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Associations of calcium and milk product intakes with incident, sporadic colorectal adenomas

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Abstract

Calcium intake has been consistently, modestly inversely associated with colorectal neoplasms, and supplemental calcium reduced adenoma recurrence in clinical trials. Milk products are the major source of dietary calcium in the US, but their associations with colorectal neoplasms are unclear.

Data pooled from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma (n=807 cases, 2,185 controls) were analyzed using multivariable unconditional logistic regression. Residuals from linear regression models of milk with dietary calcium were estimated as the non-calcium, insulin-like growth factor 1-containing component of milk.

For total, dietary, and supplemental calcium intakes, the adjusted odds ratios (ORs) comparing the highest to the lowest intake quintiles were 0.94 (95% confidence interval [CI] 0.69–1.30), 0.86 (CI 0.62–1.20), and 0.99 (CI 0.77–1.27), respectively. The corresponding ORs for consumption of total milk products, total milk, non-fat milk, total milk product residuals, and non-fat milk residuals were, respectively, 0.99, 0.90, 0.92, 0.94, and 0.95; all CI's included 1.0. For those who consumed any whole milk relative to those who consumed none, the OR was 1.15 (CI 0.89–1.49).

These results are consistent with previous findings of modest inverse associations of calcium intakes with colorectal adenoma, but suggest that milk products may not be associated with adenoma.

Keywords

Calcium; milk; dairy; colorectal neoplasia; case-control studies

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer deaths among men and women combined in the United States (1). Various lifestyle and dietary factors have been found to be important risk factors for colorectal cancer and adenomatous polyps (adenomas), including calcium intake, which has been consistently, albeit modestly, associated with lower risk (2–4).

A major proportion of calcium intake in the average American diet is from milk products, which include, but not exclusively, milk, cheese, and fermented milk products. Milk product consumption has been fairly consistently associated with lower risk for colorectal cancer and adenomas, though the high fat content of some products, such as certain high fat cheeses, was hypothesized to increase risk by increasing bile acid excretion (5). However, studies of high-fat milk products and cheese consumption with risk for colorectal cancer have been inconsistent (6).

Although greater milk product consumption increases dietary calcium intake, it may simultaneously contribute to increased intake of insulin-like growth factor 1 (IGF-1). Serum IGF-1 levels, though primarily determined by endogenous factors, were associated with several dietary factors, including milk products, fish, poultry, vegan diets, and total protein intake (7–9). “Conventionally-produced” milk contains 14% statistically significantly higher levels of IGF-1 than does organic milk (10), and calcium and milk consumption were positively associated with levels of IGF-1 and its molar ratio with IGF binding protein 3 (IGFBP-3) (11, 12). Though it is unclear whether IGF-1 from milk products is absorbed in the human intestinal tract, circulating radioactively labeled IGF-1 from milk was detected after ingestion in rats (13). This is concerning since higher circulating IGF-1 levels are associated with certain cancers, including breast, prostate, and colorectal (12, 14–16). It is unclear whether IGF-1 intake from milk product consumption is associated with risk for colorectal neoplasms.

To address these gaps in knowledge, we investigated associations of calcium and milk products and a novel estimate of the non-calcium component of milk with risk for incident, sporadic colorectal adenomas.

MATERIALS AND METHODS

Study Population

Data for this study were pooled from three colonoscopy-based case-control studies of incident, sporadic colorectal adenoma. The protocols for the Minnesota Cancer Prevention Research Unit Case-Control Study (CPRU; 1991–1994) and the Markers of Adenomatous Polyps studies I (MAP I; North Carolina, 1995–1997) (17) and II (MAP II; South Carolina, 2002) (18) were previously published. Analyses using the pooled data were also previously published (19, 20).

Briefly, the studies, conducted by the same principal investigator in three states, recruited patients scheduled for outpatient, elective colonoscopy by community gastroenterology

practices using identical participant recruitment and data collection protocols. In the CPRU study, two additional sets of controls were recruited: 1) patients being screened for colon cancer using flexible sigmoidoscopy in the same community practices as the colonoscopy-based controls (patients found to have a polyp on sigmoidoscopy had a subsequent colonoscopy), and 2) persons randomly selected from the general population in the Minneapolis-St. Paul metropolitan region as previously described (18). For the colonoscopy- and sigmoidoscopy-based participants, all self-reported data, including medical, lifestyle, and dietary history, were collected before case or control status was determined. The study protocols for all studies were approved by the respective institutional review boards of the corresponding institutions, and all participants provided informed consent.

The same eligibility criteria were used for all studies, which included English-speaking participants 35–74 years of age, with no known genetic syndromes associated with colonic neoplasia, and no history of inflammatory bowel disease, cancer (excluding non-melanoma skin cancer), or colorectal adenoma. Cases were defined as patients with first ever pathology-confirmed adenoma(s) at colonoscopy while controls were those with no adenomatous or hyperplastic polyps found at colonoscopy (all studies) or sigmoidoscopy (CPRU), and the CPRU community controls who reported no history of colorectal neoplasms. For our pooled analysis, all cases were combined into one case group, and all control groups were combined into one control group.

