Effect of Calcium Supplementation on the Risk of Large Bowel Polyps

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**Background:** Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas. However, few studies have examined the effect of calcium on the risk of different types of colorectal lesions or dietary determinants of this effect. **Methods:** Our analysis used patients from the Calcium Polyp Prevention Study, a randomized, double-blind, placebo-controlled chemoprevention trial among patients with a recent colorectal adenoma. Nine hundred thirty patients were randomly assigned to calcium carbonate (1200 mg/day) or placebo. Follow-up colonoscopies were conducted approximately 1 and 4 years after the qualifying examination. We used general estimating equation (GEE) and generalized linear regression analyses to compare the calcium treatment effects for various types of polyps with that for tubular adenomas. Additionally, we examined the interaction between calcium treatment and baseline intake of dietary calcium, fat, and fiber. All P values were obtained using Wald tests based on the corresponding models. All tests of statistical significance were two-sided. **Results:** The calcium risk ratio for hyperplastic polyps was 0.82 (95% CI = 0.67 to 1.00), that for tubular adenomas was 0.89 (95% CI = 0.77 to 1.03), and that for histologically advanced neoplasms was 0.65 (95% CI = 0.46 to 0.93) compared with patients assigned to placebo. There were no statistically significant differences between the risk ratio for tubular adenomas and that for other types of polyps. The effect of calcium supplementation on adenoma risk was most pronounced among individuals with high dietary intakes of calcium and fiber and with low intake of fat, but the interactions were not statistically significant. **Conclusion:** Our results suggest that calcium supplementation may have a more pronounced antineoplastic effect on advanced colorectal lesions than on other types of polyps. [J Natl Cancer Inst 2004;96:921–5]

Extensive experimental animal evidence indicates that high calcium intake exerts an antineoplastic effect in the large bowel (1–3), but epidemiological studies have been inconsistent (4,5). Stronger evidence suggests that calcium protects against colorectal adenomas. Although epidemiologic studies on this point have also been conflicting (6–12), two randomized, placebo-controlled trials of calcium carbonate supplementation reported modest reductions in the risk of recurrent adenomas (13,14). No clinical trial data pertaining to the effects of calcium intake on colorectal cancer are available, and it is possible that the protective effect observed in the adenoma trials does not extend beyond the early stages of carcinogenesis (15). The clinical trial data reported to date used all adenomas as an endpoint, making no distinction among gradations of histologic characteristics or degree of dysplasia.

There are other important uncertainties regarding the chemopreventive effects of calcium. Only limited data are available regarding the calcium intake required for adenoma chemoprevention, although in one recent analysis, it appeared that an intake of about 700 mg daily would suffice, with little or no further benefit at higher intakes (16). In addition, it is not clear how other aspects of diet might alter the effects of calcium. In some animal studies, a high-calcium diet had the greatest effect among animals on a high-fat diet, and in other studies there was no effect of calcium in animals maintained on a lower fat intake (17). It has also been proposed that dietary fiber may bind to calcium in the gut; if so, a high-fiber diet might interfere with the chemopreventive effects of calcium (18,19). These possible interactions have not been well studied in humans.

To explore in greater detail the chemopreventive effect of calcium supplements, we analyzed data from a large multicenter trial of the effect of calcium supplementation on the recurrence of large bowel adenomas (13). Specifically, we examined the effect of calcium treatment on the risk of hyperplastic polyps, tubular adenomas and adenomas with advanced histology or large size. Additionally, we investigated the interactions between calcium supplementation and dietary calcium, fat, and fiber intakes on the risk of different types of colorectal polyps.

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See “Notes” following “References.”

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SUBJECTS AND METHODS

Our analysis is based on data from the Calcium Polyp Prevention Study, a randomized, double-blind, placebo-controlled chemoprevention trial (13). Study participants each had a history of at least one colorectal adenoma excised within the 3 months before entry and had no known polyps remaining in the entire large bowel after complete colonoscopic examination. After a 3-month run-in period, patients were randomly assigned to calcium carbonate (1200 mg/day) or placebo. At study enrollment, intakes of dietary calcium, fat, and fiber were assessed with a validated semiquantitative food frequency questionnaire (20). Written informed consent was obtained from each participant, and the study was approved by the Institutional Review Board of every participating institution.

