Calcium Supplementation and Prevention of Colorectal Neoplasia: Lessons From Clinical Trials

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Dietary calcium has long been implicated as a protective factor for colorectal cancer and adenomas. Investigation of this nutrient was triggered by mechanisms proposed in the early 1980s based on in vivo and in vitro studies (1,2). Fast-forward to more than 20 years later, and we find ourselves debating the importance of this nutrient in the etiology of colorectal neoplasia. Examination of the abundant amount of observational data is a worthwhile exercise. Although some inconsistencies are evident across studies, the picture that emerges from most prospective studies of colorectal cancer and calcium intake suggests a threshold effect in that risk reduction is seen at intakes of approximately 600–1000 mg/day, with no further protection beyond these levels (3–5). These findings might explain the null effects observed in the Women’s Health Initiative (6), in which women were randomly assigned to receive 1000 mg of calcium carbonate and 400 IU of vitamin D₃ daily. Baseline mean calcium intake in these women was 1151 mg/day, resulting in a total calcium intake of approximately 2150 mg/day, levels that, based on the prospective data, are consistent with no effect. As a result, we are still left with the unanswered question of whether calcium supplementation would convey protection among individuals with low or moderately low baseline intakes of this nutrient.

Observational data on colorectal adenoma incidence, prevalence, and recurrence provide an equivocal picture of the association than those for colorectal cancer, with modest inverse associations seen for dietary intake of calcium in some studies and for supplemental intake in other studies and still other studies reporting no relationship [summarized in (7)]. However, by contrast to the lack of effect of supplemental calcium in colorectal cancer trials, it has been shown to reduce rates of adenoma recurrence in randomized controlled trials (8,9). It is interesting that higher levels of calcium intake have been associated with reduced risk of adenoma recurrence as compared to levels associated with colorectal cancer. For example, in the Calcium Polyp Prevention Study (8), 1200 mg of elemental calcium was associated with a modest risk reduction in adenoma recurrence of 15%–19%; baseline mean intake of dietary calcium was approximately 890 mg/day. Even more compelling are the findings in this issue of the Journal (10) indicating that the protective effect of calcium supplementation for colorectal adenoma recurrence extends as long as 5 years after cessation of supplementation and that this effect is slightly stronger than that observed during the intervention phase.

One of the major criticisms of adenoma recurrence trials is that the relatively short (i.e., 3–5 years) follow-up time is often used as
an explanation for null effects of the agents tested. In the case of calcium supplementation, however, not only is the shorter period of intervention sufficient to demonstrate efficacy but also the protective effect appears to extend beyond the intervention period. A puzzling finding, however, is that although a stronger and statistically significant effect of the intervention was observed for recurrence of advanced neoplasms during the intervention phase (relative risk [RR] = 0.65, 95% confidence interval [CI] = 0.46 to 0.93) (11), no reduction was observed after supplementation ended (RR = 0.85, 95% CI = 0.43 to 1.69). Because the advanced adenoma endpoint analyses are based on post hoc hypotheses, it is not possible to draw any conclusion regarding the effect of calcium on this important outcome. Another area to explore in these analyses is the potential interactions of calcium with vitamin D and nonsteroidal anti-inflammatory drugs, as has been previously done by the investigators (12,13).

Where do we go from here—and, more important, what public health recommendations related to calcium do we provide for risk reduction of colorectal cancer? This is an important question, especially given a recent recommendation for mandatory enrichment of the US food supply with calcium and vitamin D, primarily to reduce osteoporosis and colorectal cancer (14). The most recent American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention (15) indicate that individuals should consume recommended levels of calcium (1000 mg/day for adults up to age 50 years and 1200 mg/day for those older than 50 years). These guidelines also note that it would be sensible for men to limit intake of calcium to less than 1500 mg/day due to the possible increased risk of prostate cancer associated with higher intakes. Indeed, published reports indicate a higher risk of advanced or fatal prostate cancer associated with higher intakes of calcium (16,17). Because no protection for colorectal cancer is apparent at higher levels of calcium intake, this recommendation is justified. However, it is unknown whether risk of adenoma recurrence is reduced at lower levels, given that clinical trials have only tested higher doses (1200 and 2000 mg) and that the published observational studies assessing recurrence endpoints provide mixed results (7,18,19).

Large clinical trials of calcium and colorectal cancer are unlikely to be launched in the near future. However, should the opportunity arise, we should consider taking into account that, as is the case for many nutrients, individuals with lower rather than higher nutrient intakes are likely to benefit the most from supplementation and that those who have already exceeded the threshold of prevention may experience no added protection. Additionally, trials of adenoma recurrence should consider combinations of calcium and other agents. More important, it is time that we move to test these combinations in high-risk populations, such as individuals with advanced adenomas or those with a family history of colorectal cancer. Lastly, we must not forget that the major method of reducing risk of colorectal cancer mortality is through the removal of polyps. Given that a large proportion of the age-eligible population does not undergo screening for colorectal cancer (20), efforts must continue to increase rates of screening. This, along with increasing physical activity levels, is likely to result in lower morbidity and mortality from this malignancy.

References