Author’s response to reviews

Title: Reproductive factors and oesophageal cancer in Chinese women: a case-control study

Authors:

Zu-Hui Chen (chenzhgz@163.com)
Jian-Li Shao (jianlishao@yahoo.com.cn)
Jin-Rong Lin (jrlin@163.com)
Xia Zhang (xiazhang2001@163.com)
Qing Chen (chengingepi@163.com)

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Author’s response to reviews: see over
Dear Editor,

We are pleased to have received your email dated February 24, 2011, in which we were encouraged to submit a revision of the manuscript entitled “Reproductive factors and oesophageal cancer in Chinese women: a case-control study” we submitted to BMC Gastroenterol. We have addressed all the concerns of reviewers and improved our English according to the reviewers’ suggestions.

On the following pages, please find our point-by-point responses to the reviewers.

We wish to thank you and three reviewers for many constructive comments and suggestions that have greatly enhanced the quality of the manuscript. We hope the concerns have been addressed adequately in this revision.

Sincerely,

Zu-Hui Chen, Jian-Li Shao, Jin-Rong Lin, Xia Zhang, Qing Chen
College of Clinical Medicine, Jinan University
School of Public Health and Tropical Medicine, Southern Medical University
Response to reviewers’ comments on the manuscript entitled "Reproductive factors and oesophageal cancer in Chinese women: a case-control study" submitted by Chen et al to BMC Gastroenterol for publication

Reviewer: Ian Beales

Major compulsory revisions

1. The main issues relates to the histological types of cancer studied here. There seems to be no doubt that adenocarcinoma and squamous carcinoma are different aetiologies and pathogenesis and it would not be at all surprising if they had different relationships to parity etc. The current data needs representing to provide the relationships with the two different cancers. In addition how where these cancers diagnosed

Response: Thanks for the comment and suggestions. We have added statements “Squamous cell carcinoma was the most frequent histological type, which comprised 93.2% (68 cases) of all cases” into the results section (lines 9-10, page 8). Because only 5 cases were adenocarcinoma, so we did not present our results by histological type. However, we did sensitivity analysis restricted to the dominant type, squamous cell carcinoma, and the results did not substantially changed (lines 19-21, page 10). We have added statements “All cases recruited in this study were examined endoscopically and histologically confirmed” into the method section (lines 10-11, page 6) to clarify how these cancers were diagnosed.

2. What effects were made to confound for other medications - it seems quite clear that aspirin and NSAID use protects against some forms of oesophageal cancer, was this analyzed?

Response: Thanks for the comment. We did asked subjects to report any regular medication (line 3, page 7). We also considered further adjustment for aspirin or NSAID use in multivariable models but the estimated ORs did not substantially changed. Also because only a very small proportion of the subjects (lower than 10% for both cases and controls) had regular use of such medicines, medication was not
included in the final models.

3. Some more definition is needed for some of the potential confounding factors - how was reflux characterised in this study? Oesophageal cancer is typically associated with weight loss but how was the BMI related to the cases defined?

**Response:** According to the reviewer’s suggestion, we have added statements

“Similar to previous studies, history of gastroesophageal reflux was estimated by asking subjects about recurrent heartburn and regurgitation, which are the cardinal symptoms of gastroesophageal reflux, occurring at least once weekly at least 5 years before the diagnosis (for cases) or the interview (for controls). To avoid reverse causality, subjects were asked to report their anthropometric measures five years before the diagnosis (for cases) or the interview (for controls)” into the method section (lines 3-8, page 7).

4. Please provide the relevant code numbers for the ethics and governance approvals

**Response:** We have added such information into the method section in the revised manuscript (lines 10-12, page 7).

**Minor revisions**

5. First is spelt incorrectly in the conclusions

**Response:** Thanks for carefully reading our manuscript. We have corrected the typo.
Reviewer: Martin Retegard

Major Compulsory Revisions

1) In the background, it needs to be emphasised that the risk factors for squamous cell cancer and adenocarcinoma are different and that the sex difference is mainly observed for the latter type. The growing incidence of adenocarcinoma but not squamous cell carcinoma also needs to be mentioned.

