Reviewer's report

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

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Reviewer: Visalini Nair-Shalliker

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This fascinating paper demonstrates the importance of adjusting for a measure (albumin) of not just clinical significance, but also of biological significance (albumin corrected for calcium). Both variables were highly correlated and thus inclusion in the model would have resulted problems of co-linearity, as evidenced when calcium was adjusted for albumin. However the correction for calcium levels brought about a significant difference.

The prospective nature of this study, and the large sample size for each of the cancer supports the significance of these findings. The explanation for the findings is well founded.

Major concern:

Although the question posed by the authors is on the link between calcium and colorectal cancer risk, the authors have separated these cancers as colon and rectal cancers, in separate analysis. We were introduced to the topic as issue related to COLORECTAL cancer i.e., “A role of dietary calcium in colorectal cancer prevention has been suggested (1), but there is lack of epidemiological evidence linking serum calcium and gastrointestinal cancer risk.” in the Abstract and Introduction and further in Discussion, The separation by the author into 2 separate cancers is useful, however to support what is mentioned in the Abstract, Introduction and Discussion, the analysis will also require an additional table with both these cancers combined.

Minor concerns:

There are a few errors:

(i) In Results section, para 2, the p-value should be 0.03 and not 0.04:
[e.g. HR for colon cancer 0.92 (95% CI: 0.82 – 1.02), 0.94 (0.84 – 1.05), and 0.88 (0.79 – 0.98) for the 2nd, 3rd, and 4th quartiles of calcium, respectively; P-value for trend 0.04].

Also this sentence sho
uld specify that this effect was only evident when adjusted for age at index measurement, as this effect was not evident when the model was adjusted for SES, sex, albumin and CCI.

(ii) The authors state that the risk was higher in those with higher albumin-corrected calcium quartiles. This is true. However they go on to state
that additional adjustment with sex, SES, CCI albumin eliminated the inverse association; This is not true. The higher risks were in fact observed by using albumin corrected calcium levels after adjusting for age, and adjustment for these additional factors only improved the significance.

(iii) They assumed effect modification by sex, hence could they please state what the \( \pm \)-interaction is; even if stratification was based on face value.

(iv) There is a lot of data in this study. It would be nice if they could discuss the data in the order of the table. Eg. Following the discussion of colon cancer in women in table 3, they then skipped to oesophageal cancer which is the first cancer that is listed in this table.

(v) There is no mention of rectal cancer.

(vi) In Results para 4, they make a significant claim but data not shown; please include data in table. Maybe data can be included in Table 4, and the current data in Table 4 can be classed as ‘data not shown” since results are insignificant.

In sum, this is a well written paper that should bring attention that the complex effects of calcium homeostasis on cancer risk is not straight forward.

**Level of interest:** An article of outstanding merit and interest 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:**

'I declare that I have no competing interests'.