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Associations of Calcium, Vitamin D, and Dairy Product Intakes with Colorectal Cancer Risk Among Older Women: the Iowa Women's Health Study

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Abstract

Calcium and, to a lesser extent, dairy products are consistently modestly inversely associated with colorectal cancer (CRC). Dairy products may contain components other than calcium and fat, such as insulin-like growth factor-1, that may affect CRC risk.

In the prospective Iowa Women's Health Study, calcium, dairy product, and vitamin D intakes were assessed using a semiquantitative food frequency questionnaire. To investigate dairy products independent of their calcium components, we estimated residuals from linear regression models of their associations with dietary calcium.

Of the 35,221 55–69-year-old cancer-free women at baseline in 1986, 1,731 developed CRC during follow-up through 2012. For those in the highest relative to the lowest intake quintiles, the adjusted hazards ratios and 95% confidence intervals from multivariable Cox proportional hazards regression models for overall and distal CRC were 0.81 (0.67–0.98; $P_{\text{trend}}=0.004$) and 0.59 (0.44–0.80; $P_{\text{trend}}=0.003$), respectively, for total calcium; and 0.79 (0.66–0.94; $P_{\text{trend}}=0.01$) and 0.69

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DISCLOSURE STATEMENT

The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the National Cancer Institute. The National Cancer Institute had no influence on the analysis and interpretation of the data, the decision to submit the manuscript for publication, or the writing of the manuscript.

(0.53–0.90; $P_{\text{trend}}=0.003$) for total dairy products, respectively. The various dairy product residuals were not associated with CRC.

These results support that, among women, calcium and dairy products may be inversely associated with CRC—perhaps primarily distal CRC—but suggest that the non-calcium, non-fat component of dairy products may not be associated with CRC.

Keywords

Calcium; Dairy products; Milk; Colorectal cancer; Cohort study

INTRODUCTION

Colorectal cancer (CRC) remains the second leading cause of cancer deaths among men and women combined in the United States (1). Calcium and vitamin D have been consistently associated with modestly lower risk of incident CRC (2–4). Additionally, dairy products, which are a major contributor of dietary calcium intake in the American diet, have also been generally, although somewhat less consistently, associated with lower risk for CRC (5–7).

Evidence from clinical trials of calcium and vitamin D support the various mechanisms by which these nutrients may protect against colorectal neoplasms, including binding of damaging secondary bile acids and free fatty acids (8), promotion of differentiation and apoptosis in colonic epithelial cells (9, 10), modulation of the APC colon carcinogenesis pathway (11, 12), and protection against oxidative DNA damage (13). Although dairy products contain dietary calcium and have been inversely associated with CRC risk, they can also contain insulin-like growth factor 1 (IGF-1). Although circulating IGF-1 concentrations are largely determined by endogenous factors, they are positively associated with milk intake and dairy calcium (14, 15), and circulating radioactively-labeled IGF-1 from milk was detected in rats (16). Additional evidence from animal and *in vitro* studies suggest that other components of milk, such as amino acids, may also affect circulating IGF-1 concentrations by increasing the expression of the gene encoding IGF-1 (17) or by decreasing clearance of IGF-1 from the circulation (18). Higher circulating IGF-1 concentrations are of concern because of their reported direct associations with colorectal, prostate, and breast cancer risk (15, 19–21).

The associations of calcium, vitamin D, and dairy product intakes with CRC in the Iowa Women's Health Study were previously published using data collected through 1990, which included 212 incident CRC cases (22). Therefore, the findings reported herein serve as an update to the previously published report, and include colorectal sub-site analyses and a new approach to investigating associations of dairy product components with incident CRC.

MATERIALS AND METHODS

Study Population and Design

Details on the study design and protocols of the prospective Iowa Women's Health Study were previously described (23). Briefly, questionnaires were mailed in 1986 to 99,826

women aged 55 – 69 years randomly selected from Iowa driver's license information in 1985, and 41,836 (42.7% of eligible women) returned completed questionnaires designed to collect demographic, medical history, lifestyle, and dietary data. Participants were followed for mortality and cancer incidence, with follow-up surveys mailed in 1987, 1989, 1992, 1997, and 2004.

Dietary Assessment

Dietary intakes and vitamin and mineral supplement use were collected at baseline using a 127-item semi-quantitative Willett food frequency questionnaire, for which the validity and reliability in the study population was previously reported (24). Dairy product consumption was assessed referencing common serving sizes, and included milk (whole, low-/non-fat), cream, non-dairy creamer, sour cream, ice cream/ice milk, yogurt, butter, margarine, and various cheeses. Diet was only comprehensively reassessed in 2004, at which time only 68.3% of the participants remained alive (therefore, only baseline exposure information was used in the present analyses).

