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Dairy Foods, Calcium, and Colorectal Cancer: A Pooled Analysis of 10 Cohort Studies

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Background: **Studies in animals have suggested that calcium may reduce the risk of colorectal cancer. However, results from epidemiologic studies of intake of calcium or dairy foods and colorectal cancer risk have been inconclusive.** ***Methods:*** **We pooled the primary data from 10 cohort studies in five countries that assessed usual dietary intake by using a validated food frequency questionnaire at baseline. For most studies, follow-up was extended beyond that in the original publication. The studies included 534 536 individuals, among whom 4992 incident cases of colorectal cancer were diagnosed between 6 and 16 years of follow-up. Pooled multivariable relative risks for categories of milk intake and quintiles of calcium intake and 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided.** ***Results:*** **Milk intake was related to a reduced risk of colorectal cancer. Compared with the lowest category of intake (<70 g/day), relative risks of colorectal cancer for increasing categories (70–174, 175–249, and ≥250 g/day) of milk intake were 0.94 (95% CI = 0.86 to 1.02), 0.88 (95% CI = 0.81 to 0.96), and 0.85 (95% CI = 0.78 to 0.94), respectively (P_{trend}<.001). Calcium intake was also inversely related to the risk of colorectal cancer. The relative risk for the highest versus the lowest quintile of intake was 0.86 (95% CI = 0.78 to 0.95; P_{trend} = .02) for dietary calcium and 0.78 (95% CI = 0.69 to 0.88; P_{trend}<.001) for total calcium (combining dietary and supplemental sources). These results were consistent across studies and sex. The inverse association for milk was limited to cancers of the distal colon (P_{trend}<.001) and rectum (P_{trend} = .02).** ***Conclusion:*** **Higher consumption of milk and calcium is associated with a lower risk of colorectal cancer. [J Natl Cancer Inst 2004;96:1015–22]**

Colorectal cancer is the third most common incident cancer worldwide *(1)*, and international differences in incidence have been hypothesized to be related to diet *(2)*. Evidence from animal studies has suggested that high calcium intake may reduce colonic carcinogenesis *(3)*. In humans, calcium supplements have been shown to reduce colonic epithelial cell proliferation *(4)* and risk of recurrent colorectal adenomas *(5)*, and low-fat dairy foods reduce proliferation and normalize differentiation of colonic epithelial cells *(6)*.

Results from epidemiologic studies of consumption of dairy foods and calcium and colorectal cancer risk have been inconclusive, with most studies reporting weak, statistically nonsignificant inverse associations *(7–10)*, perhaps reflecting limited sample sizes. In this study, we examined the associations between the consumption of dairy foods and calcium and colorectal cancer risk in a pooled analysis of 10 cohort studies from North America and Europe. Most of the individual studies included in our analysis have published results of intakes of calcium *(11–18)* and dairy foods *(11,12,14,16,18–20)* on colorectal cancer risk. For most of these studies, follow-up was extended in the current analysis relative to the time of follow-up in the original published results.

METHODS

Population

The Pooling Project of Prospective Studies of Diet and Cancer has been described elsewhere *(21,22)*. For the colorectal cancer analyses, we identified 10 prospective studies *(11–13, 16–18,20,23,24)* that met the following predefined criteria: at least 50 people diagnosed with incident colorectal cancer; as-

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sessment of long-term dietary intake; and validation of either the dietary assessment method itself or a closely related instrument. Because most studies included only one sex, studies that included women and men were analyzed as two separate cohorts. The person-time experienced during follow-up of the Nurses' Health Study *(17)* was divided into two segments to take advantage of the more detailed dietary assessment completed in 1986. On the basis of the underlying theory of survival data, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people *(25)*.

Exclusion Criteria

For the primary data from each study, we applied the exclusion criteria used by that study *(11–13,16–18,20,23,24)*, and then we further excluded participants if they had $\log_e$-transformed energy intakes beyond three standard deviations from the study-specific $\log_e$-transformed mean energy intake of the population. We also further excluded participants if they reported a history of cancer other than nonmelanoma skin cancer at baseline.

Case Definition

In each study, incident colorectal cancers were ascertained by self-report with subsequent medical record review *(17)*, linkage with a cancer registry *(11–13,18,23,24)*, or both *(16,20)*. In some studies *(13,16–18,23,24)*, additional linkage with a death registry was used.

Dietary Assessment

The baseline food frequency questionnaire for each study inquired about typical consumption of food items, generally over the past year. The number of questions on dairy foods on the food frequency questionnaires ranged from one in the New York State Cohort *(24)* to 20 in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study *(16)*. We examined associations between colorectal cancer risk and three groups of dairy foods (milk, cheese, and yogurt) because these groups were measured in most of the studies. Other dairy foods that were measured in at least half of the studies were examined separately.

