Reviewer’s report

Title: Inorganic phosphate and the risk of cancer in the Swedish AMORIS study

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Reviewer: Janneke Hogervorst

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Reviewer comments for “Inorganic phosphate and the risk of cancer in the Swedish AMORIS study”

Major compulsory revisions

1) The introduction is too brief and vague. What’s really missing in the Introduction is in what raw foods Pi occurs, in what foods it occurs as a processing agent and in what kind of beverages it occurs. If people would want to reduce their Pi intake because of the message in your paper, they would not now know of which foods they would to reduce intake. Also, not knowing the foods makes it very hard to judge the potential for confounding in your analyses.

   What does “hidden” mean?

   The sentence starting with “Despite” is hard to follow. It may help to elaborate a bit more on the subjects in this sentence; there is room in the Introduction, I think.

   The transitions between parts of the introduction are not always logical to me, eg., “However” in the last sentence does not seem to follow logically from the previous sentence. Also “Despite” seems odd to me in the sentence starting with “despite”.

2) The history of lung disease (which ones?) sounds like a very poor proxy for smoking to me, especially for the amount of smoking. Is asthma included as well, for instance? I think that people with asthma smoke less than people who don’t have asthma. Since the risk of many cancers (e.g. for pancreatic and lung cancer smoking is the strongest known risk factor) is increased by smoking, this worries me. Of course, the severity of confounding here depends on how strong the correlation between serum Pi and smoking is, but right now that is impossible to judge from your paper, because there is no information on the food sources of Pi. Another question: does smoking have an effect on Pi levels?

Minor essential revisions:

-Abstract first sentence: what is meant by extracellular?

-Abstract, results: the “e.g. is a bit odd. It should be oesophagus, not stomach, in women

-Introduction: better: “denoted the potential link between Pi and the development of cancer in humans”

-Last sentence of introduction: better: “cancer risk in humans”
Abstract: the conclusion does not seem to convey the main findings.

Page 2: please write out AMORIS in full first

Page 2: Should it be Registry instead of Register?

Page 2: How can one unite “healthy” with “outpatients” in the description of the CALAB database?

Page 3: write SES in full first

Page 3: “the censuses”?

Page 3: a reference to the method to measure Pi would be useful, same for other compounds that were measured.

Page 4: you adjust for glucose, but since diabetes modifies Pi metabolism, it would be good to also check if diabetes is an effect modifier of the association between Pi and cancer.

Page 4: I am not sure if you should adjust for glucose (and history of diabetes: double adjustment!), alkaline phosphatase, season and creatinine. They all potentially influence serum Pi levels and correcting for them may lead to overcorrection. Are the risk estimates different if you do not adjust for those variables?

Page 4: The results in Table 1 are not reported in the results section, except for employment. Are there any meaningful differences between the two groups?

Page 5: it is Multivariable-adjusted, not multivariate

Page 5: The first sentence relates to men and women together, please state so.

Page 5: the results after exclusion of first 3 years of FU seem the same to me.

Page 5: why only mention the HR per SD of Pi for men and women together? For increases or decreases in risk, you should mention whether they are statistically significant or not (throughout whole paper).

Page 5: part about different cancers in men: please indicate that these results can be found in Table 3, same for part about women (table 4)

Page 5: for men: also other cancer was statistically significantly increased.

Page 5: There was an association between NHL and standardized (please add “standardized” all the time) Pi levels in men, but the dose-response relationship over the quartiles was not linear. That should be added.

Page 5: endocrine apart (other than is better than apart from) from the thyroid. Also apart from prostate and testis, right? Please add this. What then is included in this category? Also, the trend over the quartiles is not linear.

Page 5: men: there is also a borderline statistically significant inverse relationship with colorectal cancer.

Page 5: women: there is also a (borderline) statistically significant positive trend (as indicated by p for trend) over the quartiles for laryngeal cancer, although case numbers are very small.

Page 5, part about women: what cancers are in the other endocrine category?
Page 6: first sentence: increase in colorectal cancer risk not reflected by quartile analysis. Please add.

Page 6: It is cancer of the endometrium, not endometrial.

Page 6: First part of the discussion: also briefly describe here the results for the individual cancer types.

Page 6: Second section: “Recent experimental studies in rodents”


Page 6: “promote colonic cell hyperplasia and hyperproliferation”, but in men you rather see the opposite.

Page 6: So there appears to be a U-shaped dose-response curve for Pi and cancer risk in mice?

Page 7, first sentence: “Consistent with previous experimental studies in rodents”. However, you did not describe that the sex difference you observed was also shown in the rodent studies, so what is consistent? Strictly speaking, you showed that higher Pi was related to a decreased risk of overall cancer in women, not that lower Pi was related to an increased risk.

Page 7: Sentence about weakening after exclusion of first 3 years can be deleted as this weakening was almost negligible. Reverse causation is unlikely to explain both a less decreased risk in women and a less increased risk in men.

Page 7: Second section: It should be non-melanoma skin cancer.

Page 7: “consistent positive association between standardized Pi levels”: standardized can be deleted? I do not understand how the positive association you saw here in humans can corroborate the prior biological findings linking BOTH HIGH AND LOW dietary Pi to a significantly increased tumor formation in mice.

Page 8, first sentence: non-melanoma

Page 8, sentence starting with “On the other hand”: suggest to rephrase: For cancer of the brain/central nervous system, we observed no clear association with Pi levels, despite…”

Page 8: Please provide references for “not confirmed in observational studies”

Page 8: How does estrogen directly regulate circulating Pi?

Page 8: Insert gynecological before cancer in the sentence with “inverse association between Pi levels and cancer risk in women”

Page 8, last sentence: It should be encoding

Page 9: “mainly selected by analyzing”, rephrase e.g. in “mainly selected based on the availability of blood samples from health (not “healthy”) check-ups…”

Page 9: The last two sentences of the discussion seem to be put there as “oh yeah, and also this is kind of a drawback”, but actually this missing information on smoking (!) and alcohol may severely compromise the validity of your whole study.
Page 9, conclusion: biological studies? Our findings provide, not provides. Also, again you say increased risk in women with low Pi, but better: decreased risk in women with high Pi. You should also mention that some cancers show a positive association in women, and that the inverse association for total cancer seems driven by the endocrine cancers.

-In discussion and conclusion, I miss suggestions on how to go further from here. What other research is needed, can any dietary recommendations be given, etc.

-References: some journal titles are written in full, some are abbreviated. Sometimes epub is put after the page numbers. Please remove.

-Table 3 and 4 titles: part about adjustment should be in the legend of the tables.

-Table 4: the HRs and CIs of the 3rd and 4th quartile for endometrial cancer are exactly the same. Please check if this is correct.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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