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Calcium Intake and Survival after Colorectal Cancer Diagnosis

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Disclosure of Potential Conflicts of Interest

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Abstract

Purpose—Although evidence suggests an inverse association between calcium intake and colorectal cancer incidence, the influence of calcium on survival after colorectal cancer diagnosis remains unclear.

Experimental Design—We prospectively assessed the association of postdiagnostic calcium intake with colorectal cancer-specific and overall mortality among 1,660 nonmetastatic colorectal cancer patients within the Nurses' Health Study and the Health Professionals Follow-up Study. Patients completed a validated food frequency questionnaire between 6 months and 4 years after diagnosis and were followed up for death. Multivariable hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression.

Results—Comparing the highest with the lowest quartile intake of postdiagnostic total calcium, the multivariable HRs were 0.56 (95% CI, 0.32–0.96; $P_{\text{trend}} = 0.04$) for colorectal cancer-specific mortality and 0.80 (95% CI, 0.59–1.09; $P_{\text{trend}} = 0.11$) for all-cause mortality. Postdiagnostic supplemental calcium intake was also inversely associated with colorectal cancer-specific mortality (HR, 0.67; 95% CI, 0.42–1.06; $P_{\text{trend}} = 0.047$) and all-cause mortality (HR, 0.71; 95% CI, 0.54–0.94; $P_{\text{trend}} = 0.008$), although these inverse associations were primarily observed in women. In addition, calcium from diet or dairy sources was associated with lower risk in men.

Conclusions—Higher calcium intake after the diagnosis may be associated with a lower risk of death among patients with colorectal cancer. If confirmed, these findings may provide support for the nutritional recommendations of maintaining sufficient calcium intake among colorectal cancer survivors.

Introduction

Colorectal cancer remains the third most common type of cancer diagnosed in both sexes in the United States, and the number of colorectal cancer survivors continues to grow in the United States (1, 2). As of January 2016, over 1.5 million Americans were colorectal cancer survivors (3). To deliver quality cancer care, the Institute of Medicine highlighted the

importance of healthful lifestyle changes including weight management, physical activity, and a healthy diet for cancer survivors (4). However, research that defines the benefits of lifestyle changes among cancer survivors is limited, particularly for diet recommendations (5). Hence, there is an urgent need to investigate dietary factors in relation to survivorship among patients with established colorectal cancer.

Currently, about 43% of the U.S. population (including almost 70% of older women) is using supplemental calcium (6). Calcium may biologically influence colorectal carcinogenesis by reducing proliferation of colonic epithelial cells (7), inducing apoptosis (8), and inhibiting colonic *KRAS* mutations (9). In fact, the most comprehensive review by the World Cancer Research Fund and American Institute for Cancer Research concluded that supplemental calcium intake probably protects against colorectal cancer development (10). Moreover, three (11–13) controlled clinical trials have reported an inverse association between calcium and/or other supplements and the risk of colorectal adenoma recurrence, whereas others (14, 15) found no association, although there were variations in their intervention treatments among these studies (11–15). Despite considerable research on calcium intake and colorectal cancer risk, the influence of calcium intake on colorectal cancer survival is much less studied. Few existing studies (16–20) reported null associations between prediagnostic calcium intake and colorectal cancer survival. To our knowledge, only the Cancer Prevention Study II (CPS-II) cohort has examined postdiagnostic calcium intake and reported a statistically significant 28% reduced risk for all-cause mortality and a marginally statistically significant 41% reduced risk for colorectal cancer–specific mortality comparing extreme quartile intake groups (20). Clearly, more studies are warranted to confirm and better characterize these potentially important associations. Furthermore, we are not aware of any previous studies assessing the association between changes in calcium intake after colorectal cancer diagnosis (e.g., difference between prediagnostic and postdiagnostic intake) and cancer survival. This issue is important, because cancer survivors and clinicians want to know whether lifestyle changes (e.g., increasing intake of calcium) after the diagnosis may provide benefits.

Therefore, we conducted this study to investigate postdiagnostic calcium intake in relation to survival among patients with colorectal cancer by utilizing data from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Compared with previous studies including CPS-II (16–20), our cohorts have longer follow-up periods, larger number of colorectal cancer patients, and detailed information on prediagnostic and postdiagnostic calcium intake as well as clinicopathologic factors.

Materials and Methods

Study cohort

Participants in this study were selected from among 173,229 men and women in NHS (121,700 women) and HPFS (51,529 men). For NHS, the recruitment for U.S. female registered nurses ages 30 to 55 years was completed in 1976. For HPFS, the recruitment for U.S. male professionals ages 40 to 75 years was completed in 1986. In each cohort, questionnaires were administered biennially to collect and update information on

demographic characteristics, lifestyle factors, and medical history, with follow-up rates over 90%.