Studies provided data for the intake of calcium from food only (dietary calcium) and from food and supplements (total calcium), if available. Because the amount of calcium in multivitamins was not estimated in the Adventist Health Study *(20)* and in the New York State Cohort *(24)*, we used the calcium values for generic multivitamins (130 mg/day) in the Nurses' Health Study food frequency questionnaire database to derive total calcium intakes for these studies. The correlations for dietary calcium between intakes estimated by the food frequency questionnaire and either multiple diet records or 24-hour recalls ranged from 0.48 to 0.70 *(26–29)* (A. Wolk and L. Sampson: personal communications). We used the regression-residual method *(30)* to adjust nutrient intakes for a total energy intake of 1600 kcal/day for women and 2100 kcal/day for men.

Among dietary covariates, there were no missing data for nutrients. In most studies, less than 1% of the participants in each study had missing values for intake of red meat and alcohol.

Nondietary Covariates

Each study collected baseline information on nondietary covariates by using self-administered questionnaires. Most studies assessed age, smoking habits, physical activity, education, height, weight, multivitamin use, and, among women, oral contraceptive use and postmenopausal hormone use. The proportion of missing values was generally less than 5% in each study that measured the covariate. We categorized the covariate information in a consistent manner across studies.

Statistical Analysis

Primary data for dairy food and calcium intakes were modeled as categorical variables with uniform absolute intake cut points across the studies. Intake cut points were chosen to ensure a good number of cases in each category and to minimize exclusion of individual studies from any of the intake categories. Calcium intake was also categorized by study-specific quantiles on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study *(23)* and The Netherlands Cohort Study *(12)*, each of which used a case–cohort design *(31)* and on the distributions of the whole cohort in the remaining studies. To calculate the P_{trend}, we assigned participants the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models.

Each study was analyzed with the Cox proportional hazards model. The assumptions of proportionality were satisfied. Epicure software *(32)* was used for the Canadian National Breast Screening Study *(23)* and The Netherlands Cohort Study *(12)*, and SAS PROC PHREG *(33)* was used for the remaining studies. We stratified the data by age at baseline and by the year that the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the questionnaire was returned until the date of colorectal cancer diagnosis, death, or end of follow-up, whichever came first. Multivariable relative risks (RRs) were adjusted for smoking (never, past smoker with <20 years' duration, past smoker with 20–39 years' duration, past smoker with ≥40 years' duration, current smoker of <25 cigarettes per day and <40 years' duration, current smoker of ≥25 cigarettes per day and <40 years' duration, current smoker of <25 cigarettes per day and ≥40 years' duration, or current smoker of ≥25 cigarettes per day and ≥40 years' duration), body mass index (<23, 23 to <25, 25 to <30, or ≥30 kg/m^2 of body surface area), education (less than high school, high school graduate, or more than high school), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, or ≥1.75 m for women; <1.70, 1.70 to <1.75, 1.75 to <1.80, 1.80 to <1.85, or ≥1.85 m for men), physical activity (low, medium, or high), family history of colorectal cancer (no, yes), use of nonsteroidal anti-inflammatory drugs (no, yes), use of multivitamins [no, yes <6/week, yes ≥6/week, or yes missing dose for the Health Professionals Follow-up Study *(17)*, Iowa Women's Health Study *(11)*, and Nurses' Health Study *(17)*; no, yes for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study *(16)*, The Netherlands Cohort Study *(12)*, and New York State Cohort *(24)*], energy intake (continuous), alcohol intake (0, >0 to <5, 5 to <15, 15 to <30, ≥30 g/day), red meat (quartiles), and dietary folate (quintiles). For women, the relative risks were also adjusted for history of oral contraceptive use (no, yes) and postmenopausal hormone use (premenopausal, ever, never). If

Table 1. Characteristics of the cohort studies included in the pooled analysis of dairy foods and calcium intake and colorectal cancer

