Reviewer's report

Title: Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma. A prospective study of 580,000 subjects within the Me-Can project.

Version: 1 Date: 23 October 2013

Reviewer: Adana Llanos

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General comments

The manuscript by Lindkvist B and colleagues presents findings from a large prospective study to support previously reported associations of obesity with increased risk of esophageal adenocarcinoma and decreased risk of esophageal squamous cell carcinoma. This manuscript also demonstrated an association between features of the metabolic syndrome and EAC. While this paper presents important, interesting findings regarding associations between metabolic risk factors and esophageal cancer, there are multiple issues that should be addressed before this paper will be in a form appropriate for publication.

Major compulsory revisions

1. Abstract: Define mid blood pressure for clarity in the results section of the abstract.

2. Abstract: It would be important for readers to understand the implications for this study's findings. Thus, a sentence or two should be added to the conclusion section of the abstract to make clear what the findings add to the literature and if there are important implications that should be noted.

3. Introduction: More details are needed in the introduction. This would be helpful for a reader that may not be well-versed in this topic. Furthermore, adding information about the importance of studying the associations that were examined in this study.

4. Methods: More detailed methods are necessary regarding the measurement of glucose, total cholesterol and triglycerides in the blood. Were plasma or serum samples used for these measurements? Did sample type differ by cohort? Was there any consistency in the use of one sample type over another for each assay? What quality control methods were used to ensure reproducibility and reliability of the assays?

5. Methods: In the description of the end-point assessment, it was not clear how follow-up was defined for each cohort. Please provide more details. Relatedly, more details are needed regarding data collection for each of the outcomes of interest. This section was not clear at all.

6. Results: A brief overview of the baseline characteristics of the Me-Can cohort is necessary in the text. For example, what are the proportions for gender, age,
BMI, etc. Also, what was the mean follow-up time for these participants?

7. Results: The presentation of the findings should be re-organized in a way that is easier for the reader to follow along with. Findings from the tables are not presented in a logical way, so the reader is left to flip through the tables to determine where cited values are shown and this is distracting.

8. Results (and Table 4): Please provide p-trend for findings in Table 4 and present those when the finding are discussed in the text.

9. Discussion: The discussion should be reorganized for improved readability. For instance, the discussion of the strengths and weaknesses should be moved to the end of the discussion (just prior to the conclusions section). Overall the discussion doesn’t flow well and the implications of the study’s findings in the context of the literature could be done in a more scholarly manner.

10. Discussion: The subheadings should be removed entirely.

11. Discussion: On page 14, the location of the following in-text citation is inappropriate and should be revised from “An increased risk of esophageal cancer in general related to hypertension diagnosed below the age of 60 years was recently reported in a study from the Saskatchewan Health database, but we know of no studies to date, exploring the possible association between hypertension and ESCC or EAC [41]” to “An increased risk of esophageal cancer in general related to hypertension diagnosed below the age of 60 years was recently reported in a study from the Saskatchewan Health database [41], but we know of no studies to date, exploring the possible association between hypertension and ESCC or EAC.” In this section, a more scholarly discussion of the present study’s findings in the context of the literature is needed.

12. Discussion: A more scholarly discussion of the present study’s findings, related to the association of serum glucose and EAC and ESCC, in the context of the literature is needed.

13. Discussion: A more scholarly discussion of the present study’s findings, related to the association of serum/plasma lipids and EAC and ESCC, in the context of the literature is needed. While the authors state that “there is no evidence for such an association in the literature,” other studies have examined similar associations and as such, they should be cited in this paper. Here are two citations that may be useful for this section: Wulaningsih W et al., J Cancer Epidemiol 2012;2012: 792034 (article ID), 10 pages and Sako A et al. Cancer Letters 2004;208:43-49, as well as some of the references cited by these authors.

14. Discussion: A more scholarly discussion of the present study’s findings, related to the association of features of the metabolic syndrome and esophageal cancer, in the context of the literature is needed. A good citation for this section would be Ryan AM et al. Cancer Epidemiology 2011;35:309-319.

Minor essential revisions

15. Tables 2 and 3: In the footnotes, correct “Se text” to “See text.”
Discretionary revisions

16. Methods (Statistical analysis): The authors should consider rewording the description of their interaction analysis to something similar to the following: “Interactions between smoking and additional factors were tested by including cross-product terms in the regression models.”

17. Results: On page 10, the last sentence, consider rewording “High BMI” to “Higher BMI.”

18. Results: On page 11, first full paragraph, consider rewording “High mid BP” to “Higher mid BP.”

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

**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.