Response: Thanks for the comments and suggestions. According to the reviewer’s suggestions, we have revised the manuscript and added such information into the revised manuscript (paragraph 2, the background section).

2) It also needs to be mentioned that the sex difference is age-related, as suggested by Derakhshan et al 2009 Gut and Rutegard et al 2010 European Journal of Cancer. Furthermore, there is ample evidence that risk factors do not seem to be distributed in a skewed fashion between the sexes, as suggested by Lindblad et al 2006 Cancer Causes and Control.

Response: We have added such information and the references provided by the reviewer in the revised manuscript (lines 19-21, page 4).

3) Furthermore, there is a pertinent recent meta-analysis on reproductive factors that needs to be included and commented in the introduction and the discussion: Cronin-Fenton et al 2010 European Journal of Cancer.

Response: Thanks very much for providing the updated information. We have added this study in the references (lines 12-14, page 5).

4) In the methods, it needs to state what if every type of cancer warranted exclusion from the study; specifically, various types of skin cancers such as basal cell carcinoma and squamous cell cancers might not be a reason to exclude those patients, as these more benign tumours might not influence selection. It might be helpful also to make clear whether controls were included if they ever had suffered from cancer. There is also a need to state why only 2 controls were picked, as opposed to the standard 4-5
per case.

**Response**: Thanks for the valuable comment. In our study, controls were required to be without any history of any type of cancer (line 14 page 6). For some practical reasons (mainly costs), we were not able to interview more controls. However, we discussed such limitation in the revised manuscript as “Increasing the number of controls to a control-case ratio of 4 can, at least to some extent, increase the study power, which needs consideration in future studies” (lines 15-17, page 10).

5) I would certainly like to see data on breastfeeding as well, as this previously has been showed to be the only determinant influencing oesophageal adenocarcinoma risk. If this information is not available, this might turn out be a major disadvantage to this study.

**Response**: Thanks for the valuable comment. However, we did not collect information of breastfeeding, which might be a disadvantage of this study although most of the cases in this study were squamous cell carcinomas.

6) In the methods, it should also be clearly stated whether the performed tests were predefined, what reasons prompted the chosen cut-offs in exposure categories. There is a certain risk of multiple testing and one gets the impression that the authors are out on a "fishing expedition".

**Response**: Thanks for the valuable comments. We have re-analyzed our data and also revised the statements in the method section according to the reviewer’s suggestions (line 21, page 7 to lines 1-3, page 8; table 2).

7) In results, the distribution of adenocarcinoma and squamous cell carcinoma needs to be added.

**Response**: Thanks for the suggestion. We have added such results in the revised manuscript (lines 9-10, page 8).

8) The stratified analysis in the discussion must be mentioned in the methods section;
for now, it seems to have appeared magically.

**Response**: Thanks for the suggestion. We have added such description in the method section (lines 3-5, page 8).

**# Minor Essential Revisions**

1) In table 1, it would be much preferable to include a column with p values (instead of just stating "p < 0.05" or not).

**Response**: Thanks for the comment. We have added exact p values in table 1.

2) In the discussion, I would like to see a more refined discussion about the consequences of choosing controls from a cohort not randomly selected. There is a certain risk that people seeking routine health examination may be more afflicted by risk factors than the general population, and any bias this may pose must be at least commented upon.

**Response**: We have revised the manuscript according to the reviewer’s comments (lines 9-12, page 10).

3) It must be an understatement to claim that "...the two histological types... may differ in etiology to some degree". There are substantive differences, e.g. shown by Lagergren et al 1998 NEJM and Lindblad et al 2005 Cancer Causes and Control. This needs to be revised accordingly.