Two follow-up colonoscopies after randomization were planned for each subject at approximately 1 and 4 years after the qualifying exam. Each colorectal lesion found during follow-up was histologically examined by the pathologist at the local clinical center and by the study pathologist, who categorized mucosal lesions with regard to histologic type and degree of dysplasia using standard criteria (21). In cases of disagreement regarding the presence or absence of neoplasia, the study pathologist’s diagnosis was accepted.

For this analysis, polyps were classified into different histologic categories: hyperplastic polyps, tubular adenomas, and “advanced histology neoplasms.” Advanced histology neoplasms included tubulovillous adenomas (25%–74% villous component), villous adenomas (≥75% villous component), severe dysplasia (carcinoma in situ), and invasive cancer. Neoplastic polyps were also classified into two size categories: small (<1 cm in diameter) and large (≥1 cm in diameter). An “advanced adenoma” was defined as a lesion that was large or that had advanced histology.

Statistical Analysis

Analysis was by intention-to-treat. The association of calcium treatment assignment with polyp risk was assessed using risk ratios (RRs) and 95% confidence intervals (CIs) calculated with generalized linear regression analyses using a logarithmic linkage and a binomial distribution (22). This model allows the results to be interpreted in terms of risk ratios as opposed to odds ratios. We used generalized estimating equation (GEE) methodology (23) in analyses that compared the calcium risk ratios for various types of polyps with that for tubular adenomas. In these comparative analyses, we simultaneously modeled the various polyp types using randomized treatment assignment, type of polyp, and the interaction of these two factors as predictors. Age, sex, and clinical center were included as adjustment factors. Multiple observations per subject arose in this analysis because we considered different lesion types in the same model (hyperplastic polyps, tubular adenomas, and more advanced lesions), and individual subjects may have had multiple lesion types at the same examination. The GEE estimation methodology was used to account for possible dependence among the multiple possible polyp types observed in each patient. P values for the comparison of calcium treatment effects between polyp types and tubular adenomas were based on the differences in log risk ratios. All tests of statistical significance were two-sided.

Using generalized linear regression, we evaluated the interactions of treatment assignment with dietary calcium, total dietary fat, and total dietary fiber. The estimated intakes of these nutrients were adjusted for caloric intake using residuals computed from the linear regression of the log of the nutrient intake on the log of caloric intake (24). Age- and sex-adjusted calcium risk ratios within tertiles of baseline calorie-adjusted dietary calcium, fat, or fiber were computed separately, according to polyp type, using maximum likelihood techniques. Clinical center was excluded from these models because of the sparseness of available data in analyses of advanced adenomas. The calcium risk ratios were essentially unaffected, however, by the presence or absence of the clinical center variable. We tested for the statistical significance of the interactions by adding product interaction terms to the regression models. We also performed linear tests of trend for the calcium effect across tertiles of baseline dietary calcium, fat, and fiber. All P values were obtained using Wald tests based on the corresponding models. All tests of statistical significance were two-sided.

RESULTS

Of the 930 subjects, 913 completed at least one follow-up examination in the 4 years after random assignment. Subjects randomly assigned to placebo (n = 459) or to calcium (n = 454) had similar characteristics at study entry (Table 1). The mean age of the study participants was 60.9 years (standard deviation ± 9.1), and 72.3% were men. Although those assigned to calcium had slightly higher dietary calcium and total caloric intake, these differences were clearly compatible with chance.

Among the 913 subjects, 279 (30.6%) had at least one hyperplastic polyp detected, and 382 (41.8%) had one or more tubular adenomas. Fewer subjects had adenomas with advanced histology (112 [12.3%]) or adenomas that were large (55 [6.0%]) (Table 2). All types of polyps occurred less frequently in the calcium treatment group than in the placebo group (Table 2). There was a modest reduction in risk for all adenomas (RR = 0.86, 95% CI = 0.75 to 0.99) considered together. As previously reported, calcium treatment assignment was associated with a similar reduction in risk for both small and large neoplasms (Table 2). In contrast, there were more pronounced differences in the calcium risk ratios within histologic categories of adenomas.

