Calcium Intake and Risk of Colon Cancer in Women and Men

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Background: **Calcium has been hypothesized to reduce the risk of colon cancer, and in a recent randomized trial, calcium supplementation was associated with reduction in the risk of recurrent colorectal adenomas. We examined the association between calcium intake and colon cancer risk in two prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).** ***Methods:*** **Our study population included 87 998 women in NHS and 47 344 men in HPFS who, at baseline (1980 for NHS and 1986 for HPFS), completed a food frequency questionnaire and provided information on medical history and lifestyle factors. Dietary information was updated at least every 4 years. During the follow-up period (1980 to May 31, 1996 for the NHS cohort; 1986 to January 31, 1996 for the HPFS cohort), 626 and 399 colon cancer cases were identified in women and men, respectively. Pooled logistic regression was used to estimate relative risks (RRs), and all statistical tests were two-sided.** ***Results:*** **In women and men considered together, we found an inverse association between higher total calcium intake (>1250 mg/day versus ⩽500 mg/day) and distal colon cancer (women: multivariate RR = 0.73, 95% confidence interval [CI] = 0.41 to 1.27; men: RR = 0.58, 95% CI = 0.32 to 1.05; pooled RR = 0.65, 95% CI = 0.43 to 0.98). No such association was found for proximal colon cancer (women: RR = 1.28, 95% CI = 0.75 to 2.16; men: RR = 0.92, 95% CI = 0.45 to 1.87; pooled RR = 1.14, 95% CI = 0.72 to 1.81). The incremental benefit of additional calcium intake beyond approximately 700 mg/day appeared to be minimal.** ***Conclusions:*** **Higher calcium intake is associated with a reduced risk of distal colon cancer. The observed risk pattern was consistent with a threshold effect, suggesting that calcium intake beyond moderate levels may not be associated with a further risk reduction. Future investigations on this association should concentrate on specific cancer subsites and on the dose–response relationship. [J Natl Cancer Inst 2002;94: 437–46]**

Animal studies have suggested that calcium may be involved in the etiology of colon cancer *(1–5).* Calcium can bind secondary bile acids and ionized fatty acids, which can promote epithelial cell proliferation in the colon *(6–8);* calcium may also directly decrease epithelial cell proliferation *(9).*

Results from epidemiologic studies are inconsistent. Although some studies do not support a benefit *(10–13),* the majority of studies have found a weak but statistically nonsignificant inverse association between high calcium intake and risk of colorectal or colon cancer *(14–19).* In two male prospective cohorts, the Western Electric Study and the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, higher calcium intake was statistically significantly associated with lower risk of colorectal cancer *(20,21).* Lack of repeated dietary measurements in most observational studies, possibly resulting in misclassification of long-term nutrient intake, may have contributed to these inconsistent results.

Randomized trials *(22–27)* conducted to assess the relationship between supplemental calcium intake and recurrence of colorectal adenomas, which are precursors for colorectal cancers, or other biomarkers, such as fecal bile acid concentrations or colorectal mucosal cell proliferation, have also yielded inconsistent results. In recently published results from a randomized clinical trial, the Calcium Polyp Prevention Study *(27),* daily supplementation with 1200 mg of calcium resulted in a statistically significant 20% decreased risk of recurrent colorectal adenomas. Because only one relatively high dose was examined, the dose–response relationship could not be established from this study. Because the relationship between surrogate markers and the ultimate endpoint is complex and only a small propor-

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See "Notes" following "References."

tion of colon adenomas progress to cancer *(28),* establishing the association between calcium intake and colon cancer remains important.

We had previously investigated the association between calcium intake and risk of colorectal cancer in two large cohorts of U.S. women and men—the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), respectively. Consistent with most other epidemiologic studies *(15,17–19,29),* we found a modest inverse, but not statistically significant, association between calcium intake and risk of colorectal *(16)* and colon cancer *(14).* However, these studies had insufficient power to exclude effects of the magnitude suggested by the recent randomized trial *(27).* The extended follow-up and better assessment of long-term diet through multiple dietary assessments in these two cohorts allowed us to increase the statistical power to examine moderate associations, to assess dietary and supplemental calcium separately, to define the dose–response relationships, to examine risk by subsites within the colon, and to investigate whether other factors modified the relationship between calcium and colon cancer risk.

Subjects and Methods

NHS Cohort

In 1976, 121 700 registered U.S. nurses from 30 to 55 years of age were mailed a questionnaire requesting information on various exposures and medical diagnoses *(30).* Follow-up questionnaires were mailed to the participants every 2 years to update this information. A 61-item semiquantitative food frequency questionnaire was included in the 1980 mailing, and 98 462 women returned this questionnaire. Food frequency questionnaires containing 121–136 items were also incorporated into the 1984, 1986, 1990, and 1994 follow-up questionnaires. Overall follow-up rates have been very high. Up to 1996, the follow-up as a percentage of potential person-years was 98% complete. This study was approved by the Human Research Committee at the Brigham and Women's Hospital (Boston, MA).

HPFS Cohort

In 1986, 51 129 U.S. male dentists, podiatrists, pharmacists, optometrists, osteopaths, and veterinarians, from 40 to 75 years of age, were mailed a questionnaire *(31).* As in the NHS, information on medical history and exposure has been updated by biennial follow-up questionnaires. In 1986, participants were also requested to complete a 131-item semiquantitative food frequency questionnaire. Participants were also mailed a food frequency questionnaire in 1990 and 1994. Up to 1996, the follow-up as a percentage of potential person-years was 97% complete. This study was approved by the Harvard School of Public Health Human Subjects Committee.

