PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Dose-response relationship between cigarette smoking and site-specific cancer risk: protocol for a systematic review with an original design combining umbrella and traditional reviews
AUTHORS	Lugo, Alessandra; Bosetti, Cristina; Peveri, Giulia; Rota, Matteo; Bagnardi, Vincenzo; Gallus, Silvano

VERSION 1 – REVIEW

REVIEWER	Giuseppe Gorini Cancer Prevention & Research Institute (ISPO), Florence, Italy
REVIEW RETURNED	18-Aug-2017

GENERAL COMMENTS	The aim of this review is to provide updated data on the risk functions of dose-response relationships between smoking and cancer-specific risks. Firstly, an umbrella review will be conducted to find meta-analyses, pooled-analyses and systematic reviews of observational studies providing data on the association between smoking and cancers. Secondly, these analyses will be updated with recent articles not already included in the above reviews. Thirdly, a review of all original articles included in the umbrella reviews plus the updates will be evaluated in order to obtain measures of association between smoking variables (intensity, duration, time since stopping, etc.) and cancer risk. This protocol is well-structured and well written . I suggest to publish using this version, without any change. It is perfectly adherent to the journal standards since it addresses questions in public health and epidemiology and since it is relevant to clinicians. As requested by the journal, no results or conclusions were found in the protocol.

REVIEWER	Frits van Osch Maastricht University, The Netherlands University of Birmingham, United Kingdom
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	The authors succeeded in writing a clear protocol in which their considerations for restrictions in the review are well-explained in sufficient detail for most parts. This protocol proposes a large project which, in my opinion, could summarise evidence on the role of smoking behaviour in cancer incidence in an insightful and transparent way (e.g. through the publicly available website).

	Nevertheless, I think there are a few minor points that need to be discussed more thoroughly in the protocol, as listed below: - The authors could be clearer on that all cancers will be included in the introduction and abstract. It is mentioned specifically on page 8, line 26 and in my opinion this is one of the main reasons that makes this an interesting protocol. - Please provide an explanation for why no quality scores will be assigned and why no reviews will be excluded a priori (page 9, line 52). This could mean that pooled estimates are convoluted by point estimates that are not reliable. - Please give a rationale for why current and former smoker estimates will be combined if presented separately (page 14, line 39). I think combining these estimates might mean losing some information (e.g. on dose-response relationships, former vs current smoker, time exposed to smoke) and therefore a clear rationale is needed when combining these estimates.

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1
General comment: the aim of this review is to provide updated data on the risk functions of dose-response relationships between smoking and cancer-specific risks. Firstly, an umbrella review will be conducted to find meta-analyses, pooled-analyses and systematic reviews of observational studies providing data on the association between smoking and cancers. Secondly, these analyses will be updated with recent articles not already included in the above reviews. Thirdly, a review of all original articles included in the umbrella reviews plus the updates will be evaluated in order to obtain measures of association between smoking variables (intensity, duration, time since stopping, etc.) and cancer risk.
This protocol is well-structured and well written. I suggest to publish using this version, without any change.
It is perfectly adherent to the journal standards since it addresses questions in public health and epidemiology and since it is relevant to clinicians. As requested by the journal, no results or conclusions were found in the protocol.
Response: We thank the reviewer for his very favourable general comment.

REVIEWER #2
General comment: The authors succeeded in writing a clear protocol in which their considerations for restrictions in the review are well-explained in sufficient detail for most parts. This protocol proposes a large project which, in my opinion, could summarise evidence on the role of smoking behaviour in cancer incidence in an insightful and transparent way (e.g. through the publicly available website). Nevertheless, I think there are a few minor points that need to be discussed more thoroughly in the protocol, as listed below.
Response: We thank the reviewer for his favourable general comment.

Comment 1: The authors could be clearer on that all cancers will be included in the introduction and abstract. It is mentioned specifically on page 8, line 26 and in my opinion this is one of the main reasons that makes this an interesting protocol.
Response 1: We appreciate this comment. Following the reviewer's suggestion, we stressed this important aspect both in the Abstract and in the Introduction section.

Comment 2: Please provide an explanation for why no quality scores will be assigned and why no reviews will be excluded a priori (page 9, line 52). This could mean that pooled estimates are convoluted by point estimates that are not reliable.

Response 2: According to the umbrella review, no quality assessment for systematic reviews or meta-analyses will be applied, since the main aim of this umbrella review is to comprehensively find all the available original publications reporting data on the association between smoking and cancer risk. Once we will have collected all the original publications for each cancer site, it is relevant to consider a quality assessment for the corresponding papers. However, this is out of the scope of our review and, frankly, we do not have currently resources to reassure the conduction of this task. Imagine that, only for lung cancer, we expect to identify something like 1000 original publications. This may explain how such a task may be time-consuming and could affect the feasibility of the study. Since we understand the relevance of such a quality evaluation, we will consider, at least for selected neoplasms, the assignment of a quality (risk of bias) score to the original publications in order to conduct sensitivity analyses (e.g., excluding the publications with a relatively low quality score). We, therefore, added a paragraph to the "3. Review of all publications" section in order to clarify this point.

Comment 3: Please give a rationale for why current and former smoker estimates will be combined if presented separately (page 14, line 39). I think combining these estimates might mean losing some information (e.g. on dose-response relationships, former vs current smoker, time exposed to smoke) and therefore a clear rationale is needed when combining these estimates.

Response 3: We completely agree with the reviewer and we do not want to lose information. Actually, our idea is to provide pooled estimates separately for current, former and ever smokers, compared to never smokers. We will have therefore 3 pooled estimates. For completeness reasons, we will also combine estimates for current and former smokers to obtain ever smokers only in case the RR for ever smokers is not explicitly available in the article. Now we clarified this aspect in the "data analysis" paragraph.

VERSION 2 – REVIEW

REVIEWER	Frits van Osch Maastricht University / University of Birmingham
REVIEW RETURNED	04-Sep-2017

GENERAL COMMENTS	All previously mentioned issues were adequately addressed in the revised version of the protocol and therefore I would advise to move forward with publishing this version of the protocol.