Author's response to reviews

Title: Cumulative Asbestos exposure and Mortality from Asbestos Related Diseases in a Pooled Analysis of 21 Asbestos Cement Cohorts in Italy

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Cumulative Asbestos exposure and Mortality from Asbestos Related Diseases in a Pooled Analysis of 21 Asbestos Cement Cohorts in Italy

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Environmental Health

Reviewer reports:

Reviewer #1: This is well written, most interesting studies proving a detailed insight on the health impact of asbestos on workers engaged in the manufacture of asbestos-cement products in Italy.
The design and analysis of the study fulfill the standards of validity requested in epidemiological studies. Aims, methods and results are clearly reported.

In this frame, a few points appear to deserve a more thorough discussion, namely:

- In the evolving international scenario of asbestos production and use, what is the state of the asbestos-cement industries? Are there reports suggesting that the work procedures described in this paper may still be present somewhere?

>> The asbestos cement industry was very slow in introducing new technology. The core of the asbestos cement production process is still the “Hatschek Process”, that was first developed in early 1900. The technical improvements that were introduced over the years and were relevant for the reduction of asbestos exposure were: the transport of asbestos in plastic bags, the use of wet mixing process, the transfer of asbestos from one department to another by pneumatic transport, the use of automatic machines to open the bag in atmospheric depression and the general adoption of better cleaning and dust control systems with filtered exhaust. The cessation of the use of amphiboles was a major step for the reduction of the occurrence of asbestos related diseases.

We had conducted a search regarding production process in some countries, as the pace of introduction of technological improvements may have been different.

A paper was found in the literature on the current status of the asbestos cement industry in India that reported the use of “Hatschek Process” and measured the intensity of exposure in the order of 0.05 – 0.07 f/ml of chrysotile [Ansari et al, 2007]. These levels of exposure are apparently reassuring but may not be an accurate representation of the conditions of asbestos cement industry in the country as the sample was very limited and reports on poor work conditions were also published [Burki 2010; Kemp 2010].

Brazil has been one of the largest producers of asbestos and of asbestos cement. During the last few years legislation on the use of asbestos has been issued leading to the ban, but previously asbestos cement has been produced in large amounts [Kazan Allen 2018]. A report by Berman [1986] described the work conditions as follows: “The situation at smaller, Brazilian-owned firms is reputed to be disastrous from the standpoint of workers’ exposure to asbestos dust at the point of production”, and: “At a large asbestos cement manufacturing plant owned by Eternit, however, exposure to asbestos dust (according to company records) seemed to be kept under 2.0 fibers per cc, the present standard for the United States”. The paper by Berman did not report major technological advancements, with the exception of better handling of raw asbestos using plastic bags and prompt repair of damaged sacks. It should also be noted that he referred to the 1976 PEL for asbestos exposure, that was later reduced to 0.2 f/cc in June 1986 shortly after the publication of the paper. Reports from the industry site about proper working conditions were
challenged by scientists assisting workers’ trade unions [Rangè 1998; Giannasi et al, 1997]. A warning regarding asbestos exposure in the asbestos cement industry was raised in a review regarding asbestos in Latin America [Marsili et al 2014].

Little is known about work processes in Russia [Izmerov et al, 1998] and other countries that are large producers of asbestos cement, such as China.

A statement was added in the paper to briefly summarize the information, in page 5-6, with some references.

-Why does the different behavior of pleural and peritoneal mesothelioma after exposure cessation appear to be such a crucial point?

>> The ‘traditional’ model of the relation of asbestos exposure and mesothelioma [Newhouse et al 1976; Peto et al 1982] did not differentiate between the anatomical location of mesothelioma, as did most of the early epidemiological papers on asbestos effects. We realized from our previous work [Magnani et al 2008; Barone Adesi et al, 2008], in agreement with other authors [Hodgson and Darnton 2000] that the epidemiological pattern of pleural and peritoneal mesothelioma were different, as they showed different shapes of the relation of incidence and exposure and also a different relation of incidence and latency time. The most likely explanation is the different distribution of asbestos fibers in the body, that interest the pleura more directly and the peritoneum only after internal transportation [Misericocchi et al, 2008]. The message we want to stress is that epidemiological observations should focus on the two mesothelioma locations separately. Of course this objective requires very large studies to be addressed, given the rarity of peritoneal mesothelioma.