Outcome Assessment

Through 2012, 1,731 incident CRC cases (International Classification of Diseases for Oncology codes (ICD-O-3) 18.0, 18.2 – 18.9, 19.9, 20.9) were identified through linkage with the State Health Registry of Iowa, which is part of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (25). Deaths were ascertained through the State Health Registry of Iowa and the National Death Index.

Statistical Analyses

After excluding participants with a self-reported history of cancer (excluding non-melanoma skin cancer) at baseline and those missing 30 food frequency questionnaire questions or who had unreasonable self-reported total energy intakes (< 600 or $> 5,000$ kcal/day), the final sample size was 35,221.

Calcium, vitamin D, and dairy product intakes were categorized into quintiles. Due to low consumption, supplemental vitamin D was categorized as no consumption and low/high groups based on the population median, and whole milk was categorized as no consumption and quartiles of intake. Because of the high correlation between dietary calcium and milk intake (Pearson $r=0.87$), we examined the associations of whole and low-/non-fat milk adjusted for dietary calcium using residuals from linear regression models of each milk variable with dietary calcium intake. This method was modeled after the energy adjustment residual method (26) with the dependent variable being milk and the independent variable being dietary calcium. This procedure yielded a zero correlation of the residuals with dietary calcium. Our intent was that the residuals would be an indirect indicator of the non-calcium component of milk, which contains other components, such as IGF-1. To also investigate the non-calcium and non-fat component of milk, we examined models additionally adjusted for energy-adjusted total fat. The same procedure was followed for total dairy products. All residuals were also categorized into quintiles, except those for whole milk, which were categorized as no whole milk consumption and quartiles of residuals.

Follow-up time for CRC cases was calculated as the time from the date of completion of the baseline questionnaire to the date of CRC diagnosis. For non-cases, follow-up time was calculated as the time from the baseline questionnaire to one of the following: 1) date of death occurring in Iowa, 2) date when the participant moved out of Iowa if known, 3) the midpoint between the date of last contact in Iowa and the first known date outside of Iowa or the end of the follow-up period if the participant moved from Iowa at an unknown date, 4) the midpoint between the date of last contact in Iowa and the date of death if death did not occur in Iowa, or 5) the end of follow up (December 31, 2012), whichever was earliest.

Participant baseline characteristics were compared using chi-square tests for categorical variables and general linear models for continuous variables. Cox proportional hazards models were used to calculate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate associations of calcium, vitamin D, dairy product intakes, and residuals of dairy products with incident CRC. Trend tests across quantiles of intake were conducted using median values as a continuous variable. Proportional hazards assumptions were tested using Log-Log survival curves, Schoenfeld residuals, and extended Cox models for each exposure and potential covariate.

Potential confounders were selected on the basis of biological plausibility, previous literature, and whether inclusion of the variable changed the adjusted HR for the primary exposure by 10%. Variables considered as potential confounders included age (continuous); family history of CRC in a first-degree relative (yes/no); college education or higher (yes/no); smoking status (current/past/never); alcohol consumption (grams/day); physical activity level (low/moderate/high); postmenopausal hormone use (ever/never); body mass index (BMI, continuous); intakes of total energy (kcal), total and saturated fat (g/day), total vitamin D (IU/day) (for the calcium and dairy product models), total magnesium (mg/day), total vitamin E (mg/day), red and processed meats (servings/week), dietary fiber, and total fruits and vegetables (servings/week); and a dietary oxidative balance score (continuous). The dietary oxidative balance score was created using a previously described equal-weight method (27) as a score comprised of anti- (carotene, lutein, lycopene, vitamins C and E, omega-3 fatty acids, flavonoids) and pro-oxidant (dietary iron, omega-6 fatty acids, saturated fat) nutrients. The covariates for the final models are shown in the Tables' footnotes.

To assess potential effect modification, we conducted analyses stratified by age ($\leq$ median age of 61 yrs.), family history of CRC in a first degree relative, education (less than vs. college education or higher), smoking status, alcohol consumption (any/none), physical activity level, postmenopausal hormone use, BMI ($\leq$ median of 26.1 kg/m²), the dietary oxidative balance score (low/high), and median intakes of total energy ($\leq$ 1,717 kcal/day), total ($\leq$ 68.5 g/day) and saturated fats ($\leq$ 23.7 g/day), total magnesium ($\leq$ 287.4 mg/day), total vitamin E ($\leq$ 9.7 mg/day), total meats ($\leq$ 12.5 servings/week), red meats ($\leq$ 5 servings/week), processed meats ($\leq$ 1 serving/week), and total fruits and vegetables ($\leq$ 35 servings/week). We also conducted stratified analyses by total vitamin D intake ($\leq$ 338 IU/day) in the calcium and dairy product models, and by total calcium intake ($\leq$ 1,029 mg/day) in the vitamin D models.

