Reviewer’s report

Title: Serum calcium and risk of gastrointestinal cancer in the Swedish AMORIS study

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Reviewer: Qi Dai

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In this large-scale prospective study, the authors examined the associations between serum concentrations of calcium and albumin-corrected calcium and risk of esophageal, stomach, colon and rectal cancer. The findings are interesting and may potentially have important implications. However, I have some concerns regarding the interpretations of the results.

Major Compulsory Revisions

1) It is known that serum level of calcium is regulated within a narrow range by PTH and other factors. There is no obvious evidence that dietary calcium is highly correlated with serum level of calcium. The authors also mentioned in the discussion that “extracellular calcium homeostasis is mainly affected by vitamin D and PTH rather than dietary calcium”. Furthermore, in the current study, corrected serum level of calcium was linked to an increased risk of colon cancer while previous meta-analysis of cohort studies found that high dietary calcium was linked to a reduced risk of colorectal cancer. Thus, if dietary calcium is indeed correlated with corrected serum calcium, the correlation should be an inverse one.

Therefore, instead of summarizing previous studies of dietary calcium together with serum calcium in the introduction and the beginning of the discussion, which would indicate a strong link between dietary calcium and serum calcium, the authors should give the background at the beginning of the introduction that serum calcium is mainly regulated by PTH, not dietary calcium. Thus, readers could understand this from the beginning.

2) The authors also discussed that high serum calcium can be caused by hyperparathyroidism, including both primary and secondary or high levels of vitamin D. This is very likely since serum calcium is regulated by these factors. It is possible that hyperparathyroidism is linked to increased risk of total mortality, colon cancer and esophageal cancer as well as an elevated level of serum calcium. The large-scale EPIC cohort found high PTH levels were related to an increased risk of colorectal cancer. Thus, hyperparathyroidism and/or high PTH can be the underlying confounding factor for the observed association in the current study. Unfortunately, PTH levels were not included in the study.

Minor Essential Revisions

1) The authors mentioned that “measures closer to diagnosis date may provide a better assessment of gastrointestinal cancer death. ……” However, follow-up
time from baseline measurements until gastrointestinal cancer diagnosis was adjusted in the analysis”. This argument may not be valid because diagnosis of cancer could substantially change the serum calcium levels. In addition, most of participants were not diagnosed with cancer. Thus, adjustment for follow-up time could not correct this bias.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No