Study	Follow-up period	Sex*	Baseline cohort size	No. of cases	Mean (SD) intake of: Milk† (g/day)	Cheese‡ (g/day)	Yogurt§ (g/day)	Dietary calcium‖ (mg/day)	Total calcium‖ (mg/day)
Adventist Health Study	1976–1982	W	18 403	95	419 (349)	8 (8)	—	833 (124)	880 (139)
		M	12 896	74	436 (349)	9 (8)	—	1051 (123)	1087 (136)
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	1985–1995	M	26 987	184	687 (385)	25 (28)	14 (37)	1049 (312)	1052 (314)
Canadian National Breast Screening Study	1980–1993	W	56 837	284	201 (203)	22 (24)	30 (63)	674 (255)	—
Health Professionals Follow-up Study	1986–1996	M	47 673	408	219 (251)	11 (13)	20 (51)	836 (320)	931 (413)
Iowa Women's Health Study	1986–1998	W	34 603	796	275 (266)	11 (13)	11 (38)	749 (286)	1031 (484)
The Netherlands Cohort Study	1986–1993	W	62 573	501	187 (153)	23 (18)	53 (57)	868 (259)	—
		M	58 279	646	199 (178)	23 (19)	42 (56)	928 (289)	—
New York State Cohort	1980–1987	W	22 550	296	137 (87)	—	—	828 (209)	873 (220)
		M	30 363	492	139 (85)	—	—	867 (223)	904 (233)
New York University Women's Health Study	1985–1997	W	13 258	116	203 (241)	17 (22)	38 (61)	810 (306)	—
Nurses' Health Study (a)	1980–1986	W	88 651	220	215 (242)	14 (15)	22 (55)	723 (299)	732 (311)
Nurses' Health Study (b)	1987–1996	W	68 540¶	420	222 (230)	13 (13)	28 (55)	719 (254)	1068 (496)
Sweden Mammography Cohort	1987–1998	W	61 463	460	156 (130)	27 (19)	104 (108)	913 (255)	—
Total			534 536	4992					

*W = women; M = men.

†Milk included skim, low-fat, medium-fat, whole, evaporated, and butter milk. Values in parentheses are standard deviations (SD).

‡Cheese included high-fat, low-fat, hard, and other cheese. — = none.

§Yogurt included low-fat and regular yogurt and yogurt dressing.

‖Energy-adjusted values. Dietary calcium indicates calcium from food only. Total calcium indicates calcium from food and supplements.

¶These women are a subset of the women included in the Nurses' Health Study (a) and are not included in the total.

there were missing data for a measured covariate within a study, an indicator variable was created for missing responses for that covariate. Two-sided 95% confidence intervals (CIs) were calculated. A random-effects model was used to combine the study-specific $\log_e$ relative risks *(34);* the study-specific relative risks were weighted by the inverse of their variance. Tests of heterogeneity were conducted by using the Q statistic *(34,35).*

We evaluated whether total calcium intake was nonlinearly associated with colorectal cancer by comparing the nonparametric regression curve using restricted cubic splines to the linear

Table 2. Pooled relative risks of colorectal cancer for categories of dairy food intake*

Cases and RRs	Intake category (g/day)				P_{trend}	*P*, test for between-study heterogeneity for top category	*P*, test for between-study heterogeneity due to sex for top category
Milk†							
	<70	70–174	175–249	≥250			
No. of cancer cases	4946	1065	1360	1154			
Age-adjusted RR (95% CI)	1.00 (referent)	0.94 (0.86 to 1.02)	0.87 (0.80 to 0.95)	0.84 (0.77 to 0.92)	<.001	.66	.85
Multivariate‡ RR (95% CI)	1.00 (referent)	0.94 (0.86 to 1.02)	0.88 (0.81 to 0.96)	0.85 (0.78 to 0.94)	<.001	.63	.49
Cheese, excluding cottage, ricotta, and cream cheese							
	<5	5–13	14–24	≥25			
No. of cancer cases	4146	1173	906	932			
Age-adjusted RR (95% CI)	1.00 (referent)	1.05 (0.96 to 1.15)	1.09 (0.96 to 1.23)	1.12 (0.98 to 1.28)	.13	.15	.20
Multivariate‡ RR (95% CI)	1.00 (referent)	1.03 (0.94 to 1.12)	1.06 (0.95 to 1.18)	1.10 (0.98 to 1.24)	.21	.37	.18
Yogurt							
	0	1–24	25–74	≥75			
No. of cancer cases	3837	687	485	725			
Age-adjusted RR (95% CI)	1.00 (referent)	0.93 (0.84 to 1.02)	0.85 (0.72 to 1.01)	0.90 (0.81 to 0.99)	.09	.82	.67
Multivariate‡ RR (95% CI)	1.00 (referent)	0.95 (0.86 to 1.04)	0.88 (0.74 to 1.04)	0.93 (0.83 to 1.03)	.34	.72	.59

*RR = relative risk; CI = confidence interval. For context, the weight is 224 g for 8 oz of milk, 28 g for 1 oz of cheese, and 227 g for 1 cup of yogurt.

†The New York State Cohort was not included in the top category due to limited intake distribution.