We also assessed associations of all primary exposure variables with proximal (cecum through the transverse colon; ICD-O-3 codes 18.0 – 18.9) and distal (splenic flexure through sigmoid colon; ICD-O-3 codes 18.5 – 18.7) colon cancer, recto-sigmoid junction/rectal cancer (ICD-O-3 codes 19.9 and 20.9), and distal colon/rectal cancer.

We conducted sensitivity analyses in which we excluded CRC cases or deaths that occurred within 1, 2, and 6 (see below) years after enrollment to assess the potential influence of pre-morbid health conditions. Because aspirin and non-steroidal anti-inflammatory drug use have been strongly and consistently inversely associated with risk for colorectal neoplasia (28, 29), but questions on them were not included until 1992, after 6 years of follow-up, all analyses were repeated using 1992 as the baseline date to assess for potential confounding and effect modification by aspirin/non-steroidal anti-inflammatory drug use.

A two-sided P value < 0.05 or a 95% confidence interval that did not include 1.0 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Selected baseline characteristics of the study population by quintiles of total calcium intake are presented in Table 1. At baseline, the mean age was 62 years, 99% were white, and 3% had a history of a first-degree relative with colon cancer. Participants consumed a daily average of 1,798 kcal of total energy, 804 mg of dietary calcium, and 2.5 servings of dairy products. Those in the higher relative to those in the lower quintiles of total calcium intake were less likely to smoke, more likely to currently take or have previously taken postmenopausal hormones, more likely to have higher levels of physical activity, and, on average, had the lowest BMI, and higher intakes of dietary fiber, total meats, and total fruits and vegetables.

The estimated associations of calcium and dairy product intakes with incident CRC are presented in Table 2. For those in the highest relative to those in the lowest quintile of intakes, total calcium was associated with a statistically significant 19% lower risk (HR, 0.81; 95% CI, 0.67–0.98; P_{trend} 0.004). Although not statistically significant, dietary and supplemental calcium were both estimated to be associated with approximately 15% lower risk. For those in the highest relative to those in the lowest intake categories, total dairy products were associated with statistically significant 21% lower risk (HR, 0.79; 95% CI, 0.66–0.94; P_{trend} 0.01), while the estimated HRs for the associations of high- and low-fat dairy products with risk were minimally less than 1.0. For specific milk types (whole vs. low/non-fat), there was limited heterogeneity of intakes, and the estimated HRs for their associations with risk were, in general, minimally less than 1.0 (Supplemental Table 1). Also shown in Supplemental Table 1 are the estimated associations of 1) total, dietary, and supplemental vitamin D and 2) the various dairy product residuals (i.e., the dairy product variables fully adjusted for dietary calcium, thus representing the non-calcium components of dairy products, and the low-/non-fat dairy residuals that were additionally adjusted for fat, thus representing the non-calcium/non-fat components of milk), which were also close to the null. We found no evidence of effect modification of any calcium or dairy product variable-

CRC associations by any of the potential effect modifying variables listed in the methods section (data not shown).

We also investigated supplemental calcium and vitamin D use, alone and in combination. As shown in Table 3, participants who reported taking both calcium and vitamin D supplements, relative to those who reported not taking either supplement, had statistically significant 15% lower risk (HR, 0.85; 95% CI, 0.75–0.97) of CRC.

As can be seen in Table 4, our primary exposure variables were more strongly inversely associated with cancers of the distal colon/rectum than with proximal colon cancers. The estimated risks for distal CRC among participants in the highest relative to the lowest intake categories of total, dietary, and supplemental calcium, and total dairy products were 41%, 25%, 37%, and 31% lower, respectively. However, the corresponding findings for proximal colon cancer were all close to the null. When the associations were assessed in relation to colon (all sites except rectum), distal colon (excluding rectum), and rectum (Supplemental Table 2), risks for distal colon and rectal cancers were similar, and the findings for all colon cancers (i.e., excluding rectal) were similar to those for all CRCs combined. Associations of supplemental calcium and vitamin D use, alone and in combination, with risk of cancers of various colorectal subsites (data not shown) were not materially different from the associations with overall CRC risk shown in Table 3 and Supplemental Table 1.

In the sensitivity analyses, exclusion of those who died or were diagnosed with CRC within 1, 2, or 6 years after enrollment did not materially change any of the associations (data not shown). When the analyses were repeated using 1992 as the baseline date, no evidence of confounding or effect modification by regular aspirin or non-steroidal anti-inflammatory drug use (data not shown) was observed.

