Author's response to reviews

Title: Association between tooth loss and orodigestive cancer mortality in an 80-year-old community-dwelling Japanese population: a 12-year prospective study

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Prof. Stefano Petti, Editor

BMC Public Health

Dear Prof. Petti,

Thank you very much for your reply as well as sending the comments from the Editor and two Reviewers concerning our manuscript (MS: 8412771438323344), entitled “Association between tooth loss and orodigestive cancer mortality in an 80-year-old community-dwelling Japanese population: a 12-year prospective study.”. After reviewing those carefully, we made several changes to the text and tables, and added a new figure. As a result, we believe that the revised version has been greatly improved and is now acceptable for publication in BMC Public Health.

Changes in the revised manuscript are underlined, while our responses to the reviewers are shown following. We sincerely thank the reviewers for their valuable insights and you for your interest in our work.

We would be grateful if the manuscript could be reviewed and considered again for publication in your journal.

Yours sincerely,

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Following are our replies to the comments of the Editor and two Reviewers:
Editor:

1. The most important shortcoming lies in statistical analysis and inference. Indeed, tooth loss and edentulousness are not necessarily suggestive of periodontal disease at advanced stage, but they are also markers of low socio-economic status, while the present analysis did not account for the important confounding effect of socio-economic level (e.g., occupation, study level, etc.).

   • We do not have any information about income and education levels for the participants, though information regarding community area, which is known to be an SES factor is available. Additional analyses including place of residence were then performed, and the results have been added to the Results section and the Model 3 in Table 2 of the revised version: “Furthermore, those associations remained significant (HR: 1.07, 95% CI: 1.01-1.13), when place of residence as a part of socioeconomic status was added in the final model (Model 3 in Table 2).”

2. Observational studies report that periodontal disease (estimable through tooth loss adjusted for socio-economic level) is significantly associated with death for cardio-vascular diseases (CVDs) and it is not associated with death for cancer (see, for example, Watt RG et al, PLoS One 2012;7(2):e30797). In the present study, CVDs and tooth loss/edentulousness did not result significantly associated. This is not an impossible result, but Authors must explain why their results are at odds with the published literature on this argument.

   • Regarding the difference in outcome between tooth loss and CVD, some explanation has been added to the Discussion section: “On the other hand, we found no significant association between tooth loss and CVD mortality, which is inconsistent with the recent other study, as reported by Watt et al [15]. This difference may be due to the difference in subject age (the mean age of their study was approximately 50 years old in that study).”

3. Bivariate analysis displayed in Table 1 is usually made to choose the variables to include in the multivariate analysis, while the strongest predictor of patients’ death, that is, physical activity was not used for the multivariate analysis while a non-significant predictor, that is, systolic blood pressure was included.

   • Multivariate analysis including physical activity was performed and the results are now shown in Model 2 in Table 2. Furthermore, systolic blood pressure was deleted from the analysis, because bivariate analysis showed an insignificant association.
Reviewer I

Major compulsory revisions:

1. **Sex HR should be stressed, since a stronger association with females was found.**

   - “Sex HR should be stressed”, results of the Kaplan-Meier analyses have been added to the revised version (as a new Fig. 1), along with some explanations to the text: “The survival curves of subjects who survived during the 12-year follow-up period in the four groups divided by the number of remaining teeth in all subjects, as well as by sex are presented in Figure 1. The survival rate of all subjects was lowest in the edentulous subjects, though there was no significant difference among the four teeth groups (Fig. 1A). As illustrated in Figure 1B, the survival rate for males was also lowest in the 1-9 teeth group, though there was no significant difference among the four teeth groups. In contrast, the survival rate for females was lowest in the edentulous groups, being significantly lower than that in the group with 20 teeth or more teeth ($\chi^2 = 3.93, P = 0.047$). Thus, a stronger association was found in females.”

2. **Has the inter-examiner reproducibility been tested? If so, what were the variables used, and what method was used?**

   - As for “inter-examiner reproducibility”, dental examinations were performed by 3 trained dentists, as described in our previous study (Ansai, T. et al. BMC Public Health, 2010). Additional explanations have been added to the text: “Dental health conditions including number of teeth were also examined by three dentists with comparable skills, as previously described [11]. Briefly, the examiners performed all oral examinations using criteria recommended by the World Health Organization [12]. To confirm inter-examiner reliability, duplicate examinations were conducted, and the agreement for dental health conditions (dental caries, missing, filling) was 92%.”

Minor essential revisions:

1. **It would be more formal if “face to face” is replaced for some expression like “personal interview”.**

   - The phrase “face to face” has been rewritten according to the reviewer’s suggestion: “…in a personal interview performed by trained public health nurses.”

2. **(Discussion) “We have limited power for evaluation…” Power should be replaced for a more suitable word, like ability or similar.**

   - The word, “power” has been changed according to the reviewer’s suggestion: “Third,
evaluation of the mortality risk for specific cancers was limited because of the small number of site-specific orodigestive cancer deaths.”

Reviewer II

Major compulsory revisions

1. It has been well establish that both general health (cancer including oral cancer) and oral health (tooth loss) are highly associated with socioeconomic status. It might be possible in this study that participants with poorer socioeconomic status during their lifespan have both high tooth loss and cancers and finally death from cancer. I speculate, the inclusion of socioeconomic status of the participant will impact highly on the results and the relationship of tooth loss and orodigestive cancers.

