Reviewer's report

Title: A case-control study of glycemic index, glycemic load and dietary fiber intake and risk of adenocarcinomas and squamous cell carcinomas of the esophagus: the Australian Cancer Study

Version: 2 Date: 28 July 2014

Reviewer: Natasha Tasevska

Reviewer's report:

This manuscript investigates the association of GI, GL, and different types of dietary carbohydrates with risk of adenocarcinomas and squamous cell carcinomas of the esophagus in a case-control study design. There is limited evidence on dietary etiology of esophageal cancer, which marks raising incidence rates. Therefore, this analysis has a potential to add to the existing body of knowledge on this topic, despite the biases associated with its retrospective study design. Authors found dietary fiber strongly inversely associated with all three investigated subtypes of esophageal cancer. They also found GL, total carbohydrates and starch intake inversely associated with squamous cell carcinoma. This is a well written manuscript based on carefully conducted data analysis, however may benefit from further sensitivity analyses. Smoking and alcohol intake are strong risk factors for squamous cell carcinoma and some of the associations observed here may have been due to residual confounding. The 4-level smoking variable is rather crude and does not distinguish former from current smokers or smoking intensity and duration. Further investigation of the possible confounding effect of smoking in particular may strengthen the manuscript.

Major compulsory revisions

1) No stratified analyses have been reported except for gender. Have authors conducted stratified analysis by BMI, alcohol or smoking or they only investigated interactions? Please clarify and revise. Nonetheless, it will be very useful to report findings from stratified analysis by smoking (never vs. ever smokers) to see whether the inverse associations for ESCC will be observed in never smokers.

2) Was smoking and/or alcohol consumption associated with GL, carbohydrate, starch or total sugars intake? Smoking and consumption of alcohol are usually inversely associated with GL and sugars intake, so the strong inverse associations for these exposures may have been observed as a result of a negative confounding from smoking and alcohol.

3) It’s interesting that total sugars are the only exposure that shows an opposing trend between EAC and ESCC. Authors do not mention that there was a positive association between sugars and risk of EAC although it was not statistically
significant. Given obesity is a strong risk factor for EAC, and BMI may be a mediator in this association, have you tried omitting BMI from the model?

4) The limitations of the analysis should include the crude measure of smoking exposure and the potential residual confounding from smoking and alcohol, as well as from unknown/unmeasured confounders; and recall bias associated with self-reported diet, BMI, and other relevant exposures.

Minor essential revisions

Line 14: According to Table 1, protein intake was significantly lower only in ESCC cases.

Line 119-127: Please explain how you decided which covariates to include in your final model.

Line 134: Do you mean ‘total sugars’? It’s unclear, given ‘sugar’ may refer to sucrose or table sugar. Please revise throughout.

Line 155-158: According to Table 1, the difference in physical activity level is significant only in ESCC cases.

Line 162-163: see comment for Line 14.

Line 190: No Supplementary Figure 2 has been included in the submitted manuscript. Is there a supplementary Figure 1?

Table 1: Values for “reflux symptoms - never” have been misplaced and corresponding value for EGJAC is missing.

Table 2: Number of cases and controls do not add up to those reported in the title row. For GL, carbohydrate, starch and sugars, same number of cases is reported for both EAC and EGJAC.

Table 3: Again, number of cases and controls do not add up to those reported in the title row.

Figure 1: Please report GL ranges by quartiles by gender in a legend.

Discretionary revisions

Squamous cell and adenocarcinomas of the esophagus have distinct etiologies. Hence, it would be useful to briefly discuss in the introduction the main risk factors for squamous cell vs. adenocarcinoma, given these are important confounders in your analysis.


Line: 96: Please specify which reference instrument the FFQ was validated against and what were the validity estimates for the exposures of interest (i.e.
total carbohydrates, total sugars, etc.

**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.