Reviewer's report

Title: Macronutrients, Vitamins and Minerals Intake and Risk of Esophageal Squamous Cell Carcinoma in a Population at Risk for Esophageal Cancer

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Reviewer: András Keszei

Reviewer's report:

In their manuscript, Jessri M. and colleagues describe a hospital based case-control study of esophageal squamous cell carcinoma in an Iranian population investigating associations with macro- and micronutrients.

Major Compulsory Revisions:

1. As the validity of a case-control study depends strongly on how controls are selected, readers should be given an opportunity to assess the control selection method. Hence I propose to present the details of the diseases (or groups of diseases) for which the controls were admitted to the hospitals, rather than indicating that the diseases had to be unrelated to smoking and alcohol abuse, etc.

2. Matching in case-control studies introduces bias that has to be taken into account in the analysis[1]. In my view, the authors should adjust for age and gender in their analysis as these variables were used in the matching procedure. It should also be considered to present age and gender adjusted estimates as well, in order to allow comparison with the fully adjusted estimates.

3. Beside smoking status, smoking duration and intensity are also associated with ESCC[2] in Italy, but in Iranian populations as well[3]. It is not clear from the methods section if these smoking related variables were considered. If yes, please make it clear, if not, I suggest adding them to the analysis.

4. In northern Iran there are marked differences in nutrient intake between rural and urban populations[4]. Please present the distribution of urban and rural residents in your study, and include it in the analysis if appropriate.

5. Opium use is an important risk factor for esophageal cancer in Iran[5]. The authors state that questions on opium use were not answered by the study participants; however, this could have caused confounded estimates, and should be discussed as a limitation in the discussion section.

6. Several naturally continuous variables were categorized (age, BMI, physical activity MET). This could have been necessary for the analysis, but increases the possibility of residual confounding[6]. I suggest discussing this limitation.

7. I also suggest presenting the descriptive statistics for the original continuous variables (age, BMI) as well (mean, median, standard deviation, range, as appropriate) in table 1.
8. It is not clear to me where the recommendations for daily intake of nutrients come from, and what the percentage values refer to in the recommendation column of table 5. In the last paragraph of the statistical analysis section the authors state that WHO/FAO recommendations were used for vitamins and minerals. Where did the values for macronutrients originate from? In the cited paper (reference 59), Bollschweiler et al. use the recommendation for daily consumption by the German Nutritional Society (DACH 2000), but no values for macronutrients are given. I am also not sure about the similarities between the DACH 2000 and WHO recommendations. In any case, are the recommended values used in table 5 and figure 1 different from each other? If yes, why? If not, I don’t see why the proportions of compliers for sodium in table 5 do not match with the proportions in figure 1. What is the rationale for presenting the complier proportions in different formats? If there is no compelling reason to do so, I would recommend using either a table or a figure for all nutrients and minerals.

9. I assume that analyses were done in separate logistic models for all nutrients (if this is not so, please make it clear). In this case the statement in the 2nd paragraph of the discussion section about the assessment of the combined impact of all macronutrients is misleading.

10. There is a strong association between ESCC and fried and barbecued meals, as noted by the authors in the last sentence of the 3rd paragraph of the discussion section, and supported by previous studies. One would also expect to see an association between cooking habits and certain macronutrients. This could result in confounding. Could the authors comment on this?

11. In the discussion section the sentence “An increased association of vitamin B12 with ESCC risk was not shown to be significant, although similar to Mayne et al.’s study [69], there was a trend increasing this direction.” is not clear. It seems to suggest that a non-significant positive association was found between vitamin B12 and ESCC in the current study. However, the OR estimates in table 3 (0.53 and 1.01 for tertiles 2 and 3, respectively) suggest otherwise.

12. Please indicate in the discussion that the finding of a strong inverse association of ESCC with vitamin D intake is not in line with all studies (see for example[7]).

13. In the discussion section, in the sentence “Dietary antioxidants (vitamin C, #-carotene and vitamin E [27,33,38,39,59,99] have been shown to decrease the ESCC risk through several mechanisms; [28,33,67,83,100] such as deactivating excited oxygen molecules and preventing lipid peroxidation [27,28,33,34,38,59,63,67,83,85,100].” it is not clear to what statement does the first set of citations refer to. Furthermore, citations 33, 34, 59, 83, 85, and 100 are epidemiological studies that do not directly support the statement about the mechanisms involving excited oxygen molecules or prevention of lipid peroxidation.

14. I do not understand why the authors cite reference 69 in the discussion section in the sentence: “However, an interventional study in China failed to show a reduction in esophageal cancer incidence rate in individuals taking 120mg/day vitamin C for 5.25 years [69,110].” Reference 69 is a multicenter case-control
study from the US.

15. In the discussion, in the following sentence “Some epidemiological studies have suggested a role for higher salt intake in carcinogenesis; although salt is not a carcinogen per se, it acts as an irritant to the esophageal protective mucosal layer, which results in an inflammatory regenerative response, increased DNA synthesis, and cell proliferation [23] and may also enhance carcinogenesis induced by other carcinogens [111].” I fail to see how reference 111 supports the statement that salt may enhance carcinogenesis induced by other carcinogens. Could you please explain?

16. Please indicate in tables 2. and 3. the number of individuals and the range of nutrients in each exposure category.

Minor Essential Revisions

1. Please present confidence intervals in the abstract. It will be useful for those who will not read the whole paper, especially given the small sample size.

2. In the method section of the abstract, smoking as well as tobacco use is indicated as variables used in the analyses. In the main text only smoking is presented.

3. Please explain abbreviations when first used (example SFA and PUFA in the abstract).

4. In the introduction section, in the sentence starting with “The incidence rate of this disease is 5-10 per 100,000 …” it is not clear whether “this” refers to ESCC or EC.

5. Materials and Methods: Was individual matching or frequency matching performed, please indicate.

6. Materials and Methods, last sentence: “5 year groups” should come after age, not after sex.

7. Statistical analysis: Was conditional or unconditional logistic regression performed, please indicate.

8. Please indicate how the covariates were entered into the model. For example, medication use: never/ever, for each group or combined.

9. Results section, 3rd paragraph, 2nd line: remove extra comma.

10. Discussion section, 4th paragraph, 6th line: “(from solid fat, added sugar and alcohol)”

11. Table 1. Please indicate how medication was categorized.

12. Table 1. Food temperature includes beverage temperature as well?

13. Table 3. Please indicate unit for methionine.

14. Table 3. Please indicate significance for selenium.

Discretionary Revisions

1. The authors might want to consider inserting “high risk” into the title or
indicating that the study was done in Iran. This might be more informative for someone scanning the titles.

2. It might be worthwhile to be more specific about “dietary factors” in the objectives in the abstract.

3. As the main topic of the manuscript is the association between ESCC and nutrients, I would first state the conclusions regarding the associations in the conclusion section of the abstract.

4. In the limitations section the authors note that supplement use is uncommon in this population. This could be viewed as an advantage, in my view, and could be emphasized as such.


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

Quality of written English: Needs some language corrections before being published

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.