG. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. J Clin Oncol 2014;32(23):2430–9.
7. Wesa KM, Segal NH, Cronin AM, Sjoberg DD, Jacobs GN, Coleton MI, Wesa KM, Segal NH, Cronin AM, Sjoberg DD, Jacobs GN, Coleton MI, Fleischer M, Dnistrian AM, Sjølyst LB, Cassileth BR. Serum 25-hydroxyvitamin D and survival in advanced colorectal cancer: a retrospective analysis. Nutr Cancer 2015;67(3):424–30.
8. Facciorusso A, Del Prete V, Muscatello N, Crucinio N, Barone A. Prognostic role of 25-hydroxyvitamin D in patients with liver metastases from colorectal cancer treated with radiofrequency ablation. J Gastroenterol Hepatol 2016;31(8):1483–8.
9. Yang L, Chen H, Zhao M, Peng P. Prognostic value of circulating vitamin D binding protein, total, free and bioavailable 25-hydroxyvitamin D in patients with colorectal cancer. Oncotarget 2017;8(25):40214–21.
10. Maalmi H, Walter V, Jansen L, Boakye D, Schöttker B, Hoffmeister M, Cooney RV, Chai W, Franke AA, Wilkens LR, Kolonel LN, Le Marchand L, C-reactive protein, lipid-soluble micronutrients, and survival in colorectal cancer patients. Cancer Epidemiol Biomarkers Prev 2012;21(7):1278–88.
11. Maalmi H, Walter V, Jansen L, Boakye D, Schöttker B, Hoffmeister M, Brenner H. Association between blood 25-hydroxyvitamin D levels and survival in colorectal cancer patients: an updated systematic review and meta-analysis. Nutrients 2018;10(7):896.
12. Custers JA, Gielissee MF, Janssen SH, de Witt JH, Prins JB. Fear of cancer recurrence in colorectal cancer survivors. Support Care Cancer 2016;24(2):555–62.
13. Elferink MAG, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JHW. Magnesium-dependent vitamin-D-resistant activation and function. J Am Osteopath Assoc 2018;118(3):181–9.
14. Elferink MAG, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JHW. Magnesium-dependent vitamin-D-resistant activation and function. J Am Osteopath Assoc 2018;118(3):181–9.
15. Deng X, Song Y, Manson JE, Signorello LB, Zhang SM, Shrubsole MJ, Ness RM, Seidner DL, Dai Q. Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. BMC Med 2011;13:187.
16. Uwitonze AM, Razzaque MS. Role of magnesium in vitamin D activation and function. J Am Osteopath Assoc 2018;118(3):181–9.
17. RosanoﬀA, Dai Q, Shapess SA. Essential nutrient interactions: does low or suboptimal magnesium status interact with vitamin D and/or calcium status? Adv Nutr 2016;7(1):25–43.
18. Reddy V, Sivakumar B. Magnesium-dependent vitamin-D-resistant rickets. Lancet 1974;303(7864):963–5.
19. Lips P. Interaction between vitamin D and calcium. Scand J Clin Lab Invest Suppl 2012;243:60–4.
20. Yang B, McCullough ML, Gagostar SM, Jacobs EJ, Bostick RM, Fedirko V, Flanders WD, Campbell PT. Calcium, vitamin D, dairy products, and mortality among colorectal cancer survivors: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2014;32(22):2335–43.
21. Yang W, Ma Y, Smith-Warner S, Song M, Wu K, Wang M, Chan AT, Boushuizen HC, Weijenberg MP. Magnesium, vitamin D status and mortality: results from a randomized trial in a population of survivors of colorectal cancer. Eur J Nutr 2015;54(1):21–9.
22. Crockett SD, Barry EL, Mott LA, Ahnen DJ, Robertson DJ, Anderson JC, Wallace K, Burke CA, Bresalier RS, Figueiredo JC, et al. Calcium and vitamin D supplementation and increased risk of serrated polyps: results from a randomised clinical trial. Gut 2018;67(3):475–86.
23. Winkels RM, Heine-Broring RC, van Zutphen M, van Harten-Wijngaarden S, Kok KE, de Vries JL, Falkenburg HJFM, van der Harst P, Westendorp RGJ. Magnesium, vitamin D status and survival in colorectal cancer survivors. Support Care Cancer 2014;22(7):1721–8.
24. Van den Ouweland AM, Beijers AM, van Daal H. Overestimation of 25-hydroxyvitamin D3 by increased ionisation efficiency of 3-epi-25-hydroxyvitamin D3 in LC–MS/MS methods not separating both metabolites as determined by an LC–MS/MS method for separate quantification of 25-hydroxyvitamin D3, 3-epi-25-hydroxyvitamin D3 and 25-hydroxyvitamin D2 in human serum. J Chromatogr B 2014;967:195–202.
25. van den Ouweland AM, Beijers AM, van Daal H. Overestimation of 25-hydroxyvitamin D3 by increased ionisation efficiency of 3-epi-25-hydroxyvitamin D3 in LC–MS/MS methods not separating both metabolites as determined by an LC–MS/MS method for separate quantification of 25-hydroxyvitamin D3, 3-epi-25-hydroxyvitamin D3 and 25-hydroxyvitamin D2 in human serum. J Chromatogr B 2014;967:195–202.
26. Aranow C. Vitamin D and the immune system. J Invest Med 2011;59(6):881–6.
27. Koole JL, Bours MJL, Breedveld-Peters JIL, van Roekel EL, van Dongen MCJM, Eussen SJPM, van Zutphen M, van Duijnhoven FJJ, Boshuizen HC, Weijenberg MP. Evaluating the validity of a food frequency questionnaire in comparison with a 7-day dietary record for measuring dietary intake in a population of survivors of colorectal cancer. J Acad Nutr Diet 2020;120(2):245–57.
28. Dutch Nutrition Center. Nederlands voedingsstofbeeld (NEVO) [Internet]. Bilthoven, Netherlands: Rijksinstituut voor Volksgezondheid en Milieu; 2011 [cited 19 April, 2019]. Available from: http://nevo-online.rivm.nl/.
29. Zgaga L, Theodoratou E, Farrington SM, Din FV, Ooi LY, Glodzid K, Johnston S, Tenesa A, Campbell H, Dunlop MG. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. J Clin Oncol 2014;32(23):2430–9.