Author's response to reviews

Title: Epidemiological patterns of asbestos exposure and spatial clusters of incident cases of malignant mesothelioma from the Italian national registry

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Author's response to reviews: see over
Dear Editor of BMC Cancer,

Please find below the point-by-point response to your requests and to reviewers’ comments.

**Editor’s requests:**

1. A specific statement was included in the Methods section concerning the public availability of data collected by the Italian registry of malignant mesothelioma (ReNaM). The authors of the manuscript include the research team of ReNaM and the directors and expert members of regional operative centers.

2. All the corrections proposed by the reviewers were reported in the text and a careful English language revision was made before resubmission.

**In response to referee no. 1:**

As suggested Table 3 was reedited in order to make it more clear and concise.

**In response to referee no. 2:**

1. The potential usefulness of using Bayesian methods, never applied before to analyze the spatial clustering of incidence cases of mesothelioma in our knowledge (previous studies were on mortality data, see Lopez-Abente 2006 and, for Italy, Fazzo 2012, that did not use indeed a Bayesian approach), is explicitly recalled in the Introduction. The findings of this study seem to confirm the effectiveness of the Bayesian spatial analysis.

2. As suggested by the reviewer, the aim of the study was reworded making it more clear.

3. Besides the figures already in the text, i.e. those mapping smoothed RR estimates (only municipalities with RR>1 are mapped to better show the identified clusters), according to reviewer’s suggestion, we included maps depicting SIRs and the distribution of the posterior probability of RR>1 respectively. These further maps could be inserted as additional files in the paper. We prefer, however, to keep the maps of the four Italian areas separated because they are more readable. This is also in line with the choice of using the area age-specific rates for the calculation of the expected cases.

4. We are aware that the municipality of residence often does not coincide with that of working location. Unfortunately information about the municipality of the workplaces causing asbestos exposure at individual level is not available at the moment in the central database, as now more clearly stated in the Methods section. As reported in the revised text: “Nevertheless, the presence of such kind of occupational sources was verified within each cluster by sharing the analysis findings with regional operative units.” Also considering the complex influences between occupation and residence, we are confident that the corresponding bias is small in our study, as discussed in the Discussion section. Moreover: “The direct definition of municipality of occupational exposure is on going through a further collaboration effort with the operational regional centers. This future step will allow to minimize the misclassification in geographical attribution of exposure and to improve the accuracy of our findings.”

5. **In response to referee no. 3:**
1. The typing mistake was corrected.

2. The assessment of asbestos exposure was performed though individual interview by using a standardized questionnaire. The questionnaire template and the guidelines for the collection of data and for the definition of mesothelioma cases by exposure (and diagnostic certainty) are reported in reference 11 (no. 17 in the revised version), as more explicitly stated. Moreover a sentence was added in the Method section to better clarify how residential exposure had been defined at individual level. A minimum distance from the identified source of exposure was not fixed a priori for the case definition. As reported in the Discussion: “the availability of precise information about the source of residential exposure made possible to correctly attribute to each industrial sites the environmental cases occurring among residents”.

3. The reference editing error was corrected.

4. As suggested Table 3 was reedited in order to make it more clear and concise.

5. We agree with reviewer that the four maps are better separated (renamed as Figure 1, 2, 3 and 4 in the revised version). Table 2 describes clusters ordered by geographic area (even if some clusters actually cross over the boundaries between areas), as does the revised version of Table 3. Instead, exposure patterns are presented and discussed in the text at national level in order to provide useful information for public health purposes.

In response to referee no. 4:

1. Minor essential revisions:
   
   A. We fully agree with the reviewer’s suggestion to report more data about the percentage of mesothelioma cases attributed to asbestos exposure in the Background section. We reworded the imprecise sentence and added references of other relevant recent studies (Rake 2009, Lacourt 2014).
   
   B. We corrected all the mistakes the reviewer had signalled and we would like to thank him for his help in language editing.
   
   C. Several statements in the Background section were changed referring more clearly to bias affecting ecological studies due to the lack of individual exposure data and citing some of the studies suggested (Chang 2013, Cox 2013). We also inserted two sentences in the Discussion section on this particular issue: “The availability of individual data allowed to overwhelm the possibly biased approaches using spatial distance from putative environmental sources as proxy of exposure (Cox 2003). On the other hand this study does confirm the correspondence between spatial clustering of mesothelioma cases and either occupational or environmental sources of asbestos exposure as identified case by case through expert-based assessment.”
   
   D. Even if these circumstances had been ascertained by the personnel of regional operational units in several industries through technical investigation, they can not be generalized. So we have made the corrections the reviewer suggested to avoid any misunderstanding.
2. Discretionary revisions: The issue posed by the reviewer is of some interest but a full reanalysis of the data is time demanding and likely besides the scope of this study. However we verify by some additional stratified analyses that:

A. The percentage of cases with certain (pathologically proven) diagnosis is not generally different when only cases included in clusters are considered (78.2% vs. 77.8%), but seems to vary among territorial areas (North West: all 73.1%; cluster-only: 72.7%; South&Islands: all 79.7%; cluster-only: 79.3%; Centre: all 82.4%; cluster-only: 84.4%; North East: all 84.4%; cluster-only: 85.8%), likely reflecting a non homogeneous quality of diagnosis due to the regionally-based national healthcare system. Because the number of expected cases was calculated for each municipality based on age-specific rates of respective area this difference is expected to be scarcely influent. Nevertheless, it is possible that a low percentage of certain diagnoses may affect the detection of small clusters by spatial analysis reducing the number of observed cases.

B. A territorial variation is also observed in the percentage of cases with defined exposure (interviewed): Centre: 79.5%; North East: 85.9%; North West: 78.3%; South&Islands: 60%. As reported in the Discussion section: “...the effectiveness of identification of the modalities of exposure is not fully consistent among regions since the percentage of interviewed subjects varies between 45% and 95% depending on available resources and knowledge.” This issue is discussed as a limitation of our study concerning the quality of data. On the other hand, in accordance with the study aims, the choice of including in the spatial analysis all recorded mesothelioma cases appears mainly suitable for areas as the South Italy were the percentage of interviews is low, since it warrants a higher specificity. It is advisable that increased funding will lead in the future to a more homogeneous accurateness of exposure assessment over the national territory.

Thank you for your consideration and we look forward to hearing from you.

Dr Marisa Corfiati, MD, PhD