Dietary and Supplemental Calcium and the Recurrence of Colorectal Adenomas[1]

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Abstract

The association between calcium intake and the risk of colorectal neoplasia remains controversial. This analysis prospectively investigated the association between dietary and supplemental calcium intake and recurrent colorectal adenomas. Participants were part of a multicenter, randomized clinical trial of antioxidant vitamins. The study endpoints were adenomas detected between surveillance colonoscopies conducted at approximately 1 year and 4 years after study entry. Baseline intake of energy-adjusted calcium derived from a food frequency questionnaire was used as the main exposure of interest. Calcium supplement use was assessed by semiannual questionnaires. Logistic regression was used to compute odds ratios and 95% confidence limits, and Poisson regression was used to estimate rate ratios. Subjects in the fifth quintile of dietary calcium had an adjusted odds ratio of 0.72 (95% confidence interval, 0.43–1.22) compared to those in the lowest quintile. Investigation of the numbers of adenomas yielded stronger findings: the rate ratio for the fifth quintile *versus* the first was 0.63 (95% confidence interval, 0.39–1.02). Dietary calcium seemed to have a greater effect among individuals with a high-fat diet than among those with a low-fat diet; however, the interaction was not statistically significant. Use of calcium supplements was not related to adenoma recurrence. These results suggest that a high calcium intake may be associated with a reduction in risk of recurrent adenomas, especially among individuals on a high-fat diet.

Introduction

Colorectal cancer clearly has environmental determinants: incidence varies around the world; and migrants from low-risk to high-risk areas experience a rapid increase in rates compared to those of their host country (1, 2). Diet is thought to play an important role in the etiology of this cancer: dietary patterns characterized by relatively large intakes of fat (especially from red meats) and relatively low intakes of fruit and vegetables have repeatedly been associated with an increased risk (3–5).

It has been hypothesized that dietary calcium may exert a protective effect on colorectal cancer risk through the precipitation of bile acids in the bowel lumen (6), thus reducing their potential to irritate the mucosa and exert a proliferative effect (7). Indeed, some, but not all, studies have observed an inverse association between dietary calcium intake and the risk of colorectal cancer (8–12). The mechanism proposed suggests that calcium will have a greater protective effect on individuals with a high-fat diet, an association that has been observed in some animal studies (13).

The great majority of colorectal cancers are thought to originate as adenomatous polyps (14, 15), and many aspects of the epidemiology of these preneoplastic lesions parallel that of colorectal cancer (16, 17). Consequently, investigation of adenomas clarifies the early stages of carcinogenesis in the large bowel. The goal of this analysis was to investigate prospectively the association between dietary and supplemental calcium intake and recurrent adenomas among participants in a chemoprevention clinical trial of antioxidant supplementation.

Patients and Methods

The Antioxidant Polyp Prevention Study was a multicenter, randomized clinical trial of supplementation with β-carotene or ascorbic acid and α-tocopherol in combination as preventive agents against the recurrence of large bowel adenomas. The principal findings of the study have been published; the study agents did not affect adenoma recurrence (18). The six study sites were the Cleveland Clinic, Dartmouth-Hitchcock Medical Center, the Lahey Clinic Medical Center, the University of California at Los Angeles/Kaiser Sunset, the University of Iowa, and the University of Minnesota. At each center, colonoscopy reports and pathology logs were used to identify patients who had at least one histologically confirmed adenoma removed during the 3 months before study entry. To be eligible for inclusion in the study, patients also must have undergone complete colonoscopy and been judged to be free of additional polyps, been less than 80 years old, been in good health, and agreed not to take vitamin preparations containing the study agents. Patients were excluded for invasive large bowel cancer, familial polyposis, inflammatory bowel disease, and malabsorption syndromes or any condition that might be worsened by dietary supplementation with β-carotene, vitamin C, or vitamin E (including a history of kidney stones or thrombophlebitis). All subjects provided informed consent at study entry.

