Peer Review File

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Review Comments

General comment: *The authors provided a short review on the effect of calcium and vitamin D on metachronous polyp based on a recent publication on JAMA Oncology. The authors may want to consider the following points in revising their manuscript.*
Generally, the manuscript was well written. The authors reviewed the randomized trials to assess the effect of calcium and/or vitamin D on metachronous polyp.
Reply: Thank you for your comment. We appreciate your feedback on the manuscript.

Comment 1*: However, the authors did not include the results from two large-scale randomized trials to evaluate the effect of vitamin D and vitamin D plus calcium on incident of cancer and colorectal cancer. The Women's Health Initiative (WHI) reported in 2006 that supplementation of calcium plus vitamin D did not reduce risk of incident colorectal cancer compared to the placebo arm. In 2019, the Vitamin D and Omega-3 Trial (VITAL) revealed that supplementation of vitamin D did not decrease risk of incident cancer, including colorectal cancer, compared to the placebo arm.*
Reply 1: Thank you for your suggestion in this regard, in fact, although both clinical trials were indirectly mentioned in the paper (one of them through a meta-analysis cited in the text), both studies are relevant enough to be explicitly mentioned in the text.
Changes in text: We have added an explicit mention of the two trials mentioned (see page 2, lines 5 and 22).

Comment 2: *Thus, it is critical to first understand the gaps between observational studies and randomized trials. It is possible that in addition to calcium, other beneficial compounds, including nutrients, account for the inverse associations between dairy products and risk of colorectal cancer found in observational studies.*

Reply 2: Thank you for pointing this out. We did not intend to state that their calcium and vitamin D content is solely responsible for their effect, but only to mention it as a possible contributor. We have clarified this in the text.

Changes in text: The sentence referring to dairy products has been modified with the intention of not implying certainty as to whether their protective effect is due to calcium and vitamin D (see page 1, line 9): "The mechanism by which dairy products prevent colonic carcinogenesis is not clearly established, but their high calcium and vitamin D content is among the components potentially involved."

Comment 3: *On the other hand, a number of potential confounding factors may explain the inverse associations between serum vitamin D and risk of colorectal cancer. For example, physical activities are positively associated with serum vitamin D levels because outdoor physical activities lead to sun exposure. Conversely, the BMI is inversely correlated with serum vitamin D levels.*

Reply 3: Thank you for your comment. Regarding the cofactors mentioned, we would like to point out that the studies reviewed in the text (observational and randomized trials) analyze the effect of calcium and vitamin D supplements regardless of the serum levels of both substances, and not the relationship between these levels and the risk of colorectal cancer. However, it is true that both physical activity and BMI are factors related both to the appearance of adenomas and CRC and to vitamin D levels and should therefore be taken into account when assessing their effect at all levels.

Changes in text: We have modified the text by mentioning the need to

take into account physical activity and the presence of obesity when carrying out new studies on the subject (see page 4, line 18): “there are many factors influencing the development of adenomas and advanced adenomas, like diet, physical activity, obesity, tobacco, and alcohol consumption. To accurately evaluate the effect of vitamin D or calcium supplementation on adenoma recurrence those variables should be controlled.”