Reviewer’s report

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

Version: 2 Date: 3 June 2014

Reviewer: Emily White

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This paper reports on a well designed and analyzed cohort study of the association between cadmium intake from diet and prostate cancer risk. It is well written and the results are appropriately discussed.

Minor essential revisions:

1. The authors need to make clearer that the limitation of this study is the exposure assessment. First, they need to report on how well a FFQ can assess cadmium intake from diet. Are there any studies on, for example, cadmium assessed from a FFQ vs toenail cadmium? If not, then cite validity/reliability studies of other minerals from diet, and generalize about how well minerals are measured from a FFQ. Second, one limitation of the FFQ that should be mentioned is that it is not a measure of total cadmium exposure, the likely true exposure of interest, if cadmium exposure also comes from smoking and occupational exposures.

2. The authors need to report their results based on other, more strict definitions of aggressive prostate cancer. Most definitions used in epi studies yield a relatively small percent of prostate cancer cases who meet the definition of aggressive, while in this study, two-thirds of prostate cancer cases were classified as aggressive (840 of 1267 in Table 2). Is this because PSA screening is uncommon in Denmark? Often Gleason 4+3 (or 8+) is considered aggressive, not 7s with pattern 3+4. To my knowledge, few studies have used PSA values to define aggressive nor used the T part of TNM. Some studies have used prostate cancer as cause of death to define aggressive prostate cancer. Perhaps several definitions could be used to be more comparable to other epi studies.

3. The discussion of reference 27 (Platz et al.) is misleading. Page 5 states “One study indicated that prostate cancer risk was lower in men with high dietary zinc intake, indicating that a high zinc intake may modify a possible harmful effect of cadmium intake (27)” This study is again cited on page 10 as showing a slightly lower prostate cancer risk among men with moderate to high zinc intake, and the paragraph goes on to say the present study and another one (ref 26) did not find effect modification of the cadmium-prostate cancer association by zinc intake. However, the Platz et al. study explicitly examined the toenail zinc-toenail cadmium interaction in prostate cancer risk and found no evidence of interaction (p for interaction =0.9). So: 1) finding a small decrease in risk associated with zinc “intake” does not support a zinc-cadmium interaction, and should not be cited as providing support for that interaction, 2) it should be stated that the Platz
et al study looked at the interaction of cadmium with zinc, with no evidence of any interaction, and 3) the Platz study should not be referred to as one of zinc or cadmium “intake” as that implies intake from food. It should be called a study of zinc and cadmium “exposure” or “toenail” zinc and cadmium.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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.