Author's response to reviews

Title: Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer

Authors:

  Peter N Lee (PeterLee@pnlee.co.uk)
  Barbara A Forey (BarbaraForey@pnlee.co.uk)
  Katharine J Coombs (KatharineCoombs@pnlee.co.uk)

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Author's response to reviews: see over
Reviewer's report 1

Title: Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer

Version: 1 Date: 8 February 2012

Reviewer: Geoffrey C Kabat

Reviewer's report:

This is a prodigious piece of work, which synthesizes the results of studies of the association of smoking with risk of lung cancer during the twentieth century. The authors have done a meticulous job of selecting studies (and avoiding double-counting from multiple reports), extracting the available information, and conducting meta-analyses on all major aspects of smoking, as well as examining heterogeneity among studies. The findings are both important and, in some cases, surprising. They provide an extremely valuable summation of what is known from epidemiologic studies of smoking and lung cancer, and they raise certain questions for future study. Just to mention several of the major findings that struck me: the heterogeneity of the association of smoking with lung cancer by geographic location, the fact that the association does not differ significantly between Blacks and Whites, and that there was no evidence of heterogeneity between those with occupational exposures and those without such exposures. Other valuable points are that pack-years is not a valid measure of exposure and that the lower risk of lung cancer among smokers of filter cigarettes compared to smokers of non-filter
cigarettes cannot be explained by accounting for compensation due to switching from a higher to a lower tar cigarette, as argued in NCI Monograph #13.

We thank Dr Kabat for the considerable time he clearly took in carefully looking through our extremely long paper, and his kind remarks. We answer his comments below, using Times New Roman in bold to distinguish from their original comments in Arial not bold. We should also note that since submission of the paper, while carrying out further work on other projects, we found some minor errors in our database and analysis procedures. The main errors resulted in

(1) the incorrect omission of results for CPS I females in some meta-analyses,
(2) the incorrect classification of study KREUZE as a principal study, when it was in fact subsidiary to study BOFFET, and
(3) the incorrect use of 90% (rather than 95%) confidence limits for study HIRAYA.

The present version corrects these errors and as a result many meta-analysis estimates are slightly changed. However changes are minor, and the conclusions generally unchanged.

I have only relatively minor comments, below.

Specific comments

p. 14. The authors might explain for the general reader the objective of meta regression – i.e., to examine the influence of 6 different factors on the results.
The relevant sentence now reads “Following preliminary meta-regressions (not shown), a “fixed model” was fitted to examine the effect on the results of six different categorical variables (sex, location, start year of study, major study type, number of lung cancer cases and number of adjustment factors).”

p. 15. Para starting with “First..” needs to refer to Table 5 – in order to orient the reader.

We could find no para starting with “First..” on p15, and as page 15 is in the Methods section it should not refer to Tables of Results. Perhaps Dr Kabat meant page 20 where Table 5 is introduced, and there is a paragraph starting “First..”. The beginning of this paragraph has been amended to read:

“First, the RRs for all three outcomes are markedly heterogeneous. As shown in Table 5, H is estimated as 22.84 for all lung cancer, 5.17 for squamous and 8.78 for adeno (p < 0.001).”

p. 23. Last line. “This results” Should be “This result” -- need a comma after “counter-intuitive”

We have made the suggested changes

p. 50, line 14. Should be “smoke fewer cigarettes”

We have made the suggested change

We have extended the first paragraph of the section “Type of Cigarette Smoked” to read

“The conclusions drawn from the results in Table 14 are consistent with those drawn by one of us in a review of the relationship between lung cancer and type of cigarette conducted in 2001 [24]. This is unsurprising, because the data sets considered are very similar. The conclusions are also very similar to those of a review by Kabat carried out in 2003 [REF INCLUDED].“

I found the years preceding the refs used in the figures confusing. For example, the main ref for CARPEN is 120. In Fig. 23 CARPEN is preceded by 1991. But if one looks up ref. #120, which is London et al., it was published in 1995. So there is something confusing about this numbering scheme.

