Peer Review File

Reviewer A

Yan et al have performed a cross-sectional analysis of associations between uric acid level and a self reported diagnosis of prostate cancer in a dataset from the NHANES. The reason for this study is conflicting prior data regarding a role of markers of inflammation, uric acid and prostate cancer incidence. They seek to add to this body of literature through this analysis. Overall, they report no significant association in this cross sectional study in the entire population between serum uric acid and prostate cancer, including after multivariable modeling to account for confounding. In a subpopulation of patients >60 years old, a lower uric acid was associated more likelihood of diagnosis of prostate cancer. Given the nature of the study, this is hypothesis generating that there may be a link between uric acid metabolism, inflammation and prostate cancer. Weaknesses of the study include that it is an older data set (1999-2010) and no information regarding severity/clinical significance of prostate cancer was available. The validity of this self reported prostate cancer diagnosis during a time when there was potentially overdiagnosis of non-clinically significant (grade group 1) prostate cancer due to screening trends should probably be acknowledged to be a limitation.

Reply: Thanks for your valuable comments. The aforementioned comments offer a comprehensive overview of our article.

Other comments:

Comment 1:

Abstract background: appreciate that association between uric acid levels and prostate cancer is "debatable" but why are you doing this study -- what are the scientific reasons to consider a link between uric acid and prostate cancer?

Reply 1: Thanks for your valuable comments. As you say, there may be a link between uric acid metabolism, inflammation, and prostate cancer. Some authors propose that the uric acid play a critical role in protection against cancer by the suppression of inflammation [1-3].

Changes in the text: We added some data in abstract background (see Page 2, line 2-3).

[1] Singh S, Jaiswal S, Faujdar G, Priyadarshi S. Comparison of serum uric acid levels between localised prostate cancer patients and a control group. Urologia. 2024 Feb 12:3915603241228892. doi: 10.1177/03915603241228892. Epub ahead of print. PMID: 38344978.

[2] Akinloye O, Adaramoye O, Kareem O. Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma. Pol Arch Med Wewn. 2009 Sep;119(9):526-32. PMID: 19776696.

[3] Benli E, Cirakoglu A, Ayyıldız SN, Yüce A. Comparison of serum uric acid levels between prostate cancer patients and a control group. Cent European J Urol. 2018;71(2):242-247. doi: 10.5173/ceju.2018.1619. Epub 2018 Jun 12. PMID: 30038817; PMCID: PMC6051366.

Comment 2:

Abstract Results line 13-14 and Results 3.2 line 3: "borderline significant associated" is a misleading term. While I understand that the p- value is close to being considered significant (close to <0.05 but >0.05), most statistically appropriately this should be stated as "not significantly associated"... I would think it is ok to comment in discussion that there was an overserved nonsignificant trend toward this finding that may be identified with a larger sample size.

Reply 2: We feel great thanks for your professional comments. We strongly agree with the reviewer's opinion.

Changes in the text: We have modified our text as advised in Abstract (see Page 2, line 14) and in Discussion (see Page 9, line 3-6).

Comment 3:

Discussion line 22: "adversely" correlated, do you mean inversely?

Reply 3: Thanks for your nice comment. I mean inversely correlated and it has been modified.

Changes in the text: We have modified our text as advised in Discussion (see Page 7, line 17).

Comment 4:

Discussion paragraph 2: in the discussion of limitations, as above, discuss that data on PCa significance/severity is not available in this dataset. Furthermore, the likelihood of diagnosis of non-clinically significant prostate cancer was higher in that era due to screening trends.

Reply 4: We feel great thanks for your professional comments. We added the above in the Discussion section.

Changes in the text: We have modified our text as advised in Discussion (see Page 8, line 27-28 and Page 9, line 1-2).

Comment 5:

Can the authors comment on whether it would be more appropriate to do this analysis with age matching between prostate cancer cases and controls?

Reply 5: Thanks for your nice comment. The NHANES employs a complex, multistage probability sampling design to select a nationally representative sample. Although the sample size of this paper is 7860, it represents tens of millions of Americans, and age matching may lose a large number of population data in the control group.

1. Please check if any references should be added since you mentioned *studies*.
   - Many observational *studies* have rigorously controlled for confounding variables, however, there may still be some unmeasured or unknown variables that affect the results.
   - Moreover, a small number of prostate cancer cases or a short follow-up period in some observational *studies* may cause a loss of this association.

   Reply: We have added references to the corresponding content.

   Changes in the text: We have modified our text as advised (see Page 11, line 3; Page 11, line 5).

2. Tables:

   1) Please indicate the full name of "BMI" in Table 1-2 foot.

   Reply: We have indicated the full name of "BMI" in Table 1-2 foot.

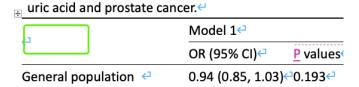   Changes in the text: We have modified our text as advised (see Page 19; Page 21, line 4).

   2) Table 1: the (%) is repeated. Please remove.

Age, n (%)		
< 60 years	14 (9%)	3,961 (68%)
≥ 60 years	301 (91%)	3,584 (32%)
Race, n (%)		
Non-Hispanic White	204 (82%)	4,155 (78%)
Other Race	111 (18%)	3,390 (22%)

Reply: We have removed the (%) in Table 1.

Changes in the text: We have modified our text as advised (see Page 17-18).

3) Table 2: Please add a head for the first column.

uric acid and prostate cancer.

	Model 1	
	OR (95% CI)	P values
General population	0.94 (0.85, 1.03)	0.193

Reply: We have added a head for the first column.

Changes in the text: We have modified our text as advised (see Page 20).

3. Please check if any references should be added since you mentioned *studies*.

- Many observational *studies* have rigorously controlled for confounding variables, however, there may still be some unmeasured or unknown variables that affect the results.
- Moreover, a small number of prostate cancer cases or a short follow-up period in some observational *studies* may cause a loss of this association.

Reply: We have added references to the corresponding content.

Changes in the text: We have modified our text as advised (see Page 11, line 3; Page 11, line 5).