Supplemental Calcium in the Chemoprevention of Colorectal Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The aim of the review was to assess the evidence for the effectiveness of calcium in reducing the recurrence of adenomas and the occurrence of colorectal cancer among populations at high, intermediate, and low risk of the disease.

Methods: A systematic review of randomized controlled trials (RCTs) was performed to compare calcium alone, and with other agents, versus placebo. Nine databases (Cochrane Library, MEDLINE, PreMEDLINE, *CINAHL*, EMBASE, Web of Science, Biological Abstracts, the National Research Register, and Current Controlled Trials) were searched for published and unpublished trials. Searches were not restricted by either language or date of publication. All searches were completed in January 2010. Database thesaurus and free text terms for calcium and adenomas or colorectal cancer were used to search for trial reports; additional terms were used to search for other agents of interest, such as NSAIDs and folic acid. Search terms consisted of a combination of terms for colorectal cancer (eg, *colon* or *colorectal* and *neoplasm* or *cancer* or *adenoma*) and terms for calcium and RCTs. The initial searches were conducted in June 2008, with update searches in January 2010 to identify more recent studies. The reference lists of relevant studies were also searched for additional papers not identified by the search of electronic databases. Studies had to satisfy the following criteria to be included: RCTs about calcium, with or without other chemopreventive agents, in adults with familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer, or a history of colorectal adenomas, or with no increased baseline risk of colorectal cancer. Meta-analysis was performed. For discrete and numerical outcomes, relative risks (RRs) and risk differences were reported with 95% CIs. The random-effects model was used to account for clinical and methodologic variations between trials.

Results: The original and update searches of electronic databases produced 3835 citations, of which 6 studies (8 papers) met the inclusion criteria. Supplemental calcium had no effect on the number of adenomas in 1 small trial of patients with FAP. Meta-analysis of 3 trials in individuals with a history of adenomas showed a statistically significant reduction in the RR for adenoma recurrence (RR = 0.80 [95% CI, 0.69–0.94], $P = 0.006$) for those receiving calcium 1200 to 2000 mg/d, but no effect was seen in advanced adenoma (RR = 0.77 [95% CI, 0.50–1.17], P = NS). Meta-analysis of 2 trials in populations with no increased baseline risk for colorectal cancer suggested that calcium, with or without vitamin D, had no effect on the RR for colorectal cancer (RR = 0.62 [95% CI, 0.11–3.40], P = NS).

Conclusion: Published reports indicated that supplemental calcium was effective for the prevention of adenoma recurrence in populations with a history of adenomas, but no similar effect was apparent in populations at higher or lower risk. (Clinicaltrials.gov identifier: NCT00486512. (*Clin Ther.* 2010;32:789–803) © 2010 Excerpta Medica Inc.

Key words: adenoma, calcium, colorectal cancer, recurrence, risk.

INTRODUCTION

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine and is the second most common fatal cancer in western Europe and the United

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States.[1,2] Incidence of colorectal cancer increases with age, with the median age at diagnosis being between 70 and 74 years for both colon and rectal cancer patients.[3,4] Risk factors for the development of colorectal cancer include genetic syndromes, family or individual history of adenomas, and environmental factors related to diet and lifestyle.[5,6] Approximately 5% of colorectal cancers are associated with the genetic syndromes familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome),[7,8] and up to 20% occur in individuals who have a family history of the disease but for whom no specific disease-causing mutations can be identified.[9,10] The occurrence of colorectal cancer is otherwise sporadic, with the remaining 75% of patients having neither a clear family history nor any known predisposing condition.[11]

Colorectal cancer typically develops from adenomatous polyps arising from the lining of the intestine; indirect evidence suggests that adenomas may be present for ≥10 years before malignancy develops.[12–14] The size and number of adenomas, as well as their histologic type and the presence of epithelial dysplasia, are thought to affect the risk of colorectal cancer development. Individuals in whom adenomatous polyps are identified undergo polypectomy (ie, removal of polyps) and are invited to attend routine endoscopic surveillance.[15] The overall 5-year survival rate for colorectal cancer in the United Kingdom is ~50%, but it varies according to the stage of disease at diagnosis.[16] The clinical effectiveness of several drug and micronutrient interventions for the prevention of colorectal cancer, its precursor (adenomatous polyps), or both in populations at differing risks for being diagnosed with colorectal cancer has been investigated and synthesized in a number of systematic reviews.[17] These interventions include NSAIDs, folic acid, and antioxidants (eg, vitamin A, vitamin C, vitamin E, selenium, β-carotene).[18–23] Aspirin and celecoxib have been found to have some chemopreventive effect in populations with a history of colorectal adenomas,[17,18] but the other agents appear to have no significant benefit and, in the case of folic acid, may even be harmful.[21]

Therefore, the purpose of the present work was to systematically review the existing evidence concerning the clinical effectiveness of calcium in reducing the recurrence of colorectal adenomas in populations with FAP/HNPCC or a history of adenomas (ie, with a high or intermediate risk), and in reducing the occurrence of colorectal cancer in the general population with no increased baseline risk of the disease (ie, no known personal or family history of colorectal polyps). Two previous reviews have examined the effect of supplemental calcium on adenoma recurrence in individuals with a history of adenomas,[24,25] but a search of the literature identified no other systematic review or meta-analysis of randomized controlled trials (RCTs) that addressed this question for all relevant populations in terms of colorectal cancer, as well as for the outcomes of advanced adenomas and colorectal cancer.

METHODS

A literature search was performed to identify relevant research using database thesaurus and free text terms for calcium and adenomas or colorectal cancer. A validated study design filter to identify RCTs was used.[26] This search also included terms for other agents of interest, such as NSAIDs and folic acid, because this review was conducted, in part, as one element of a larger assessment of numerous potential chemopreventive agents for colorectal cancer. Nine databases were searched for published and unpublished trials: Cochrane Library, MEDLINE, PreMEDLINE, *CINAHL*, EMBASE, Web of Science, Biological Abstracts, the National Research Register, and Current Controlled Trials. Search terms consisted of a combination of terms for colorectal cancer (eg, *colon* or *colorectal* and *neoplasm* or *cancer* or *adenoma*) and terms for calcium and RCTs. Searches were not restricted by either language or date of publication. The initial searches for all relevant agents were conducted in June 2008, with update searches performed in January 2010 to identify any more recent calcium studies. The reference lists of relevant studies were also searched for additional papers not identified by the search of electronic databases.

Studies had to satisfy the following criteria to be included in the review: RCTs of calcium (with or without other chemopreventive agents) in adults with FAP, HNPCC, or a history of colorectal adenomas, or with no increased baseline risk of colorectal cancer. Relevant comparators were specified as either placebo or agents other than calcium. Relevant outcomes included the recurrence of adenomas or advanced adenomas, or the occurrence of colorectal cancer. Institutional review board approval and consent were not inclusion criteria for this review.

All citations identified by the searching process were screened by 1 of 3 reviewers (C.C., K.C., or D.P.) to determine whether they met the inclusion criteria. For quality-control purposes, a double check for appropriate