

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cigarette Smoking and the Risk of Nasopharyngeal Carcinoma: A Meta-Analysis of Epidemiological Studies
AUTHORS	Long, Mengjuan; Fu, Zhenming; Li, Ping; Nie, Zhihua

VERSION 1 – REVIEW

REVIEWER	Peter Lee Director P N Lee Statistics and Computing Ltd Sutton Surrey United Kingdom I am a long term consultant to the tobacco industry.
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	<p>While this paper describes a careful and detailed review of the evidence on smoking and nasopharyngeal carcinoma it could be improved in a number of ways, as summarized below:</p> <ol style="list-style-type: none">1. There is some confusion between the terms nonsmoker and never smoker. In strict English, a nonsmoker is someone who does not currently smoke, and therefore includes former smokers. However, I am fairly sure that the authors mean lifelong nonsmokers when they say nonsmokers. I would get round the problem by initially referring to “lifelong nonsmokers (i.e. never smokers)” and then using the term “never smokers” consistently afterwards.2. Related to this is the unmentioned problem of “never smoker of what?” Are we talking of never smokers of cigarettes (which may include pipe or cigar smokers) or never smokers of any tobacco product? The same problem arises with the definition of cigarette smoking. Are results equally acceptable for those who smoke cigarettes only, or who are mixed smokers of cigarettes and other products? What about studies who only present results for smoking of any product?3. The analyses described in Table 3 do not (and should) include tests of significance of heterogeneity over levels of a factor. It is inappropriate, for example, to carry out separate analyses for males and females, find that estimates are significant for males but not for females, and then emphasise this in the discussion, if in fact there is no significant variation by gender in the effect estimates. The proper analysis is to first test whether effect estimates vary significantly by gender, and then only emphasise differences if they do. If there is no significant variation, simply say that there was no significant evidence of variation by gender. It is a gross error to
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attempt to explain differences which statistically do not exist. Looking briefly at your results the variation by histological type seems real, but that by gender is consistent with chance variation.

4. It is unclear whether the authors only used effect estimates provided directly in the publications or whether they derived some estimates from data provided. For example, if the authors presented estimates for current and former smoking, it is possible (using the methodology of Hamling et al1) to derive an effect estimate for ever smoking.

5. At the end of the introduction it is stated that the authors “sought to provide a summary of available literature of high quality...”. It is also stated that the studies were graded for quality using the Newcastle-Ottawa Scale. However, there is no definition of what constitutes “high” quality, or whether any studies were rejected on the basis of low quality.

6. The authors refer in the information to a previous meta-analysis by Xu et al involving 28 case-control studies and four cohort studies. The present paper includes 17 case-control studies and four cohort studies. The paragraph refers to nine of Xu’s studies that were excluded for various reasons, and to four new studies. This would explain why the number of studies in the present review is smaller by 5 (9–4), but not why it is smaller by 11 (28–17). Some explanation is needed.

7. Selection of pack-years as the only dose-response measure in Table 3 seems strange, especially as it is a combination of two distinct dimensions (daily consumption and years smoked) which may have differing relationships to NPC risk. It would be useful to see results by consumption and duration separately.

8. There seemed to be no legends for the Figures (at least in the material provided to me for review).

9. The Tables are referred to in the text as I, II and III, but are headed 1, 2 and 3.

10. A figure (2) is provided showing results for ever smokers. It would be useful to see also figures for current and former smoking.

11. It seems bizarre that in the dose-response analysis reference is made to a linear relationship with pack-years when the graph shown to illustrate this shows a curved relationship. Perhaps it would be useful to show the fitted line in the figure. Reference to “cumulative number of pack-years” is incorrect. Pack-years itself is a cumulative measure.

12. In paragraph 4, there is the phrase “pointless in terms of statistics”. What does this mean?

13. In the sensitivity analysis, the study of Ji 2001 is removed. It is stated that the between-study heterogeneity dropped strikingly, but it should be made clear whether it remained statistically significant. Looking at Figure 1 it also seems that Turkoz 2001 is a clear outlier. It would be of interest to see whether removing that also reduced (and perhaps eliminated) the significant heterogeneity.

14. Table 3 refers to “age of onset”. To avoid a reader thinking this might refer to “age of onset of NPC”, call it “age of onset of smoking”.

