Reviewer's report

Title: Dietary cadmium intake and risk of prostate cancer: A Danish prospective cohort study

Version: 2
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Reviewer: Bettina Julin

Reviewer's report:

This is an overall well written manuscript on the association between cadmium exposure from food and risk of prostate cancer in a Danish cohort. The statistical analyses are appropriate and straightforward. My main concern relates to the lack of adjustments for energy intake.

- Major Compulsory Revisions

1. Associations between components of the diet and disease cannot be considered primary effects if they are simply the results of differences in total energy intake between cases and non-cases (resulting from differences in body size, physical activity and metabolism). Individual differences in total energy intake produce variations in intake of specific dietary components unrelated to dietary composition because the consumption of most nutrients are positively correlated with total energy intake. Thus, energy-adjustment is standard practice in nutritional epidemiology and is based on the concept that the composition of the diet, independent of total caloric intake, is of primary interest. This adjustment also reduces the artificial between person variation introduced by under and over-reporting of food intake by the FFQ.

   It is recommended that the authors energy-adjust their estimates of cadmium exposure. Alternative they should energy-adjust the dietary cadmium exposure at least in a sensitivity analysis. There are regression models for this e.g. Willett and Stampfer, Am J Epid 1986).

   Another crucial point is whether dietary exposure to cadmium can be well-assessed using FFQs. The authors doesn't mention if their estimates of the average daily dietary exposure to cadmium using a FFQ has been compared with another assessment instrument or biological marker (e.g. urinary or blood cadmium concentrations). If yes, what were the results? Is the FFQ in itself validated?

2. Background. The introduction is very long and the paper would gain by making the introduction more focused.

3. Background, Second paragraph. It is unclear what PTWI the authors are referring to. EFSA has estimated a TWI and JECFA has estimated a PTM. Please clarify.
4. Ascertainment of prostate cancer. I miss a headline for the description of outcome assessment, e.g. "Outcome assessment and follow-up" or "Ascertainment of prostate cancer" or similar. For the paper to read better, this section should be placed after the "Exposure assessment" section, but before the "Statistical analyses" section.

5. The definition of non-aggressive disease needs clarification.

6. Statistical analyses, paragraph 2 and Table 2. The authors state that out of the 1567 total prostate cases, 400 cases were excluded due to missing information on aggressiveness status, which leaves 1167 cases available for subtype classification. In Table 2, however, they report 840 aggressive cases and 427 non-aggressive cases, summing up to 1267 cases. Please explain.

- Minor Essential Revisions.

7. Exposure assessment. The estimation of the daily cadmium exposure from food deserve a bit more detail. For example, were the cadmium concentrations of the specific food items averaged over several samples and approximately how many samples? In the FFQ, did you ask for the consumption of whole dishes or only individual food items? If you asked for the consumption of whole dishes - when using FoodCalc, did you consider reduction in weight and consequently cadmium concentration for that specific food item? When data was not available for certain food items, why did you choose to go forward in time and not backwards?

8. Do the authors have data on diabetes status of the participants? Since diabetes is associated with decreased risk of prostate cancer and the dietary advice given to diabetics is likely to lead to an increased exposure to cadmium diabetics could confound the association between cadmium and prostate cancer.

9. Ascertainment of prostate cancer. PSA levels have been used to define advanced prostate cancer which is not a common practice everywhere. In addition, the use of PSA 15 as a cut-off does seem a bit low. In a sensitivity analysis, could you use a higher cut point or even exclude PSA from the definition?

Furthermore Gleason sum = 7 is included as a criteria for the definition of advanced prostate cancer. Since numerous studies suggest that Gleason 3 + 4 tumors have a better prognosis than Gleason 4 + 3 tumors, it may be interesting to only include the 4 + 3 pattern in the definition of advanced prostate cancer or to exclude Gleason sum = 7 from the definition.

10. Table 3. Is this the results for total prostate cancer? This should be made clearer in the header.

11. Discussion, first paragraph. The authors state that the study by West et al. (1991) did not find any significant association between dietary Cd exposure and prostate cancer, regardless of age-group or aggressiveness of the disease. In fact, West et al. actually report an association for all tumors among older men
(OR 1.8; 95% CI: 1.1-3.1, comparing the highest quartile of Cd exposure with the lowest).


13. Typo. Page 9, line 231. ”...and we did not found...”. Please revise to ”...and we did not find...”

- Discretionary Revisions

14. Exposure assessment, first paragraph. The authors may want to state that they are estimating the average dietary cadmium exposure.

15. Results, first paragraph. The authors may want to add the number of aggressive and non-aggressive cases here.

16. A meta-analysis regarding dietary cadmium intake and risk of cancer was recently published. The authors may want to cite this paper: "Cho YA, Kim J, Woo HD, Kang M. Dietary cadmium intake and the risk of cancer: a meta-analysis. PLoS One. 2013 Sep 17;8(9):e75087. doi: 10.1371".

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.