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Title: Calcium supplementation for the prevention of colorectal adenomas: A systematic review and meta-analysis of randomized controlled trials.

Authors: Stefanos Bonovas, Gionata Fiorino, Theodore Lytras, Alberto Malesci, Silvio Danese.

Editor comments

We have read your comments carefully.
The language has been polished, the "Comments section" has been added in the revised manuscript, the references have been carefully checked, and Figure-1 is provided also as a Word file (separately), so that you can edit it easily.

Reviewer 1

This study presented the effect of calcium supplementation on colorectal adenoma recurrence through a meta-analysis of clinical trials. Three trials included patients who had colorectal adenoma, but underwent colonoscopy, and one trial included colorectal cancer patients.

Major comments are as follows;

(1) Abstract. For "Therefore, it is safe to say that calcium does not appear to strongly reduce the risk of adenomas; however, there is evidence to suggest a modest overall risk reduction", author may need to revise the conclusion. Given a significant inverse association (13% or 11% reduction), "it is safe to say that calcium does not appear..." it maybe somewhat strong to state no strong association because even 13% or 11% could be substantial with a long follow-up. We can rather say that it is a modest risk reduction.

Reply: Change made (Abstract, page 3, last paragraph).

(2) Introduction "This endpoint also avoids the size and complexity required for trials of colorectal cancer itself", this statement may not be correct for colorectal adenoma because size and types of adenomas are also clinically important to predict cancer development. Please delete it or revise it.

Reply: As per your request, the particular sentence was deleted.

(3) Authors seemed to be motivated by a recent trial of Baron et al. and this large trial found no association for calcium supplementation. Because Baron's recent trial is the largest among four trials, it has large contribution to weight. Thus, it would be better to address why this large trial found no association in the discussion session. (different population? any study design issue? lower rate of advanced adenomas recurrence compared to their previous trial? etc.)

Reply: The reviewer is right. We have been motivated by the recent trial of Baron et al. to conduct this systematic review and meta-analysis. However, there is no obvious reason why this trial found no association (e.g. study population, study design, etc).

(4) please also address the mechanism through which calcium decreases colorectal cancer risk in the discussion section.

Reply: The following paragraph has been added in the revised manuscript (Discussion, page 13):
"Our knowledge on the underlying mechanism is incomplete. It has been proposed that calcium may protect against neoplasia in the large bowel by binding bile and fatty acids, thus decreasing their proliferative and carcinogenic effects on colonic epithelial cells."

(5) in figure 1, it is not clear how n=27 becomes n=4. please clearly address no. of studies excluded and the reasons.

Reply: Figure 1 was modified appropriately (page 25).

Minor comments are as follows;

(1) Introduction "However, even after polypectomy, rates of adenoma recurrence may be up to 50 percent" please state duration of follow-up. How long did those studies follow patients and found 50% of recurrence?

Reply: The phrase *"within 3 years of follow-up"* was added in the revised manuscript (page 5).

(2) In Table 1, authors can cite the references that actually provided information on RR estimates. For additional citations for each study, please specify them into the text.

Reply: Change made in Table 1 (page 30).

(3) please indicate what n and N are in the footnote of figure 3.

Reply: Change made in Figure 3 (page 27).

<u>Reviewer 2</u>

In figure 3 and 4 please explain n and N.

Reply: Changes made in Figure 3 (page 27) and Figure 4 (page 28).

Could you discuss and give evidence on the development of colorectal carcinomas among the patients with adenomas?

Reply: The following paragraph was added in Introduction section (page 5):
"Most colorectal tumors develop from adenomas arising from the lining of the intestine. Progression –described as the adenoma-cancer (or polyp-cancer) sequence– is characterized by morphological and histological changes. For instance, a small tubular adenoma acquires villoglandular characteristics as it grows. On the molecular level, the adenoma-cancer sequence reflects an accumulation of genomic defects. Generally, a single adenoma has a risk of progressing into neoplasia of 0.25% per year, depending on its size, location, histological type, and the presence of dysplasia."

What is the clinical significance of fixed and random effects?

Reply: The following paragraph was added in Methods section (page 8):
"Under a fixed-effects model, we assume that the included studies share a common true effect, and the pooled effect is an estimate of the common effect size. Under a random-effects model, we assume that the true effects vary between the studies, and the pooled effect is a weighted average of the effects reported in the different studies. The random-effects model often leads to broader confidence intervals (i.e., it is a more conservative approach)."