Table 1. Baseline characteristics in the Calcium Colorectal Polyp Prevention Trial among subjects completing at least one study examination (N = 913)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 459)</th>
<th>Calcium (n = 454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>322 (70)</td>
<td>338 (74)</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.0 ± 9.1</td>
<td>60.9 ± 9.1</td>
</tr>
<tr>
<td>Daily dietary intake†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>861.9 ± 419.9</td>
<td>890.5 ± 453.1</td>
</tr>
<tr>
<td>Fat, g</td>
<td>88.1 ± 42.9</td>
<td>87.6 ± 41.4</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>16.2 ± 7.8</td>
<td>16.6 ± 8.0</td>
</tr>
<tr>
<td>Calories, kcal</td>
<td>2008.1 ± 757.7</td>
<td>2044.4 ± 762.6</td>
</tr>
<tr>
<td>No. of previous adenomas‡</td>
<td>2.6 ± 2.8</td>
<td>2.4 ± 2.5</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation, unless otherwise noted.
†Dietary information was missing for 10 subjects in the placebo group and 13 subjects in the calcium group.
‡Lifetime number of colorectal adenomas found and removed before randomization.
mas. The risk ratio for tubular adenomas in subjects assigned to calcium compared with those assigned to placebo was 0.89 (95% CI = 0.77 to 1.03), while that for advanced histology neoplasms was much lower (0.65, 95% CI = 0.46 to 0.93; \(P_{\text{difference}} = .12\)). Among subjects assigned to calcium, the risk ratio for advanced neoplasms (i.e., those with advanced histology or large size) was 0.73 (95% CI = 0.53 to 1.00; \(P_{\text{difference}} = .27\)). Calcium treatment conferred a risk ratio of 0.82 (95% CI = 0.67 to 1.00; \(P_{\text{difference}} = .47\)) for hyperplastic polyps.

There were some indications that baseline dietary patterns modified the effect of calcium supplementation, particularly for advanced histology neoplasms. For tubular adenomas, there were no substantial differences in the calcium risk ratios across tertiles of baseline dietary calcium, fat, or fiber (Table 3). However, for advanced neoplasms, treatment was associated with a reduction in risk only among those in the highest tertile of dietary calcium (RR = 0.27, 95% CI = 0.12 to 0.63; \(P_{\text{trend}} = .10\)) (Table 3). Conversely, dietary fat seemed to counteract the effects of calcium supplementation. Among subjects in the lowest tertile of total dietary fat intake, those randomly assigned to calcium had a substantial reduction in risk of advanced histology neoplasms relative to those who were randomly assigned to placebo (RR = 0.51, 95% CI = 0.25 to 1.06), but for those in the highest tertile of fat intake, calcium supplementation provided a smaller reduction (RR = 0.90, 95% CI = 0.42 to 1.90; \(P_{\text{trend}} = .29\)). Subjects who had high intake of total dietary fiber experienced more pronounced effects of calcium supplementation than those with lower fiber intake (\(P_{\text{trend}} = .26\) (Table 3). None of these interactions achieved conventional statistical significance, however.

### DISCUSSION

In this randomized, double-blind, placebo-controlled trial, supplementation with calcium carbonate reduced the risk of all types of colorectal polyps. However, the protective effect seemed particularly pronounced for the advanced histologic lesions that are most strongly associated with invasive colorectal

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**Table 2.** The effect of randomized calcium treatment on the risk of different types of large bowel polyps

<table>
<thead>
<tr>
<th>Polyp type</th>
<th>Placebo*</th>
<th>Calcium*</th>
<th>RR (95% CI)</th>
<th>(P) value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polypl</td>
<td>154</td>
<td>125</td>
<td>0.82 (0.67 to 1.00)</td>
<td>.47</td>
</tr>
<tr>
<td>Tubular adenoma</td>
<td>204</td>
<td>178</td>
<td>0.89 (0.77 to 1.03)</td>
<td>—</td>
</tr>
<tr>
<td>Advanced histology neoplasm§</td>
<td>68</td>
<td>44</td>
<td>0.65 (0.46 to 0.93)</td>
<td>.12</td>
</tr>
<tr>
<td>Small neoplasm</td>
<td></td>
<td>221</td>
<td>190</td>
<td>0.86 (0.75 to 0.99)</td>
</tr>
<tr>
<td>Large neoplasm</td>
<td></td>
<td>32</td>
<td>23</td>
<td>0.72 (0.43 to 1.21)</td>
</tr>
<tr>
<td>Advanced adenoma¶</td>
<td>75</td>
<td>54</td>
<td>0.73 (0.53 to 1.00)</td>
<td>.27</td>
</tr>
</tbody>
</table>

*Number of subjects with at least one hyperplastic or neoplastic polypl. Four hundred fifty-nine subjects in the placebo group and 454 in the calcium group had at least one endoscopy.