   • Regarding the inclusion of socioeconomic status (SES) in our results, we do not have information about income and education levels for the participants, though information regarding community area, known to be an SES factor is available. Additional analyses including place of residence were performed and the results have been added to the Results section and the Model 3 in Table 2 of the revised version.: “Furthermore, those associations remained significant (HR: 1.07, 95% CI: 1.01-1.13), when place of residence as a part of socioeconomic status was added in the final model (Model 3 in Table 2).”

2. Is Fukuoka Prefecture an urban community or mixed patches of urban, rural, suburban communities? If it has both rural and urban communities then I think it would be reasonable to included participant's rural and urban status in regression models. It has been evident that people from rural background have poorer oral health and general health including cancer due to various reasons including limited access to health services. I would not be surprised if after adjusting to rural and urban the relationship of tooth loss and cancer might disappear.

   • As for the difference among communities in the prefecture, additional analyses were performed and the results are presented in Table 2, as noted above. Consequently, the significant relationship between tooth loss and total cancer has been disappeared in the final model. On the other hand, the relationship between tooth loss and orodigestive cancer remained significant even after full adjustment.

3. If the outcome data is dead/alive due to orodigestive cancer and all we know is that it occurred sometime in the last 12 years. In this case, hazard ratio is inappropriate to use as the exact time of death not known and death can be anytime between 0 to 12 years.
Regarding the limitation of hazard ratio. Kaplan-Meier analyses were performed, and the results are now presented as a new figure (Fig. 1).

4. Discuss the other possible reasons for this association of tooth loss and orodigestive cancers. For example, 1) tooth loss just might be a marker for poorer general health and cancers and not a risk factor, 2) tooth loss alters dietary choices and pattern and chewing ability and swallowing etc.

As for other possible reasons for the association between tooth loss and orodigestive cancer, additional explanation has been added to the text of revised Discussion section: “Tooth loss reduces chewing ability and swallowing ability [19], thus altering dietary choices, and may lead to consumption of a less healthy diet, which might be associated with cancer.”

Methods

1. Some subjects with a history of cancer at baseline were excluded. How many subjects were excluded?

- Three subjects with a history of cancer at the baseline have been excluded, which is noted in the revised text (page 5, line 13).

2. Discuss the impact of low response rate on the study results. discuss the possible reasons for this low response rate 41(5.9%) and explain the reasons for the lost.

- The explanation in the original version regarding response rate was confusing. The sentence has been rewritten in the Results section of revised version: “Of the 697 participants originally examined, 41 subjects (5.8 %) had moved away during the 12 years, giving a follow-up rate of 94.2%.

3. Describe the sample size calculation.

For sample size calculation, results of power analysis have been added to the text of the Methods section: “Power analysis was performed using the software package G-Power. The statistical power of this study was found to be 86.9%, with sample sizes of 242 for n1 and 414 for n2, an effect size of 0.25, and an a value of 0.05 set (two tailed t-test).”

Results

1. Page 9, line 5: " No significant associations between cardiovascular or pneumonia deaths.........". There was no data or methodology discussed for cardiovascular or pneumonia.

- Regarding CVD and pneumonia, additional analysis results have been added to
Table 2 and the text in the revised version: “No significant associations of cardiovascular or pneumonia death and tooth loss were observed in the final model (HR: 1.018, 95% CI: 0.99–1.04; HR: 0.994, 95% CI: 0.97–1.02, respectively) (Table 2).”

**Discussion**

1. Please justify some of the comments in discussion section. eg page 10, line 7: “Even after extensive adjustment for recognized confounders, tooth loss was significantly associated with an increased risk of all-cause and cancer mortality, but not of cardiovascular and pneumonia mortality." justify this conclusion about cardiovascular and pneumonia as no data on these two variables.

   - As described above, regarding CVD and pneumonia, additional analysis results have been added to Table 2 and the text in the revised version.

2. Abnet et. al, used tooth loss as dichotomous variable and this study used it as continuous variable. Please discuss why this study used tooth loss as a continuous variable and how it can impact results as compared to using tooth loss as dichotomous variable. The only reason given for the use of continuous variable is on page 12 “continuous variable of number of missing teeth would be better used to standardize the assessment of tooth loss.” it is not very clear statement for readers that how it can be more standardize assessment?

   - We have added some text to explain why tooth loss was used as a continuous variable in this study: “Those results indicate that cut-off values for number of teeth utilized there have not been standardized. Because of this disparity, we employed the number of missing teeth as a continuous variable in the present study, as it basically represents an accumulated burden of severe periodontal disease as the number increases. However, the association might not always be linear, as the association between CVD mortality and the number of missing teeth was shown to be non-linear in the study of Tu et al [5]. A similar situation has been also been found in periodontal disease assessments. Periodontal disease is generally diagnosed by probing and its diagnosis of periodontal disease is not straightforward, thus it would be inappropriate to use for determination of the underlying disease status. As pointed out by Tu and Gilthorpe [16], an alternative method is to use the number of lost teeth, as tooth loss appears to be a better indicator than probing as a marker of lifetime oral health, and is less prone to measurement error. International standardization regarding evaluation by tooth loss or periodontal disease is required.

**Minor essential revisions**

**Introduction**
1. Add a definition of orodigestive cancer.

• A definition of orodigestive cancer is now provided in the Background section of the revised version: “Orodigestive cancers were defined as cancers in the oral cavity and pharynx, esophagus, stomach, pancreas, liver, and colon, rectum or anus, as described in a recent report [8].