15. The English, though clear enough, could be improved in a number of places.

Limiting attention to the first few pages:

1.	Abstract – objective – line 3	“evidence of a reliable
2.	Abstract – Eligibility – line 2	“All studies had to evaluate the”
3.	Abstract – Results – line 4	“..... in that the risk
4.	Abstract – Results – line 8	“This finding also existed

	<p>What finding? This is very unclear</p> <p>5. Abstract – Results – final sentence “had a greater risk” Greater risk than what? Than never smokers, or people starting later?</p> <p>6. Introduction – Para 1 – line 2 “Despite NPC being rare”</p> <p>7. Introduction – Para 2 – line 2 “for the occurrence”</p> <p>8. Introduction – Para 2 – line 5 “..... some studies failing to find”</p> <p>Reference</p> <p>1. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008;27:954-70.</p>
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REVIEWER	<p>Kazuya Ishikawa Kanazawa University Japan I declare that I have no significant competing financial, professional or personal interests.</p>
REVIEW RETURNED	29-May-2017

GENERAL COMMENTS	<p>The manuscript “Cigarette Smoking and the Risk of Nasopharyngeal carcinoma: A Meta-Analysis of Epidemiological Studies” by Mengjuan Long and colleagues presents cigarette smoking is one of the risk factors of nasopharyngeal carcinoma (NPC).</p> <p>The manuscript is well written and the analysis is well conducted in large. I think that Epstein-Barr virus (EBV) is the most important factor in the patients with NPC. In the NPC case not related to EBV, smoking can be the risk factor of NPC.</p> <p>Here are the minor comments.</p> <p>1) The authors should present the characteristic of EBV in the Table. 2) NPC has the regionality. Are there regionalities in NPC caused by smoking?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Peter Lee
Director
P N Lee Statistics and Computing Ltd. Sutton. Surrey. United Kingdom

Please state any competing interests or state ‘None declared’: I am a long term consultant to the tobacco industry.

Response: We agree that any competing interests should be stated. Thus, we have provided this information and stated ‘None declared’ in the revised manuscript (Marked copy- Page 16, Line 9).

Reviewer 1 COMMENTS FOR THE AUTHOR:

While this paper describes a careful and detailed review of the evidence on smoking and nasopharyngeal carcinoma it could be improved in a number of ways, as summarized below:

1. There is some confusion between the terms nonsmoker and never smoker. In strict English, a nonsmoker is someone who does not currently smoke, and therefore includes former smokers. However, I am fairly sure that the authors mean lifelong nonsmokers when they say nonsmokers. I would get round the problem by initially referring to “lifelong nonsmokers (i.e. never smokers)” and then using the term “never smokers” consistently afterwards.

Response: We agree and have reworded the term “nonsmoker” to “never smoker” throughout the revised manuscript.

2. Related to this is the unmentioned problem of “never smoker of what?” Are we talking of never smokers of cigarettes (which may include pipe or cigar smokers) or never smokers of any tobacco product? The same problem arises with the definition of cigarette smoking. Are results equally acceptable for those who smoke cigarettes only, or who are mixed smokers of cigarettes and other products? What about studies who only present results for smoking of any product?

Response: In our research, never smokers meant that people did not smoke any tobacco product. We have added this definition in the revised manuscript (Marked copy- Page 6, Line 17-18). Three of 21 eligible studies presented results for smoking of different tobacco products, and we extracted data for smoking cigarettes only. The other 18 studies referred to cigarette smokers and did not mention pipes or cigars or any other tobacco products. Since data about mixed smokers of cigarettes and other products was scarce, we could not address this issue in the current meta-analysis. However, we agree this is an important question warrants further research, thus, we mentioned this as a limitation of our manuscript in the revised manuscript (Marked copy- Page 15, Line 12-13).

3. The analyses described in Table 3 do not (and should) include tests of significance of heterogeneity over levels of a factor. It is inappropriate, for example, to carry out separate analyses for males and females, find that estimates are significant for males but not for females, and then emphasise this in the discussion, if in fact there is no significant variation by gender in the effect estimates. The proper analysis is to first test whether effect estimates vary significantly by gender, and then only emphasise differences if they do. If there is no significant variation, simply say that there was no significant evidence of variation by gender. It is a gross error to attempt to explain differences which statistically do not exist. Looking briefly at your results the variation by histological type seems real, but that by gender is consistent with chance variation.

Response: The results presented in Table III showed heterogeneity of data among eligible studies included in each stratified analysis. We did not test whether effect estimates vary significantly by levels of a selected factor.