**Response**: We have revised the manuscript according to the reviewer’s comments (the second paragraph, the background section).

4) Linguistic check is needed.

**Response**: Thanks for the suggestion. We have carefully checked and refined the English language.
Reviewer: Neal D Freedman

Major Compulsory Revisions

1. It is very important for the authors to distinguish esophageal cancers by histological type. In China, nearly all esophageal cancers have a squamous histology. In Western countries, however, esophageal adenocarcinoma is more common. The authors should acknowledge that risk factors for these two cancers are very different. For example, alcohol is a strong cause of esophageal squamous cell carcinoma, but not esophageal adenocarcinoma. Obesity, on the other hand, substantially increases adenocarcinoma risk but has little to no association with squamous cancer risk.

Response: Thanks for the valuable comments. We have revised the manuscript according to the reviewer’s suggestions (the second paragraph, the background section).

The authors should specify the histology of cancers in their study.

Response: Thanks for the suggestion. We have added such results in the revised manuscript (lines 9-10, page 8).

More importantly, the authors should restrict their discussion of previous studies to those of esophageal squamous cell carcinoma.

Response: Thanks for the comment. We have removed those of adenocarcinoma from paragraph 1 in the discussion section.

2. The sex-ratio varies substantially by geographic region and histologic type. The highest sex ratio has been seen for esophageal adenocarcinoma in Western countries. Incidence rates for esophageal squamous cell carcinoma are more similar in both sexes, though higher in men than women in many populations. But, in several parts of China with extremely high rates of esophageal cancer, the sex ratio is nearly 1:1. What is the sex ratio in Guangzhou, China? The authors should provide specific data about incidence rates in the region of the current study. Are a similar proportion of male and female patients diagnosed at the hospital and treated? In some parts of the
world, men with esophageal cancer are more likely to receive a hospital diagnosis and treatment than women with esophageal cancer.

**Response**: Thanks for the comments. We have provided information on incidence of oesophageal cancer in Guangzhou in the revised manuscript (lines 5-7, page 6).

During the study period, there were totally 357 male and 92 female primary oesophageal cancer cases diagnosed in the hospital, showing a similar sex ratio to the whole population.

3. How were the categories for analysis, in Table 2, chosen? For example, there are very few cases and controls in the oldest category of age at first birth. The first and third categories of age at menarche and age at menopause are also very small. Since the first category of age at menarche and age at menopause serves as the referent group, small numbers in this group leads to instability in the risk estimates. The authors should create tertiles or quartiles based on the controls for these variables. Categorizing the exposures in this way will increase the precision of the risk estimates. It is especially important due to the small sample size of the current study.

Also, could the authors analyze years of menstruation? (age at menopause – age at menarche)

**Response**: Thanks for the valuable comments. We have re-analyzed our data and also revised the statements in the method section according to the reviewer’s suggestions (line21, page 7 to lines 1-3, page 8; table2). Results for years of menstruation were also added in the revised manuscript.

4. Where the authors able to collect additional information on other related exposures such as types and duration of contraceptive use (i.e oral contraceptives, IUD), hysterectomy and oophorectomy, breast feeding, or menopausal hormone therapy?

**Response**: Thanks for the comment. We did collected information on any regular medication, including oral contraceptive use and menopausal hormone therapy. But only very few (less than 10% for any medicine) subjects ever used, so we did not reported the results. We were not able to collect information breastfeeding, which
might be a disadvantage of this study although previous studies showed that HRT was only associated with adenocarcinoma risk not squamous cell cancer (the dominant type in this study). We were either not able to collect information on hysterectomy and oophorectomy, which is indeed a disadvantage of this study.

Minor issues not for publication

1. Conclusions, first paragraph, replace "firs" with "first"
2. Abstract, Background, "is still lacked" should be "is still lacking"

Response: Thanks for carefully reading our manuscript. We have corrected these typing errors.