Assessment of Nutrient Intake

The food frequency questionnaires inquired about the average frequency of consumption of selected foods and beverages during the past year. Participants chose from nine possible answers ranging from never or less than one serving per month to six or more servings per day. We computed nutrient intakes by multiplying the frequency of consumption of a specific food or beverage item by its nutrient content and then summed the contributions from all foods and beverages. Nutrient intakes were energy adjusted using the residuals method *(32).*

Calcium intake from dairy sources alone was calculated by summing the contributions of all dairy products and food items containing dairy products, such as mashed potatoes (milk), clam chowder (milk), or pizza (cheese) (*see* Appendix I). Calcium intake from nondairy sources was computed by subtracting calculated dairy calcium intake from total dietary calcium intake. Total milk intake was calculated as the sum of intake of skim milk, whole milk, and 1%–2% milk (skim milk and 1%–2% milk were combined into one question before the 1994 questionnaire), and total intake of fermented milk products was computed by summing the intake of sour cream, yogurt, and cheese intake for each participant.

On each biennial questionnaire (except for the 1980 NHS questionnaire), participants were also asked to provide information on their current use and dosage of calcium supplements (<400 mg/day, 400–900 mg/day, 901–1300 mg/day, and ⩾1301 mg/day). Participants who did not respond to one or more of the follow-up questionnaires were assigned the information from the most recently completed questionnaire. Current calcium supplement users who did not supply information on dosage of calcium supplementation were assigned to the 400–900 mg/day category, the category with the highest frequency among current calcium supplement users.

The reproducibility and validity of the food frequency questionnaires administered in the NHS and HPFS cohorts have been described previously *(33–36).* Pearson correlation coefficients between calcium intake computed from the food frequency questionnaires and average intake of two 1-week diet records of 127 men was 0.53 for calcium both with and without supplements *(35);* for 191 women, the correlation coefficients for calcium were 0.63 with and 0.70 without supplements (Sampson L: personal communication). Overall, there was a good correlation between calcium intake from the food frequency questionnaires and the dietary records of both women and men. The difference in the correlation between women and men was compatible with statistical variability because of the relatively small sample size.

Exclusion of Participants at Baseline

Participants without a completed food frequency questionnaire at baseline (i.e., 1980 for NHS cohort, 1986 for HPFS cohort) or participants with unreasonably high (>3500 calories/day for women; >4200 calories/day for men) or low intakes (<600 calories/day for women; <800 calories/day for men) and those who had left a large number of items blank (>10 items for women; >70 items for men) were excluded from the analysis. We also excluded participants with a history of ulcerative colitis or previous cancer (except for nonmelanoma skin cancer). This left us with 87 998 women and 47 344 men for follow-up (1980 to May 31, 1996 for the NHS cohort; 1986 to January 31, 1996 for the HPFS cohort).

Case and Death Ascertainment

We asked participants who had reported a diagnosis of colon or rectal cancer on the follow-up questionnaires for permission to obtain and evaluate their hospital and pathology reports. Those reports were reviewed by physicians, who extracted information on histology, anatomic location, and stage of cancer. Only primary adenocarcinomas were included in our analysis.

Between 1980 and May 31, 1996, 529 incident female colon cancer cases were identified; between 1986 and January 31, 1996, 313 male colon cancers were identified. All female and

male colon cancer cases were confirmed by medical records. Because the vast majority of colorectal cancer cases are colon cancer cases, we also included 97 female and 86 male colorectal cancer cases with missing information on anatomic site in our analysis, yielding a total of 626 female and 399 male cancer cases for the analysis. These additional cases were confirmed by medical records, by autopsy or death reports, or by reconfirming the self-reported diagnosis from the participants. Exclusion of these cases yielded similar results. Colon cancers located in the cecum, ascending colon, or transverse colon were considered proximal (right-sided) colon cancers, whereas those located in the descending or sigmoid colon were considered distal (left-sided) colon cancers.

The National Death Index or reports from family members were used to ascertain death among participants. We also requested permission to obtain and evaluate medical records from next of kin of participants who had died of cancer and had not already been recorded in our database.

Statistical Analysis

Starting from the month the baseline questionnaire was returned, each participant contributed follow-up time until the month in which cancer was diagnosed, the date of death, or if they were noncases (alive and not diagnosed with colorectal cancer), the end of the study period (May 31, 1996 for the NHS cohort; January 31, 1996 for the HPFS cohort), whichever came first. Incidence rates were calculated by dividing the number of incident colon cancer cases by the number of total person-years.

We adjusted relative risks [RR] for potential confounders by implementing the Mantel–Haenzel estimator *(37)* and pooled logistic regression *(38,39).* Data from each cohort were first analyzed separately and then, when appropriate, RRs were pooled by the use of a method described by DerSimonian and Laird *(40).* Categories of calcium intake were based on increments of 100 mg/day calcium; above 800 mg the increments were 801–1000 mg/day and 1001–1250 mg/day. The upper cut point depended on the range of intake and thus was lower for dairy calcium compared with total calcium. Smaller increments (i.e., 25–50 mg/day) were used for nondairy calcium because of the limited distribution. All categories were defined *a priori.* The basic multivariate model included known and suspected nondietary risk factors (age, family history, body mass index, physical activity, pack-years of smoking before age 30, and aspirin use) as well as red meat and alcohol consumption. Potential confounding effects of single nutrients were examined separately because many dietary variables are strongly correlated. Having several correlated nutrients as well as their interactions together in one multivariate model would have resulted in multicolinearity and, thus, less reliable estimates. However, the nutrients such as total fat, fiber, iron, methionine, folate, vitamin D, vitamin E, vitamin C, total vitamin A, or carotene intake as well as multivitamin use, when added separately to the basic multivariate models, did not change the overall results and were therefore not added to the final models. In addition, potential confounding of endoscopy was also examined. Trend tests were conducted by using median intake of the defined calcium categories as exposure scores. All P values are two-sided.