For example, heterogeneity among 19 studies referred to the pooled OR and its 95%CI for ever smokers was 1.56 (1.32-1.83), and heterogeneity of the ORs for ever smokers among 19 studies was 66.8%. There was significant heterogeneity in ORs for ever smokers among 19 studies (P value was <0.01). Table 3 did not show whether effect estimates vary significantly by levels of smoking (i.e. current smoker versus former smokers).

4. It is unclear whether the authors only used effect estimates provided directly in the publications or whether they derived some estimates from data provided. For example, if the authors presented estimates for current and former smoking, it is possible (using the methodology of Hamling et al1) to derive an effect estimate for ever smoking.

Response: As for publications without available effect sizes, crude effect estimates and 95% CIs were directly derived from data provided (for example: N, sample size for different groups). Since most of the studies provided effect estimate for ever smoking directly, we did not use the methods mentioned in Hamling’s article. These had been stated in Methods section in the revised manuscript (Marked

copy- Page 6, Line 5-7).

5. At the end of the introduction it is stated that the authors “sought to provide a summary of available literature of high quality...”. It is also stated that the studies were graded for quality using the Newcastle-Ottawa Scale. However, there is no definition of what constitutes “high” quality, or whether any studies were rejected on the basis of low quality.

Response: We agree that the term “high quality” was not appropriate in the text and thus was deleted. The sentence has been rewritten in the revised manuscript (Marked copy- Page 5, Line 1).

6. The authors refer in the information to a previous meta-analysis by Xu et al involving 28 case-control studies and four cohort studies. The present paper includes 17 case-control studies and four cohort studies. The paragraph refers to nine of Xu’s studies that were excluded for various reasons, and to four new studies. This would explain why the number of studies in the present review is smaller by 5 (9–4), but not why it is smaller by 11 (28–17). Some explanation is needed.

Response: We stated that only publications in English were included (Marked copy- Page 5, Line 14). There were four studies in Chinese (three case-control studies: Cai 1996, Huang 2002, Liao 2005; one cohort study: Zhang 2004) and one in French (Bendjemana 2011) eligible for Xu’s meta-analysis. Another one (Ma 2011) was excluded after reviewing its abstract for it mainly described functional gene polymorphism and risk of NPC and did not provide data for relationships between cigarette smoking and NPC risk, which did not conform with our strict selection criteria. As a result, there were total of 15 studies excluded and four new studies were added (15-4=11).

7. Selection of pack-years as the only dose-response measure in Table 3 seems vstrange, especially as it is a combination of two distinct dimensions (daily consumption and years smoked) which may have differing relationships to NPC risk. It would be useful to see results by consumption and duration separately.

Response: We have tried to analyze relationships of daily consumption and duration to NPC risk separately. However, most eligible studies did not provide data for duration. Consequently, we decided to see results by pack-years and intensity of smoking (i.e. daily consumption) respectively, which could indicate the effects for duration to a certain degree.

8. There seemed to be no legends for the Figures (at least in the material provided to me for review).

Response: We have edited legends for our figures and uploaded them as images.

9. The Tables are referred to in the text as I, II and III, but are headed 1, 2 and 3.

Response: We agree and have corrected them in the tables.

10. A figure (2) is provided showing results for ever smokers. It would be useful to see also figures for current and former smoking.

Response: We have compared the relationship between current/former smokers and the risk of NPC development, and the results were displayed in the Table III. However, we did not present their funnel plots because our research already had five figures.

11. It seems bizarre that in the dose-response analysis reference is made to a linear relationship with pack-years when the graph shown to illustrate this shows a curved relationship. Perhaps it would be

useful to show the fitted line in the figure. Reference to “cumulative number of pack-years” is incorrect. Pack-years itself is a cumulative measure.

Response: After being reprogrammed, the figure now shows a linear relationship with pack-years and the new Figure 3 is presented. As for the term “cumulative”, we have deleted it in the text.

12. In paragraph 4, there is the phrase “pointless in terms of statistics”. What does this mean?

Response: It was not clearly stated and the phrase has been modified as “statistically insignificant” in the revised manuscript (Marked copy- Page 10, Line 25).

13. In the sensitivity analysis, the study of Ji 2011 is removed. It is stated that the between-study heterogeneity dropped strikingly, but it should be made clear whether it remained statistically significant. Looking at Figure 1 it also seems that Turkoz 2001 is a clear outlier. It would be of interest to see whether removing that also reduced (and perhaps eliminated) the significant heterogeneity.

