Author's response to reviews

Title: Cardiorespiratory Fitness, Body Mass Index, and Cancer Mortality: A Cohort Study of Japanese Men

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Author's response to reviews: see over
Reviewer's report:

Synopsis. The authors conducted a cohort study of Japanese male workers to address whether higher fitness is associated with a lower risk of cancer mortality in men with a higher BMI. As a result, the authors found an inverse association of cardiorespiratory fitness with risk of cancer mortality in smokers (current and past) but not in never-smokers. The authors also found that an inverse association of fitness with risk of cancer mortality was not modified by weight status. This paper provides important information for cancer prevention in an Asian population. However, this study is limited by small number of deaths due to cancer, leading to wide confidence intervals. I have several minor comments as below.

SS=> We appreciate your thoughtful comments.

- Major Compulsory Revisions
- Introduction
1) 3rd paragraph, there is some duplication in meaning between the sentences “we intend to extend our previous study, which investigated CRF and cancer mortality” and “, extending our previous investigation of CRF in relation to cancer mortality (ref)”. Please, reconsider.
SS=> Thank you for your suggestion. We have now deleted the last sentence (L109-110).

- Methods
2) Section for Participants, when the interview to confirm the presence of disease including asthma and so on was done? Please specify where appropriate for clarity.
SS=> Thank you for your suggestion. We have now added information to the "Participants" section (L122 and L124-125) for clarity.

3) Please simply describe how the authors calculate man-years in the Data analysis section.
SS=> Thank you for your suggestion. We have now added sentences to the "Data analysis" section (L171-172).

5) It would be informative to describe the coverage rate of the retired men by the members list kept by the Tokyo Gas Retiree Office in the Mortality surveillance section. Most of the retired men were registered in the list?
SS=> Thank you for your suggestion. Most of the retired men were registered; only 3.4% were not.
We have now added information to the "Mortality surveillance" section (L166-168).

- Results
6) 2nd and 3rd paragraphs, please show hazard ratios and 95% confidence intervals for major results.
SS=> Thank you for your suggestion. We have now added hazard ratios and 95% confidence intervals (L236 and L245).
7) The sum of never-smokers and smokers (defined as past and current) is 7,704. This number is less than total number of workers remained for main analysis (n = 8,760). Could you kindly explain?

SS=> Thank you for picking up this error. We made a mistake with the comment under table 2 regarding the definition of smokers. We did analysis only among current smokers because past smokers had a wide variance of smoking history. So, we have now added "current" before smokers (L232, L235, L502, Table 2, and Figure 1).

- Figure 1
8) Please describe total number of participants as well as number of cases in each of the combined categories of BMI and fitness where appropriate.

SS=> Thank you for your suggestion. Please note, the numbers in Figure 1 don't represent the total number of participants due to the exclusion of past smokers.

- Minor Essential Revisions
- Abstract
9) Please check whether the use of abbreviations for CRF and BMI are correct.

SS=> Thank you for your suggestion. We have now revised the abbreviations for CRF and BMI to be consistent (L53, 56, 57, 63, 67, and 78).

- Methods
10) “self-administered questionnaire was administered”
This can be rephrased to avoid redundancy.

SS=> Thank you for your suggestion. We now have deleted the "self-administered" part (L141).

- References
11) Please check the followings at least for correctness.
Ref 11. THomas -> Thomas?
Ref 17. P Peel -> Peel?

SS=> Thank you for picking up these errors of reference. We have now revised the text as you suggested (Ref 11, 13, 17, and 35).

- Discretionary Revisions
- Abstract
12) Conclusion section, the authors may stress the conclusion derived from joint analysis; the present conclusion appears to be derived from single association of CRF with cancer mortality.
Thank you for your comment. However, we have respectfully chosen to concentrate on the CRF results instead of the results from the joint analyses since there was no statistically significant interaction between BMI and CRF in this study.

- Discussion
13) Limitations section, the present study was conducted among workers, who are generally healthy. Therefore, caution may be required to generalize present results to general population or non-working population.

We agree with your comment, so we have now inserted this limitation in L359-361.

- Key Words
14) It might be better to add “cancer mortality” to keywords (rather than smoking) to describe this study.

Thank you for your suggestion. However, we already included "cancer mortality" in the title so this would be picked up in a search for the term. Thus, we didn't change the keywords.

Level of interest: An article of importance in its field
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.
Reviewer's report:
Generally speaking, this manuscript had long showed significant association between CRF and cancer mortality independently of BMI, which has been published in 2003 by Dr. Sawada, but they found "no clear relationship between BMI and cancer mortality and notably they did not find statistically significant interaction between BMI and CRF either". In other words, they did not report positive novel findings from their previous publication. For these reasons, the originality of this study is not high at all. It was thought that it was necessary to raise the quality of the study by increasing the case numbers of the cancer death that was an endpoint in increasing target people and more longer follow-up periods for an observation period in future.