To evaluate long-term nutrient intake, we used the repeated dietary information from the baseline and all follow-up food frequency questionnaires (i.e., NHS: 1980, 1984, 1986, 1990, and 1994; HPFS: 1986, 1990, and 1994) and computed a cumulative average nutrient intake, which is the average of all available nutrient intakes for a participant up to the beginning of each follow-up cycle *(41).*

On the 1980 questionnaire, women were also asked to report whether they had changed their milk intake considerably over the past 10 years. Because consistency in milk intake over time may be a good indicator for consistent calcium intake, we also investigated associations between calcium intake and colon cancer risk after exclusion of women with a change in milk intake. In men, the baseline questionnaire did not include a comparable question on changes in overall milk intake.

Results

Baseline characteristics for both cohorts by categories of total calcium intake are shown in Table 1. Most baseline characteristics did not differ appreciably by categories of total calcium intake. However, participants with higher calcium intake were less likely to be smokers and had higher intakes of vitamin C, vitamin E, carotene, phosphorus, and total fiber and lower intake of red meat. The participants with higher calcium intake were also more likely to be multivitamin supplement users and aspirin users.

The percentage of women who were using calcium supplements increased from 24% in 1984 (information on calcium supplementation was not obtained in the 1980 baseline questionnaire) to 41% in 1994. In men, the percentage of calcium supplement users did not change considerably over time; in 1986, 16% and in 1994, 14% of all men reported current calcium supplement use. Dairy products or food items containing dairy products (*see* Appendix I) contributed most to dietary calcium, 61% in women (1984 food frequency questionnaire) and 58% in men (1986 food frequency questionnaire). In both cohorts, calcium intake from nondairy sources was relatively low. For example, in the NHS (1984 food frequency questionnaire), the 90th percentile of calcium intake from nondairy sources was 336 mg/day, whereas from dairy sources it was 766 mg/day; in the HPFS (1986 food frequency questionnaire), the 90th percentile of calcium intake from nondairy sources was 377 mg/day, whereas from dairy sources it was 858 mg/day.

Table 2 shows multivariate-adjusted RR by category of cumulative average calcium intake in both cohorts. Multivariate adjustment did not substantially alter the age-adjusted estimates. In men, associations were similar for total, dietary, and dairy calcium. In men, total and dietary calcium intake above the second lowest category (>601–700 mg/day) was associated with an approximately 30% lower risk of colon cancer. In women, there was no appreciable association between cumulative updated calcium intake and colon cancer. In both cohorts, no evidence for an inverse association between higher intake of nondairy calcium (after exclusion of calcium supplement users) and colon cancer risk was found. There was also no association between nondairy calcium and colon cancer risk among participants with low (<500 mg/day) or among those with high ($\geq$500 mg/day) dairy calcium intake (data not shown).

When we examined calcium intake at baseline (i.e., in 1980 for women and in 1986 for men) without updating dietary information, associations between calcium intake and colon cancer risk were similar in men. However, in women, inverse associations between dietary calcium intake at baseline and colon cancer risk were slightly stronger than those observed for the cu-

Table 1. Baseline characteristics by categories of total calcium intake: Nurses' Health Study (1980–1996) and Health Professionals Follow-up Study (1986–1996)

	Total calcium intake, mg						
	<500	501–600	601–700	701–800	801–1000	1001–1250	>1250
Nurses' Health Study							
Characteristics*							
No. participants	20 599	13 457	13 173	10 945	14 608	9580	5636
Mean age, y	46.3	46.6	46.7	46.8	46.7	46.7	47.1
Current smokers, %	33.5	29.8	27.4	27.7	26.5	26.1	26.0
Aspirin users, %	32.5	34.1	33.8	33.0	32.8	31.4	30.8
Family history, %	8.0	7.7	7.7	7.8	7.9	8.0	7.6
Previous polyps, %	0.7	0.9	0.9	0.9	0.8	0.9	1.1
Previous endoscopy, %	9.6	9.7	9.6	10.0	9.8	10.4	10.1
Postmenopausal, %	33.4	32.9	32.8	32.7	32.6	32.8	33.7
Mean BMI, kg/m^2	24.4	24.4	24.4	24.4	24.5	24.5	24.7
Current multivitamin supplementation, %	27.3	30.7	32.9	35.2	38.0	40.9	46.2
Mean daily intake†							
Calories, kcal	1573	1570	1554	1536	1563	1599	1562
Calcium, mg	397	552	650	749	890	1110	1502
Vitamin D, IU	174	222	253	292	344	424	619
Total fat, g	74.4	72.2	70.8	68.8	66.9	64.8	61.3
Phosphorus, mg	921	1026	1095	1164	1263	1417	1669
Folate, mcg	293	337	352	379	400	419	521
Methionine, g	1.7	1.8	1.8	1.9	1.9	2.1	2.2
Alcohol, g	8.2	7.0	6.4	5.9	5.5	4.7	3.7
Vitamin E, IU	52.5	59.4	60.9	67.8	78.8	82.6	117
Vitamin C, mg	246	272	281	310	342	366	450
Total carotene, mcg	6450	7615	8155	8624	9100	9101	9485
Total fiber, g	12.3	13.5	14.0	14.4	14.6	14.3	14.0
Beef as main dish, servings/day	0.5	0.4	0.4	0.3	0.3	0.3	0.2
Health Professionals Follow-up Study							
Characteristics							
No. participants	4714	6090	7047	6678	8916	6413	7486
Mean age, y	54.0	54.0	53.7	54.1	54.4	54.6	55.9
Current smokers, %	14.2	11.1	10.0	9.3	8.1	8.9	7.9
Aspirin users, %	26.4	27.4	28.3	29.5	30.0	31.2	31.3
Family history, %	9.3	8.3	8.5	7.9	8.2	8.4	8.5
Previous polyps, %	4.0	4.0	3.4	3.4	3.3	3.5	3.5
Previous endoscopy, %	23.6	24.1	25.4	26.3	26.4	26.5	27.0
Postmenopausal, %	NA	NA	NA	NA	NA	NA	NA
Mean BMI, kg/m^2	25.5	25.7	25.7	25.6	25.5	25.4	25.4
Current multivitamin supplementation, %	27.2	30.1	33.9	39.0	43.3	50.0	60.5
Mean daily intake†							
Calories, kcal	1924	1981	2004	1983	1958	2104	1941
Calcium, mg	432	554	651	749	889	1118	1655
Vitamin D, IU	193	231	265	314	368	460	626
Total fat, g	73.4	73.5	72.7	71.7	70.2	70.5	68.4
Phosphorus, mg	1133	1219	1285	1351	1428	1527	1696
Folate, mcg	354	401	432	462	497	529	626
Methionine, g	2.1	2.1	2.1	2.2	2.2	2.2	2.3
Alcohol, g	17.6	13.9	12.6	10.8	9.6	9.8	8.0
Vitamin E, IU	60.9	63.5	69.5	79.4	92.2	115.1	200.5
Vitamin C, mg	297	327	351	377	422	472	680
Total carotene, mcg	7712	9168	9623	9965	10 548	10 116	11 290
Total fiber, g	17.8	20.0	20.8	21.5	22.3	21.5	21.9
Beef as main dish, servings/day	0.3	0.3	0.3	0.3	0.2	0.2	0.2