‡Multivariable relative risks were adjusted for smoking (never, past smoker <20 years' duration, past smoker 20–39 years' duration, past smoker ≥40 years' duration, current smoker <25 cigarettes per day and <40 years' duration, current smoker ≥25 cigarettes per day and <40 years' duration, current smoker <25 cigarettes per day and ≥40 years' duration, or current smoker ≥25 cigarettes/day and ≥40 years' duration), body mass index (<23, 23 to <25, 25 to <30, or ≥30 kg/m^2), education (less than high school, high school graduate, or more than high school), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, or ≥1.75 m for women; <1.70, 1.70 to <1.75, 1.75 to <1.80, 1.80 to <1.85, or ≥1.85 m for men), physical activity (low, medium, or high), family history of colorectal cancer (no, yes), use of nonsteroidal anti-inflammatory drugs (no, yes), use of multivitamins (no, yes <6/wk, yes ≥6/wk, or yes missing dose for the Health Professionals Follow-up Study, Iowa Women's Health Study, and Nurses' Health Study (a) and (b); no, yes, for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Netherlands Cohort Study, and New York State Cohort), energy intake (continuous), alcohol intake (0, >0–<5, 5–<15, 15–<30, ≥30 g/day), red meat (quartiles), and dietary folate (quintiles). For women, the relative risks were also adjusted for history of oral contraceptive use (no, yes) and postmenopausal hormone use (premenopausal, ever, never).

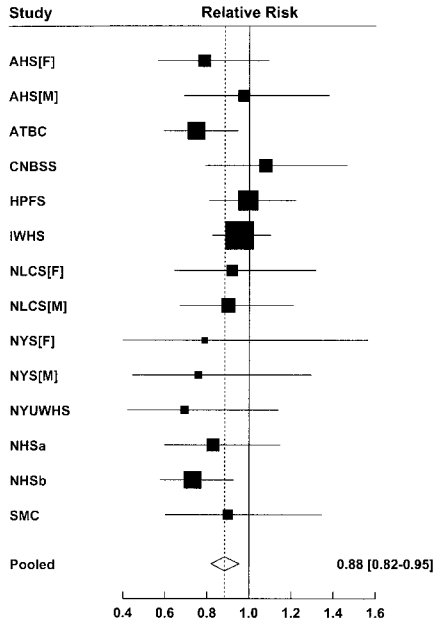

Fig. 1. Study-specific and pooled multivariable relative risks of colorectal cancer for each 500-g/day (approximately two 8-oz glasses) increase in milk intake. The **black squares** and **horizontal lines** correspond to the study-specific relative risks and 95% confidence intervals for a 500-g/day increase in milk intake. The area of the black squares reflects the study-specific weight (inverse of the variance), which is related to sample size and intake variation. The **diamond** represents the pooled multivariable relative risk and 95% confidence interval. The **dashed line** represents the pooled multivariable relative risk. Studies that included data on both sexes were considered as individual cohorts and are designated by F (female) and M (male), respectively. AHS = Adventist Health Study; ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; CNBSS = Canadian National Breast Screening Study; HPFS = Health Professionals Follow-up Study; IWHS = Iowa Women's Health Study; NLCS = Netherlands Cohort Study; NYSC = New York State Cohort; NYUWHS = New York University Women's Health Study; NHSa = Nurses Health Study (a); NHSb = Nurses Health Study (b); SMC = Sweden Mammography Cohort.

model using the likelihood ratio test and by visual inspection of the graphs *(36,37).* Studies were combined into a single dataset stratified by study for these analyses. Four knot positions were specified at the 5th (406 mg/day), 35th (716 mg/day), 65th (997 mg/day), and 95th percentiles (1667 mg/day) for calcium intake based on the intake distribution across all studies.

To evaluate heterogeneity, we tested for variation in relative risks by sex and vitamin D intake by using meta-regression models *(38).* We evaluated whether associations differed by subsite of the large bowel (proximal colon, distal colon, and rectum), using a Wald test *(39,40)* to test the null hypothesis of no difference among the $\log_e$ rate ratios.

RESULTS

During follow-up, which ranged from up to 6 to 16 years across the 10 cohort studies, 4992 incident cases of colorectal cancer were documented (Table 1). Milk intake was the lowest (137 g/day) in the New York State Cohort and highest (687 g/day) in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. By contrast, yogurt consumption was the highest (53 g/day and 104 g/day) in The Netherlands Cohort Study and Sweden Mammography Cohort, respectively, in which milk intakes were low. On the other hand, in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and most of the U.S. cohorts, more than 50% of the participants did not consume yogurt.

Milk consumption was inversely related to colorectal cancer risk (Table 2). Compared with participants who consumed less than 70 g/day of milk, the pooled multivariate relative risks for colorectal cancer were 0.94 (95% CI = 0.86 to 1.02) for those who consumed 70–174 g/day, 0.88 (95% CI = 0.81 to 0.96) for those who consumed 175–249 g/day, and 0.85 (95% CI = 0.78 to 0.94) for those who consumed 250 g/day or more (test for between-study heterogeneity, $P = .63$; $P_{trend} < .001$). The inverse associations with milk consumption were similar in women and men; the pooled multivariable relative risks for participants who consumed 250 g/day or more of milk compared with participants who consumed less than 70 g/day were 0.84 (95% CI = 0.75 to 0.94) for women (n = 3188) and 0.90 (95% CI = 0.74 to 1.10) for men (n = 1804) (test for between-study heterogeneity due to sex, $P = .49$). Each 500-g/day (approximately two 8-oz glasses) increase in milk consumption was associated with a 12% reduced risk of colorectal cancer (Fig. 1). The inverse association for milk consumption was highly consistent across studies (test for between-study heterogeneity, $P = .64$). Cheese intake was weakly positively associated and yogurt intake was weakly inversely associated with colorectal cancer risk, but trends for neither were statistically significant (Table 2).