After a 3-month placebo run-in period, 864 patients were randomly assigned to treatment groups using a 2 × 2 factorial design with blocking by study center. The two factors were: (*a*)

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Table 1 Characteristics at study entry by energy-adjusted baseline dietary calcium

	Calcium quintile				
	1	2	3	4	5
No. (%) with adenoma recurrence	56 (39.4)	57 (40.1)	58 (40.9)	46 (32.4)	43 (30.5)
% Male	83.1	85.9	79.6	71.8	71.6
Age (yr)[a]	59.3 ± 7.7	61.3 ± 8.2	61.9 ± 8.3	61.3 ± 8.5	61.9 ± 8.5
Study center					
Cleveland Clinic	26 (18.3)	24 (16.9)	22 (15.5)	33 (23.2)	20 (14.2)
Dartmouth	26 (18.3)	21 (14.8)	24 (16.9)	22 (15.5)	29 (20.6)
Iowa City	21 (14.8)	24 (16.9)	23 (16.2)	22 (15.5)	23 (16.3)
Lahey Clinic	14 (9.9)	20 (14.1)	28 (19.7)	20 (14.1)	19 (13.5)
Los Angeles	33 (23.2)	34 (23.9)	25 (17.6)	20 (14.1)	28 (19.9)
Minneapolis	22 (15.5)	19 (13.4)	20 (14.1)	25 (17.6)	22 (15.6)
No. of prior adenomas[a]	2.6 ± 2.2	3.2 ± 5.8	2.2 ± 2.0	2.5 ± 1.8	2.2 ± 2.0
Median size of the largest adenoma (cm)	0.4	0.3	0.4	0.4	0.4
Median intake/day					
Calcium (mg)	469	724	772	962	1370
Saturated fat (g)	26.4	28.7	25.8	25.9	25.4
Total fat (g)	82.4	88.5	75.1	72.0	75.5
Total energy (kcal)	1875	1956	1780	1785	1922

[a] Mean ± SD.

placebo or 25 mg/day of β-carotene; and (*b*) placebo or the combination of 1 g/day of vitamin C and 400 mg/day of vitamin E. The study included two follow-up colonoscopic examinations, the first at approximately 1 year after the qualifying colonoscopy (year 1), and the second approximately 3 years later (year 4). At each colonoscopy, all raised mucosal lesions were excised and examined histologically. The polyps were classified as neoplastic (adenoma) or nonneoplastic (hyperplastic, lymphoid follicle, and so forth).

The participants' diets were assessed by the standardized food frequency questionnaire developed by the National Cancer Institute (19); this was completed at enrollment and at the end of the study. In addition, at enrollment and every 6 months, the participants were sent a questionnaire regarding illnesses and hospitalizations, adherence to the study protocol, and use of vitamin supplements, including β-carotene; vitamins C, D, and E; nutritional supplements (including calcium); and over-the-counter medications. Use of calcium supplements was ascertained from responses to these questionnaires.

In this analysis, as in the trial itself, the primary endpoint was colorectal adenomas in the interval after the year 1 examination, up to and including the year 4 colonoscopic examination. Adenomas detected at the year 1 colonoscopy were not used as the principal study endpoints, because of concerns that some of these might represent small adenomas that were missed at the qualifying colonoscopy and would not truly be recurrent adenomas.

The exposures considered were dietary calcium as reported at baseline and the use of calcium supplements as reported at baseline and on interval questionnaires. We hypothesized that calcium intake would be associated with a reduced proportion of patients who would have at least one new (recurrent) adenomatous polyp detected during the interval from the year 1 to (and including) the year 4 colonoscopic examinations.

ORs[3] and 95% CIs for having at least one recurrent adenomatous polyp were used as measures of association. These were calculated by unconditional multiple logistic regression (20). Energy adjustment was achieved using the residuals from the regression of the log of dietary calcium on the log of total caloric intake (21). Quintiles of energy-adjusted calcium were used as the exposure of interest; the cutpoints for the quintiles were 610, 752, 879, and 1044 mg/day. In logistic regression models, these quintiles were adjusted for age, sex, study center, the exact interval between the year 1 and year 4 examination, the log of total calories consumed, and the quintile of residuals of total fat intake. The supplement models were adjusted for age, sex, study center, and the length of the interval between the year 1 and year 4 exams. Because the study agents did not have any substantial effect on recurrence, treatment assignment was omitted from the analyses. Adjusted trend tests were performed, treating the calcium residuals as a continuous variable.

We used Poisson regression to investigate the relationship between calcium intake and the number of adenomas occurring per patient. These models yield RRs that can be interpreted as the ratio of the adjusted mean number of adenomas in one group divided by that in another (reference) group. The dispersion parameter for the models was estimated by the Pearson χ^2 statistic divided by its degrees of freedom. SEs were adjusted accordingly (22).