*Standardized for age at baseline; BMI = body mass index; IU = international unit; NA = not applicable.
†Nutrients are adjusted for total energy intake by regression analysis.

mulative updated intake variable (lowest versus highest category: RR = 0.83; 95% confidence interval [CI] = 0.64 to 1.09).

In men, a higher total milk intake at baseline (>1.1 servings/day versus 0.5 servings/day) suggested a lower risk of colon cancer (RR = 0.58; 95% CI = 0.29 to 1.17), but this is not the case in women (RR = 0.93; 95% CI = 0.76 to 1.15). Results were similar when analysis was restricted to women without a change in milk intake over the past 10 years. In men, intake of fermented milk products was not associated with colon cancer risk (data not shown). In women, there was a slight but not statistically significant association between higher intake of fermented milk products at baseline and risk of colon cancer (>1 serving/day versus ≤0.07 servings/day: RR = 0.86; 95% CI = 0.63 to 1.16), but this association was attenuated when we used the cumulative updated intake of fermented milk products.

When we examined risk by cancer site, inverse associations between higher calcium intake and colon cancer were observed for distal colon cancer, whereas no associations were observed for proximal colon cancer (Table 3). After pooling RR estimates

Table 2. Multivariate-adjusted relative risks (RRs) and 95% confidence intervals (CIs) of colon cancer by categories of cumulative average calcium intake in Nurses' Health Study (NHS) (1980–1996) and Health Professionals Follow-up Study (HPFS) (1986–1996)

	NHS				HPFS	
	Total		No change in milk intake		Total	
	No. case subjects	Multivariate RR† (95% CI)	No. case subjects	Multivariate RR† (95% CI)	No. case subjects	Multivariate RR† (95% CI)
Total calcium, mg						
⩽500	70	1	52	1	47	1
501–600	79	1.19 (0.86 to 1.64)	56	1.18 (0.81 to 1.73)	48	0.69 (0.46 to 1.04)
601–700	83	1.07 (0.77 to 1.47)	56	1.05 (0.72 to 1.55)	58	0.69 (0.47 to 1.01)
701–800	90	1.18 (0.86 to 1.63)	50	0.97 (0.65 to 1.44)	51	0.60 (0.40 to 0.90)
801–1000	130	1.04 (0.77 to 1.40)	71	0.85 (0.58 to 1.23)	81	0.67 (0.47 to 0.97)
1001–1250	106	1.05 (0.77 to 1.44)	59	0.96 (0.65 to 1.41)	54	0.62 (0.42 to 0.92)
>1250	68	0.94 (0.66 to 1.33)	39	0.91 (0.59 to 1.42)	60	0.64 (0.43 to 0.95)
		P_{trend} = .35		P_{trend} = .30		P_{trend} = .17
Dietary calcium, mg*						
⩽500	78	1	60	1	53	1
501–600	83	1.16 (0.85 to 1.58)	58	1.11 (0.77 to 1.59)	60	0.76 (0.53 to 1.11)
601–700	74	0.99 (0.72 to 1.36)	45	0.86 (0.58 to 1.27)	53	0.57 (0.39 to 0.84)
701–800	77	1.26 (0.91 to 1.73)	44	1.04 (0.70 to 1.55)	45	0.52 (0.35 to 0.78)
801–1000	59	0.77 (0.55 to 1.09)	33	0.65 (0.42 to 1.01)	74	0.67 (0.47 to 0.96)
>1000	54	0.97 (0.68 to 1.38)	33	0.96 (0.62 to 1.49)	71	0.67 (0.46 to 0.96)
		P_{trend} = .21		P_{trend} = .15		P_{trend} = .24
Dairy calcium, mg						
⩽200	60	1	43	1	67	1
201–300	64	0.85 (0.60 to 1.22)	47	0.92 (0.61 to 1.40)	66	0.79 (0.56 to 1.11)
301–400	89	1.09 (0.78 to 1.52)	55	1.02 (0.68 to 1.53)	58	0.66 (0.46 to 0.94)
401–600	128	1.06 (0.78 to 1.45)	77	1.01 (0.69 to 1.48)	85	0.72 (0.52 to 1.00)
601–800	53	0.88 (0.61 to 1.28)	31	0.87 (0.55 to 1.40)	39	0.69 (0.46 to 1.03)
>800	31	0.78 (0.50 to 1.21)	20	0.86 (0.49 to 1.49)	41	0.78 (0.53 to 1.16)
		P_{trend} = .26		P_{trend} = .38		P_{trend} = .33
Nondairy calcium, mg						
⩽250	180	1	124	1	80	1
251–275	79	1.09 (0.84 to 1.43)	51	1.04 (0.75 to 1.45)	52	0.91 (0.64 to 1.30)
276–300	59	0.98 (0.73 to 1.32)	33	0.78 (0.53 to 1.17)	55	0.89 (0.63 to 1.26)
301–350	78	1.24 (0.95 to 1.63)	48	1.17 (0.83 to 1.64)	98	1.01 (0.75 to 1.37)
>350	29	1.03 (0.70 to 1.54)	17	0.97 (0.57 to 1.64)	71	1.02 (0.73 to 1.43)
		P_{trend} = .43		P_{trend} = .91		P_{trend} = .37