We also examined colorectal cancer risk associations with intake of other dairy foods, including cottage or ricotta cheese, butter, cream, and ice cream, which were measured in at least five studies. Participants who consumed more than 25 g/day (highest intake category) of cottage or ricotta cheese had an RR of 0.83 (95% CI = 0.72 to 0.96) compared with those who did not consume cottage or ricotta cheese (lowest intake category). Other dairy foods were not statistically significantly related to a reduced risk of colorectal cancer (data not shown). The association with fermented dairy fluid products, which include yogurt, buttermilk, and sour cream, was similar to that of yogurt; the relative risk for participants who consumed the most compared with those who consumed the least was 0.91 (95% CI = 0.82 to 1.00).

Because the association between dairy foods and colorectal cancer risk may vary by cancer site, we analyzed associations for cancers of the colon (proximal and distal colon) and rectum separately (Table 3). The associations for milk consumption varied by cancer site (test for common effects by cancer site, $P = .03$), and the inverse association was limited to cancers of the distal colon and rectum. The associations between cheese or yogurt consumption and colorectal cancer risk were not statistically significantly different across the cancer site of the large bowel.

High intakes of dietary and total calcium (i.e., from diet and supplements) were associated with a lower risk of colorectal cancer (Table 4). When we limited the analysis of dietary calcium to the subset of studies with total calcium intake, the results were similar to those shown in Table 4 (data not shown).

To examine more extreme contrasts, we compared the top and bottom deciles of calcium intake. The RRs for colorectal cancer were 0.79 (95% CI = 0.67 to 0.88; $P_{trend} = .004$) for dietary calcium and 0.70 (95% CI = 0.59 to 0.83; $P_{trend} < .001$) for total calcium intake. When we evaluated absolute intake categories of calcium intake across studies, the results were consistent with those from quantile analyses. Compared with participants with an intake of less than 500 mg/day (referent),

Table 3. Pooled multivariable relative risks (95% confidence interval) by cancer site of colorectal cancer according to dairy food intake*

Cancer site	Intake category (g/day)				P_{trend}	*P*, test for between-study heterogeneity for top category	*P*, test for between-study heterogeneity due to sex for top category	*P*, test for common effects by cancer site (proximal colon, distal colon, and rectum) for top category
				***Milk*†**				
	<70	70–174	175–249	≥250				
Colon (n = 3482)	1.00 (referent)	0.94 (0.85 to 1.04)	0.88 (0.80 to 0.97)	0.88 (0.79 to 0.99)	.01	.76	.80	
Proximal (n = 1732)	1.00 (referent)	1.00 (0.87 to 1.16)	0.91 (0.79 to 1.06)	0.99 (0.85 to 1.15)	.56	.79	.65	
Distal (n = 1471)	1.00 (referent)	0.89 (0.76 to 1.04)	0.85 (0.73 to 0.98)	0.73 (0.62 to 0.87)	<.001	.99	.64	
Rectal (n = 1437)	1.00 (referent)	0.94 (0.77 to 1.15)	0.89 (0.76 to 1.05)	0.80 (0.66 to 0.96)	.02	.34	.36	.03
				Cheese, excluding cottage, ricotta, and cream cheese				
	<5	5–13	14–24	≥25				
Colon (n = 2912)	1.00 (referent)	1.03 (0.92 to 1.16)	1.02 (0.86 to 1.22)	1.14 (0.95 to 1.36)	.38	.10	.30	
Proximal (n = 1505)	1.00 (referent)	1.05 (0.91 to 1.20)	0.93 (0.77 to 1.12)	1.21 (1.00 to 1.45)	.20	.78	.46	
Distal (n = 1238)	1.00 (referent)	1.00 (0.84 to 1.20)	1.11 (0.88 to 1.39)	1.03 (0.84 to 1.26)	.94	.61	.60	
Rectal (n = 1208)	1.00 (referent)	1.06 (0.90 to 1.26)	1.19 (0.98 to 1.44)	1.08 (0.86 to 1.36)	.28	.31	.47	.47
				Yogurt				
	0	1–24	25–74	≥75				
Colon (n = 2724)	1.00 (referent)	0.98 (0.88 to 1.09)	0.86 (0.75 to 1.00)	0.89 (0.78 to 1.01)	.22	.76	.71	
Proximal (n = 1396)	1.00 (referent)	0.96 (0.82 to 1.12)	0.76 (0.60 to 0.96)	0.85 (0.68 to 1.06)	.13	.18	.84	
Distal (n = 1166)	1.00 (referent)	1.05 (0.89 to 1.24)	1.03 (0.84 to 1.27)	0.93 (0.76 to 1.14)	.64	.75	.74	
Rectal (n = 1129)	1.00 (referent)	0.88 (0.73 to 1.00)	0.98 (0.72 to 1.33)	1.03 (0.86 to 1.25)	.73	.75	.23	.41