Results

Of the 864 patients enrolled in the clinical trial, 751 underwent both year 1 and year 4 colonoscopic examinations. Of the 113 patients who did not receive both exams, 44 died, 32 did not wish to continue in the study, 19 moved or became too ill to continue, and 18 dropped out for unknown reasons. Nine patients did not complete any interval questionnaires, leaving 742 patients for the analyses of the effects of calcium supplementation. An additional 33 patients did not provide baseline dietary information, leaving 709 patients for the dietary calcium analysis.

The subjects in each energy-adjusted dietary calcium quintile were similar in their distribution of age, study center, and the number of prior adenomas removed. However, the percentage of women was higher in quintiles 4 and 5 (Table 1). During the study interval, 260 of the 709 patients (36.7%) had at least

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; RR, rate ratio.

Table 2 ORs for the development of at least 1 right- or left-side adenoma and RRs of the numbers of right- or left-side adenomas, according to energy-adjusted baseline dietary calcium quintile

Quintile of dietary calcium intake	*N* (with/without adenomas)	Logistic regression	Poisson regression
		Adjusted OR (95% CI)[a]	Adjusted RR (95% CI)[a]
Overall			
1	56/86	1.00	1.00
2	57/85	1.02 (0.62–1.67)	1.51 (1.04–2.20)
3	58/84	1.08 (0.66–1.78)	1.04 (0.69–1.56)
4	46/96	0.85 (0.51–1.42)	0.77 (0.49–1.22)
5	43/98	0.72 (0.43–1.22)	0.63 (0.39–1.02)
P[b]		0.30	0.005
Right side[c]			
1	36/106	1.00	1.00
2	39/103	1.10 (0.63–1.90)	1.98 (1.20–3.27)
3	33/109	0.87 (0.50–1.54)	1.16 (0.67–2.03)
4	28/114	0.83 (0.46–1.49)	0.96 (0.52–1.75)
5	23/118	0.63 (0.34–1.16)	0.68 (0.36–1.31)
P[b]		0.14	0.05
Left side[c]			
1	33/109	1.00	1.00
2	34/108	0.99 (0.56–1.74)	1.05 (0.67–1.63)
3	36/106	1.10 (0.62–1.93)	0.91 (0.57–1.45)
4	23/119	0.66 (0.36–1.23)	0.59 (0.34–1.01)
5	27/114	0.76 (0.42–1.40)	0.58 (0.34–0.99)
P[b]		0.14	0.01

[a] Adjusted for age, sex, study center, length of time between the year 1 and year 4 examinations, total energy intake, and energy-adjusted baseline dietary fat.
[b] *P* for trend with calcium residual as a continuous variable.
[c] Right side, cecum, ascending colon, and transverse colon; left side, splenic flexure, descending colon, and rectum.

one large bowel adenoma detected and confirmed histopathologically. Adenomas were found in 39.4% of the patients in calcium intake quintile 1 and in 30.5% of those in quintile 5.

The risk of at least one recurrent adenoma was modestly and nonsignificantly reduced in calcium intake quintiles 4 and 5; the adjusted OR for quintile 5 *versus* quintile 1 was 0.72 (95% CI, 0.43–1.22) with a *P* of 0.30 (Table 2). There was no further reduction in risk with higher intake: the OR in the highest decile of calcium intake was 0.83 (95% CI, 0.44–1.58). Findings in the right large bowel (proximal to the splenic flexure) and left large bowel (splenic flexure to rectum) were broadly similar (Table 2).

The adjusted RRs displayed more marked patterns. The RR for quintile 5 of energy-adjusted calcium intake *versus* quintile 1 was 0.63 (95% CI, 0.39–1.02). Despite an elevated RR in quintile 2, there was a highly significant trend of decreasing numbers of adenomas with increasing calcium intake ($P = 0.005$; Table 2). The inverse association of decreasing numbers of adenomas with increasing calcium intake was particularly marked in the left colorectum (Table 2).

Among the 742 patients included in the analysis of calcium supplementation, 8.7% of males and 36.5% of females reported at least some supplement use at baseline or during the trial. Users and nonusers were similar in their distributions of age and prior adenomas. A higher proportion of Los Angeles center participants used supplements than participants at other centers. As seen in Table 3, supplementation during the trial resulted in a modest reduction in the risk of adenoma recurrence among individuals who reported taking calcium on more than 30% of the interval forms: the adjusted OR was 0.76 (95% CI, 0.42–1.38). However, the RRs calculated from the Poisson regression suggested that supplementation was not related to the number of recurrent adenomas.