DISCUSSION

The results of our study support that calcium and total dairy product intakes are inversely associated with risk of incident CRC among older women. These findings are consistent with those from the same study population after follow up through 1990 (22), and with others around the world (2). Our results also suggest that total calcium and dairy product intakes may be primarily inversely associated with left-sided CRC among women. Overall, we found that the estimated inverse associations of dietary and supplemental calcium with risk were minimally weaker than those for total calcium, but of similar magnitudes to each other. Also, taking supplemental calcium and vitamin D concomitantly was inversely associated with risk of CRC. The estimated inverse associations of high- and low-fat dairy products with risk were much weaker than those for total dairy products but of similar magnitudes to each other. Finally, our results do not suggest that the non-calcium/non-fat components of dairy products are associated with incident CRC.

Calcium and vitamin D are hypothesized to reduce risk for colorectal neoplasms by various mechanisms. Calcium binds secondary bile acids and free fatty acids in the gut, thus reducing exposure of colonic epithelial cells to their damaging effects, and through direct effects on colonic epithelial cell proliferation and differentiation (30–32). Vitamin D

promotes bile acid catabolism and modulates > 200 genes involved in cell cycle regulation, DNA repair, immunomodulation, and protection against oxidative stress and inflammation (8, 33–35).

Calcium has also been consistently, modestly inversely associated with colorectal neoplasms in observational studies. A meta-analysis of total or dietary calcium intakes and CRC risk from 17 cohort studies reported a statistically significant summary relative risk (RR) of 0.77 (95% CI, 0.71–0.81) for those in the highest relative to the lowest quantiles of calcium intakes (36). The most recent dose-response meta-analysis of 15 cohort studies reported a statistically significant summary RR of 0.92 (95% CI, 0.89–0.95) per 300 mg/day increase in total or dietary calcium intake (37). From a recent pooled analysis of eight prospective studies of calcium and colorectal adenoma risk, a statistically significant 5% lower risk of adenoma per 300 mg/day increase in total calcium intake was reported, and when three of the eight studies were pooled for an analysis of supplemental calcium alone, risk of adenoma was statistically significantly 4% lower per 300 mg/day increase in supplemental calcium intake (38).

Evidence from clinical trials also supports a protective effect of calcium supplementation against colorectal neoplasms. In three (39–41) of four (39–42) clinical trials of colorectal adenoma recurrence, supplemental calcium modestly reduced recurrence; in a meta-analysis of the trials, the summary relative risk (RR) of recurrence was 0.80 (95% CI, 0.68–0.93) (43). Another clinical trial found no evidence that supplemental calcium and vitamin D in combination reduced invasive CRC incidence (RR, 1.08; 95% CI, 0.86–1.34); however, only 60% of participants reported taking at least 80% of their study pills, low doses of calcium (1,000 mg/day) and vitamin D (400 IU/day) were administered, and the follow-up time may have been inadequate to assess CRC development (44).

Our finding of an inverse association of concomitant use of supplemental calcium and vitamin D with CRC risk suggests a synergistic effect of these nutrients in relation to the disease. Unfortunately, because we did not measure serum 25-OH-vitamin D concentrations—the best measure of total vitamin D exposure—we were unable to assess possible synergism between total calcium intakes and total vitamin D exposure in our study population. However, there is other evidence to support possible synergism between calcium and vitamin D in relation to colorectal carcinogenesis. In the Calcium Polyp Prevention Trial (n = 803), there was a 29% reduction in adenoma recurrence among those randomized to calcium 1,200 mg/day, relative to placebo, among those with greater than the study population median serum 25-OH-vitamin D concentration (> 29.1 ng/mL) at baseline, but not among those with serum 25-OH-vitamin D concentrations less than the median at baseline (45). A more recent, modified 2×2 factorial trial of 1,200 mg/day calcium and/or 1,000 IU/day vitamin D₃ supplementation and colorectal adenoma recurrence, reported a non-statistically significant 7% lower risk (RR = 0.93; 95% CI: 0.80, 1.08) among those randomized to both agents relative to neither agent, but not relative to calcium supplementation alone (RR = 1.01; 95% CI: 0.88, 1.15) (42). In chemoprevention trials among colorectal adenoma patients, favorable changes in biomarkers of risk for colorectal neoplasms in normal colonic tissue were reported in those supplemented with calcium and vitamin D; for some biomarkers, the estimated treatment effects were stronger among those

randomized to both agents (9–12). Evidence from these studies, taken together with our findings, supports further research into the possibility that calcium and vitamin D may interact to reduce risk for colorectal carcinogenesis.