The incident colorectal cancer cases were defined as a primary tumor with International Classification of Diseases-9 codes of 153 and 154. Participants from the two cohorts were asked for written permission to obtain medical records and pathologic reports if they reported colorectal cancer on biennial questionnaires. For nonresponders, we searched the state cancer registries and the National Death Index to identify deaths and to ascertain any colorectal cancer diagnosis that contributed to death or was a secondary diagnosis (21). For all deaths attributable to colorectal cancer, we requested permission to review medical records from next-of-kin. All possible colorectal cancer cases were further confirmed through review of medical and pathologic records. A study physician who was blinded to exposure data abstracted information on tumor anatomic location, stage, and histology type.

By the end of June 1, 2012, for the NHS, and January 31, 2012, for the HPFS, 3,924 cases of colorectal cancer were identified. After exclusion (see the flow chart in Supplementary Fig. S1), a total of 1,660 participants ($n = 1,022$ in the NHS and 638 in the HPFS) who were diagnosed with colorectal cancer and completed the food frequency questionnaire (FFQ) after diagnosis were included in this study. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Study outcomes

Deaths and causes of death among 1,660 included colorectal cancer patients were identified through review of the National Death Index, and family members or the postal system in response to the follow-up questionnaires. Over 98% of deaths have been identified using these methods (21).

Assessments of calcium intake

Assessment of calcium intake and other dietary factors was described in detail elsewhere (22–24). Briefly, in each cohort, self-reported dietary information was collected at baseline and updated almost every 4 years using a validated (25–27) semiquantitative 131-item (or more) FFQ. In addition, we collected information on calcium supplements and multivitamin use in each biennial questionnaire. We used the composition database from the U.S. Department of Agriculture to calculate nutrient intake by multiplying the frequency of each food consumed by the nutrient content per serving of that food, and summing across all foods and beverages (22, 23). Consistent with previous studies from the same cohorts (22, 23), we calculated individual's total calcium intake by summing calcium from dietary sources including fortified foods plus supplements. The calcium from dairy sources alone was calculated by summing the contributions of all dairy products and food items containing dairy products. Calcium from nondairy sources was calculated by subtracting dairy calcium intake from total dietary calcium intake (22, 23). Supplemental calcium intake in this study included calcium from both calcium supplement use and multivitamin use (22, 23).

The FFQs used in this study have been validated among 173 women from the NHS (27) and among 127 men from the HPFS (25). The energy-adjusted correlation coefficients of total

calcium intake comparing the FFQ and the average of multiple 1-week diet records (four for women and two for men) were 0.63 for women (27) and 0.61 for men (25). The correlation coefficients for dietary calcium intake were 0.70 for women (27) and 0.60 for men (25).

To avoid potential impact of active treatment and consistent with our previous study from the same cohorts (28), postdiagnostic intake in the current analysis was defined as dietary intake reported on the first FFQ collected at least 6 months but no more than 4 years after diagnosis (median, 2.1 years). Prediagnostic intake assessment was based on the last FFQ reported before colorectal cancer diagnosis (median, 1.9 years).

Assessment of covariates

We inquired on covariates including adult body weight, physical activity (METs-hours/week), cigarette smoking, and aspirin use every 2 years. Other dietary factors including intakes of alcohol, vitamin D, folate, red meat and processed meat, and fat were collected and updated almost every 4 years using validated FFQs in each cohort (25, 26).

Statistical analysis

Person-years of follow-up were calculated from the return date of the FFQ that was used for postdiagnostic assessment to death, or the end of the study period (June 1, 2012, for the NHS, January 31, 2012, for the HPFS), whichever came first. In the colorectal cancer-specific mortality analysis, death from colorectal cancer was the primary end point, and deaths from other causes were censored. In the all-cause mortality analysis, death from any cause was the end point.