In Fig 23 “1991 CARPEN” are the values of START and REF, as indicated by the headings of the figure. As explained in the description of the figures “START” is the start year of the study, and “REF” is the study reference. This applies to all the forest plots (Figures 1 to 23). There was no intention to give either the date or first author of the publication from which the data derived. Though REF is the same as the first author of the principal publication, this is not always the case, as in this example. It does not seem necessary to make any change to the paper here.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: No competing interests
Reviewer's report 2

Title: Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer

Version: 1 Date: 30 April 2012

Reviewer: C. Arden Pope

Reviewer's report:

General Comments:

1. This is an ambitious attempt to provide a systematic review and meta-analysis of the epi evidence of smoking and lung cancer. It is restricted to studies with 100+ lung cancer cases and to studies in the 1900s. The large body of studies involved and the number and complexity of the issues make this a highly challenging undertaking. It is no small effort to just carefully review this analysis. The review has included a large amount of judgment calls (most of which are reasonably well documented) but many of which readers and reviewers could quibble with. There is also an element of “trust us, we’ve got this right” that is unavoidable in such a large and complicated review. However, in general I am impressed with the remarkable effort, the apparent attempt at comprehensiveness, and the systematic well-documented approach. I find this to be a well-written and extremely useful review.

2. Figures and Tables. Dense but well done and very informative.

We thank Dr Pope for the considerable time he clearly took in carefully looking through our extremely long paper, and his kind remarks. We answer his comments below, using Times New Roman in bold to distinguish from their original comments in Arial not bold. We should also note that since submission of the paper, while carrying out further work on other projects, we found some
minor errors in our database and analysis procedures. The main errors resulted in

(1) the incorrect omission of results for CPS I females in some meta-analyses,
(2) the incorrect classification of study KREUZE as a principal study, when it was in fact subsidiary to study BOFFET, and
(3) the incorrect use of 90% (rather than 95%) confidence limits for study HIRAYA.

The present version corrects these errors and as a result many meta-analysis estimates are slightly changed. However changes are minor, and the conclusions generally unchanged.

Major Compulsory Revisions:

1. Page 2, Abstract. The results section of the Abstract (and to a large degree, throughout the report) the primary emphasis is on the heterogeneity of the results. While heterogeneity is well documented and should be included and discussed, for me the most overarching result is the remarkable consistency and coherency of the results. For me the results section of the Abstract should be completely rewritten to more closely reflect the way the results are summarized at the beginning of the Discussion section on page 45. For example, using the existing abstract and the text on page 45, a suggested rewritten results section of the abstract is:

Abstract Results:
A total of 287 studies (19 subsidiary) were identified. The review and meta-analyses demonstrated a clear and highly consistent relationship of smoking to overall lung cancer risk. A smoking-lung cancer relationship was
observed for ever smoking (RR 5.55, CI 5.12-6.01), current smoking (RR 8.48, 7.68-9.36), ex smoking (4.30, 3.93-4.71), and only pipe/cigar smoking (2.92, 2.38-3.57). The smoking-lung cancer relationship was much larger for squamous cell carcinoma (RR for current smoking, 16.91, 13.14-21.76) than for adenocarcinoma (4.21, 3.32-5.34). The smoking-lung cancer risk relationship was evident in both sexes (with somewhat higher RR in males), in all continents studied (with RR highest for North America and lowest for Asia, particularly China), and in prospective and case-control studies. That this relationship is causal was supported by evidence of a dose-response to amount smoked, duration of smoking, tar level and fraction smoked, and with earlier age of starting to smoke, and decreasing with duration of quitting. It is also supported by minimal sensitivity of RR estimates to amount of adjustments for covariates.

We agree with Dr Pope that the emphasis might usefully be altered in the abstract along the lines indicated. However, the suggested rewrite had a few limitations – no mention of heterogeneity at all, no mention of some specific results we felt important (e.g. mentholation, no association of pipes with adeno, no handrolled cigarettes), and interpretation of the findings in the results section. The suggested revision for the Results and Conclusions section of the Abstract, shown below, will hopefully now satisfy him.