SS=> We appreciate your thoughtful comments.

1. Is the question posed by the authors well defined?
There was contradiction in the hypothesis that "higher CRF and moderate BMI would be associated with lower cancer mortality risk independently and jointly with the lowest risk among individuals in the highest CRF group and moderate BMI group". When CRF and BMI are independently associated with cancer mortality, there would be no interaction between CRF and BMI.

SS=> Thank you for your comments. We have tried to improve clarity by rewording L103-106 to “We hypothesized that higher CRF and moderate BMI would each be associated with lower cancer mortality risk, independent of the other factor, and also that the lowest risk would occur among individuals in the joint group of highest CRF and moderate BMI.”

2. Are the methods appropriate and well described?
1) The statistical analysis on the interaction of smoke with BMI and CRF is rigorous and well considered.
SS=> Thank you for your comment.

2) Although VO2max makes the low fitness group as the reference, what is the reason for having set 2nd tertile of BMI as reference?
SS=> Thank you for your question. Previous papers have reported that there were U shape relationships between BMI and cancer mortality. Thus, we used as reference the group with the lowest risk – the 2nd tertile.

3) With respect to the BMI,
Firstly "participants with BMI less than 18.5 were excluded to minimize potential bias from undiagnosed cancer that may have led to weight loss". However, patients with cancer usually undergo weight loss at the late stage of cancer. What's more the percentage of BMI less than 18.5 is not few in fit Japanese population. Therefore at the primary analyses, that exclusion may not be done while it could be done in the sensitivity analysis.
Thank you for your suggestion. We chose to exclude men with BMI <18.5 in primary analyses because there were only 279 people with a BMI lower than 18.5. We did conduct a sensitivity analysis including the 279 people; the results were the same.

Secondly, participants were divided into tertiles and "the second tertile was used as the reference group which had a reference that published in 2011 with data were from a large study of East Asians. However, the tertile and using the second tertile as the reference group is not convincing. In that report BMI 22.5-27 group showed lowest mortality while this BMI range is overlapped with the second tertile (21.6-23.6) and the third tertile (23.7-37.4) in this present manuscript.

Thank you for your suggestions. The East Asians large study (Ref.23) and other primary studies in this field (Ref. 4, 6, 7, and 8) reported that there was U shape relationship between BMI and cancer mortality. Thus, we tried to confirm whether there was also a U shape relationship between BMI and cancer mortality in this study. To maximize statistical power in our study and to also approximately match the referent groups from other studies at around BMI 23 (Ref. 4: 22.5-24.9, Ref. 6: 23.5-24.9, and Ref. 7: 23.0-24.9), we chose to use tertile cut points.

Thirdly, in Figure I, "BMI were divided according to classification from WHO". It is confusing that why they did not keep consistent to use BMI tertile. Additionally, there was no number of two groups of BMI<25 and BMI >=25 showed in the result section or in the figure 1.

Thank you for your question. In this particular analysis, we wanted to display the results based on clinically used BMI categories, but not relative distributions. Thus, we divided BMI according to WHO classifications.

Also, we have now added the numbers of both groups in Figure 1 according to your suggestion.

3. Are the data sound?  Yes.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?  Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data? In terms of the combined effects of CRF and BMI, this manuscript found no interaction between BMI and CRF. It is still needed to further discuss. In the Table 2, author did not have any explanation about association between cancer mortality and CRF regardless of BMI in smoker's group only.

Thank you for your suggestions. We have now added additional information to the "Results" section (L236-237).

Table 3 shows the cancer death rate is related to CRF in the 2nd tertile of BMI, and not in 1st and 3rd tertile of BMI. However, author did not explain for this result.

Thank you for your suggestions. We have now revised the sentences to the "Results" section (L247-251).
Table 4 shows that significant association between CRF and cancer mortality is observed in the group of follow-up period less than 10 years, but not in longer follow-up period. The reason is not explained.

SS=> Thank you for your suggestions. We have now added a potential explanation in L257-259.

I guess that order of the cause-specific cancer mortality in Japanese is different from North American. However, total cancer mortality is associated with CRF in both Japanese and north American. Is it thought that the mechanism is common?

SS=> The mechanisms are believed to be common, so we now add this in L315-316 in the "Possible mechanisms" section.

6. Are limitations of the work clearly stated?
Limitation were clearly stated while there could be other considerations. The sample were recruited just from a company so the results may not be generalized to other Japanese population.

SS=> We agree with your comments, and we now have inserted this limitation in L359-361.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.

8. Do the title and abstract accurately convey what has been found?

9. Is the writing acceptable
The writing in the results of the abstract is confusing, especially the last sentence.

SS=> We agree with your comment, so we have now revised the last sentence (L67-75).