†Risk ratio (RR) adjusted for age, sex, and clinical center. CI = confidence interval.

‡P values for difference of log risk ratios between tubular adenomas and other polyp types. All tests of statistical significance were two-sided.

§Advanced histology neoplasm is defined as tubulovillous or villous adenoma, carcinoma in situ, or invasive cancer (n = 10).

¶Small neoplasms were <1 cm and large neoplasms were ≥1 cm in diameter. Polyp size was unavailable for two subjects in the placebo group; consequently, the risk ratios for small and large neoplasms were based on 911 subjects.

¶¶Advanced adenoma is defined as a lesion that was large or that had advanced histology.

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**Table 3.** The effect of calcium treatment on the risk of different types of large bowel polyps, stratified by baseline calorie-adjusted intakes of dietary calcium, fat, and fiber*

<table>
<thead>
<tr>
<th>Nutrient†‡</th>
<th>Tubular adenoma &amp; Advanced histology neoplasm†</th>
<th>Placebo/calciu$m§</th>
<th>RR (95% CI)</th>
<th>Placebo/calciu$m§</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary calcium</td>
<td>Tertile 1 148/149</td>
<td>64/55</td>
<td>0.76 (0.47 to 1.21)</td>
<td>21/15</td>
<td>0.68 (0.33 to 1.39)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2 158/159</td>
<td>71/57</td>
<td>0.82 (0.51 to 1.30)</td>
<td>21/18</td>
<td>0.94 (0.48 to 1.86)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3 144/153</td>
<td>64/61</td>
<td>0.82 (0.51 to 1.30)</td>
<td>24/8</td>
<td>0.27 (0.12 to 0.63)</td>
</tr>
<tr>
<td></td>
<td>(P_{\text{trend}})</td>
<td>.82</td>
<td>—</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Dietary fat</td>
<td>Tertile 1 143/154</td>
<td>72/64</td>
<td>0.71 (0.44 to 1.12)</td>
<td>22/13</td>
<td>0.51 (0.25 to 1.06)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2 140/157</td>
<td>68/65</td>
<td>0.70 (0.44 to 1.12)</td>
<td>25/15</td>
<td>0.46 (0.23 to 0.92)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3 167/130</td>
<td>59/44</td>
<td>0.94 (0.58 to 1.52)</td>
<td>19/13</td>
<td>0.90 (0.42 to 1.90)</td>
</tr>
<tr>
<td></td>
<td>(P_{\text{trend}})</td>
<td>.41</td>
<td>—</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>Tertile 1 148/149</td>
<td>59/59</td>
<td>0.96 (0.60 to 1.55)</td>
<td>19/17</td>
<td>0.90 (0.45 to 1.83)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2 150/147</td>
<td>62/57</td>
<td>0.91 (0.57 to 1.46)</td>
<td>27/13</td>
<td>0.46 (0.23 to 0.94)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3 152/145</td>
<td>78/57</td>
<td>0.58 (0.36 to 0.92)</td>
<td>20/11</td>
<td>0.49 (0.22 to 1.07)</td>
</tr>
</tbody>
</table>

*RR = risk ratio; CI = confidence interval. Risk ratios were adjusted for age and sex.

†Advanced histology neoplasm is defined as tubulovillous or villous adenoma, carcinoma in situ, or invasive cancer.

‡Baseline dietary information was available for 891 subjects. Each tertile shows number of subjects in each experimental group (placebo/calciu$m$). Tertile 1 is the lowest.

§Number of neoplasms analyzed in placebo/calciu$m$ groups.

Wald tests were used to generate \(P\) values. All tests of statistical significance were two-sided.
cancer (25–27). The protective effect of supplemental calcium appeared to be strongest in subjects whose baseline dietary calcium intake was in the highest tertile, suggesting that a total calcium intake of greater than 1200 mg/day may be required to optimize chemopreventive efficacy. There were also indications that high intake of dietary fat may counter some of the benefits of supplemental calcium but that high intake of total dietary fiber did not interfere with the calcium effects.