“Results

287 studies (20 subsidiary) were identified. Although RR estimates were markedly heterogeneous, the meta-analyses demonstrated a relationship of smoking with lung cancer risk, clearly seen for ever smoking (random-effects RR
5.50, CI 5.07-5.96) current smoking (8.43, 7.63-9.31), ex smoking (4.30, 3.93-4.71) and pipe/cigar only smoking (2.92, 2.38-3.57). It was stronger for squamous (current smoking RR 16.91, 13.14-21.76) than adeno (4.21, 3.32-5.34), and evident in both sexes (RRs somewhat higher in males), all continents (RRs highest for North America and lowest for Asia, particularly China), and both study types (RRs higher for prospective studies). Relationships were somewhat stronger in later starting and larger studies. RR estimates were similar in cigarette only and mixed smokers, and similar in smokers of pipes/cigars only, pipes only and cigars only. Exceptionally no increase in adeno risk was seen for pipe/cigar only smokers (0.93, 0.62-1.40). RRs were unrelated to mentholation, and higher for non-filter and handrolled cigarettes. RRs increased with amount smoked, duration, earlier starting age, tar level and fraction smoked and decreased with time quit. Relationships were strongest for small and squamous cell, intermediate for large cell and weakest for adenocarcinoma. Covariate-adjustment little affected RR estimates.

Conclusions

The association of lung cancer with smoking is strong, evident for all lung cancer types, dose-related and insensitive to covariate-adjustment. This emphasises the causal nature of the relationship. Our results quantify the relationships more precisely than previously.”

2. The analysis regarding publication bias seems incomplete, lacking context, and scattered. On page 45, the brief discussion of publication bias results is somewhat suggestive of publication bias. Yet the results are clearly mixed. First, there is a clear and well-documented selection bias in this review and
meta-analyses. It is well justified to focus on the studies with a substantial number of lung cancer cases (100+). However, by doing so, tests of overall publication bias are less easy to interpret. Clearly the authors understand this issue. On page 52 as part of the discussion of “Number of cases”, they note the tendency for RRs to be higher in larger studies and also note that this tendency is in the opposite direction to that predicted from publication bias. They also note that the explanation is unclear. A similar discussion is given on page 58. I think that this issue should be addressed more directly. It may be true that if studies with less than 100 lung cancer cases were included, there may be compelling evidence of publication bias. However, my reading of this paper is that the evidence of publication bias is weak and/or mixed at best. If this is true, it should be clearly stated in the paper. If it is not (if the authors think that there is clear publication bias), the relative size of this bias should be addressed.

Associated with each meta-analysis conducted, of which there were very many, we carried out and reported (in the detailed tables) the results of Egger’s test of publication bias. Rather than give these results every time we reported a meta-analysis estimate, which we felt would have unnecessarily made the paper longer (and more boring), we decided in section Q of the results section, on page 45, to summarize the findings for the main analyses, and to present limited funnel plots. We also feel that attempting to estimate the magnitude of any publication bias (made more complex by our decision to consider only studies involving 100 or more lung cancer cases) would be extremely difficult, and of doubtful value. We do not trust methods that attempt to correct for publication bias anyway, as they are based on unverifiable assumptions. In fact we believe that the evidence
of publication bias is not that strong, and certainly does not affect the main conclusions of the paper.

However, in answer to Dr Pope’s comment, we have made a number of changes. Firstly, in the main tables 5 (ever smoking), 8 (current smoking) and 12 (ex smoking) we have include the p value associated with Egger’s test. We have also expanded section Q somewhat, which now reads:

“Q. Publication bias

Some results of Egger’s test [17] for publication bias are presented in Tables 5, 8 and 12, with further results given in Additional file 5 : DetailedAnalysisTables, but have not previously been referred to in the text. For ever smoking there is evidence of publication bias for all lung cancer (p < 0.001) and adeno (p < 0.01), but not for squamous (p ≥ 0.1). For current smoking, some evidence of publication bias is seen for all lung cancer (p < 0.05), but not for squamous or adeno (p ≥ 0.1). For ex smoking, there is again evidence of bias for all lung cancer and for adeno (p < 0.001) but not for squamous. Figures 24 (all lung cancer), 25 (squamous) and 26 (adenoid) show funnel plots for ever smoking. Where asymmetry is seen, this in the direction of there being more higher-weight RRs above the mean. This is consistent with the evidence in Table 5 of higher RRs for larger studies. Inspection of a funnel plot for ex-smoking for all lung cancer (data not shown) also showed the high weight RRs tended to be above the mean.”