Cox hazard regression models were used to calculate HRs and 95% confidence intervals (CI) of death, with time since diagnosis as the time scale, accounting for left truncation due to differences between patients in the timing of postdiagnostic assessment (29). Both stage I–III colorectal cancer patients and colorectal cancer patients with unknown stage were included in the analysis. We tested proportional hazards assumption by including the interaction term between total calcium and calcium by food source and follow-up time into the model, and found no evidence for violation of this assumption (all $P > 0.05$). We adjusted for tumor differentiation, anatomic subsites, year of diagnosis, prediagnostic calcium intake, postdiagnostic body mass index (BMI), physical activity, smoking, multivitamin use, and other supplement use (defined by the sum of vitamin A, C, E, selenium, and zinc), and intake of alcohol, vitamin D, folate, total fat, and total calorie. We simultaneously stratified age, tumor stage, and study cohort (sex) in the Cox regression model. We categorized energy adjusted calcium intake into quartile categories based on the distribution of each cohort. Given no evidence of significant between-study heterogeneity for total and supplemental calcium (P values for heterogeneity by gender > 0.05), we combined results from the two cohorts to maximize the statistical power. However, we did not pool results for postdiagnostic dietary or dairy calcium because there was significant heterogeneity between the two cohorts. The trend tests were conducted using the median of each category of calcium intake as a continuous variable, and P value for trend was calculated using a Wald test (30). Consistent with our previous studies (22, 23), we also presented the HRs of mortality per 300 mg daily increment of calcium intake. In addition,

we evaluated the influence of calcium on survival by different food sources (i.e., dietary calcium, dairy calcium, and supplemental calcium intake). Furthermore, we evaluated changes in calcium intake after colorectal cancer diagnosis (i.e., difference between prediagnostic and postdiagnostic intake) and cancer survival. Subgroup analyses were conducted by lifestyle and clinicopathologic factors. Test of interaction was conducted using the likelihood ratio test by comparing the model with product terms between stratified covariate and calcium intake with the models without these terms. Consistent with previous studies from our cohorts (31–33), we excluded participants with missing values on exposure data at baseline.

We conducted several sensitivity analyses. First, considering the possible selection bias by exclusion of patients from study due to lack of postdiagnostic dietary data, we also applied inverse probability weighting (IPW) method (34). In this method, complete cases (i.e., individuals without missing data) are weighted by the inverse of their probability of being a complete case. The weight was inverse of the probability of calcium data availability estimated based on a model for calcium data availability status (34). Second, prediagnostic versus postdiagnostic calcium intake were dichotomized into low (the first and second quartile categories) versus high (the third and fourth quartile categories), resulting in four mutually exclusive categories based on pre- and postdiagnostic intakes [low (prediagnostic)-low (postdiagnostic), low-high, high-low, and high-high]. These four groups were evaluated in relation to survival. Third, we also repeated analysis by excluding unspecified tumor stage patients. In addition, we repeated analysis that included stage IV colorectal cancer patients. Fourth, we further adjusted for the 2010 alternative healthy eating index (AHEI-2010) score in replacement of dietary covariates in the models, including postdiagnostic alcohol consumption and postdiagnostic intake of total fat, folate, and vitamin D, multivitamin use, and other supplement use. Last, we evaluated the association between calcium supplement use (i.e., supplemental calcium intake from calcium supplement use only but not from multivitamin use) and mortality among colorectal cancer survivors. We used SAS 9.4 for all analyses (SAS Institute).

Results

During a median follow-up of 9.4 years, we documented a total of 1,660 patients with colorectal cancer, of which 646 deaths were identified, including 210 colorectal cancer-specific deaths. Participants with higher total calcium intake were slightly older, more physically active, less likely to smoke and drink alcohol, and more likely to use aspirin and consume vitamin D, total folate, and total fat (Table 1).

Postdiagnostic total calcium intake was inversely associated with colorectal cancer-specific mortality and all-cause mortality. Results were similar in three models (Table 2). Comparing the highest with the lowest quartile intake of postdiagnostic total calcium, the multivariable HRs were 0.56 (95% CI, 0.32–0.96; $P_{\text{trend}} = 0.04$) for colorectal cancer-specific mortality and 0.80 (95% CI, 0.59–1.09; $P_{\text{trend}} = 0.11$) for all-cause mortality. These inverse associations remained when we used the IPW method (Supplementary Table S1).

Postdiagnostic supplemental calcium intake was inversely associated with colorectal cancer-specific mortality (HR comparing the highest with the lowest quartile intake, 0.67; 95% CI, 0.42–1.06; $P_{\text{trend}} = 0.047$) and all-cause mortality (HR, 0.71; 95% CI, 0.54–0.94; $P_{\text{trend}} = 0.008$, Table 2). To tease out the possible association of supplemental calcium intake from multivitamin sources, we assessed the association on calcium supplement use only and found similar results (Supplementary Table S2). In subgroup analysis, we investigated whether the association between total calcium intake and mortality differed by other possible predictors of cancer survival, including age, smoking, alcohol consumption, BMI, physical activity, aspirin use, vitamin D, cancer locations, and stage, and found no statistically significant interactions (Table 3).

Compared with patients who did not appreciably alter their supplemental calcium intake (amount of change <150 mg/day), those who increased intake by at least 300 mg/day had an HR of 0.64 (95% CI, 0.40–1.00) for colorectal cancer-specific mortality. However, those who decreased their intake at least 300 mg/day had an HR of 1.23 (95% CI, 0.72–2.11; $P_{\text{trend}} = 0.01$; Table 4). In addition, compared with low-low intake groups (low intake level before cancer diagnosis and low after cancer diagnosis), the inverse associations generally appeared stronger in low-high groups (Supplementary Table S3). After we excluded colorectal cancer patients with unspecified tumor stage ($n = 208$) or included stage IV patients ($n = 91$), the results did not materially change (Supplementary Table S4). Likewise, when we adjusted for the AHEI-2010 dietary pattern score in replacement of all dietary covariates in the models, the results were very similar to those in the main analysis (data not shown).

When stratified by sex, we observed significant inverse association between supplemental calcium intake and mortality among women but not with dietary or dairy calcium intake (Supplementary Table S5). In men, intake of total calcium, dietary calcium, and dairy calcium was associated with lower risk of mortality, but supplemental calcium intake was not associated with risk of mortality (Supplementary Table S6). There was no association between prediagnostic calcium intake and mortality among colorectal cancer patients in our cohorts (Supplementary Table S7).

Discussion

In this large cohort of patients with nonmetastatic colorectal cancer, we found that higher postdiagnostic calcium intake, especially supplemental calcium intake, was independently associated with lower risk of colorectal cancer-specific and all-cause mortality. These observations, along with our previous findings of inverse associations between calcium intake and colorectal cancer risk (22, 35), provide additional support for the role of calcium intake in both colorectal cancer development and prognosis.

Consistent with an inverse association between calcium intake and colorectal cancer incidence (22, 35–37), the current study suggested that patients who had higher calcium intake after diagnosis had substantially lower risk of mortality. Only one published study to date has assessed the risk of all-cause and colorectal cancer-specific mortality associated with postdiagnostic calcium intake. This study, conducted among 1,111 colorectal cancer patients from the CPS-II cohort, reported an inverse association for both all-cause mortality

and colorectal cancer-specific mortality (20), which were generally consistent with our findings. Similar to previous studies (16–20), we found no association between prediagnostic calcium intake and mortality among colorectal cancer patients.

Some potential mechanisms might explain the observed beneficial associations. *In vitro* studies showed that calcium could promote E-cadherin expression, suppress beta-catenin/T-cell factor activation (38, 39), and activate p38 mitogen-activated protein kinase cascade through activation of calcium-sensing receptor (CASR; refs. 40, 41), thereby regulating the balance between proliferation, differentiation, and apoptosis of colonic epithelial cells, and inhibit malignant progression. Besides CASR-mediated effects, other potential mechanisms include reduced solubility of damaging bile acids (42), fatty acids (36), and heme (43) in the colonic lumen and direct effects on reducing proliferation of colonic epithelial cells (7). We are not aware of any randomized clinical trials that were specifically designed to test the effect of calcium intake on colorectal cancer survival, although several clinical trials were conducted among patients with colorectal adenoma, and inconsistently showed that daily treatment with calcium and/or other supplements was associated with lower risk of colorectal adenoma recurrence (11–15). However, we do not have data on colorectal cancer recurrence for this study.

We observed significant inverse associations with higher supplemental calcium intake for both all-cause mortality and colorectal cancer-specific mortality, especially in women. The ingestion of calcium supplements, but not for calcium-rich foods, may lead to an acute increase in serum calcium (44, 45). This increase could be sustained in the long term leading to a persistent decrease in serum parathyroid hormone (PTH; refs. 46, 47). The reduced PTH concentrations could be associated with colonic neoplasm occurrence and progression (48, 49). Thus, higher supplemental calcium intake might have a more pronounced effect on cancer survival. Alternatively, calcium supplement users may have had more healthy behaviors or use of other supplements, which may in turn have a lower risk of mortality. However, the inverse associations persisted in this study after we adjusted for multivitamin use and other supplement use as well as a wide range of potential prognostic factors. In our cohorts, supplemental calcium intake contributed to 25% (1990s) to 35% (2000s) of total calcium intake in women but only contributed to 3% (1990s) to 8% (2000s) in men (22). Thus, the much lower intake average and less frequent use might partially explain the null associations with supplemental calcium intake among men. Our results might have an important implication for clinical practice if validated in future studies. In men, however, we observed significant inverse associations with total, dietary, and dairy calcium intake. This was unexpected, and the possible difference might be due to chance. Clearly, we should interpret these results cautiously because of the very limited number of patients in men. Overall, differential association between calcium and mortality by gender or by food sources warrants further investigation.

Strengths of our study include prospective cohort design, large sample size, relatively long follow-up, detailed collection of prediagnostic and postdiagnostic data, and validated colorectal cancer outcomes including diagnosis and death. In addition, the availability of the prediagnostic data allowed us to evaluate the associations between changes in intake after diagnosis and mortality.

There are several limitations. First, assessment of calcium intake using FFQs was subject to measurement errors, but the FFQs used in our cohorts have been comprehensively validated (25–27). Second, as an observational study, residual confounding cannot be totally ruled out, although our detailed data resources enabled us to adjust for a wide range of potential confounders.

Third, due to the limited number of colorectal cancer patients with tumor molecular biomarker data, we did not consider or adjust for tumor molecular markers such as microsatellite instable status in the current analysis. Other limitations of this study include the lack of detailed data on cancer treatment and recurrence, as well as information on adherence to treatment, and treatment adverse effects. However, over 65% of patients had stage I or stage II disease in the analysis, in which surgery alone would generally be the standard of care. In addition, adjuvant therapy was largely standardized and correlated with disease stage. Thus, adjusting for tumor stage may reduce such potential confounding bias by treatment. Furthermore, in a subset of patients who provided chemotherapy data (43%), there was no difference in total calcium intake between those who received chemotherapy and those who did not.

In summary, we observed that higher postdiagnostic calcium intake, including from supplement use, might be associated with lower risk of death among colorectal cancer patients. Our findings need to be confirmed by further studies, including possible clinical trials of calcium supplementation in patients with nonmetastatic colorectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix Figure A1.

Flow chart of the study population in the Nurses' Health Study (1980–2012) and Health Professionals Follow-up Study (1986–2012)

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Translational Relevance

Calcium may decrease the risk of developing colorectal cancer. However, the influence of calcium consumption on survival after colorectal cancer diagnosis remains unclear. We prospectively assessed the association of postdiagnostic calcium intake with colorectal cancer-specific and overall mortality among 1,660 colorectal cancer patients within the Nurses' Health Study and the Health Professionals Follow-up Study. We found that postdiagnostic calcium intake, especially from supplements, may reduce risk of death among colorectal cancer patients. These results were consistent with the only prospective study examining the association between calcium intake and mortality after colorectal cancer diagnosis in the Cancer Prevention Study II cohort. If validated in future studies, our findings support nutritional recommendations of maintaining sufficient calcium intake among colorectal cancer survivors.

Table 1.
Characteristics of colorectal cancer patients according to energy-adjusted calcium intake after cancer diagnosis

	Quartile of postdiagnostic total calcium intake ^a			
	Quartile category 1 (n = 414)	Quartile category 2 (n = 415)	Quartile category 3 (n = 416)	Quartile category 4 (n = 415)
Age, years	65.6	67.3	68.4	70.6
White, %	97.6	97.1	98.0	97.7
BMI, kg/m ²	26.3	26.5	26.4	26.3
Activity, METS-hours/week	17.2	19.5	21.6	20.3
Smoking pack years	18.6	17.8	16.8	14.1
Current smoking, %	13.3	9.6	8.6	7.9
Multivitamin use, %	37.3	52.7	66.2	74.1
Regular aspirin use, % ^b	32.0	33.0	33.3	41.4
Family history of colorectal cancer, %	20.9	22.1	21.6	19.3
Food and nutrient intakes				
Alcohol, g/day	9.3	7.2	7.4	6.7
Total folate intake, µg/day	498	613	725	834
Total calcium intake, mg/day	572	878	1,246	1,892
Dietary calcium intake, mg/day	558	766	891	1,032
Dairy calcium intake, mg/day	252	399	516	605
Supplemental calcium intake, mg/day ^c	28	126	361	863
Total vitamin D, IU/day	306	420	612	756
Total fiber, g/day	20.0	21.7	21.2	22.1
Total fat, g/day	63.2	59.4	58.5	57.4
Tumor subsite, %				
Proximal colon	36.4	37.9	41.7	45.3
Distal colon	36.0	34.5	30.4	24.5
Rectum	21.8	21.9	21.4	25.4
Unspecified	5.8	5.7	6.4	4.8
Tumor grade, %				
Well differentiated	16.0	15.4	16.1	12.2

	Quartile of postdiagnostic total calcium intake ^a			
	Quartile category 1 (n = 414)	Quartile category 2 (n = 415)	Quartile category 3 (n = 416)	Quartile category 4 (n = 415)
Moderately differentiated	58.2	59.3	52.3	58.3
Poorly differentiated	11.4	13.3	15.2	11.5
Unspecified	14.5	12.0	16.4	18.0
Tumor stage, %				
Stage I	33.3	36.6	36.7	29.9
Stage II	29.8	27.3	26.1	33.6
Stage III	24.8	23.7	22.4	25.9
Unspecified	12.1	12.4	14.9	10.6

Abbreviation: METS, metabolic equivalent task.

^aWe created the quartile categories separately for women and men. Percentages were calculated for the categorical variables, and means were calculated for continuous variables. All variables were age-standardized except age.

^bAspirin use was defined as users who took 2 standard (325 mg) tablets/week.

^cSupplemental calcium intake in this study included calcium from both calcium supplement use and multivitamin use.

Table 2.

Total and supplemental calcium intake after cancer diagnosis in relation to mortality among colorectal cancer patients^a

	Quartile category 1	Quartile category 2	Quartile category 3	Quartile category 4	Per 300 mg/day	P trend
Total calcium intake						
Median intake, mg/day	582	864	1,222	1,875		
Colorectal cancer specific mortality						
Number of events	58	68	50	34		
Model 1 ^b HR (95% CI)	Referent	1.19 (0.81–1.73)	0.90 (0.58–1.37)	0.62 (0.38–1.01)	0.90 (0.81–0.99)	0.045
Model 2 ^c HR (95% CI)	Referent	1.18 (0.79–1.76)	0.83 (0.52–1.33)	0.57 (0.33–0.98)	0.89 (0.80–0.99)	0.044
Model 3 ^d HR (95% CI)	Referent	1.18 (0.79–1.77)	0.82 (0.51–1.32)	0.56 (0.32–0.96)	0.89 (0.79–0.99)	0.038
All-cause mortality						
Number of events	194	192	138	122		
Model 1 ^b HR (95% CI)	Referent	1.09 (0.88–1.35)	0.83 (0.65–1.06)	0.78 (0.60–1.02)	0.92 (0.87–0.98)	0.02
Model 2 ^c HR (95% CI)	Referent	1.11 (0.88–1.39)	0.87 (0.66–1.14)	0.80 (0.59–1.08)	0.93 (0.87–1.00)	0.11
Model 3 ^d HR (95% CI)	Referent	1.11 (0.88–1.39)	0.87 (0.66–1.15)	0.80 (0.59–1.09)	0.93 (0.87–1.00)	0.11
Supplemental calcium intake ^e						
Median intake, mg/day	0	37	259	960		
Colorectal cancer specific mortality						
Number of events	103	41	30	36		
Model 1 ^b HR (95% CI)	Referent	0.78 (0.53–1.15)	0.56 (0.37–0.86)	0.64 (0.42–0.98)	0.86 (0.77–0.97)	0.01
Model 2 ^c HR (95% CI)	Referent	0.75 (0.50–1.13)	0.53 (0.33–0.85)	0.68 (0.43–1.07)	0.89 (0.78–1.01)	0.057
Model 3 ^d HR (95% CI)	Referent	0.73 (0.48–1.12)	0.51 (0.32–0.83)	0.67 (0.42–1.06)	0.88 (0.78–1.00)	0.047
All-cause mortality						
Number of events	301	144	103	98		
Model 1 ^b HR (95% CI)	Referent	0.95 (0.77–1.17)	0.80 (0.63–1.02)	0.65 (0.50–0.84)	0.88 (0.82–0.94)	0.0001
Model 2 ^c HR (95% CI)	Referent	1.01 (0.80–1.27)	0.86 (0.67–1.12)	0.73 (0.55–0.96)	0.90 (0.84–0.97)	0.01
Model 3 ^d HR (95% CI)	Referent	0.98 (0.77–1.23)	0.85 (0.65–1.10)	0.71 (0.54–0.94)	0.90 (0.83–0.97)	0.008

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^a Postdiagnostic intake at least 6 months but no more than 4 years after diagnosis to avoid potential impact of active treatment.

^b Cox model stratified by **age** at diagnosis (<55, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and 75 years), cancer **stage** (I, II, III, and unspecified), and **gender** (men, women), with additional adjustments for tumor **grade** of differentiation (well differentiated, moderately differentiated, poorly differentiated, and unspecified), tumor **subsite** (proximal colon, distal colon, rectum, and unspecified), **year** of diagnosis (continuous), prediagnostic intake of total calcium (in quartiles).

^c Model 1 + postdiagnostic **BMI** (<23, 23 to 24.9, 25 to 27.4, 27.5 to 29.9, 30 kg/m²), postdiagnostic **physical activity** (<3, 3 to 8.9, 9 to 11.9, 12 to 17.9, 18 METS-hours/week), postdiagnostic regular use of **aspirin** (yes or no), and postdiagnostic **smoking** (0, 1 to 9, 10 to 19, 20 to 40, 40 pack years), postdiagnostic **alcohol** consumption (<5, 5 to 14.9, 15 g/d), and postdiagnostic intake of total **fat**, **folate**, and **vitamin D** (all in quartiles).

^d Model 2 + **multivitamin** use (yes or no) + **other supplement** use (defined by the sum of vitamin A, C, E, selenium, and zinc).

^e Supplemental calcium intake in this study included calcium from both calcium supplement use and multivitamin use.

Table 3.

Stratified analyses of postdiagnostic total calcium intake with mortality among colorectal cancer patients^a

	Colorectal cancer-specific mortality			All-cause mortality		
	Number of events/patients	Per 300 mg/day HR (95% CI)	P for interaction	Number of events/patients	Per 300 mg/day HR (95% CI)	P for interaction
Age			0.15			0.61
<65 years	96/601	0.95 (0.82–1.11)		205/601	0.95 (0.86–1.06)	
65 years	114/1,059	0.84 (0.73–0.96)		441/1,059	0.92 (0.86–1.00)	
Smoking			0.28			0.42
Never	4/425	1.13 (0.71–1.79)		30/425	1.02 (0.85–1.23)	
Ever	206/1,235	0.88 (0.78–0.99)		616/1,235	0.94 (0.88–1.00)	
Alcohol consumption			0.09			0.78
<10 g/day	163/1,217	0.90 (0.80–1.02)		479/1,217	0.94 (0.87–1.01)	
10 g/day	47/443	0.80 (0.63–1.01)		167/443	0.91 (0.81–1.02)	
BMI ^b			0.71			0.80
<25 kg/m ²	99/695	0.85 (0.73–1.00)		277/695	0.92 (0.85–1.01)	
25 kg/m ²	103/918	0.91 (0.79–1.04)		337/918	0.94 (0.86–1.02)	
Physical activity ^c			0.54			0.92
<9 METS-hours/week	105/745	0.90 (0.79–1.04)		333/745	0.94 (0.87–1.02)	
9 METS-hours/week	83/855	0.85 (0.73–1.00)		282/855	0.94 (0.85–1.02)	
Regular aspirin use			0.46			0.18
No	153/1,082	0.87 (0.77–0.98)		429/1,082	0.91 (0.85–0.98)	
Yes	57/578	0.94 (0.78–1.12)		217/578	0.98 (0.89–1.08)	
Total vitamin D intake			0.72			0.40
<800 IU/d	182/1,377	0.90 (0.80–1.01)		561/1,377	0.91 (0.85–0.98)	
800 IU/d	28/283	0.87 (0.70–1.08)		85/283	0.97 (0.86–1.09)	
Multivitamin use			0.21			0.84
No	88/698	0.82 (0.69–0.98)		295/698	0.94 (0.85–1.03)	
Yes	122/962	0.93 (0.82–1.06)		351/962	0.93 (0.86–1.01)	
Cancer subsite			0.24			0.29
Colon	144/1,199	0.93 (0.82–1.05)		467/1,199	0.96 (0.89–1.03)	

	Colorectal cancer-specific mortality				All-cause mortality			
	Number of events/patients	Per 300 mg/day	HR (95% CI)	P for interaction	Number of events/patients	Per 300 mg/day	HR (95% CI)	P for interaction
Rectum	58/369		0.82 (0.68–0.99)		140/369		0.89 (0.79–0.99)	
Cancer stage				0.52				0.18
I to II	83/1,056		1.04 (0.86–1.26)		388/1,056		0.98 (0.90–1.07)	
III	94/396		0.83 (0.70–0.99)		162/396		0.88 (0.77–1.01)	

^aPostdiagnostic intake at least 6 months but no more than 4 years after diagnosis to avoid potential impact of active treatment. Cox model stratified by **age** at diagnosis (<55, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and 75 years), cancer **stage** (I, II, III, and unspecified), and **gender** (men, women), with additional adjustments for tumor grade of **differentiation** (well differentiated, moderately differentiated, poorly differentiated, and unspecified), tumor **subsite** (proximal colon, distal colon, rectum, and unspecified), year of **diagnosis** (continuous), prediagnostic intake of total calcium (in quartiles), postdiagnostic **BMI** (<23, 23 to 24.9, 25 to 27.4, 27.5 to 29.9, 30 kg/m²), postdiagnostic **physical activity** (<3, 3 to 8.9, 9 to 11.9, 12 to 17.9, 18 METS-hours/week), postdiagnostic regular use of **aspirin** (yes or no), and postdiagnostic **smoking** (0, 1 to 9, 10 to 19, 20 to 40, 40 pack years), postdiagnostic **alcohol** consumption (<5, 5 to 14.9, 15 g/d), and postdiagnostic intake of total **fat**, **folate**, and **vitamin D** (all in quartiles), and other **supplement use** (defined by the sum of vitamin A, C, E, selenium, and zinc).