Response: Our research conducted the sensitivity analysis by deleting each study in turn to investigate the influence of every single study to the overall estimate. “Sensitivity analysis and publication bias” section had stated that the odds ratios remained significant when the study of Ji 2011 was removed in the revised manuscript (Marked copy- Page 11, Line 5-10). And the heterogeneity reduced partly while the results also remained significant when the study of Turkoz 2001 was removed (OR, 1.50; 95% CI, 1.28-1.76; heterogeneity: $I^2=62.4%$, $P<0.01$). We have added this information in Results section in the revised manuscript (Marked copy- Page 11, Line 13-15).

14. Table 3 refers to “age of onset”. To avoid a reader thinking this might refer to “age of onset of NPC”, call it “age of onset of smoking”.

Response: We agree and have rewritten it in the Table 3.

15. The English, though clear enough, could be improved in a number of places.

Limiting attention to the first few pages:

1). Abstract – objective – line 3 “evidence of a reliable

Response: We agree and have modified the sentence to “evidence of a reliable” in the Objective in the revised manuscript (Marked copy- Page 2, Line 4).

2). Abstract–Eligibility–line 2 “All studies had to evaluate the”

Response: We agree and have modified the sentence to “All studies had to evaluate the...” in the Eligibility in the revised manuscript (Marked copy- Page 2, Line 8).

3). Abstract–Results–line 4 “... in that the risk ...”

Response: We agree and have modified the sentence to “... in that the risk...” in the Results in the revised manuscript (Marked copy- Page 2, Line 16).

4). Abstract–Results–line 8 “This finding also existed ...”

What finding? This is very unclear

Response: We have modified the sentence to “Significantly increased risk also existed...” in the Results in the revised manuscript (Marked copy- Page 2, Line 20-21).

5). Abstract–Results–final sentence “had a greater risk ...”

Greater risk that what? Than never smokers, or people starting later?

Response: We have modified the sentence to “greater risk than those starting later for ...” in the Results in the revised manuscript (Marked copy- Page 4, Line 23).

6). Introduction–Para 1–line 2 “Despite NPC being rare ...”

Response: We agree and have modified the sentence to “Despite NPC being rare...” in the Introduction in the revised manuscript (Marked copy- Page 4, Line 3).

7). Introduction–Para 2–line 2 “for the occurrence ...”

Response: We agree and have modified the sentence to “for the occurrence...” in the Introduction in the revised manuscript (Marked copy- Page 4, Line 8).

8). Introduction–Para 2–line 5 “...some studies failing to find ...”

Response: We agree and have modified the sentence to “some studies failed to find...” in the Introduction in the revised manuscript (Marked copy- Page 4, Line 12).

Reviewer 2

Kazuya Ishikawa

Kanazawa University. Japan

Please state any competing interests or state ‘None declared’: I declare that I have no significant competing financial, professional or personal interests.

Response: As mentioned in the response to the reviewer 1, we have provided this information and stated ‘None declared’ in the revised manuscript (Marked copy- Page 16, Line 9).

Reviewer 2 COMMENTS FOR THE AUTHOR:

The manuscript “Cigarette Smoking and the Risk of Nasopharyngeal carcinoma: A Meta-Analysis of Epidemiological Studies” by Mengjuan Long and colleagues presents cigarette smoking is one of the risk factors of nasopharyngeal carcinoma (NPC).

The manuscript is well written and the analysis is well conducted in large. I think that Epstein-Barr virus (EBV) is the most important factor in the patients with NPC.

In the NPC case not related to EBV, smoking can be the risk factor of NPC.

Here are the minor comments.

1) The authors should present the characteristic of EBV in the Table.

Response: We agree that NPC has strong association with EBV. However, data regarding characteristic of EBV is not available in the literatures included in this study. Thus, we cannot present characteristic of EBV in the Tables.

2) NPC has the regionality. Are there regionalities in NPC caused by smoking?

Response: We agree that NPC has regionality. Although smoking tended to be associated with the risk of NPC in some regions, the association was not statistically heterogeneous among regions. We have mentioned these results in the revised manuscript (Marked copy- Page 10, Line 1-8).

VERSION 2 – REVIEW

REVIEWER	Peter Lee P N Lee Statistics and Computing Ltd Sutton Surrey United Kingdom I am a long term consultant to the tobacco industry
REVIEW RETURNED	16-Aug-2017

GENERAL COMMENTS	I thank the authors for the attention they have paid to my earlier comments and have no further major comments. The text of the paper, though reasonably clear, could be slightly improved by professional editing.
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