Author's response to reviews

Title: "Occupational exposure and sinonasal cancer: a review and meta-analysis"

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Author's response to reviews: see over
Answers to reviewers:

First reviewer:

1. “This meta-analysis is potentially interesting, since this topic is relatively new. Although the most part of the methodology is well written, there are some important limits in the first part of the study. Using the following keywords, [(nasal sinus) AND/OR (paranasal sinus)] AND [(cancer)] AND [(odds ratio) OR (relative risk) OR (prevalence ratio) OR (hazard ratio)] – SCOPUS 138 documents, GOOGLE Scholar 6,420 documents. PubMed provided only 70 papers, so it is not possible to say that the majority of observational studies were identified by the Authors”.

   The search was performed through PubMed using the following key words: “sinonasal”, “cancer”, “occupational”, “risk”, “epidemiology”, and no other search engines were used. Therefore it is possible that not all the observational studies in the universe of occupational epidemiology literature have been identified. Nevertheless PubMed provides a fulfilling selection of studies and has been chosen as the most suitable to the aim of this paper.

2. “Histologically, several groups of neoplasms were included: adenocarcinoma, squamous cell carcinoma, anaplastic carcinoma, transitional-cell carcinoma, epidermoid carcinoma, adenoid cystic carcinoma, mucinous adenocarcinoma, anaplastic carcinoma, respiratory cells carcinoma and other histologic subgroups. With so many forms of cancer, a rationale is necessary that justifies the idea that the effect of the investigated carcinogens is the same for this heterogeneous group of neoplasms.”

   Sinonasal cancer (SNC) has been defined as target organ of several occupational exposures by the IARC (Young C et al 2012; Siemiatycki J et al 2004). From the search on PubMed several histologic types resulted, but the risk estimates related to SNC as a whole and, in some studies, to squamous cell carcinoma (SCC) and adenocarcinoma (AC), that represent the histotypes most involved in occupational exposure to carcinogens (e.g. Bimbi et al. 2004 found that only 1.6% other than AC resulted exposed to wood and leather dust).

   Consequently, in the present meta-analysis the pooled risk estimates have been calculated on all SNC grouped together and, when data were available, the effect of the selected carcinogens has been distinguished between AC and SCC. Other histotypes are not represented in the retrieved occupational studies, and so could not be used in this meta-analysis. At this regard the methods section and table 2 have been modified.

   Grouping together all SNC types could have certainly reduced the causal role of occupational exposure. Anyway, they are mostly represented by AC and SCC (75%), therefore analyses are reasonably representative of the risk between SNC and occupational exposure to carcinogens. These issues are now integrated and discussed in the text.

3. “The funnel plots corroborate the hypothesis that studies are discrepant, as the typical shape of funnel is not visible in any of the investigated carcinogens.”

   This sentence is unclear: the funnel plot is one method available to researchers for the detection of publication bias. The informal examination for asymmetry of funnel plot is subjective so that the same graph may be interpreted differently by different observers. Therefore asymmetry is formally evaluated by using statistical approaches (Begg’s method, Egger’s test, Trim and Fill method are examples). In the
present study the Egger’s test was used (the degree of funnel plot asymmetry is measured by the intercept from regression of standard normal deviates against precision), and evidence of publication bias was detected only for wood dust exposure, where indicated minor risks for smaller studies. Details are reported in the Appendix.

4. “If the Authors wish to perform such a complex meta-analysis, they should perform a thorough literature search as above described and to distinguish between different forms of cancer, at least those forms that cannot be considered similar from the histological point of view.”

The rationale of this meta-analysis is to investigate the effect of occupational carcinogens on SNC risk by using PubMed results, available for all the forms of sinonasal cancer grouped together and for the epithelial subtypes of adenocarcinoma and squamous cell carcinoma. The text has been modified accordingly.

Second reviewer:

1. “Occupational exposure to carcinogens is an interesting topic and this review focuses on particular forms of neoplasm (C30-C31) that are seldom investigated. However, the topic is very extended, since many carcinogens and many neoplasms are included in this analysis. More specifically, the number of neoplasms included in the same analysis is high and it is hard to imagine that a given carcinogen has the same effect on so many different histological types and that exposure levels are similar for different occupations. In addition, the risk exists that studies on occupational medicine which found non-significant associations between exposure and outcome are not accepted for publication. Therefore, despite the control for publication bias, the pooled risk could be overestimated.”

The effect of occupational carcinogens investigated in the present study is described in the searched literature for all the forms of sinonasal cancer (SNC) grouped together and specifically for the epithelial subtypes of adenocarcinoma (AC) and squamous cell carcinoma (SCC). It is reasonable that a given carcinogen could have different effects on other histological types, but these are not described in the occupational epidemiology currently available on SNC. This is now discussed more accurately in the text.

The fact that “studies on occupational medicine which found non-significant associations between exposure and outcome are not accepted for publication” and consequently excluded from the meta-analysis, and that the pooled risk could be overestimated, is an issue meta-analyses must deal with. This is particularly problematic when data come solely from the published scientific literature, as studies are not uniformly likely to be published in scientific journals. The use of funnel plots to control for publication bias could be purely subjective and a number of quantitative methods are often used in the literature. In the present meta-analysis evidence for publication bias (measured by using the Egger’s test) was detected only for wood dust exposure, where minor risks for smaller studies are suggested. Details on this method are reported in the Appendix.

Finally it is likely that exposure levels could be different according to different occupations, but – as detailed in the methods section on classification of exposures – on the basis of the HSE method (Young C et al 2012) and of the available information provided by the studies, analyses were performed considering the carcinogens involved rather than the corresponding occupations, with the purpose to investigate previously suggested associations and to increase the power to identify risk factors for SNC.
2. “I think that a narrative review using the references reported by the authors could be better than the meta-analysis which could rise problems of result interpretation.”

The text has been revised according to the referees’ comments and now the results are consistent with the aim of the meta-analysis. In fact, with the restriction to AC and SCC histotypes, the authors think that the meta-analysis findings overtake the interpretation problems.