The initial sample sizes of each study were: 574 cases and 707 colonoscopy, 538 sigmoidoscopy, and 550 community controls combined as one control group for CPRU; 184 cases and 236 colonoscopy controls for MAP I; and 49 cases and 154 colonoscopy controls for MAP II. Participants were excluded from this pooled analysis if their total energy intake estimated from the self-reported Willett semi-quantitative food frequency questionnaire (FFQ) was >6,000 or <600 kilocalories daily, or if 10% of their FFQ data was missing. The final sample size for this pooled case-control study was 787 incident, sporadic adenoma cases and 2,033 controls.

Dietary Assessment

From the above noted FFQ, calcium intake was assessed as total, dietary, and supplemental intake, and milk product consumption was assessed as individual and total milk products. Total milk products included milk, creams, ice cream and sherbet, fermented dairy products, cheeses, and butter. Milk intake was categorized as whole and non-/low-fat milk.

Statistical Analyses

The characteristics of the cases and the controls were compared using the Pearson's chi square and Fisher's exact tests for categorical variables and the Student *t* test for continuous variables.

Calcium (total and dietary) and milk product intakes (total and non-fat milk) were categorized into quintiles based on the study- and sex-specific distributions among the controls. Whole milk was dichotomized as any or no intake, and supplemental calcium intake was categorized into three groups (none and according to the median dose among those who took supplemental calcium). Since dietary calcium was highly correlated with

milk intake, in order to examine the association of non-fat milk adjusted for dietary calcium, residuals from the linear regression models of non-fat milk with dietary calcium intake were determined. This method was patterned after the energy adjustment residual method (21) with the dependent variable being non-fat milk and the independent variable being dietary calcium. The intent was that the calcium-adjusted residuals would represent a possible indirect indicator of the non-calcium, non-fat components of milk (such as IGF-1). The same procedure was followed for total milk products. All calcium-adjusted residuals were categorized into study- and sex-specific quintiles and used in logistic regression models in which dietary calcium was included because of its expected independent association with adenoma.

Multivariable unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the categorized exposure variables of interest with adenomas. In addition, the associations of calcium and milk intakes with various categories of adenomas were examined, and associations were stratified by potential effect-modifying variables which were dichotomized according to the study- and sex-specific medians among the controls.

Potential confounding variables considered included study, age, sex, education, hormone replacement therapy use (females), family history of colorectal cancer in a first-degree relative, regular (once per week) aspirin or nonsteroidal anti-inflammatory drug (NSAID) use (yes/no), intakes of total energy (continuous), total fat (continuous; adjusted for total energy using the residual method), dietary fiber (continuous), fruits and vegetables (continuous), red and processed meats (continuous), calcium (continuous), vitamin D (continuous), magnesium (continuous), and an oxidative balance score (OBS; continuous). The OBS was created using a previously described equal-weight method (20) and was comprised of lifestyle (physical activity, smoking, alcohol intake, and obesity measures [body mass index, BMI; waist-to-hip ratio, WHR]) and dietary variables (total carotene, lutein, lycopene, vitamins C and E, linoleic and linolenic acids, flavonoid, glucosinolate, dietary iron, and saturated fat). Criteria for inclusion of covariates in the final models included: 1) biological plausibility, 2) previous literature, 3) their associations with the primary exposure and outcome variables, and 4) whether inclusion of the variable in the models changed the logistic regression coefficient of the primary exposure variable by 10%. Initial models were adjusted for study, age, and sex, and the final full models were additionally adjusted for total energy intake, regular aspirin or NSAID use, family history of colorectal cancer, total fat intake, and the OBS as well as supplemental calcium intake in total milk products and milk models and dietary calcium intake in total milk product and milk residual models.

We also conducted several sensitivity analyses. All analyses were repeated separately by study to analyze possible differences before and after US Food and Drug Administration (FDA) approval of bovine somatotropin (bST) use in conventional milk production in 1993 (22), which increases milk production through the growth hormone-IGF-1 axis (23). The CPRU study, which began in 1991, was analyzed independently of the two MAP studies, which began after 1993. We also considered potential confounding by the OBS components individually rather than combined into the OBS. Finally, we assessed designating

participants who reported taking supplemental calcium <2 years as non-supplemental calcium users.

The lowest category of each exposure variable was used as the referent category, and a test for trend was calculated using the sex-specific median of each category of the exposure variable. All statistical tests were conducted using SAS version 9.3 software (SAS Institute Inc., Cary, North Carolina). All tests were 2-sided, and a two-sided *P* value of <0.05 or a 95% confidence interval that did not contain 1.00 was considered statistically significant.

RESULTS

Selected characteristics of the study participants are presented in Table 1. Cases were more likely to be male, current smokers, and not regularly take an NSAID. On average, cases consumed greater total energy and total fat but less total calcium, particularly from supplemental calcium. Cases were also, on average, 4 years older and had a slightly higher BMI and WHR. Among the cases, 31% had multiple adenomas, 27% had at least one adenoma >1.0 cm in diameter, and the largest or most advanced adenoma was pedunculated in 22%, villous or tubulovillous in 23%, and in the right colon in 14%.

Dietary calcium intake was associated with a 14% lower risk of incident, sporadic colorectal adenomas upon comparison of the highest versus lowest quintiles of intake after multivariable adjustment, although the finding was not statistically significant (Table 2). The separate findings for total and supplemental calcium were closer to the null and not statistically significant.

The estimated associations of total milk products, total milk, or non-fat milk consumption with adenoma were slightly inverse and not statistically significant (Table 3). Consumption of any whole milk was associated with a non-statistically significant 15% higher risk for colorectal adenoma after multivariable adjustment. There was a suggestion of a U-shaped association of total milk product residuals with adenoma, with approximately 30–40% statistically significant lower risk among those in the third and fourth quintiles after multivariable adjustment, whereas the findings for non-fat milk residuals were null. We also assessed associations of milk products and milk product residuals separately for the CPRU and MAP studies (data not shown) to examine potential differences before and after the FDA approved bST use in 1993 (22), but there was little difference in the associations for adenoma risk by study period (early 1990s vs. late 1990s – early 2000s).

Possible differences in the associations of calcium and milk product intakes with adenoma according to various demographic, lifestyle, and dietary risk factors were also examined. Of particular interest was NSAID use, which may particularly strongly mask modest associations of dietary factors with colorectal neoplasms. Among those who did not regularly take NSAIDs, the estimated associations were slightly more inverse for total and dietary calcium, total milk products, total milk, non-fat milk, and total milk product residuals (Tables 2 and 3). There were no strong or consistent patterns to indicate effect modification by other demographic or lifestyle factors (data not shown).

We also examined whether the investigated associations differed according to adenoma characteristics. Based on the largest adenoma, total calcium was more strongly inversely associated with adenomas of more advanced characteristics (larger size, more dysplasia) or located in the distal colon (Table 4).

In sensitivity analyses, we found no evidence of important differences in our findings according to the separate CPRU and MAP studies, when the OBS components were included in the models individually rather than combined into the OBS, nor when we re-categorized participants who reported taking supplemental calcium for less than 2 years as non-supplemental calcium users.

We analyzed associations of calcium/magnesium and calcium/phosphorus ratios and of calcium according to magnesium and phosphorus intakes since some previous studies suggested that magnesium and phosphorus intakes may influence the effects of calcium by competing for absorption and transport (24, 25). Similarly, since calcium and vitamin D are closely metabolically linked, we repeated all analyses according to serum 25-hydroxyvitamin D₃ (25[OH]D₃) levels among those with available measures (n = 613 cases, 751 controls [we previously reported that serum 25(OH)D₃ levels were inversely associated with adenoma in this same pooled population(19)]). However, there were no strong, clear patterns or statistically significant findings observed in any of the associations (data not shown).

DISCUSSION

The results from this study, although mostly not statistically significant, are consistent with previous extensive literature that higher calcium intakes are associated with modestly lower risk for incident, sporadic colorectal adenoma. We found no evidence that milk product intake was associated with adenoma except for a suggestion of a U-shaped association with total milk product residuals. Also, we found no evidence that the results for milk product residuals differed among the studies conducted before and after bovine somatotropin approval.

Calcium is hypothesized to reduce risk for colorectal cancer and adenomas by binding with secondary bile acids and free fatty acids in the colon and subsequently reducing epithelial cell exposure to their damaging effects and lowering the risk for colorectal cancer and adenomas (26, 27). Additionally, calcium directly inhibits proliferation and induces differentiation of colonic epithelial cells (28, 29).

Inverse associations of calcium intake with colorectal cancer and adenomas were consistently reported in numerous epidemiologic studies. Of 46 observational studies of calcium and colorectal cancer (20 prospective cohort and 26 case-control studies), 35 (76%) found inverse associations, of which 13 were statistically significant. In addition, several meta-analyses reported on the calcium-colorectal cancer association (4, 30–32). From a recent pooled analysis of 17 cohort studies on total or dietary calcium intake in relation to incident colorectal cancer, a summary relative risk (RR) of 0.77 (95% CI 0.71–0.81) was reported (31). A pooled analysis of 13 case-control studies reported a similar summary OR

of 0.77 (95% CI 0.71–0.84), although there was substantial heterogeneity of unidentified source(s). The most recent meta-analysis of 15 cohort studies on total and dietary calcium intake reported a summary RR of 0.92 (95% CI 0.89–0.95) per 300 mg/day increase in calcium intake (4).

Fewer studies investigated the calcium-colorectal adenoma association but support the results of the colorectal cancer studies. Among 16 observational studies (6 prospective cohort and 10 case-control studies), 15 (94%) reported inverse associations, of which 4 were statistically significant. Additionally, in a meta-analysis of 7 prospective studies, a statistically significant 13% lower risk of adenomas was reported among those in the highest relative to the lowest levels of total calcium intake (33). In the same meta-analysis, 8 additional prospective studies were pooled in a dose-response analysis in which a statistically significant 5% lower risk of adenomas per 300 mg/day increase in total calcium intake was reported. Analysis of 3 of these 8 studies also yielded a statistically significant finding of 4% lower risk for adenoma per 300 mg/day increase in supplemental calcium intake. Although we found no substantial inverse association with total or supplemental calcium, we found dietary calcium intake to be modestly, inversely associated with adenomas.

Milk products are a major source of dietary calcium in the US. However, some milk products also contain a high percentage of total and saturated fat, which may offset calcium's potential protective effects. Although dietary fats stimulate bile acids release, epidemiological studies, in general, do not support the hypothesis that total fat intake increases colorectal cancer risk (34).

Due to the high calcium content of milk products, observational studies also examined associations of milk product intakes with colorectal cancer risk. We reviewed 56 observational studies (28 prospective cohort and 28 case-control studies) that included either total or specific milk products, with or without calcium. Of 23 studies that included total milk products, 19 (83%) reported inverse associations, with 6 being statistically significant. Of 36 studies that included milk, 24 (67%) reported inverse associations, with 8 being statistically significant. Several meta-analyses of milk products and colorectal cancer were also conducted (5, 6, 30, 31, 35, 36). In a recent meta-analysis of 15 cohorts, only non-fermented milk was statistically significantly inversely associated with colorectal cancer (summary RR 0.85, 95% CI 0.77–0.93) (6). In another recent meta-analysis of 12 studies, a statistically significant inverse association of total milk products with colorectal cancer was found (summary RR 0.81, 95% CI 0.74–0.90) (36). In the same meta-analysis, a dose-response analysis of 10 cohort studies yielded a statistically significant finding of a 17% lower risk of colorectal cancer per 400 g/day increase in milk product consumption.

Fewer studies examined milk product-adenoma associations, and to our knowledge, only one systematic review of milk product consumption and adenoma risk was reported (37). In this review of 11 case-control and 2 cohort studies, there was no association of milk product consumption with adenoma. Since this review, three additional observational studies of milk product-adenoma associations were reported, with only one finding an inverse association (38). This study of French women from the E3N-EPIC prospective cohort study included

1,933 participants who completed dietary questionnaires between 1993 and 1995 and were diagnosed with a colorectal polyp by December 1997. The RRs for total milk product and milk consumption were 0.80 (95% CI 0.62–1.05; $P_{trend}=0.04$) and 0.93 (95% CI 0.73–1.19; $P_{trend}=0.36$), respectively.

Consumption of milk products may increase circulating IGF-1 levels, as suggested by a recent meta-analysis. In this meta-analysis, 10 of 13 cross-sectional studies observed a statistically significant positive correlation between milk consumption and IGF-1, though only 3 of 12 studies reported statistically significant positive correlations with total milk products (11). A possible explanation for the stronger findings for milk than for total milk products is that the IGF-1 content of products other than fluid milk, such as yogurt, may decrease with storage and fermentation (39). It is biologically plausible that higher IGF-1 levels may be present in conventional milk products due to bST use, as statistically significantly higher IGF-1 levels were reported in conventional milk than in organic milk, although levels were not statistically significantly different from those in non-organic, bST-free labeled milk (10). The use of bST upregulates the insulin-like growth factor system to increase milk production, and subsequently increases cell proliferation, decreases differentiation, and inhibits apoptosis (40, 41). It is unclear whether milk IGF-1 is absorbed in humans, but radioactively labeled IGF-1 from milk was detected in the circulation of rats (13). Also, in a 7 day feeding study of young boys, milk, but not meat, statistically significantly increased serum IGF-1 and the molar ratio of IGF-1 to IGFBP-3 by 19% and 13%, respectively, though both resulted in similar increases in protein energy percentage (42).

Positive associations were reported between IGF-1 and risk for colorectal, breast, prostate, and liver cancers (43–50), and a pooled analysis of 16 prospective nested case-control and 3 case-control studies reported a statistically significant 25% higher risk for colorectal cancer among those in the highest categories of circulating IGF-1 (51). Although milk products and IGF-1 may be independently associated with colorectal cancer risk, to our knowledge, only one study included milk intake in their analyses of IGF-1 and colorectal cancer. In this nested case-control study of 596 colorectal cancer cases, IGF-1 was positively but not statistically significantly associated with colorectal cancer upon comparison of the highest to lowest IGF-1 quintiles (OR 1.11, 95% CI 0.83–1.48) (52). However, within the lowest category of milk intake, there was a statistically significant higher risk for colorectal cancer (OR 1.43, 95% CI 1.10–1.85) per 100 ng/mL IGF-1 increase.

Although we found no evidence of an association of milk products with adenoma, our findings for our estimated total milk product residuals, which may indirectly measure other milk product components such as fat, sugars, and IGF-1, were unexpectedly U-shaped, even after adjusting for total and saturated fat. The potential reasons for this finding are unclear, but include a beneficial effect of some known component for which the plausibility is unknown, an unrecognized component of milk, or, especially given the generally low intake of milk products in this study population, chance. The inverse association of non-fat milk but the null association of non-fat milk residuals with adenoma suggests that the non-fat, non-calcium component of milk, which contains IGF-1, may not be associated with colorectal adenoma risk. However, the use of residuals as a possible indirect measure of the non-

calcium/non-fat, IGF-1-containing component of milk products is a novel approach that adds to the limited evidence on milk products and, possibly, IGF-1 and colorectal adenoma risk.

Because regular aspirin and other NSAID use has been strongly and consistently inversely associated with risk for colorectal neoplasia (53–56), we assessed whether regular use of these medications may have masked associations of calcium and milk products. We observed stronger inverse associations for total and dietary calcium, total milk products, total milk, and non-fat milk. In our review of previous studies on calcium and risk for colorectal cancer, only 7 stratified by regular aspirin and/or NSAID use. Of those, 4 reported stronger inverse associations between calcium intake and colorectal cancer or adenoma among regular users of aspirin and/or NSAIDs (57–60), 2 reported stronger inverse associations among those who did not take NSAIDs (17, 61), and 1 reported no difference in association (62). Taken together, these studies provide no consistent evidence that regular NSAID use so overwhelms any protective effect of calcium that a calcium-colorectal neoplasm association is undetectable among those who regularly take NSAIDs.

Although we found no evidence of confounding by or interactions with magnesium, vitamin D, or phosphorus, these nutrients were previously independently inversely associated with colorectal neoplasia, similar to calcium. Magnesium is involved in DNA synthesis, cell proliferation and apoptosis, and defenses against oxidative stress, which may influence colorectal carcinogenesis (63). Though studied less extensively than calcium, a meta-analysis of 8 prospective studies reported 11% lower risk for colorectal cancer (RR 0.89, 95% CI 0.79–1.00) for those in the highest to lowest categories of magnesium intake (64). However, magnesium may be antagonistic to calcium and compete for the same binding sites on plasma proteins (65), although clinical trials reported conflicting evidence (66, 67). Several observational studies analyzed the calcium/magnesium ratio and calcium intakes stratified by magnesium levels to account for this potential interaction, but the findings were inconsistent (24, 68, 69). Vitamin D has been more consistently inversely associated with colorectal neoplasms, with proposed mechanisms involving detoxification of secondary bile acids, direct effects on the cell cycle, growth factor signaling, and immunomodulation (70–73). A recent meta-analysis reported inverse associations of circulating 25(OH)D and dietary vitamin D intake with incident and recurrent colorectal adenomas (74). However, there is limited evidence on a possible combined effect of vitamin D and calcium on risk for colorectal neoplasia. Two large cohort studies reported positive interactions between calcium and vitamin D (75, 76), although a separate analysis of the Nurses' Health Study revealed no significant interaction (59). In a large randomized trial, calcium supplementation reduced colorectal adenoma recurrence (RR 0.71, 95% CI 0.57–0.89) only among those with baseline 25(OH)D levels above the median (77). Further evidence from studies of biomarkers of risk for colorectal cancer supports that calcium and vitamin D, separately and in combination, reduces cell proliferation, induces differentiation, and promotes apoptosis (78, 79). Last, phosphorus has been studied in context with calcium because of its hypothesized antagonistic effects in reducing intestinal absorption of calcium (80), and similar to our findings, there was no evidence of a calcium-phosphorus interaction in relation to colorectal neoplasms (24, 81, 82).

Our study had several limitations and strengths. First, few participants consumed supplemental calcium or whole milk. Second, we assumed that participants consumed conventional milk since data on whether the milk products they consumed was conventional or organic were not collected. It may be important to include this distinction on future dietary questionnaires. Additional limitations of this study included the general limitations of case-control studies (e.g., inability to assess temporality) and food frequency questionnaires (e.g., measurement error). Further, most study participants were white and more likely to be recommended for routine colonoscopy, thus limiting the generalizability of our findings. Finally, although a strength of the study was that our estimated total milk product and non-fat milk residual variables were fully adjusted for dietary calcium, further research is needed on the use of such residuals to estimate the non-calcium component of milk, in general, and the IGF-1 exposure from milk, in particular. Although the results did not support our hypothesis, to our knowledge, the method of using these residuals as a potential estimate of the non-calcium, non-fat, and IGF-1-containing component of milk products is novel. Additional strengths of this study included the comprehensive analysis of total, dietary, and supplemental calcium intake as well as total and specific milk product consumption.

Overall, in this pooled case-control study, our findings of a modestly lower risk for colorectal adenoma with higher intakes of calcium are consistent with those of previous studies. We introduced a novel method of potentially estimating the non-calcium, non-fat component of milk products, which contains IGF-1, and contrary to our hypotheses, found a statistically significant U-shaped association of this indirect measure of other milk components with adenomas. This latter finding, which may have been due to chance, should be assessed in future studies.

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Table 1.

Selected Characteristics of Participants in Pooled Case-Control Study of Incident, Sporadic Colorectal Adenomas^a

	Cases (n = 787)	Controls (n = 2,033)	P value
<i>Demographics</i>			
Age (years)	58.1 (9.2)	54.5 (10.9)	<0.0001
Male, %	61.3	43.0	<0.0001
White, %	94.7	96.3	0.05
Family history, % ^b	16.9	17.7	0.62
<i>Lifestyle Factors</i>			
College education or higher, %	28.5	31.8	0.10
Current smoker, %	24.2	14.1	<0.0001
Current drinker, 1–6 drinks/week, %	22.8	20.9	<0.0001
Body mass index (kg/m ²)	27.5 (5.2)	26.8 (5.0)	0.001
Waist-to-hip ratio	0.93 (0.16)	0.88 (0.15)	<0.0001
Physical activity (MET-hrs/week)	37.4 (39.4)	35.9 (34.9)	0.42
Take NSAID/aspirin, % ^c	35.4	41.3	0.004
HRT use (% females)	35.5	37.4	0.56
<i>Dietary Factors</i>			
Total energy (kcal/day)	2,069 (767)	1,985 (713)	0.01
Total fat (% total kcals)	46.4 (29.0)	35.7 (19.9)	<0.0001
Dietary fiber (g/day)	21.8 (9.4)	21.9 (10.0)	0.71
Total calcium (mg/day)	913.2 (509.5)	971.4 (523.4)	0.01
Dietary calcium	808.3 (431.3)	821.5 (433.2)	0.47
Supplemental calcium	94.8 (272.8)	129.9 (314.6)	0.003
Total magnesium (mg/day)	322.3 (120.4)	324.2 (125.2)	0.70
Total milk product (servings/day)	2.5 (1.8)	2.4 (1.8)	0.89
High fat dairy	1.4 (1.5)	1.3 (1.4)	0.08
Low fat dairy	1.1 (1.2)	1.2 (1.2)	0.05
Cheese	0.6 (0.7)	0.6 (0.6)	0.82
Fermented dairy	0.7 (0.8)	0.8 (0.7)	0.06
Total milk	0.9 (1.1)	1.0 (1.1)	0.37
Whole milk	0.1 (0.3)	0.1 (0.3)	0.27
Non-fat milk	0.9 (1.0)	0.9 (1.1)	0.22
Total fruit (servings/day)	2.3 (1.8)	2.6 (1.9)	0.0002
Total vegetable (servings/day)	3.7 (2.3)	3.7 (2.4)	0.62
Total meat (servings/day)	1.9 (1.3)	1.7 (1.1)	0.0001
Red meat	0.7 (0.5)	0.6 (0.5)	0.01
Processed meat	0.4 (0.5)	0.3 (0.4)	<0.0001

Abbreviations: MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drug; HRT, hormone replacement therapy.

^aValues presented are mean (standard deviation) unless otherwise specified.

^bFamily history of colorectal cancer in a first-degree relative.

^cRegularly take aspirin or NSAID once per week.

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Table 2.

Multivariable-adjusted Associations of Calcium Intake with Incident, Sporadic Colorectal Adenomas

Quintiles	No. of Cases/ Controls (n=787/ 2,033)	Among Non-Regular Users of Aspirin and NSAIDs						
		Initial Model ^a		Full Model ^b		No. of Cases/ Controls (n=508/ 1,187)	Full Model ^c	
		OR	95% CI	OR	95% CI		OR	95% CI
Total Calcium								
1	164/405	1.00 (ref)		1.00 (ref)		122/249	1.00 (ref)	
2	164/407	0.96	0.74, 1.26	0.98	0.74, 1.29	104/238	0.88	0.63, 1.24
3	167/409	1.00	0.77, 1.30	1.00	0.75, 1.33	106/234	0.93	0.65, 1.32
4	132/406	0.76	0.58, 1.01	0.75	0.55, 1.02	78/244	0.64	0.44, 0.93
5	160/406	0.94	0.72, 1.23	0.94	0.69, 1.30	98/222	0.91	0.61, 1.35
<i>P_{trend}</i> ^d		0.27		0.43			0.38	
Dietary Calcium								
1	167/404	1.00 (ref)		1.00 (ref)		124/243	1.00 (ref)	
2	152/408	0.89	0.68, 1.16	0.90	0.68, 1.19	91/228	0.75	0.53, 1.07
3	161/409	0.94	0.72, 1.23	0.92	0.69, 1.23	105/242	0.82	0.58, 1.17
4	148/407	0.90	0.68, 1.18	0.87	0.64, 1.17	89/234	0.75	0.51, 1.09
5	159/405	0.95	0.73, 1.25	0.86	0.62, 1.20	99/240	0.77	0.51, 1.17
<i>P_{trend}</i> ^d		0.88		0.62			0.35	
Supplemental Calcium ^e								
1	580/1,419	1.00 (ref)		1.00 (ref)		387/888	1.00 (ref)	
2	94/286	0.82	0.63, 1.06	0.86	0.65, 1.12	57/137	0.97	0.69, 1.38
3	113/328	0.86	0.67, 1.10	0.99	0.77, 1.27	64/162	1.02	0.73, 1.42
<i>P_{trend}</i> ^d		0.15		0.79			0.97	

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval.

^aAdjusted for study, age, and sex.^bAdjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted).^cAmong non-regular users of aspirin and NSAIDs, adjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, total energy intake, total fat intake (energy-adjusted).^d*P_{trend}* calculated using sex-specific median of each quintile (for total and dietary calcium) or tertile (for supplemental) of calcium intake as a continuous variable.^eSupplemental calcium intake categorized as three groups (none and according to the median dose among those who did take supplemental calcium) due to small sample size.

Table 3.

Multivariable-adjusted Associations of Milk Product Consumption with Incident, Sporadic Colorectal Adenomas

Quintiles	No. of Cases/ Controls	Among Non-Regular Users of Aspirin and NSAIDs						
		Initial Model ^a		Full Model ^{b,c}		No. of Cases/ Controls	Full Model ^{d,e}	
		OR	95% CI	OR	95% CI		OR	95% CI
	(n=787/ 2,033)					(n=508/ 1,187)		
Total Milk Products								
1	148/392	1.00 (ref)		1.00 (ref)		109/228	1.00 (ref)	
2	173/420	1.06	0.81, 1.38	1.02	0.78, 1.35	114/256	0.88	0.63, 1.22
3	145/393	1.04	0.79, 1.38	1.01	0.76, 1.35	93/213	0.93	0.65, 1.33
4	153/414	0.97	0.74, 1.28	0.94	0.71, 1.25	89/244	0.74	0.52, 1.06
5	168/414	1.11	0.85, 1.46	0.99	0.74, 1.34	103/246	0.84	0.58, 1.22
P_{trend}^f		0.63		0.84			0.27	
Total Milk								
1	140/366	1.00 (ref)		1.00 (ref)		97/217	1.00 (ref)	
2	84/258	1.01	0.73, 1.40	1.00	0.71, 1.39	48/162	0.73	0.48, 1.11
3	238/596	1.07	0.82, 1.38	1.06	0.82, 1.38	162/343	1.02	0.74, 1.40
4	152/329	1.07	0.79, 1.44	1.06	0.78, 1.45	87/163	1.12	0.76, 1.66
5	173/484	0.95	0.73, 1.25	0.90	0.68, 1.19	114/302	0.85	0.60, 1.20
P_{trend}^f		0.47		0.32			0.64	
Whole Milk^g								
1	661/1,818	1.00 (ref)		1.00 (ref)		434/1,050	1.00 (ref)	
2	126/215	1.26	0.96, 1.62	1.15	0.89, 1.49	74/137	1.01	0.73, 1.40
Non-fat Milk								
1	183/417	1.00 (ref)		1.00 (ref)		125/247	1.00 (ref)	
2	81/220	1.03	0.75, 1.43	1.07	0.77, 1.48	51/141	0.88	0.59, 1.32
3	117/337	1.08	0.81, 1.45	1.14	0.85, 1.53	75/194	0.99	0.69, 1.43
4	205/558	0.95	0.74, 1.21	0.99	0.77, 1.28	136/301	1.02	0.75, 1.41
5	201/501	0.92	0.72, 1.18	0.92	0.70, 1.19	121/304	0.83	0.60, 1.15
P_{trend}^f		0.48		0.33			0.31	
Total Milk Product Residuals								
1	177/402	1.00 (ref)		1.00 (ref)		111/227	1.00 (ref)	
2	167/408	0.92	0.71, 1.20	0.84	0.63, 1.11	120/238	0.83	0.58, 1.17
3	126/408	0.70	0.53, 0.92	0.61	0.45, 0.82	89/242	0.55	0.37, 0.80
4	130/409	0.74	0.56, 0.98	0.67	0.50, 0.90	81/234	0.58	0.40, 0.85
5	187/406	1.09	0.84, 1.42	0.94	0.71, 1.24	107/246	0.71	0.50, 1.02
P_{trend}^f		0.40		0.98			0.10	
Non-fat Milk Residuals								
1	154/401	1.00 (ref)		1.00 (ref)		88/235	1.00 (ref)	