Since dairy products are a major source of dietary calcium in the American diet, several observational studies investigated associations of total and specific dairy product intakes with CRC risk. The hypothesized mechanism of action of dairy products may be similar to that of calcium, although some dairy products also contain a high percentage of total and saturated fats. However, as summarized in a meta-analysis, epidemiologic evidence does not support the hypothesis that dietary fat intake increases CRC risk (46). A recent meta-analysis of 12 cohort studies on total dairy product intake reported a statistically significant 19% lower risk of CRC (47). Additionally, analysis of milk consumption (high versus low) and CRC risk from 10 cohort studies in that same meta-analysis yielded a RR of 0.83 (95% CI, 0.74–0.93).

Our findings of stronger associations for left-sided than for right-sided CRC are plausible, but supporting evidence from epidemiologic studies and clinical trials is limited. The left and right sides of the colorectum differ in respect to embryological origin and bile acid metabolism, and in some cases, tumors in these sites may develop along different carcinogenic pathways (48). In a meta-analysis of 60 observational studies, five provided colon subsite-specific data. In those studies, total and dietary calcium were more strongly inversely associated with distal than with proximal colon cancers, but there was no substantial difference between calcium's associations with colon and rectal cancers (36). In two of the previously mentioned calcium supplementation randomized clinical trials, there was no evidence that calcium differentially affected adenoma recurrence by colon subsite (40, 41). Thus, further investigation of calcium and dairy products in relation to risk of subsite-specific colorectal neoplasms is warranted.

Whereas we found total dairy products to be statistically significantly inversely associated with CRC risk, our estimated associations of high-fat and low-fat dairy products separately with CRC were both closer to the null. The latter findings may be attributable to the overall low milk consumption in our study population, and warrants further investigation in populations with greater milk consumption heterogeneity. Milk is the dairy product most consistently associated with CRC risk in previous studies (49). Dairy products other than milk may also contain fermented components, artificial flavorings, preservatives, and other additives, which have unknown associations with CRC risk. Additionally, all dairy products produced using conventional, non-organic methods may contain IGF-1, which has been associated with higher risk of colorectal, prostate, and breast cancers (50–53). However, our findings for calcium, total dairy products, and residuals of dairy products suggest that the observed inverse associations with CRC risk may be most attributable to the calcium component of dairy products.

We recognize several limitations in our study. The intakes of supplemental vitamin D and all milk types were low; thus, the limited heterogeneity (i.e., too few persons with sufficiently high intakes to compare to those with low intakes) would tend to yield modest associations. Other limitations include the general limitations of food frequency questionnaires (e.g.,

measurement error) and that diet and supplement use was assessed only at baseline. These types of measurement error in prospective cohort studies are considered non-differential (because participants at baseline do not know what their eventual outcomes will be), which results in attenuated estimates of the true associations. Another limitation is the lack of data on CRC screening, which also would be expected to result in attenuated observed associations. This is because no matter how high risk someone's diet or lifestyle may be, if via CRC screening (which is actually mostly colorectal adenoma detection and subsequent removal) they have their adenomas removed, they are unlikely to get CRC. So, in a sense, these patients are 'misclassified', thus attenuating what the associations may have been had there been no screening. Finally, considering the widespread recognition that circulating 25-OH-vitamin D concentrations are considered to be the best indicator of vitamin D exposure (54), future studies should utilize 25-OH-vitamin D concentrations, which were unavailable in this study.

Major strengths of this study include the long follow-up duration, prospective study design, large sample size and number of CRC cases, and the collection and assessment of multiple potential confounding/effect modifying risk factors. Additional strengths include the comprehensive analysis of calcium and total and specific dairy products, the use of residuals as a potential estimate of the non-calcium component of dairy products, and the colorectal subsite analyses.

In summary, our findings of modestly lower risk for incident CRC with higher intakes of calcium and total dairy products are consistent with the previous analysis of the Iowa Women's Health Study cohort and other studies. Our results also suggest that 1) higher intakes of calcium and total dairy products may be primarily associated with lower risk of left-sided CRCs among women, 2) our findings for dairy products may be primarily attributable to their calcium component, and 3) concomitant calcium and vitamin D supplementation may also reduce CRC risk. Future studies in populations with sufficient levels of dairy product consumption are warranted to further investigate the association of dietary and supplemental calcium and dairy products with incident CRC, overall and by subsite.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1. Selected baseline characteristics of Iowa Women's Health Study participants by quintiles of total calcium^a