*For dietary, dairy, and nondairy calcium intake; calcium supplement users were excluded from analysis.

†Basic models were multivariate adjusted for age, family history, body mass index (at baseline), physical activity (at baseline), pack-years of smoking before age 30, aspirin use (at baseline), red meat intake (at baseline), alcohol consumption (at baseline); multivariate models for NHS also included postmenopausal hormone use and menopausal status.

for men and women (those without a change in milk intake), we found an approximately 40%–50% lower risk of distal colon cancer among those subjects with a calcium intake of 701–800 mg/day or higher compared with those subjects having a calcium intake of less than or equal to 500 mg/day. When history of endoscopy, multivitamin use, or intake of total vitamin D, phosphorus, or folate were added separately to these multivariate models, RR estimates for total calcium intake were similar to those shown in Table 3.

We also investigated whether observed inverse associations between calcium intake and colon cancer risk may be explained by higher dairy product intake. Table 4 shows multivariate RR of distal colon cancer according to supplemental calcium use (at baseline) and categories of dietary calcium intake (at baseline) in both cohorts. In addition to the covariates noted in Table 2, for this analysis, multivitamin use was also included in the final models. Participants with low dietary calcium intake (⩽700 mg/day) who were not using calcium supplements were the reference category. After pooling RRs for both men and women, we found that supplemental calcium was associated with lower risk of distal colon cancer among participants in the low category of dietary calcium intake. Among participants with high dietary calcium intakes (>700 mg/day), RRs were similar for nonsupplement users and supplement users, suggesting that supplemental calcium use may not confer further benefit among participants with high dietary calcium intake. The relationships between potential risk factors (physical activity, aspirin use, multivitamin use, and vitamin D intake) were in the opposite direction for dietary and supplemental calcium; thus, the fact that we observed inverse associations for both dietary and supplemental calcium argues against residual confounding by these factors.

Table 5 shows multivariate-adjusted RRs of distal colon cancer comparing high (>700 mg/day) with low (⩽700 mg/day) calcium intake within strata of different variables. Consistent with a recent clinical trial of colorectal adenomas *(27),* inverse associations between total calcium intake and risk of colon cancer were restricted to aspirin nonusers only. In men, inverse associations between distal colon cancer and calcium intake were also more pronounced among those who had smoked at least one pack-year of cigarettes before age 30 years. In men, but not in women, RR estimates suggested an inverse association

Table 3. Multivariate-adjusted relative risks (RRs) and 95% confidence intervals (CIs) of colon cancer by categories of cumulative average calcium intake in Nurses' Health Study (NHS) (1980–1996) and in Health Professionals Follow-up Study (HPFS) (1986–1996) by cancer site

	NHS				HPFS		Pooled analysis	
	Total (1)		No change in milk intake (2)†		Total (3)		(1) + (3)	(2) + (3)
	No. case subjects	Multivariate RR* (95% CI)	No. case subjects	Multivariate RR* (95% CI)	No case subjects	Multivariate RR* (95% CI)	Pooled RR* (95% CI)	Pooled RR* (95% CI)
Proximal cancer								
Total calcium, mg								
≤500	27	1	19	1	12	1	1	1
501–600	25	0.92 (0.53 to 1.61)	18	1.05 (0.55 to 2.01)	15	0.84 (0.39 to 1.81)	0.90 (0.57 to 1.40)	0.96 (0.58 to 1.57)
601–700	37	1.18 (0.72 to 1.96)	24	1.26 (0.69 to 2.32)	19	0.87 (0.42 to 1.79)	1.07 (0.71 to 1.62)	1.08 (0.68 to 1.72)
701–800	46	1.55 (0.96 to 2.52)	27	1.50 (0.82 to 2.73)	22	0.98 (0.48 to 1.99)	1.33 (0.87 to 2.04)	1.25 (0.79 to 1.98)
801–1000	56	1.13 (0.70 to 1.81)	27	0.92 (0.50 to 1.70)	34	1.06 (0.54 to 2.07)	1.10 (0.75 to 1.63)	0.98 (0.63 to 1.54)
1001–1250	50	1.28 (0.79 to 2.08)	27	1.25 (0.68 to 2.31)	24	1.01 (0.50 to 2.05)	1.19 (0.80 to 1.77)	1.14 (0.72 to 1.81)
>1250	35	1.28 (0.75 to 2.16)	21	1.49 (0.77 to 2.86)	24	0.92 (0.45 to 1.87)	1.14 (0.72 to 1.81)	1.19 (0.75 to 1.93)
		P_{trend} = .32		P_{trend} = .33		P_{trend} = .91	P_{trend} = .41	P_{trend} = .46
Distal cancer								
Total calcium, mg								
≤500	33	1	27	1	22	1	1	1
501–600	37	1.24 (0.77 to 2.00)	26	1.06 (0.61 to 1.84)	25	0.77 (0.43 to 1.37)	1.01 (0.64 to 1.59)	0.91 (0.61 to 1.36)
601–700	40	1.16 (0.72 to 1.85)	29	1.05 (0.62 to 1.80)	25	0.64 (0.36 to 1.14)	0.88 (0.50 to 1.57)	0.83 (0.51 to 1.35)
701–800	33	0.98 (0.60 to 1.61)	16	0.61 (0.32 to 1.14)	16	0.41 (0.21 to 0.78)	0.65 (0.28 to 1.53)	0.50 (0.32 to 0.79)
801–1000	46	0.78 (0.49 to 1.25)	28	0.63 (0.36 to 1.09)	28	0.51 (0.29 to 0.91)	0.65 (0.44 to 0.98)	0.58 (0.38 to 0.85)
1001–1250	40	0.91 (0.56 to 1.48)	26	0.82 (0.47 to 1.44)	18	0.46 (0.24 to 0.86)	0.67 (0.34 to 1.30)	0.62 (0.35 to 1.10)
>1250	24	0.73 (0.41 to 1.27)	12	0.51 (0.25 to 1.07)	24	0.58 (0.32 to 1.05)	0.65 (0.43 to 0.98)	0.55 (0.35 to 0.88)
		P_{trend} = .06		P_{trend} = .03		P_{trend} = .12	P_{trend} = .01	P_{trend} = .09