A statement was added in the paper to summarize the information. (p16)

- With regards to the negative (or prevailingly non-positive) findings about laryngeal and digestive tract cancers, could the Authors expand the discussion and more address the core issue of presence or absence of a causal link?

>> Our data provide little support to the causal association with laryngeal cancer, however we should note that in men the SMRs were higher in the higher classes of TSFE (40-49 and 50+ years) and in women the two observed cases were in the mid and upper tertile of cumulative exposure and in the upper categories of TSFE. The major limits of our study are the use of mortality data and the absence of information on smoking and drinking. These limits reflect on
our possibility to draw firm conclusions regarding the causal link, even if suggested by the reviewer. The text was revised. (p16-17)

>> Even less support is provided in respect to the association of digestive tract cancer. After the exclusion of peritoneal MM the SMRs are very close to unity in both genders (Men: 0.999; 95%CI: 0.916 – 1.087; Women: 1.176; 95%CI: 0.956 – 1.432). No support is also given from the analyses by cancer site, that are presented in the paper tables. The text was revised (p17).

Reviewer #2: Major Comments

page 7 line 161: Please explain what you mean by "causes of death associated to the Healthy Worker Effect (HWE)"

>> Following the indications from literature and standard textbooks [Checkoway et al 1989], we focused our attention on cardiovascular diseases, digestive diseases and respiratory diseases, as well as on the total number of deaths. However, we also analyzed data with focus on other causes of death reported in association with the Healthy Worker Effect, namely: psychiatric diseases, neurological diseases, digestive diseases and genitourinary diseases. Mortality was lower than expected for neurological diseases (statistically significant in men) and genitourinary diseases in men (not statistically significant), corroborating the observation of HWE.

A statement was added in the paper to summarize the information, in the methods (p 7) and in the discussion (p 17-18) sections.

page 15 line 373: "A biological interpretation of the overall evidence that mesothelioma incidence does not increase indefinitely by TFSE is that asbestos fibres are slowly cleared." If this is true, shouldn't the same kind of trend be seen also in the SMR for lung cancer?

>> The model describing the relation of lung cancer and asbestos exposure includes only the cumulative exposure, while the model describing the relation of mesothelioma with asbestos exposure includes also the power function of the latency time, therefore the focus of our analyses and comments, in agreement with the debate in the literature, was more on the relation of latency for the occurrence of mesothelioma. As a matter of fact, the shape as described for the pleural mesothelioma was observed also for the SMRs for lung cancer, with TSFE (table 4 and figure 2c). The result was reported in the results and discussion sections but with nor enough evidence. In the submitted draft we did not highlight it in our comments and we thank the reviewer for the observation. The text was modified to underline this observation following the reviewer’s suggestion (p 16).
page 16 line 404: "With consideration to the possible misclassification of outcome, we underline that 89 deaths in men and 1 in women had been recorded as "other pneumoconiosis" in the death certificate, possibly attributable to incorrect reporting of asbestosis."

Can you tell something about the differential diagnostics of asbestosis? Is it possible that this could be also other way round, that other pneumoconiosis would be falsely diagnosed as asbestosis? Based on Table 2, other pneumoconioses (mainly silicoses?) seem to be much more common in the population. And is it possible that IPF/UIP could be diagnosed as asbestosis? In practice a patient can get a diagnosis of asbestosis even if the exposure had been at low level which is not in line with the Helsinki criteria. (Tossavainen A, reporter. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 1997;23(4):311-316. Wolff H, reporter, Vehmas T, reporter, Oksa P, reporter, Rantanen J, reporter, Vainio H, reporter. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health 2015;41(1):5-15)

>> First we would like to amend a typo in the text and a confusion in the table 3 headings. The number of other pneumoconioses is 32 in men and 1 in women, not 89 as we wrongly stated in line 404 (line 430 in the revised text). (it was a mismatch due to the contemporary work on another paper!). As a matter of fact, the correct number of ‘other pneumoconioses’ can be checked by computing the difference between the two figures for ‘asbestosis’ and ‘Pneumoconioses’ in table 2.