	Total Calcium Quintiles					<i>P</i> ^b
	1 (n = 7,041)	2 (n = 7,042)	3 (n = 7,050)	4 (n = 7,044)	5 (n = 7,044)	
Demographics						
Age, years	61.5 (4.2)	61.6 (4.3)	61.7 (4.2)	61.4 (4.2)	61.4 (4.2)	<0.0001
White, %	98.8	99.2	99.3	99.3	99.4	<0.0004
1 st degree relative with colorectal cancer, %	2.9	2.9	3.1	3.0	3.4	0.46
College graduate or higher, %	7.9	10.7	12.3	15.6	18.0	<0.0001
Lifestyle factors						
Body mass index, kg/m ²	27.3 (5.2)	27.1 (5.1)	27.0 (5.0)	26.9 (5.1)	26.5 (4.9)	<0.0001
Physical activity, %						<0.0001
Moderate	23.2	26.4	28.1	29.8	28.1	
High	16.9	22.6	24.2	26.9	32.6	
Current smokers, %	19.5	15.4	14.2	12.5	11.9	<0.0001
Alcohol, grams/day	3.9 (9.6)	3.7 (8.7)	3.7 (8.8)	3.7 (8.5)	3.7 (8.6)	0.51
Current or previous PHT, %	32.6	36.0	38.9	39.9	45.9	<0.0001
Dietary intakes						
Total energy, kcal/day	1,393 (408)	1,730 (494)	1,801 (561)	1,984 (589)	2,084 (695)	<0.0001
Total fat, % total energy	35.2 (6.2)	34.4 (5.6)	33.9 (5.6)	33.5 (5.4)	32.9 (5.7)	<0.0001
Dietary fiber, g/day	14.8 (5.3)	19.0 (6.4)	19.8 (7.5)	21.9 (7.9)	23.3 (9.4)	<0.0001
Total calcium, mg/day	443 (110)	734 (76.4)	1,024 (85.9)	1,321 (103)	1,957 (385)	<0.0001
Dietary calcium	425 (114)	645 (150)	800 (248)	990 (335)	1,162 (497)	<0.0001
Supplemental calcium	17.8 (56.2)	89.0 (155)	224 (235)	332 (345)	795 (499)	<0.0001
Total vitamin D, IU/day	199 (184)	309 (217)	401 (240)	495 (275)	656 (371)	<0.0001
Dietary vitamin D	134 (68.2)	202 (89.8)	251 (111)	310 (138)	360 (178)	<0.0001
Supplemental vitamin D	65.2 (173)	108 (209)	150 (340)	185 (273)	296 (350)	<0.0001
Total meat, servings/week	11.5 (5.7)	13.5 (6.5)	13.6 (6.9)	14.6 (7.2)	14.7 (7.6)	<0.0001
Total fruit and vegetable, servings/week	28.6 (13.9)	36.5 (16.1)	38.4 (19.0)	42.6 (19.6)	46.0 (24.1)	<0.0001
Total dairy, servings/week	9.0 (7.7)	13.6 (8.1)	17.2 (9.7)	21.3 (11.3)	25.3 (15.2)	<0.0001
Whole milk	0.4 (1.2)	0.7 (1.9)	1.0 (3.2)	1.2 (3.8)	1.6 (5.4)	<0.0001

Total Calcium Quintiles					
	1 (n = 7,041)	2 (n = 7,042)	3 (n = 7,050)	4 (n = 7,044)	5 (n = 7,044)
					<i>P^b</i>
Low-/non-fat milk	1.5 (2.2)	3.8 (3.0)	6.8 (6.4)	9.8 (7.3)	12.2 (9.8)
Fermented dairy	3.4 (2.8)	4.9 (3.5)	5.2 (4.3)	6.0 (4.5)	7.1 (6.9)
Cheese	3.0 (2.4)	4.4 (3.2)	4.6 (3.8)	5.2 (4.1)	6.0 (6.2)
					<0.0001
					<0.0001
					<0.0001

Abbreviations: PHT, postmenopausal hormone therapy.

^aContinuous variables are presented as means (standard deviations); categorical variables are presented as percentages.

^b*P* values from Chi-square test for categorical variables and general linear models for continuous variables

Table 2.

Associations of calcium and dairy product intakes with incident colorectal cancer among Iowa Women's Health Study Participants, 1986–2012