*Multivariate RRs were adjusted for age, family history, body mass index (at baseline), physical activity (at baseline), pack-years of smoking before age 30, aspirin use (at baseline), red meat intake (at baseline), alcohol consumption (at baseline); multivariate models for NHS also included postmenopausal hormone use and menopausal status. In HPFS, 5 of 313 confirmed colon cancer case subjects were excluded because of insufficient information on colon cancer location.

†Women with no change in milk intake are considered to have more stable calcium intake (for more information, please refer to text).

Table 4. Multivariate-adjusted relative risks (RRs)* and 95% confidence intervals (CIs) of distal colon cancer according to supplemental and dietary calcium intake (≤700 mg/day versus >700 mg/day at baseline†) in Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	Supplemental calcium	
	Never users	Current users
	RR (95% CI)	RR (95% CI)
NHS		
Total	1 (referent)	0.69 (0.48 to 1.00)
Dietary calcium, mg/day		
≤700	1 (referent)	0.65 (0.39 to 1.08)
>700	0.73 (0.52 to 1.02)	0.55 (0.32 to 0.94)
HPFS		
Total	1 (referent)	0.70 (0.43 to 1.14)
Dietary calcium, mg/day		
≤700	1 (referent)	0.33 (0.13 to 0.82)
>700	0.74 (0.52 to 1.06)	0.82 (0.45 to 1.48)
Pooled analysis*		
Total	1 (referent)	0.69 (0.51 to 0.94)
Dietary calcium, mg/day		
≤700	1 (referent)	0.52 (0.27 to 0.97)
>700	0.73 (0.57 to 0.94)	0.66 (0.44 to 0.98)

*Multivariate RRs were adjusted for variables as denoted in Table 2, plus multivitamin use; past calcium supplement users were excluded from this analysis.

†For NHS dietary intake and supplemental intake in 1984 was used, for HPFS dietary intake and supplemental intake in 1986 was used; in NHS follow-up was from 1984 to 1996; in HPFS, follow-up was from 1986 to 1996.

among those with higher fat and lower phosphorus intake, but results were not statistically significant. After pooling RRs for both women and men, intake of beef did not appear to modify the associations between calcium and risk of distal colon cancer.

Because calcium absorption is influenced by vitamin D *(42,43),* potential interactions between calcium intake and vitamin D were investigated more closely. After pooling RRs for both women and men, inverse associations between high total calcium intake (>700 mg/day) and distal colon cancer risk appeared to be restricted to participants with higher intake of vitamin D (Table 5).

Discussion

We previously reported modest inverse, but not statistically significant, associations between calcium intake and risk of colorectal cancer in these two cohorts separately *(14,16).* In the NHS cohort *(16)* we used dietary information from the food frequency questionnaires received in 1980, 1984, and 1986, whereas in the HPFS cohort *(14)* we used dietary information from only the 1986 questionnaire. In both studies we followed cases through 1992. The present analysis, with follow-up extended to 1996 and better assessment of long-term diet through multiple dietary assessments, had more power to investigate modest associations. This extended assessment also allowed us to examine dietary and supplemental calcium separately, to better define dose–response relationships, to examine risk by colon subsites, and to examine factors that may modify the associations between calcium intake and colon cancer risk. In this study, an inverse association between higher calcium intake and distal, but not proximal, colon cancer was found in both men and women. Observed risk patterns were consistent with a threshold effect of calcium intake on colon cancer risk, suggesting that even a modest increase in calcium intake may confer protection against distal colon cancer among those with low intakes. Associations were also restricted to non-aspirin users and appeared

Table 5. Multivariate-adjusted relative risks (RRs) and 95% confidence intervals (CIs) of distal colon cancer for high (>700 mg/day) versus low (⩽700 mg/day) calcium intake (cumulative update) by different variables in Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