*The relative risks were adjusted for the same covariates as the multivariate model in Table 2. Colon cancers were considered to be those from the cecum through the sigmoid colon. Tumors from the cecum to the splenic flexure were considered to be proximal colon cancers, and the remaining tumors in the colon were defined as distal colon cancers. Rectal cancers included tumors in the rectum and the rectosigmoid junction.

†The New York State Cohort was not included in the top category due to limited intake distribution.

the RRs were 0.90 (95% CI = 0.73 to 1.11) for those with an intake of 500–599 mg/day, 0.83 (95% CI = 0.66 to 1.05) for those with an intake of 600–699 mg/day, 0.79 (95% CI = 0.67 to 0.94) for those with an intake of 700–799 mg/day, 0.89 (95% CI = 0.74 to 1.06) for those with an intake of 800–899 mg/day, 0.79 (95% CI = 0.67 to 0.93) for those with an intake of 900–1099 mg/day, 0.76 (95% CI = 0.64 to 0.91) for those with an intake of 1100–1299 mg/day, and 0.74 (95% CI = 0.62 to 0.88) for those with an intake of 1300 mg/day or more (P_{trend}<.001). In nonparametric regression analyses, the plot was also suggestive of a threshold effect of total calcium intake, with little further reduction in the risk of colorectal cancer with calcium intakes of more than approximately 1000 mg/day (Fig. 2).

Additional adjustment for total vitamin E, total fat, and dietary fiber intake did not materially change the results for total calcium intake (data not shown). For dietary calcium and total calcium, the pattern of the associations by colorectal cancer disease location was similar to that observed for milk intake.

Because dairy foods are a good source of vitamin D, which has been hypothesized to reduce colorectal cancer risk *(41)*, we examined the independent effects of calcium and vitamin D intakes in the five studies with total vitamin D intake data (n = 2816 colorectal cancer cases). Spearman correlation coefficients for total calcium and total vitamin D were generally more than 0.5 across studies. In analyses in which both nutrients were included in the multivariable models, the relative risk for the highest quintile of total calcium intake compared with the lowest changed slightly but was still statistically significant (from 0.78 [95% CI = 0.69 to 0.88] to 0.83 [95% CI = 0.72 to 0.95]), and the corresponding relative risk for total vitamin D changed from 0.86 (95% CI = 0.73 to 1.01) to 0.93 (95% CI = 0.79 to 1.10) after the adjustment. Table 5 presents the results for total calcium intake by tertiles of total vitamin D intake. Although the

Table 4. Pooled relative risks and 95% confidence intervals of colorectal cancer according to energy-adjusted calcium intake

Cases and RRs	Intake quintile					P_{trend}	*P*, test for between-study heterogeneity for quintile 5	*P*, test for between-study heterogeneity due to sex for quintile 5
	1 (low)	2	3	4	5 (high)			
				Dietary calcium				
No. of cancer cases	1062	999	978	1007	946			
Age-adjusted RR (95% CI)	1.00 (referent)	0.93 (0.83 to 1.04)	0.89 (0.81 to 0.97)	0.90 (0.81 to 1.01)	0.83 (0.76 to 0.91)	<.001	.92	.36
Multivariate* RR (95% CI)	1.00 (referent)	0.94 (0.84 to 1.05)	0.91 (0.83 to 0.99)	0.93 (0.83 to 1.04)	0.86 (0.78 to 0.95)	.02	.98	.66
				Total calcium				
No. of cancer cases	665	589	627	552	552			
Age-adjusted RR (95% CI)	1.00 (referent)	0.86 (0.77 to 0.97)	0.88 (0.79 to 0.99)	0.76 (0.68 to 0.85)	0.74 (0.64 to 0.83)	<.001	.98	.72
Multivariate† RR (95% CI)	1.00 (referent)	0.87 (0.78 to 0.97)	0.90 (0.80 to 1.01)	0.79 (0.70 to 0.88)	0.78 (0.69 to 0.88)	<.001	.97	.83

*The relative risks were adjusted for the same covariates as the multivariable model in Table 2. RR = relative risk; CI = confidence interval.

†The relative risks were adjusted for the same covariates except multivitamin use as the multivariable model in Table 2.