When the effect of dietary calcium was considered within the lowest and highest two quintiles of calorie-adjusted dietary fat, there were indications of a greater effect among individuals with a high fat intake (Table 4). Among individuals with a low fat intake, the OR for calcium quintile 5 *versus* quintile 1 was 1.05 (95% CI, 0.44–2.48), but among those with a high-fat diet, the OR was 0.52 (95% CI, 0.20–1.36). The *P* in the high-fat group was 0.07; for the low-fat group, it was 0.83. However, the interaction did not achieve statistical significance ($P = 0.22$), and the Poisson regression findings regarding the numbers of adenomas were similar in the low- and high-fat groups. The effects of calcium supplements had a different pattern: there was a reduction in risk only in the low-fat dietary group (Table 4).

There was no apparent association between an increased intake of dairy foods and the calorie-adjusted risk of adenoma recurrence (Table 5). However, there was a nonsignificant reduction in the number of recurrent adenomas among individuals who had greater than 2 servings/day of dairy foods *versus* those with less than 0.5 serving/day (calorie-adjusted rate ratio = 0.74; 95% CI, 0.46–1.21). Further adjustment for dietary fat did not alter these findings (data not shown).

Discussion

In this prospective study, there were suggestions of a reduction in the risk of recurrent adenomas among subjects with high dietary calcium. The reductions in risk were consistent with chance, although many of the linear trends were at least marginally significant. We found no overall association between calcium supplementation and adenoma recurrence, although there were some indications of an inverse association with risk among subjects with a lower fat intake.

Prior studies of dietary calcium and the risk of colorectal adenomas have generally not found an association. In the Health Professionals and Nurses Health Studies, there were slight (nonsignificant) increases in the risk of polyps in the distal colon and rectum associated with increased dietary calcium (23), findings hypothesized to be partly due to the low saturated fat and high dietary fiber consumption of the participants. A case-control study in France also found a nonsignificant increase in risk associated with calcium intake (24), and two other case-control studies reported no association between dietary calcium and either colorectal adenomas or carcinomas (25, 26). However, a case-control study in Norway using a 5-day dietary record did observe insignificantly higher mean calcium intakes in the control group than in cases (especially those with larger polyps; Ref. 27). A recent case-control study found a nonsignificant increase in risk of adenoma recurrence among users of calcium supplements. However, the authors felt that the association arose largely as the result of multiple comparisons (28).

There has been more investigation of colorectal cancer. These investigations have been inconsistent, but several have reported a reduction in risk associated with high dietary calcium (8, 9, 29, 30). Our finding of an apparent threshold has also been observed previously (11, 31). A substantial protective effect was observed in a 19-year cohort study (a decreasing risk of colon cancer with increasing dietary calcium intake, and a 67% reduction in risk with daily calcium intakes in excess of 1500 mg; Ref. 32). When colon cancer was used as an outcome in the Health Professionals Follow-Up Study, a threshold effect was observed for dietary calcium, with statistically significant age- and calorie-adjusted relative risks in quintiles 2, 3, and 5 (0.61 for quintile 5 *versus* quintile 1; Ref. 33). However, after further adjustment for diet and other risk factors, the reductions

Table 3 ORs for the development of at least one adenoma and RRs of the numbers of adenomas, according to calcium supplement use

Supplement use	No. of subjects	Logistic Regression	Poisson Regression
		Adjusted OR (95% CI)	Adjusted RR (95% CI)
At study entry			
No	638	1.00	1.00
Some use	109	1.25 (0.78–2.01)	0.99 (0.63–1.55)
At study entry and during study			
No use	576	1.00	1.00
1-30% of forms	89	0.88 (0.53–1.48)	0.89 (0.55–1.45)
31-100% of forms	86	0.76 (0.42–1.38)	1.04 (0.61–1.76)
P[b]		0.82	0.40

[a] Adjusted for age, sex, study center, length of time between year 1 and year 4 examinations, total energy intake, and energy-adjusted baseline dietary fat.
[b] *P* for trend with percentage of interval questionnaires reporting calcium supplement use as a continuous variable.