	NHS		HPFS		Pooled analysis
	No. case subjects	Multivariate RR* (95% CI)	No. case subjects	Multivariate RR* (95% CI)	Multivariate RR* (95% CI)
Aspirin use at baseline					
Nonusers	184	0.63 (0.47 to 0.86)	110	0.52 (0.35 to 0.76)	0.59 (0.46 to 0.74)
Users	64	1.28 (0.74 to 2.22)	42	1.08 (0.56 to 2.12)	1.20 (0.78 to 1.83)
Pack-year(s) of smoking before age 30					
None	158	0.78 (0.56 to 1.08)	59	0.81 (0.47 to 1.39)	0.78 (0.59 to 1.04)
⩾1 pack-year(s)	90	0.70 (0.45 to 1.08)	93	0.55 (0.36 to 0.83)	0.62 (0.46 to 0.83)
Vitamin D intake†,‡					
Tertile 1	87	0.78 (0.47 to 1.29)	61	0.97 (0.56 to 1.68)	0.86 (0.60 to 1.25)
Tertile 2	80	0.74 (0.46 to 1.21)	46	0.50 (0.27 to 0.91)	0.63 (0.43 to 0.93)
Tertile 3	81	0.67 (0.39 to 1.14)	45	0.63 (0.32 to 1.27)	0.66 (0.43 to 1.00)
Total fat intake†,¶					
Tertile 1	71	0.79 (0.47 to 1.35)	51	1.08 (0.59 to 1.99)	0.91 (0.61 to 1.35)
Tertile 2	96	0.70 (0.46 to 1.06)	53	0.36 (0.21 to 0.62)	0.51 (0.27 to 0.99)
Tertile 3	81	0.79 (0.50 to 1.24)	48	0.72 (0.40 to 1.27)	0.76 (0.53 to 1.09)
Total phosphate intake†,§					
Tertile 1	88	0.68 (0.40 to 1.17)	64	0.55 (0.30 to 1.02)	0.62 (0.41 to 0.93)
Tertile 2	75	0.79 (0.49 to 1.28)	48	0.61 (0.34 to 1.10)	0.71 (0.49 to 1.03)
Tertile 3	85	0.63 (0.31 to 1.27)	40	2.22 (0.30 to 16.21)	0.83 (0.30 to 2.30)
Intake of beef as main dish					
Low (⩽1 serving/week)	113	0.58 (0.39 to 0.85)	92	0.87 (0.56 to 1.34)	0.70 (0.47 to 1.04)
High (>1 serving/week)	135	0.91 (0.64 to 1.29)	60	0.39 (0.23 to 0.67)	0.61 (0.27 to 1.39)

*Multivariate adjusted for variables as denoted in Table 2, except, if applicable, for the stratification variable.

†Since cumulative updated information was used, exact median values for each tertile vary with each follow-up period. As median values for each tertile did not differ considerably between follow-up periods, only median values from nutrient intakes at baseline (i.e., 1980 Food Frequency Questionnaire for NHS and 1986 Food Frequency Questionnaire for HPFS) are reported here.

‡Median intake: NHS: tertile 1 = 81 IU/day, tertile 2 = 197 IU/day, tertile 3 = 529 IU/day; HPFS: tertile 1 = 127 IU/day, tertile 2 = 261 IU/day, tertile 3 = 610 IU/day.

¶Median intake: NHS: tertile 1 = 57 g/day, tertile 2 = 70 g/day, tertile 3 = 83 g/day; HPFS: tertile 1 = 58 g/day, tertile 2 = 72 g/day, tertile 3 = 84 g/day.

§Median intake: NHS: tertile 1 = 915 mg/day, tertile 2 = 1113 mg/day, tertile 3 = 1387 mg/day; HPFS: tertile 1 = 1162 mg/day, tertile 2 = 1365 mg/day, tertile 3 = 1626 mg/day. IU = international units.

to be stronger among male smokers. Finally, our data also suggest that inverse associations between calcium intake and colon cancer risk are independent of intake of dairy products but may be modified by vitamin D intake.

Even though epidemiologic studies on the association between calcium and colon cancer risk have been inconsistent, modest but statistically nonsignificant inverse associations have been observed in the majority of studies *(14–19,29).* Some, but not all, case–control studies *(44–50)* have reported a statistically significant inverse association between calcium intake and colorectal or colon cancer risk. When analyses were stratified by sex, inverse associations appeared to be stronger in women *(47,50).*

In two male prospective cohorts, the Western Electric Study and the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, higher calcium intake was associated with lower risk of colorectal cancer with RR estimates (comparing lowest with highest quantile of calcium intake) ranging from 0.60 (95% CI = 0.40 to 0.90) *(21)* to 0.32 ($P \leqslant .05$) *(20).* In another prospective study of 11 888 male and female residents of a retirement community *(13),* dietary calcium intake was not associated with colorectal cancer risk. The Netherlands Cohort Study *(51)* did not observe an inverse association between total dietary calcium intake or intake of fermented dairy products and colorectal cancer risk but did suggest a modest inverse association between calcium from unfermented dairy products and colorectal cancer risk (lowest versus highest quintile: multivariate RR = 0.71; 95% CI = 0.48 to 1.05).

A recent meta-analysis of 24 studies on the association between calcium intake and colorectal adenoma or cancer *(52)* concluded that existing data are not consistent with a considerable protective effect of calcium on risk of colorectal cancer (pooled RR = 0.86; 95% CI = 0.74 to 0.98) or colorectal adenoma (pooled RR = 1.13; 95% CI = 0.91 to 1.39).

Randomized trials *(22–27)* of supplemental calcium and recurrence of colorectal adenomas (which are precursors for colorectal cancers) or other biomarkers, such as fecal bile acid concentrations or colorectal mucosal cell proliferation, have also yielded inconsistent results. In the Calcium Polyp Prevention Study, participants with a history of colorectal adenoma were randomly assigned to receive daily either 1200 mg of calcium or placebo. Supplementation resulted in a statistically significant, albeit moderate, lower risk of recurrent adenomas (RR = 0.81; 95% CI = 0.67 to 0.99) *(27).* Another recent trial from Europe *(53)* also observed a modest, but not statistically significant, decreased risk of colorectal adenoma recurrence after daily supplementation with 2000 mg of calcium (RR = 0.66; 95% CI = 0.38 to 1.17). Because only relatively high doses were examined, the dose–response relationship could not be established from these two studies.