Quintiles	No. of Cases/ Controls (n=787/ 2,033)	Among Non-Regular Users of Aspirin and NSAIDs						
		Initial Model ^a		Full Model ^{b,c}		No. of Cases/ Controls (n=508/ 1,187)	Full Model ^{d,e}	
		OR	95% CI	OR	95% CI		OR	95% CI
2	141/408	0.83	0.63, 1.10	0.86	0.64, 1.15	86/226	0.87	0.60, 1.27
3	177/408	1.09	0.84, 1.43	1.15	0.86, 1.55	123/232	1.42	0.98, 2.06
4	154/408	0.93	0.71, 1.22	0.96	0.70, 1.31	105/256	1.02	0.69, 1.50
5	161/408	0.92	0.70, 1.21	0.95	0.69, 1.31	106/238	1.06	0.71, 1.59
P_{trend}^f		0.69		0.69			0.76	

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval.

^aAdjusted for study, age, and sex.

^bFor Total Milk Products, Total Milk, Whole Milk, and Non-fat Milk, adjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted), supplemental calcium intake.

^cFor Total Milk Product Residuals and Non-fat Milk Residuals, adjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted), dietary calcium intake.

^dFor non-regular users of aspirin and NSAIDs in Total Milk Products, Total Milk, Whole Milk, and Non-fat Milk models, adjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, total energy intake, total fat intake (energy-adjusted), supplemental calcium intake.

^eFor non-regular users of aspirin and NSAIDs in Total Milk Product Residuals and Non-fat Milk Residuals models, adjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, total energy intake, total fat intake (energy-adjusted), dietary calcium intake.

^f P_{trend} calculated using sex-specific median of each quintile of calcium intake as a continuous variable.

^gWhole milk consumption categorized as dichotomous due to small sample size.

Table 4.

Multivariable-adjusted Associations of Total Calcium with Incident, Sporadic Colorectal Adenomas by Characteristics of the Largest Adenoma.

		Full Model ^a					
	Quintiles	No. of Cases/ Controls	OR	95% CI	No. of Cases/ Controls	OR	95% CI
Atypia		Mild				More Severe	
	1	86/406	1.00 (ref)		90/406	1.00 (ref)	
	2	96/407	1.11	0.79, 1.57	83/407	0.94	0.66, 1.33
	3	88/407	1.05	0.72, 1.51	57/407	0.64	0.43, 0.95
	4	63/407	0.75	0.51, 1.12	65/407	0.70	0.47, 1.04
	5	83/406	1.05	0.70, 1.57	62/406	0.68	0.44, 1.05
Location		Proximal ^b				Distal ^c	
	1	22/406	1.00 (ref)		154/406	1.00 (ref)	
	2	34/407	1.54	0.86, 2.76	143/407	0.93	0.70, 1.24
	3	25/407	1.16	0.61, 2.21	120/407	0.58	0.58, 1.07
	4	23/407	1.02	0.53, 1.99	104/407	0.67	0.49, 0.93
	5	21/406	1.07	0.52, 2.21	123/406	0.81	0.58, 1.13
Shape		Pedunculated				Sessile	
	1	55/406	1.00 (ref)		94/406	1.00 (ref)	
	2	43/407	0.75	0.48, 1.18	107/407	1.12	0.80, 1.57
	3	38/407	0.66	0.41, 1.08	84/407	0.91	0.63, 1.31
	4	32/407	0.55	0.33, 0.92	70/407	0.77	0.52, 1.12
	5	28/406	0.47	0.27, 0.84	88/406	1.01	0.68, 1.49
Size		< 1 cm				1 cm	
	1	116/406	1.00 (ref)		65/406	1.00 (ref)	
	2	123/407	1.11	0.81, 1.51	59/407	0.88	0.59, 1.32
	3	107/407	0.97	0.70, 1.36	42/407	0.65	0.41, 1.02
	4	84/407	0.77	0.54, 1.09	45/407	0.68	0.43, 1.07
	5	108/406	1.05	0.73, 1.51	38/406	0.57	0.34, 0.95
Subtype		Tubular				Villous/Tubulovillous	
	1	129/406	1.00 (ref)		46/406	1.00 (ref)	
	2	135/407	1.07	0.79, 1.45	43/407	0.91	0.57, 1.45
	3	103/407	0.84	0.61, 1.17	41/407	0.84	0.51, 1.37
	4	88/407	0.73	0.52, 1.03	40/407	0.79	0.48, 1.30
	5	113/406	0.97	0.68, 1.39	32/406	0.61	0.34, 1.08

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

^aAdjusted for study, age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fat intake (energy-adjusted).

^bCecum, ascending colon, hepatic flexure

^cTransverse colon, splenic flexure, descending colon, sigmoid colon, rectum