	Categories					<i>P</i> for trend ^a
	1	2	3	4	5	
Total calcium	n = 7,041	n = 7,042	n = 7,050	n = 7,044	n = 7,044	
Range (mg/day)	72.2–603	> 603 – 872	> 872 – 1,164	> 1,164 – 1,532	> 1,532 – 5,076	
Person-years	143,820	146,487	147,966	150,796	147,682	
No. of cases	395	404	346	293	293	
Unadjusted HR, 95% CI	1.00 Referent	1.00 0.87, 1.15	0.85 0.74, 0.98	0.70 0.60, 0.82	0.72 0.62, 0.84	<0.0001
Adjusted HR, 95% CI ^b	1.00 Referent	1.03 0.89, 1.19	0.89 0.76, 1.04	0.76 0.64, 0.90	0.81 0.67, 0.98	0.004
Dietary calcium	n = 7,042	n = 7,046	n = 7,045	n = 7,044	n = 7,044	
Range (mg/day)	72.2–470	> 470 – 634	> 634 – 812	> 812 – 1,148	> 1,148 – 4,405	
Person-years	145,512	148,013	147,594	147,449	148,182	
No. of cases	391	362	347	325	306	
Unadjusted HR, 95% CI	1.00 Referent	0.91 0.79, 1.05	0.87 0.76, 1.01	0.82 0.71, 0.95	0.77 0.66, 0.89	0.0004
Adjusted HR, 95% CI ^b	1.00 Referent	0.92 0.79, 1.07	0.90 0.76, 1.05	0.85 0.72, 1.01	0.84 0.68, 1.03	0.07
Supplemental calcium ^c	n = 17,820	n = 4,513	n = 6,091	n = 4,433	n = 2,364	
Range (mg/day)	0	> 0 – 200	> 200 – 500	> 500 – 1,000	> 1,000 – 2,700	
Person-years	368,176	94,032	130,020	95,374	49,149	
No. of cases	946	201	294	197	93	
Unadjusted HR, 95% CI	1.00 Referent	0.83 0.71, 0.97	0.87 0.77, 1.00	0.80 0.68, 0.93	0.74 0.60, 0.91	0.001
Adjusted HR, 95% CI ^b	1.00 Referent	0.87 0.75, 1.02	0.94 0.82, 1.08	0.88 0.75, 1.03	0.85 0.68, 1.06	0.16
Total dairy products	n = 6,976	n = 7,023	n = 7,090	n = 6,665	n = 7,467	
Range (servings/week)	0–7.5	> 7.5 – 11.8	> 11.8 – 18.0	> 18.0 – 24.5	> 24.5 – 143	
Person-years	144,729	147,978	149,033	139,682	155,328	
No. of cases	391	343	358	321	318	
Minimally-adj. HR, 95% CI ^d	1.00 Referent	0.85 0.73, 0.98	0.88 0.76, 1.02	0.83 0.72, 0.97	0.74 0.64, 0.86	0.0002
Fully adjusted HR, 95% CI ^e	1.00 Referent	0.86 0.74, 0.99	0.89 0.77, 1.04	0.87 0.74, 1.02	0.79 0.66, 0.94	0.01
High-fat dairy ^f	n = 6,113	n = 7,356	n = 7,191	n = 7,365	n = 7,196	

	Categories					<i>P</i> for trend ^a
	1	2	3	4	5	
Range (servings/week)	0 – 2.5	> 2.5 – 5.0	> 5.0 – 8.0	> 8.0 – 13.5	> 13.5 – 128	
Person-years	126,775	154,666	151,943	154,996	148,371	
No. of cases	309	371	351	377	323	
Minimally-adj. HR, 95% CI ^d	1.00 Referent	0.98 0.85, 1.10	0.99 0.85, 1.15	0.99 0.85, 1.15	0.88 0.76, 1.03	0.06
Fully adjusted HR, 95% CI ^e	1.00 Referent	1.00 0.86, 1.16	0.97 0.83, 1.14	1.02 0.87, 1.19	0.91 0.77, 1.08	0.14
Low-fat dairy ^g	n = 6,142	n = 5,363	n = 6,787	n = 8,532	n = 8,397	
Range (servings/week)	0	> 0 – 2.0	> 2.0 – 6.5	> 6.5 – 14.0	> 14.0 – 84.0	
Person-years	124,757	111,967	142,844	180,228	176,954	
No. of cases	312	282	349	394	394	
Minimally-adj. HR, 95% CI ^d	1.00 Referent	1.01 0.86, 1.19	0.98 0.84, 1.14	0.88 0.76, 1.02	0.88 0.76, 1.02	0.08
Fully adjusted HR, 95% CI ^e	1.00 Referent	1.02 0.87, 1.20	1.00 0.86, 1.17	0.91 0.78, 1.06	0.99 0.84, 1.17	0.91

Abbreviations: HR, hazard ratio; Minimally-adj., Minimally-adjusted; 95% CI, 95% confidence interval.

^a *P* for trend calculated using medians of each quantile.

^b Adjusted for age, family history of colorectal cancer, body mass index, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, vitamin D, magnesium, fruit and vegetable intake, red and processed meat intake, and dietary oxidative balance score (a score combining anti- and pro-oxidant dietary exposures; see text).

^c Supplemental calcium analyzed as 5 categories of intake with no intake as the reference category.

^d Adjusted for supplemental calcium.

^e Adjusted for age, family history of colorectal cancer, body mass index, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, vitamin D, magnesium, fruit and vegetable intake, red and processed meat intake, dietary oxidative balance score, and supplemental calcium.