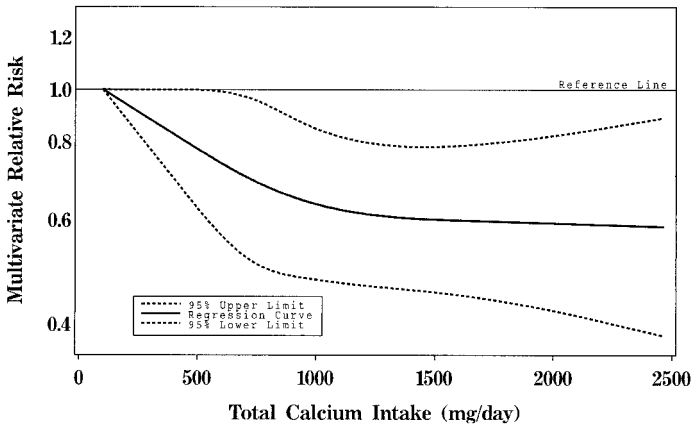

Fig. 2. Nonparametric regression curve for the relationship between total calcium intake and colorectal cancer. We excluded participants in the top 1% of total calcium intakes in each study to avoid excessive influence of extreme intakes and treated the studies as a single data set.

test for heterogeneity for the highest quintile of total calcium intake across tertiles of total vitamin D intake was not statistically significant ($P = .29$), total calcium intake was statistically significantly inversely associated with colorectal cancer risk only within the highest tertile of total vitamin D intake. We also examined the cross-classifications of these nutrients modeled as tertiles. The relative risk was the lowest (RR = 0.74, 95% CI = 0.65 to 0.84) for persons in the highest tertiles of both total calcium and total vitamin D intake compared with the lowest tertile of intake for both nutrients.

We also examined associations with milk, calcium, and vitamin D intakes when all three dietary factors were included in the model simultaneously among the five studies that measured all three dietary factors (Spearman correlation coefficients between milk and total calcium intake ranged from 0.38 to 0.78 across studies and between milk and total vitamin D intake were generally more than 0.3 across studies). The multivariate relative risk for the highest category of milk intake (≥250 g/day) was attenuated from 0.80 (95% CI = 0.70 to 0.91) to 0.84 (95% CI = 0.71 to 1.00) after simultaneous adjustment for total calcium and total vitamin D intakes. The relative risk for the highest quintile of total calcium was attenuated from 0.78 (95% CI = 0.69 to 0.88) to 0.90 (95% CI = 0.77 to 1.05). The highest quintile of total vitamin D was attenuated from 0.86 (95% CI = 0.74 to 1.01) to 0.96 (95% CI = 0.81 to 1.14).

To calculate the population attributable risk for calcium intake for women and men separately, we combined studies of the same sex into a single dataset and used the age-adjusted relative risk and prevalence of calcium intakes of less than 1000 mg/day (76% of women and 58% of men). Assuming that the association between calcium and colorectal cancer risk is causal, if individuals who consumed less than 1000 mg/day of calcium increased their intake to 1000 mg/day or more, 15% and 10% of the colorectal cancer cases in this study population would have been avoided for women and for men, respectively.

DISCUSSION

In these pooled analyses of prospective studies, we found that milk and calcium intakes were related to a lower risk of colorectal cancer. The inverse associations were consistent across studies and sex.

A growing body of evidence indicates that calcium prevents colorectal carcinogenesis by influencing a complex series of signaling events induced at various tiers of colonic cell organization *(42).* Several animal studies *(3)* and some *(4,6,43–45),* but not all *(46–49),* clinical trials have shown that consumption of calcium and dairy food reduced colonic epithelial cell proliferation. Clinical trials also have suggested that calcium intake reduced the recurrence of colorectal adenomas *(5,50).* However, none of these trials directly evaluated the effects of dairy foods or calcium on colorectal cancer risk.

Many epidemiologic studies have examined consumption of dairy foods and/or calcium and colorectal cancer risk, but their findings have been inconclusive. A meta-analysis of the published literature *(10),* which included a few of the studies in the current analyses, found an inverse association with milk intake for cohort studies (RR = 0.80 [95% CI = 0.68 to 0.95; *P* heterogeneity = .77] for high versus low intake) but not for case–control studies. The analysis found no clear association between cheese or yogurt intake and colorectal cancer, consistent with our findings. The meta-analysis did not provide data on the dose–response relationship of dairy food intake and colorectal cancer risk because published data with different intake cut points across studies were combined. For calcium intake and colorectal cancer risk, a meta-analysis of 24 studies (eight cohort and 16 case–control studies) *(8),* which included some of the studies in the current analysis, reported an RR of 0.86 (95% CI = 0.74 to 0.98) for individuals in the highest category of calcium intake compared with individuals in the lowest category. There was significant heterogeneity across the studies, whereas we found no suggestion of heterogeneity among the cohort studies included in our analysis for calcium or any of the dairy products examined.