Table 4 ORs of at least one recurrent adenoma and RRs of the numbers of recurrent adenomas, according to dietary calcium intake, by dietary fat

	Low-fat diet[a]		High-fat diet[b]	
	OR of at least one adenoma	RR of the no. of adenomas	OR of at least one adenoma	RR of the no. of adenomas
A. Quintile of dietary calcium intake				
1	1.00	1.00	1.00	1.00
2	1.55 (0.58–4.16)	1.17 (0.56–2.47)	0.72 (0.36–1.44)	1.40 (0.88–2.23)
3	1.60 (0.64–3.99)	0.86 (0.41–1.77)	0.76 (0.37–1.58)	1.03 (0.61–1.73)
4	1.27 (0.52–3.09)	0.86 (0.44–1.69)	0.43 (0.18–1.04)	0.49 (0.22–1.08)
5	1.05 (0.44–2.48)	0.69 (0.34–1.38)	0.52 (0.20–1.36)	0.54 (0.24–1.21)
P[c]	0.83	0.09	0.07	0.03
B. Calcium supplement use: Percentage of questionnaires reporting use				
None	1.00	1.00	1.00	1.00
1–30%	0.45 (0.17–1.21)	0.46 (0.17–1.24)	1.24 (0.58–2.66)	1.18 (0.68–2.06)
31–100%	0.31 (0.10–1.04)	0.51 (0.18–1.48)	1.15 (0.47–2.82)	1.58 (0.81–3.07)
P[d]	0.12	0.29	0.35	0.05

[a] Low-fat diet, lowest two quintiles of calorie-adjusted total fat intake.
[b] High-fat diet, highest two quintiles of calorie-adjusted total fat intake.
[c] *P* for trend with calcium residual as a continuous variable.
[d] *P* for trend with percentage of interval questionnaires reporting calcium supplement use as a continuous variable.

Table 5 ORs of at least one adenoma and RRs of the numbers of adenomas according to intake of dairy foods

	N (with/without adenomas)	OR of at least one adenoma[a]	RR of the no. of adenomas[a]
≤1/2 serving/day	41/83	1.00	1.00
>1/2–1.25 servings/day	94/129	1.44 (0.90–2.31)	0.99 (0.66–1.50)
>1.25–2 servings/day	59/120	0.95 (0.57–1.57)	1.04 (0.68–1.61)
>2 servings/day	66/117	1.04 (0.61–1.79)	0.74 (0.46–1.21)
Per serving/day		0.94 (0.83–1.07)	0.90 (0.80–1.01)

[a] Adjusted for age, sex, study center, length of time between year 1 and year 4 examinations, and total energy intake.

in risk were attenuated (0.81 for quintile 5; Ref. 23). This contrasts with the finding of no association between dietary calcium and adenomas in the same population (20).

Calcium supplementation has been reported to lower fecal bile acid concentration (34) and to reduce colon cancer risk in women (35). However, most studies of supplemental calcium in humans have used an endpoint of mucosal proliferation. The results of these studies have been inconsistent, with some reporting no beneficial effect (36–40), and some finding a reduction in proliferation (41–43). Small sample size and lack of blinding limit interpretation of some of these studies.

The great majority of participants in our study underwent colonoscopic examinations according to study protocol, providing uniform surveillance for adenomas. Because all subjects in the trial had had adenomas, it is unlikely that our assessment of diet was biased with respect to adenoma recurrence. However, it is possible that our results were confounded by adenoma risk factors that have not yet been identified and were not included in our study. Inaccuracies in dietary data are another possible source of error.

Although we collected information on the use of vitamin and mineral supplements (including calcium), this component of the study had several weaknesses. Limited information on calcium dosage prevented investigation of possible dose-response patterns. Also, more than half of those reporting calcium supplementation used multivitamin preparations, which typically deliver 300 mg or less per day. Thus, the null findings regarding supplements may have been due to the low dose actually received. Alternatively, it is possible that the large calcium bolus provided by supplements has a different effect than calcium contained in foods.

In summary, the results of this study lend some support to the hypothesis that increased intake of dietary calcium is associated with a decreased risk of recurrent colorectal adenoma. However, there was no evidence that calcium supplementation

decreases the risk of recurrent adenomas. Continued study of dietary and supplemental calcium is necessary to understand their possible association with colorectal cancer and the mechanisms underlying this association and to determine whether it can reduce the incidence of this disease.

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