^bThere are 47 missing values in BMI.

^cThere are 60 missing values in physical activity.

Table 4. Colorectal cancer-specific mortality and overall mortality according to changes in total and supplemental calcium intake

	Changes in calcium intake					<i>P</i> trend
	Decrease intake of less 150-increase intake up to 150 mg/d					
	Decrease intake of 300 mg/d	Decrease intake of 150–300 mg/d	Increase intake of up to 150 mg/d	Increase intake of up to 300 mg/d		
Colorectal cancer-specific mortality (<i>n</i> = 210)						
Total calcium intake						
Model 1 ^a HR (95% CI)	1.28 (0.80–2.05)	1.39 (0.86–2.24)	Referent	1.71 (1.12–2.62)	0.79 (0.53–1.16)	0.10
Model 2 ^b HR (95% CI)	1.25 (0.77–2.04)	1.57 (0.96–2.58)	Referent	1.75 (1.12–2.73)	0.79 (0.52–1.19)	0.12
Model 3 ^c HR (95% CI)	1.28 (0.78–2.10)	1.64 (0.99–2.71)	Referent	1.78 (1.14–2.79)	0.80 (0.53–1.22)	0.12
Supplemental calcium intake ^d						
Model 1 ^a HR (95% CI)	1.34 (0.82–2.18)	1.39 (0.81–2.37)	Referent	0.83 (0.47–1.46)	0.64 (0.41–0.97)	0.004
Model 2 ^b HR (95% CI)	1.24 (0.73–2.10)	1.47 (0.84–2.57)	Referent	0.71 (0.39–1.29)	0.64 (0.41–1.00)	0.01
Model 3 ^c HR (95% CI)	1.23 (0.72–2.11)	1.41 (0.80–2.48)	Referent	0.72 (0.40–1.31)	0.64 (0.40–1.00)	0.01
All-cause mortality (<i>n</i> = 646)						
Total calcium intake						
Model 1 ^a HR (95% CI)	0.94 (0.71–1.24)	1.17 (0.88–1.56)	Referent	1.21 (0.94–1.55)	0.80 (0.65–0.99)	0.13
Model 2 ^b HR (95% CI)	0.91 (0.68–1.21)	1.13 (0.85–1.51)	Referent	1.26 (0.97–1.63)	0.83 (0.66–1.04)	0.42
Model 3 ^c HR (95% CI)	0.92 (0.69–1.23)	1.14 (0.85–1.52)	Referent	1.28 (0.98–1.66)	0.84 (0.67–1.06)	0.45
Supplemental calcium intake ^d						
Model 1 ^a HR (95% CI)	0.86 (0.46–1.38)	1.00 (0.62–1.68)	Referent	0.88 (0.61–1.39)	0.70 (0.48–1.23)	0.35
Model 2 ^b HR (95% CI)	0.77 (0.43–1.38)	0.87 (0.51–1.46)	Referent	0.87 (0.55–1.38)	0.66 (0.39–1.10)	0.56
Model 3 ^c HR (95% CI)	0.77 (0.43–1.40)	0.84 (0.49–1.44)	Referent	0.89 (0.56–1.42)	0.68 (0.41–1.15)	0.68

^aCox model stratified by **age** at diagnosis (<55, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and 75 years) cancer **stage** (I, II, III, and unspecified), and **gender** (men, women, pooled analysis only), with additional adjustments for tumor **grade** of differentiation (well differentiated, moderately differentiated, poorly differentiated, and unspecified), tumor **subsite** (proximal colon, distal colon, rectum, and unspecified), **year** of diagnosis (continuous), and prediagnostic total calcium intake (in quartiles).

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^bModel 1 + postdiagnostic **BMI** (<23, 23 to 24.9, 25 to 27.4, 27.5 to 29.9, 30 kg/m²), postdiagnostic **physical activity** (<3, 3 to 8.9, 9 to 11.9, 12 to 17.9, 18 METS-hours/week), postdiagnostic regular use of **aspirin** (yes or no), and postdiagnostic **smoking** (0, 1 to 9, 10 to 19, 20 to 40, 40 pack years), postdiagnostic **alcohol** consumption (<5, 5 to 14.9, 15 g/d), and postdiagnostic intake of total **fat**, **folate**, and **vitamin D** (all in quartiles).

^cModel 2 + **multivitamin** use (yes or no) + **other supplement** use (defined by the sum of vitamin A, C, E, selenium, and zinc).

^dSupplemental calcium intake in this study included calcium from both calcium supplement use and multivitamin use.