Reviewer’s report

Title: Esophagus cancer and diabetes mellitus: A population-based case-control study in Taiwan

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Reviewer: Jennifer Drahos

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This manuscript assesses the association between diabetes and esophageal cancer cases diagnosed in Taiwan. Odds ratios were calculated for diabetes and several potential risk factors. The analysis suggests that there is no association between diabetes and esophageal cancer. The authors were unable to stratify their esophageal cancers into the two major subtypes, which has major implications to most results presented. For example, since the risk factors for each subtype are mostly distinct it is difficult to interpret the significant association with both alcoholism and reflux; which are associated with squamous cell carcinoma and adenocarcinoma respectively. The authors do address the limitation of not having site-specific data, however, it should be stated earlier and there be more emphasis on putting their results within the context of what is known for both esophageal squamous cell carcinoma and adenocarcinoma.

There are some study design concerns and some additional information is needed, as discussed below. Understanding that English may not be the primary language of the authors, there are many essential minor revisions pertaining to grammar and sentence structure that will need to be addressed. I have not provided comments for each of these, but overall the paper would benefit from further editing by an English speaking professional.

Major Compulsory Revisions:

ABSTRACT

1. Background section, line 2: “esophageal cancer using universal insurance data” Please state this is a study using Taiwan’s insurance data.

2. Results, line 7: This is somewhat unclear. Did the authors assess the association of those taking any diabetic drug verses no diabetic drug prescribed? Or did they assess only individual diabetic drugs?

3. Conclusions: The authors should consider using “associated with” the disease, rather than “predict”

INTRODUCTION

4. Page 3, Line 5: I am unsure that “(336 million) is necessary, unless the authors
would include the number after 2.8% (X million).

5. General: The authors should state the esophageal cancer (EC) incidence rate and subtype distribution (esophageal adenocarcinoma [EA] and esophageal squamous cell carcinoma [ESCC]) in Taiwan.

6. Page 3, Line 12: I think the authors mean that “Studies have revealed that the adenocarcinoma is the predominant subtype in the United States…..” Esophageal cancer is still relative uncommon in the U.S.

7. Page 3, Line 16 onward: The authors describe studies that assessed the association between adenocarcinoma and diabetes. Since most EC in Taiwan is likely ESCC, have the authors reviewed that literature? Such studies should be included, since these are more pertinent to the authors’ current study.

8. Page 4, line 3: “In addition to DM, obesity, alcohol consumption…..” This sentence is misleading and the authors should consider revising. The risk factors for the main subtypes of EA are mostly distinct. For example, alcohol consumption is a major risk factor for ESCC and obesity is a major risk factor for EA.

MATERIALS AND METHODS

9. How was the index date determined for the controls? Were random index dates assigned and then used for matching?

10. Medical records were used to determine the presence of potential risk factors. How many years prior to diagnosis of EC or index visit was data collected?

11. Was there a “clean” period prior to study selection? Many similar studies will have a 6 month to 1 year period prior to diagnosis/index visit in which exposure is not assessed. During this period cases may have been ill and in comparison to controls may have had more health care visits and more rigorous evaluation of their health status and the potential risk factors of EC. (See article: Engels et al. “Use of surveillance, epidemiology, and end results-Medicare data to conduct case-control studies of cancer among the US elderly.”) Authors should consider a clean period, although it is not necessary.

12. Periodontal disease is one of the exposures adjusted for in the models. Why was this risk factor assessed? The IDC-9CM code(s) need to be included in the Methods section.

13. For the assessment of diabetic drugs, did the authors evaluate “ever/never” for any diabetic drug? Are any of these drugs prescribed for other indications besides diabetes? In the models (Table 4) the authors did not include diabetes. This may or may not be necessary, but to what extent are the results an indication of diabetes status? It would be helpful to understand how many people had treated verses untreated diabetes in the study.

RESULTS
14. Page 7, line 3: The standard deviation 30.3 years seems very large.

15. Page 7, line 6: Authors should consider removing “co-morbidities” since the list includes NSAIDS, which may be provide some protection from EC.

16. Page 7, line 8: Authors should consider removing results in which data is not shown. Their study presented matched on age and sex and therefore could not evaluate the risk of sex.

17. Page 7, line 13: Please clarify what is meant by “use of other NSAIDS”

18. Page 7, line 14: This is the first mention of periodontal disease. This needs to be added to the methods section.

19. Table 1: Please indicate matching variables.

20. If the authors matched on year, why was there such a very large difference in the standard deviation between the cases and controls?

DISCUSSION

21. It needs to be clear within the discussion section and introduction that the study population is likely to be primarily ESCC. The beginning of the discussion section focuses on the association between diabetes and EA, but does not discuss any known association or hypothesis for an association between diabetes and ESCC.

22. Page 9, bottom page: “We have conducted an additional unmatched data analysis and found men…” Since diabetes generally increases with age it is difficult to assess the validity of that finding and furthermore one would want additional information than that single sentence provides. This sentence severely detracts from the article and the authors may consider removing.

23. Page 10, Line 3: I am not sure I agree that the distribution of ESCC and EA necessarily vary by race. The subtypes vary by geographic location and the prevalence of major risk factors in these regions, which may correlate with whether it is a developing or highly developed country. The authors may consider revising.

24. Page 12: “A three 5-year cohorts study in Taiwan.... which is apparently different from adenocarcinoma...” Were to authors explaining how the distribution of subtypes is different in Taiwan and the U.S. or that the subtypes of esophageal cancer are apparently different? Authors should remove “apparently” and clarify their statement.

CONCLUSIONS

25. First sentence is very unclear and should be edited. It may be a grammatical error, but it is not clear what is meant by “risk factor at all for esophageal cancer”.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**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.