Among the dairy items we examined, only milk consumption was statistically significantly associated with a lower risk of

Table 5. Pooled multivariable relative risks for total calcium intake by levels of total vitamin D Intake*

Tertile of total vitamin D intake	Quintile of total calcium intake					P_{trend}	*P*, test for between-study heterogeneity for quintile 5	*P*, test for between-study heterogeneity due to sex for quintile 5
	1 (low)	2	3	4	5 (high)			
1 (n = 1001)	1.00 (referent)	0.88 (0.75 to 1.03)	1.04 (0.86 to 1.25)	0.73 (0.52 to 1.01)	0.87 (0.64 to 1.18)	.08	.70	.17
2 (n = 954)	1.00 (referent)	1.00 (0.77 to 1.30)	0.88 (0.66 to 1.19)	0.87 (0.67 to 1.13)	0.96 (0.73 to 1.26)	.88	.42	.84
3 (n = 861)	1.00 (referent)	0.77 (0.58 to 1.02)	0.79 (0.60 to 1.03)	0.70 (0.54 to 0.91)	0.72 (0.55 to 0.92)	.04	.78	.29

*The relative risks were adjusted for the same covariates except multivitamin use as the multivariable model in Table 2. *P,* test for heterogeneity for quintile 5 of total calcium intake across tertiles of total vitamin D intake was .29.

colorectal cancer, although the results for most of the other dairy foods were suggestive of inverse associations. This difference may have occurred because milk had a wider intake distribution than that of other dairy products. Another explanation: U.S.-based national surveys have reported that milk is the most important contributor to dietary calcium intake *(51)*.

Calcium intake was inversely associated with the risk of colorectal cancer, with the inverse association being statistically significant only among those in the highest vitamin D intake category, although the difference in associations across vitamin D intake levels was not statistically significant. In addition, in a cross-classified analysis, the inverse association was strongest for the highest versus the lowest intakes of both nutrients together, possibly because vitamin D enhances calcium absorption and vitamin D itself may decrease colorectal cancer incidence *(52)*. In our analyses, we could not distinguish clearly between the effects of milk and calcium because of their strong correlation in most studies. Calcium in milk is highly bioavailable, which may make milk appear to be associated with colorectal cancer risk independent of total calcium intake. Also, other components in milk may contribute to the inverse association. Dairy foods contain conjugated linoleic acid and lactoferrin, which inhibit colonic carcinogenesis in animal models *(53,54)*, and the milk protein casein has antimutagenic activity on the digestive tract *(55)*. Certain microorganisms in fermented dairy foods have also been hypothesized to reduce the risk of colorectal cancer *(12)*. In our study, fermented food products such as yogurt or cheese, or fermented dairy fluids as a whole, were not strongly associated with colorectal cancer risk, but we had a limited ability to detect an association because the consumption of these foods was relatively low in most of the cohort studies.

Some of the etiologic factors for cancers of the proximal and distal colon may differ *(56,57)*. Cancers of the distal colon have been hypothesized to be more related to exogenous factors such as diet than cancers of the proximal colon *(56,57)*. We found that the inverse association between milk intake and colorectal cancer risk was limited to cancers of the distal colon and rectum, which is consistent with results of some of the previous studies *(58–60)* but not others *(61)*.

Our study has several strengths. By including only prospective cohort studies that used validated diet assessment instruments, we minimized the possibility of bias and misclassification. Furthermore, by examining the primary data instead of the published literature and applying uniform criteria to define the food and nutrient variables and other covariates, if available, we minimized potential sources of heterogeneity and improved comparability of the results across the studies. We were able to evaluate the associations across several populations with different dietary intake patterns and confirmed that the results were consistent across these studies. We examined calcium intake as study-specific quantiles as well as categories based on identical absolute intake cut points. Analyses using study-specific quantiles rank and classify participants using identical methods across studies and ensure that there are enough cases in each category. However, if distributions of intake across the studies are different, each quantile may not be comparable across studies. Analyses using identical absolute intake cut points take advantage of the actual range of intakes but assume that the intakes are measured comparably across studies. Despite these different analytic approaches and different sources of potential misclassification, we found that the results for these two approaches were consistent. Because information on calcium supplements was available in only four of the studies and the amount of calcium in multivitamins is usually small, we had limited ability to examine very high calcium intakes.

In summary, in this pooled analysis of 10 prospective studies, we found that increased consumption of milk and calcium were related to a lower risk of colorectal cancer. These data, in combination with the previous experimental studies documenting a salutary effect of calcium supplementation on colonic epithelial cell turnover and colorectal adenoma recurrence, support the concept that moderate milk and calcium intake reduces the risk of colorectal cancer.

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