Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis

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CRD summary
This review concluded that supplemental calcium was effective for prevention of adenoma recurrence in patients with a history of adenomas. There was no similar effect in patients at higher and lower risks. These conclusions reflected the evidence presented, but should be interpreted cautiously in view of the limited quality of some of the included studies.

Authors' objectives
To compare the effectiveness of calcium in reducing the recurrence of adenomas and the occurrence of colorectal cancer in patients at high, intermediate and low risk of the disease.

Searching
MEDLINE, PREMEDIATE, CINAHL, EMBASE, Web of Science, Biological Abstracts, NRR, Current Controlled Trials and The Cochrane Library were searched up to January 2010 without language restrictions. Search terms were reported. Reference lists of relevant publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared calcium (with or without other chemopreventive agents) with placebo or agents other than calcium in adults with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, a history of colorectal adenomas or with no increased baseline risk of colorectal cancer were eligible for inclusion. The primary outcomes were incidence of recurrence of adenomas or advanced adenomas and occurrence of colorectal cancer. The secondary outcome was adverse event.

Dosage regimes of calcium varied between included studies. Calcium (1,000mg to 2,000mg per day) was administered either individually or in combination with other agents (such as β-carotene and vitamins C, D and E). Treatment duration of included studies ranged from six months to seven years. Half of the included studies recruited patients with a history of adenomas; other studies recruited postmenopausal women with no baseline risk of colorectal cancer or familial adenomatous polyposis. Age of included patients ranged from 16 to 80 years.

More than two reviewers assessed studies for inclusion. Any disagreement was resolved by consensus.

Assessment of study quality
Study quality was assessed with criteria for randomisation, allocation concealment, blinding, baseline comparability, intention-to-treat analysis and power calculation.

The study quality was assessed by one reviewer and checked by a second reviewer.

Data extraction
Data were extracted on event rates to enable calculation of relative risks (RRs) with 95% confidence intervals (CIs).

Data extraction was performed by one reviewer and checked by a second reviewer.

Methods of synthesis
Studies were grouped by type of patients and combined in meta-analyses. Pooled relative risks with 95% CIs were calculated using a random-effects model. Statistical heterogeneity was assessed using $I^2$. Separate analyses were conducted on subgroups of patients. For patients with a history of adenomas, sensitivity analyses were performed by excluding unpublished data from one low-quality trial where the intervention was calcium plus antioxidants.
Results of the review
Six RCTs were included in the review. Three studies were judged to be of good quality and the others were judged to be of low quality.

For patients with familial adenomatous polyposis, one RCT (n=28 participants) showed no significant difference on the incidence of adenomas between the supplemental calcium and placebo groups.

For patients with a history of adenomas, supplemental calcium was associated with a significant reduction in risk of diagnosis of any type of adenoma compared with placebo (RR 0.80, 95% CI 0.69 to 0.94; three RCTs, n=1,279). There was no difference between treatment groups in risk of diagnosis with advanced adenoma (RR 0.77, 95% CI 0.50 to 1.17; two RCTs, n=1,186). There was no significant heterogeneity for these outcomes. Sensitivity analyses did not materially alter the results.

For patients with no increased baseline risk of colorectal cancer, there was no significant difference on the rate of colorectal cancer between the calcium (with/without vitamin D) and placebo groups (RR 0.62, 95% CI 0.11 to 3.40; two RCTs, n=37,016). A high degree of heterogeneity was observed for this outcome ($I^2=58\%$).

Four RCTs reported no adverse events or complications at doses of 1,000mg to 1,500mg per day. Two RCTs with higher doses observed adverse events. One RCT administered a dose of 2,000mg per day and reported a significant increase in all adverse events compared with the placebo group (26 out of 176 versus 12 out of 178, p=0.04).

Authors’ conclusions
Supplemental calcium was effective for prevention of adenoma recurrence in patients with a history of adenomas. There was no similar effect in patients at higher and lower risks.

CRD commentary
This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find both published and unpublished studies and there were no language restrictions; these efforts minimised the risk of publication and language biases. Sufficient attempts were made to minimise errors and biases in the review process. Appropriate criteria were used to assess study quality. Statistical heterogeneity was assessed. Appropriate methods were used to pool the results.

This review was generally well conducted. The authors’ conclusion reflected the evidence presented. However, a degree of caution might be required in interpreting these conclusions given the limited quality of some of the included studies.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further trials were required to confirm the potential chemopreventive effect of supplemental calcium demonstrated in this review. These trials should continue assessing the chemopreventive effect of supplemental calcium at different doses as well as its adverse event profile, especially in patients with a history of adenomas and general populations (such as women who do not take supplemental oestrogen).

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