^f High-fat dairy includes whole milk, cream, yogurt, ice cream, cream cheese, cottage cheese, other cheese, sour cream, and butter.

^g Low-fat dairy includes low-/non-fat milk and ice milk/sherbet, and analyzed as 5 categories of intake with no intake as the reference category.

Association of supplemental calcium and vitamin D use with incident colorectal cancer among Iowa Women's Health Study participants, 1986–2012

Table 3.

	No calcium or vitamin D	Calcium, no vitamin D	Vitamin D, no calcium	Calcium and vitamin D
All participants	n = 15,415	n = 6,996	n = 2,405	n = 10,405
Person-years	318,901	149,467	49,275	219,108
Number of cases	821	352	125	433
Unadjusted HR, 95% CI	1.00	Referent	0.91	0.80, 1.03
Minimally-adj. HR, 95% CI ^a	1.00	Referent	0.90	0.82, 1.19
Fully adjusted HR, 95% CI ^b	1.00	Referent	0.95	0.82, 1.20
			0.85, 1.23	0.75, 0.97

Abbreviations: HR, hazard ratio; Minimally-adj., Minimally-adjusted; 95% CI, 95% confidence interval.

^a Adjusted for dietary calcium and dietary vitamin D.

^b Adjusted for age, family history of colorectal cancer, body mass index, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, magnesium, fruit and vegetable intake, red and processed meat intake, dietary oxidative balance score (a score combining anti- and pro-oxidant dietary exposures; see text), dietary calcium, and dietary vitamin D.

Table 4.

Multivariable-adjusted associations of calcium and dairy product intakes with incident proximal and distal colorectal cancers among Iowa Women's Health Study participants, 1986–2012

	Categories ^c	Proximal ^a			Distal ^b		
		No. of cases	HR ^d	95% CI	No. of cases	HR ^d	95% CI
Total calcium							
	1	204	1.00	Referent	191	1.00	Referent
	2	238	1.21	0.99, 1.47	166	0.84	0.67, 1.04
	3	189	0.98	0.79, 1.21	157	0.79	0.62, 0.99
	4	162	0.87	0.69, 1.10	131	0.65	0.50, 0.84
	5	178	1.04	0.81, 1.34	115	0.59	0.44, 0.80
	<i>P for trend^e</i>		0.57			0.003	
Dietary calcium							
	1	223	1.00	Referent	168	1.00	Referent
	2	187	0.85	0.70, 1.04	175	1.00	0.81, 1.25
	3	199	0.94	0.76, 1.17	148	0.84	0.66, 1.07
	4	190	0.93	0.74, 1.17	135	0.75	0.57, 0.98
	5	172	0.92	0.70, 1.20	134	0.75	0.55, 1.02
	<i>P for trend^e</i>		0.78			0.02	
Supplemental calcium							
	1	514	1.00	Referent	432	1.00	Referent
	2	118	0.94	0.76, 1.15	83	0.80	0.63, 1.02
	3	182	1.06	0.89, 1.26	112	0.81	0.65, 1.00
	4	94	0.76	0.60, 0.95	103	1.05	0.83, 1.32
	5	63	1.03	0.78, 1.36	30	0.63	0.43, 0.92
	<i>P for trend^e</i>		0.69			0.09	
Total dairy products ^f							
	1	217	1.00	Referent	174	1.00	Referent
	2	192	0.89	0.73, 1.08	151	0.83	0.67, 1.03
	3	187	0.87	0.71, 1.07	171	0.92	0.74, 1.14
	4	197	1.03	0.83, 1.27	124	0.71	0.55, 0.90
	5	178	0.87	0.69, 1.10	140	0.69	0.53, 0.90
	<i>P for trend^e</i>		0.54			0.003	

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

^aProximal includes cecum, appendix, ascending colon, hepatic flexure, transverse colon, overlapping lesion of colon, and colon, not otherwise specified.

^bDistal includes splenic flexure, descending colon, sigmoid colon, recto-sigmoid junction, and rectum.

^cQuintiles of intake except for supplemental calcium, analyzed as 5 categories of intake with no intake as the reference category.

^d Adjusted for age, family history of colorectal cancer, body mass index, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, vitamin D, magnesium, fruit and vegetable intake, red and processed meat intake, and dietary oxidative balance score (a score combining anti- and pro-oxidant dietary exposures; see text).

^e *P* for trend calculated using medians of each quantile.

^f Multivariable hazard ratios adjusted for age, family history of colorectal cancer, body mass index, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, vitamin D, magnesium, fruit and vegetable intake, red and processed meat intake, dietary oxidative balance score, and supplemental calcium.