We have also extended the part of the discussion section on page 58. We have separated off what was the section “Other sources of bias” to separate sections
on “Publication bias” and “Bias due to misclassification of smoking status”. The rewritten first section is as follows:

“Publication bias
It is well known that researchers are more likely to wish to publish, and editors more likely to accept for publication, studies finding a statistically significant association between exposure and disease. The published literature may therefore overstate any true association or produce a false-positive relationship. As part of each meta-analysis we have carried out Egger’s test of publication bias, though results are generally shown only in the detailed tables. While evidence for such bias generally is mixed, the results for all lung cancer suggest that, where significant bias is seen, it is not in the direction of smaller studies with lower-weight RRs producing higher RRs. Rather it is, as noted above, the larger studies that tend to produce higher RRs. The reason for this finding is unclear. It should also be noted that our analyses are based only on those studies satisfying the inclusion criteria, and that one of these criteria restricted attention to studies with at least 100 lung cancer cases.

We have not attempted to try to correct for publication bias for four reasons. Firstly, we feel that evidence for its existence is not strong. Second, any adjustment for it seems unlikely to affect our main conclusions. Third, any adjustment for it would be complicated by the restriction on study size, Finally, any correction for publication bias would be open to question, as it inevitably involves assumptions that are impossible to verify.”
1. Page 2, Abstract, Background. I think that it is a bit of an overstatement to state that “no systematic review exists.” Given the various Surgeon General and other reports and reviews that have been written, there are a number of systematic reviews that exist. Specifically what is the unique contribution of this report?

We have rewritten the first sentence of the abstract to read:

“Smoking is a known lung cancer cause, but no detailed quantitative systematic review exists.”

The unique contribution of this report is the use of meta-analyses and meta-regressions and the number of smoking indices considered. There is not really the space to elaborate further in the abstract.

2. Page 2, Abstract and page 18. The sentence on tar levels in the abstract overstates the inferences allowed based on the limited number of studies, the enormous uncertainties regarding tar yields, etc. In the suggested abstract the tar results are only briefly mentioned as adding evidence to a dose-response relationship.

The only mention of tar level on page 18 is to state that “few studies provide data on tar level (11 studies, 4.1%)”. In the abstract as originally written we only stated that “RRs for all lung cancer increased with tar level..”. Dr Pope’s suggested amendment to the abstract includes the phrase “That this relationship is causal was supported by evidence of a dose-response to ....tar level..”. Though we accept and have stated that there are few studies, and that there are other uncertainties of interpretation, we see little difference between the two wordings. Indeed, whereas our original statement was merely reporting the association
found, Dr Pope’s revision is interpreting it as additional evidence of cause, which seems a stronger, not a weaker, position to take. In any case, we have revised the abstract considerably, relating to Dr Pope’s Major Compulsory Revision 1.

3. Page 27, The one-sentence paragraph just before “B. Risk from current smoking”. This one-sentence paragraph is awkward and unclear. Suggest rewrite and clarify.

The paragraph has been rewritten, we hope more clearly. It now reads:

“The fixed model (Table 7) considered how RR estimates varied by six main characteristics and additional analyses (see Additional file 5: DetailedAnalysisTables) tested whether adding in further characteristics improved the model fit, Characteristics which did not improve the fit for any of the three outcomes considered included whether there was adjustment for specific factors (such as age), the age of the subjects studied, the definition of smoking product, the definition of the unexposed base, whether the study was conducted in a population working in a risky occupation, and whether the study procedures required full histological confirmation.”

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests.