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Calcium, Magnesium, and Colorectal Cancer

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High calcium consumption may confer a reduced risk of colorectal cancer.[1,2] Dai and colleagues[3] recently reported in a case-control study that intake of calcium may be associated with a decreased risk of colorectal adenoma only when the dietary calcium:magnesium intake ratio is low. This finding provides one possible interpretation for inconsistencies in previous studies of the association of calcium intake with risk of colorectal neoplasia.[4]

Belonging to the same family in the periodic table, calcium (Ca^{2+}) and magnesium (Mg^{2+}) share the same homeostatic control system and have the potential to antagonize each other physiologically.[5] A high calcium intake reduces absorption of both magnesium and calcium,[6] whereas moderate magnesium deprivation results in negative magnesium balance but increased calcium retention[7]. Due to the potential competition between magnesium and calcium, we hypothesized that the dietary calcium:magnesium ratio may modify the effects of calcium supplementation on colorectal carcinogenesis.

We sought to test this hypothesis using data from a randomized clinical trial of calcium supplementation (1200 mg/day) to prevent adenoma recurrence over a 4-year period. The outcome measure in this analysis was the recurrence of adenomas during the pre-specified main risk period (i.e. after a year-1 colonoscopy up to and including a year-4 examination)[2]. A validated semi-quantitative food frequency questionnaire (FFQ) was given at study entry to assess usual diet.

Consistent with our hypothesis,[3] we found suggestions that the baseline dietary calcium:magnesium intake ratio modified the effect of calcium treatment on adenoma recurrence. Among subjects with the intake ratio above the median, calcium supplementation had no effect on the risk of one or more recurrent adenoma (relative risk

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[RR]=0.98 [95% confidence interval (CI)=0.75–1.28]) (Table). In contrast, among those with the baseline ratio less than or equal to the median, calcium treatment was associated with reduced risk (RR=0.68 [95%CI=0.52–0.90]; test for interaction, *P*= 0.075).

The effect of calcium treatment did not differ by magnesium intake at baseline (test for interactions *P* = 0.68). Previously, the study had shown that the effects of calcium supplementation on adenoma recurrence did not differ by baseline dietary intakes of calcium. We found no material change after adjustment for baseline dietary calcium intake. Thus, the suggestion of effect modification by the calcium:magnesium ratio cannot be attributed solely to the baseline dietary intake in either calcium or magnesium. Point estimates suggest that calcium reduces the risk of advanced adenoma regardless of the calcium:magnesium intake ratio level, a null finding that could be due to lack of statistical power. The effect of calcium on the risk of hyperplastic polyps did not differ by baseline calcium:magnesium intake ratio, but a protective effect of calcium on hyperplastic polyps was observed when baseline magnesium intake was below the median (test for interaction, *P* = 0.05).

Although not entirely consistent, prospective studies conducted in Western societies have generally found that high intake of magnesium was associated with a reduced risk of colorectal cancer.[8] Also, in a previous case-control study,[3] polyp-free controls consumed substantially higher levels of magnesium than patients diagnosed with an initial colorectal adenoma. There are several possible reasons for the null magnesium finding in this study. It is possible that the association between magnesium intake and adenoma recurrence differs from that for an initial adenoma diagnosis. Also, baseline adenomas in participants with high dietary magnesium at entry may have occurred despite that intake, and so might develop adenoma recurrence along pathways unaffected by magnesium at that level. Future studies are needed to investigate the possibility that magnesium treatment among those with a high calcium:magnesium ratio at baseline could reduce the calcium:magnesium ratio and, in turn, reduce colorectal cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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John Baron and Dartmouth College hold a use patent for the chemopreventive use of calcium supplementation, currently licensed to Pfizer. Proceeds are used to support the research of the Polyp Prevention Study Group.

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Table

Association of calcium intake with recurrence of total and subtype adenoma during main risk period, stratified by median baseline calcium:magnesium intake ratio

Calcium:magnesium ratio[a]	Placebo No. cases/Total	Calcium No. cases/Total	Adjusted RR (95% CI)[b]	Test for interaction[c]
All adenomas				
ratio ≤ median	84/217	54/198	0.68 (0.52–0.90)	*P* = 0.075
ratio > median	71/198	71/198	0.98 (0.75–1.28)	
Advanced lesions				
ratio ≤ median	20/217	13/198	0.69 (0.36–1.33)	*P* = 0.575
ratio > median	21/198	16/198	0.71 (0.38–1.32)	
Hyperplastic polyps				
ratio ≤ median	45/217	35/198	0.89 (0.60–1.34)	*P* = 0.861
ratio > median	48/198	41/198	0.83 (0.57–1.22)	

[a] 2.626 was used as the median ratio of Ca/Mg for both baseline and year 4 FFQs.

[b] Adjusted for age, sex, study center, follow-up interval, and number of lifetime adenomas at baseline.

[c] Interaction was assessed between continuous Ca/Mg ratio and calcium treatment vs. placebo.