

Peer Review File

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Reviewer Comments

1) Page 2: lines 5-9: Describe specific purposes of Cox regression and Youden index analyses separately; lines 10-11: This is a confusing statement here. The risk (incidence) of prostate cancer increases monotonically with age. So what does “inflection” mean and why should that be affected by metabolic syndrome?; line 18: Perhaps, you should state what the limitations are, at least the major ones.

: Thank you for the good comments. We revised ‘Statistical analysis’ as you pointed out: The predictive accuracy of age for prostate cancer was assessed by the Youden index and multivariate adjusted Cox regression analysis was used to analyze the effect of metabolic syndrome-like components on prostate cancer development.

Secondly, we have revised ‘lines 10-11’ as follows to avoid confusion: The risk of prostate cancer increases with age, and the best cutoff age for prostate cancer detection was 62 years (the maximum value of the Youden index). When stratified by the number of metabolic syndrome-like components, the age with the highest Youden index of each group is still 61 or 62 years.

Lastly, we added the example of limitations at the end of the abstract as follows: However, results of this study should be interpreted with consideration due to several limitations including the diversity of definitions of metabolic syndrome components.

2) Page 4, lines 21 – page 5, line 1: More detailed descriptions of the study population and health examinations will be informative. For example, how were study subjects selected and enrolled in health examinations? How many examinations did the study subjects participate in during the follow-up period, how were those participating two or more of examinations treated?

: Thank you for a good comment. We have revised ‘study population’ section as follows to help the reader understand: In Korea, a national health examination is semi-mandatory to local householder, company member and family member over the age of 40 and dependents of member once every 2 years. Therefore, during one year, about half of the population over the age of 40 undergo examination. And it is not possible to receive more than two national health examination during one

year. In this study, male subjects that had undergone a national health examination in 2009 without a previous diagnosis of any cancer were included.

3) Page 5, lines 2-4: What is meant by “the event that did not occur.”? This is not clear. What data were missing?

: Thank you for a good comment. We have revised this sentence to avoid confusion as follows: Subjects who the development of prostate cancer did not occur during the follow up period were censored and Cox regression analysis was used for these censored data. Sensitivity analysis was used to handle missing data.

4) Page 5, line 9-11: The authors should describe how the ROC and Youden index are calculated. It is this reviewer’s understanding that the ROC and/or Youden index are used as a measure of the predictability of a diagnostic test, based on test sensitivity and specificity results. Are the authors using “age” as a test for diagnosis of prostate cancer? As incidence (or morality) rates statistics indicate, we know age is a strong factor (predictor) of prostate cancer. What is the purpose of the Youden index analysis? What insights do the Youden index data provide to what is known about the effect of aging on prostate cancer?

: We agree with your opinion, but here are a few more explanations. Of course, that age is a strong predictor of prostate cancer. And it is generally known that the incidence of prostate cancer increases monotonically with age. However, we used the Youden index because we wanted to know the best cutoff age for prostate cancer detection, since the appropriate age for starting screening has become a very important issue.

In addition, we wanted to know if cut-off age is different depending on metabolic components, since we hypothesize that early screening should also be considered for men with metabolic diseases. Therefore, we also analyzed the Youden index according to the number of metabolic syndrome-like components. However, the age with the highest Youden index of each group is still 61 or 62 years. This finding is consistent with the results of the multivariate adjusted Cox regression analysis used to analyze the effect of metabolic syndrome-like components on prostate cancer development.

We would highly appreciate if you could take these points into account for publication.

5) Page 6, line 2-7, and Table 1. The authors should summarize key findings of the demographic and metabolic disease characteristics. In Table 1, percentage distributions stratified by metabolic disease components would be easier for interpretation

: We agree with your opinion and revised the Table 1 with percentage distributions stratified by metabolic disease components. In addition, we added key findings to the demographic and metabolic disease characteristics section.

6) Figures 2 and 3: Reversed.

We apologize to have made a mistake in describing figure numbers. We have changed the figure numbers each other.

7) Page 6, lines 14-16: How was the statistical difference tested using the data in Supplementary Table 1?

Thank you for a comment. We added the statistical method about supplementary table 1 to ‘Statistical analysis’ section as follows: One-way ANOVA used to test difference in the incidence rate among the non-component group, the group with 1 or 2 components, and the group with ≥ 3 components.

8) Page 6, lines 19-23: What does the highest Youden index (of 62) mean? What is the implication? Do the authors suspect (hypothesize) that metabolic disease has an effect on Youden index (by age) and why?

: As we mentioned in the Question 4), we used the Youden index because we wanted to know the best cutoff age for prostate cancer detection. In addition, age is also closely related to metabolic diseases. Therefore, we thought that it is important to see how metabolic diseases affects the association between age and the risk of prostate cancer.

9) Page 7, lines 2-8, Supplementary Table 3: In this reviewer’s view, this paragraph and Supplementary Table 3 are the most important relevant observation for the objective of this study.

: We agree with your opinion and we have changed the Supplementary Table 3 to Table 2. Thank you for a good comment.