Beneficial effects of calcium have been hypothesized to be more pronounced in the proximal colon because effects of fatty

acids and bile acids on colon cell proliferation may be stronger proximally *(52,54).* However, only few observational studies *(14,55–57)* have investigated associations by cancer site. In this analysis, inverse associations were observed between calcium intake and distal colon cancer but not for proximal cancer. In one case–control study *(55)* with 746 colon cancer case subjects and control subjects, researchers found inverse associations between calcium intake and colon cancer risk to be strongest in the sigmoid colon (per 295 mg/day increase in calcium intake: ascending colon: RR = 0.91; 95% CI = 0.78 to 1.05; transverse and descending colon: RR = 0.87; 95% CI = 0.74 to 1.01; sigmoid colon: RR = 0.86; 95% CI = 0.77 to 0.97). Another large case–control study *(57)* based on 1993 case subjects and 2410 control subjects found inverse associations between higher calcium intake and colon cancer risk to be stronger (and statistically significant) for distal colon cancers than for proximal colon cancers. Proximal cancers are commonly detected at a more advanced stage than distal colon cancers, which might have resulted in recall bias *(52).* However, inverse associations between calcium intake and colon cancer risk were also more pronounced for the sigmoid colon in a prospective cohort of 11 000 men of Japanese descent residing in Hawaii *(56)* (lowest versus highest tertile of calcium intake: sigmoid colon: RR = 1.7; 95% CI = 1.1 to 2.8; 113 case subjects). Findings from randomized clinical trials with regard to colon subsites are inconclusive. In the trial by Bonithon-Kopp et al. *(53),* inverse associations between calcium supplementation and adenoma recurrence were restricted to proximal adenomas, whereas no relationship with colon subsite was observed in the trial by Baron et al. *(27).*

Results from some epidemiologic studies *(15,17,21,29,55)* also support an inverse association between dairy product or milk intake and colorectal or colon cancer risk. Thus, the question arises as to whether one or more component(s) in dairy products other than calcium, for example, casein *(58),* may be responsible for those observed associations. In our study, supplemental calcium intake was significantly associated with decreased risk even among participants with low dietary calcium intake, suggesting that calcium may be the relevant component. Use of supplemental calcium in participants with high dietary calcium intake appeared to be of no further benefit, providing additional support for a possible threshold effect of calcium intake on colon cancer risk.

Calcium can bind secondary bile acids and ionized fatty acids, both of which have been hypothesized to promote epithelial cell proliferation in the colon *(6–8).* According to this hypothesis, people with higher fat intake should benefit most from higher calcium intake *(8).* In men, inverse associations between calcium intake and distal colon cancer risk appeared to be restricted to those with higher total fat intake, but in women, fat intake did not modify the association with calcium intake. Also, we did not observe evidence of an overall effect of total dietary fat in these cohorts. In the human body, calcium absorption is tightly regulated and primarily involves vitamin D, parathyroid hormone, and phosphorus *(42,43).* Vitamin D can increase absorption of calcium in the gastrointestinal tract and decrease renal calcium loss *(42,43).* Higher phosphorus intake may decrease calcium absorption in the gastrointestinal tract, although this may be balanced by decreased renal excretion of calcium *(59).* Our data provide some indication that participants with higher intake of vitamin D may benefit most from higher calcium intake with regard to their colon cancer risk. In men, but not in women, there was also some suggestion of a more pronounced inverse association between higher calcium intake and colon cancer risk among participants in the lowest tertile of phosphorus intake. Other factors that can affect absorption and bioavailability of calcium are dietary fiber *(43)* and the source of ingested calcium (i.e., dairy calcium versus calcium from other dietary sources, such as plant products) *(59,60).* Some components in plants, such as phytate, cellulose, or oxalate may reduce calcium absorption *(59).* In our study, calcium from nondairy sources was not associated with colon cancer risk, even among participants with low dairy calcium intake. Given that calcium intake from nondairy sources was low in our cohorts, we cannot exclude the possibility that calcium intake from nondairy sources may have been too low to exert a protective effect on colon cancer risk.

Our data also suggest that beneficial effects of calcium on colon cancer risk may be restricted to aspirin nonusers only. In the recent randomized trial of calcium supplementation and recurrent colorectal adenomas *(27),* protective effects of calcium supplementation were more pronounced among nonusers of aspirin or other nonsteroidal anti-inflammatory drugs. This finding deserves further examination.

Although residual confounding cannot be ruled out entirely, arguing against confounding as an explanation for our results are 1) similarity of age-adjusted and multivariate associations, 2) associations seen for both women and men, and 3) associations seen for both dietary and supplemental calcium separately. Our results suggest that relatively moderate calcium intake may decrease the risk of distal colon cancer but that high calcium intake may not appreciably lower risk further. Considering the public health importance of colon cancer *(61),* even a modest protective effect of higher calcium intake on colon cancer could result in the prevention of a large number of colon cancer cases. Future studies investigating this relationship should concentrate on specific cancer subsites and on better characterizing the dose–response relationship.

Appendix I

Food items included in the calculation of calcium from dairy sources were skim milk, 1%–2% milk, whole milk, yogurt (flavored and plain yogurt), ice cream, frozen yogurt, cottage cheese, cream cheese, other cheese, butter, clam chowder, mashed potatoes, pie (homemade), cake (homemade), cake (ready-made), donut, sweet roll (homemade and ready-made), muffin, pancake, pizza, chocolate, candy with chocolate, chocolate chip cookie (homemade and ready-made), white bread, and dark bread.

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NOTES

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