To date, only two observational studies have analyzed the relationship between calcium intake and histologic type of colorectal adenomas; neither reported a difference in associations between adenomatous polyps and polyps with villous features (12,28). In both studies, however, there were few advanced lesions, relatively low dietary calcium intake, and no information on calcium supplement use. In addition, control subjects did not undergo colonoscopy, a design feature that could have biased the results toward the null, because it has been estimated that between 20% and 60% of the adult population harbors colorectal adenomas (29). Several studies (30–33) have examined the association of calcium intake with the risk of larger and smaller adenomas; as in our study, associations did not differ by size of adenoma. Our finding that calcium protected against the formation of hyperplastic polyps is also consistent with the results from other studies (34,35) and suggests some similarity in risk factors for hyperplastic polyps and adenomas.

The dose of calcium required for maximal chemopreventive effect is not clear. Our findings suggest that increasing calcium intake above 1200 mg/day lowers the risk of colorectal neoplasia. However, for several reasons, our data are not suited to the estimation of the exact magnitude of the optimal calcium intake. Our findings in this regard derive from secondary analyses of food frequency questionnaires, and the relevant interaction had only borderline statistical significance. These questionnaires are often designed largely to order individuals with regard to intake (24), not to precisely measure the amount taken in. Consequently, our dietary assessment instrument may have underestimated the amount of calcium actually consumed by our subjects (36). Further investigation will therefore be needed to clarify the optimal calcium dose.

In some animal studies, a protective effect of calcium on colorectal tumors has been more pronounced in, or was even limited to, animals fed relatively high-fat diets (17,37–39). Similar findings have been observed in some human studies (10,11,16,40,41), although other studies found that calcium had a greater impact among those with relatively low dietary fat intake (42,43) or saw no interaction (44,45). In our study, higher dietary fat tended to diminish the effect of calcium, although the interactions were not statistically significant. Future studies will be needed to determine whether fat intake alters the relationship between calcium supplementation and the risk of colorectal neoplasms.

The possible interactions between intakes of dietary fiber and calcium on colorectal neoplasia have also not been well investigated. In a randomized trial of cereal fiber supplements, the inverse association of total calcium intake with risk of adenoma occurrence was stronger in the low-fiber arm than in the high-fiber arm (8). We found the calcium effects to be most pronounced among individuals who reported higher total dietary fiber intake, although this finding could have been due to chance, particularly for advanced adenomas. Other studies have reported no interaction between calcium and fiber intake (43,45) on the risk of adenomas. The possibility that dietary fiber modifies the effect of calcium will be important to explore in future studies.

It is not clear how calcium acts to reduce the risk of neoplasia in the large bowel. A commonly cited possibility is that calcium complexes with, and therefore prevents the irritating and cancer-promoting effects (46) of, bile acids and other fats in the lumen of the bowel. Indeed, these calcium/fat “soaps” have been observed (17,47,48). Nonetheless, more direct effects have also been proposed, mediated by a cell surface calcium-sensing receptor (49). Our finding that the effect of calcium supplementation was almost absent among subjects in the highest tertile of dietary fat intake is more consistent with the latter type of mechanism: dietary fat may sequester supplemental calcium in the bowel, leaving lower calcium concentrations in the water phase of stool to irritate the colorectal mucosa.

Our study has several important strengths, including its randomized design, high rate of follow-up, and uniform histologic review of all large bowel lesions. However, this analysis also has limitations. Because of the small numbers of large lesions observed in the short follow-up interval, we had limited statistical power to examine the association of calcium and different types of advanced polyps. In addition, participants in our study may be different from the general population at risk for colorectal adenomas or colorectal cancer because all of our patients had a history of previous adenomas.

In summary, calcium supplementation decreased the risk of all types of neoplastic and hyperplastic polyps. Our data suggest the potential for high calcium intake to provide more substantial chemoprotective effects for advanced polyps than for adenomas considered as a single group. Nineteen patients with adenomas would need to be treated with calcium supplementation for 4 years to prevent one histologically advanced neoplasm (50). Our findings also suggest that total calcium intakes above 1200 mg are necessary, and perhaps that high dietary fiber and modest dietary fat are required to optimize this effect. Additional data regarding nutrient interactions with calcium will help further refine optimum cancer protective strategies and may clarify the mechanisms by which calcium has its effects in the large bowel.

REFERENCES


NOTES

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