As regards the table headings of table 2, the line heading ‘Pneumoconioses’ refers to ‘All pneumoconioses’, including asbestosis. It can be checked in supplementary table 2 listing the ICD codes for each category. In order to avoid the possible confusion, table 2 was amended presenting ‘Asbestosis’ and ‘Other Pneumoconioses’.

The number of ‘Other Pneumoconioses’ is fairly small: 32 (vs 8.0 expected) in men and 1 (vs 0.04) in women.

The reviewer underlines some potential errors in the ascertainment of asbestosis that are theoretical possibilities but we do not deem as very likely in the study under consideration. The basis of information in our study is limited to the underlying cause of death, that is we can include as ‘asbestosis’ only the subjects that were diagnosed as dying because of asbestosis. This is not entirely satisfactory, but it is consistent with the information at the basis of previous retrospective studies.

Some misclassification is possible between asbestosis and ‘other pneumoconiosis’, but we cannot estimate it. We took a cautionary approach and considered in the analyses the two categories separately, focusing in particular on the ‘asbestosis’ category. In the future, we will attempt to link our data with the registry of compensations for occupational diseases, but the process is very complex because of bureaucratic restrictions and we are not sure that we will succeed. In any case, the impact of the potential misclassification between Asbestosis and ‘Other
Pneumoconioses’ is limited to a few subjects and most likely the category ‘other pneumoconioses’ includes also cases of asbestosis misdiagnosed in the death certificate. The category ‘other pneumoconioses’ included 21 silicoses and 12 ‘unspecified pneumoconioses’. The pattern of mortality by tertile of cumulative exposure of the ‘other pneumoconioses’ suggested that at least a proportion of those cases are asbestosis cases, as we observed an increasing trend, similar to that observed for the ‘asbestosis’ category but with lower SMRs: I tertile: 1 obs, 1.18 exp, SMR: 0.85 (95% CI: 0.02 – 4.72); II tertile: 6 obs, 2.46 exp, SMR: 2.44 (95% CI: 0.90 – 5.31); III tertile: 26 obs, 4.39 exp, SMR: 5.92 (95% CI: 3.87 – 8.68). This information was added in the text, at page 11.

The lack of information about other work periods did not permit to define the risk of silicosis for the decedents from ‘Other pneumoconiosis’.

IPF/UIP is in principle a potential source of misclassification of the diagnosis, but we do not have access to the clinical records and death certificates may not be sensitive enough for the epidemiological analysis of that disease. No deaths were attributed to this cause in the death certificate.

The distribution of the cases of asbestosis by cumulative exposure was discussed in the paper and in particular we stated “Five cases of death attributed to asbestosis were observed in men in the lowest tertile of cumulative exposure, corresponding to the cumulative exposure ‘up to 54.0’ f/ml*years for fibre-type-weighted-CEI”. (in submitted paper: p 16, lines 397-399). The category is coherent with the conclusions of the Helsinki Consensus conference, but we cannot exclude that some individual’s value may be underestimated due to the possible asbestos exposures before the period at work in the asbestos-cement cohort. The actual values of cumulative exposure for these 5 cases were: 0.16, 3.83, 14.85, 28.31 and 37.57. We cannot exclude that the first three cases have a misclassification of their real exposure and therefore we prefer not to present these data in detail, but we will consider the reviewer’s opinion in this respect.

Given the fact that a specific paper on asbestosis is announced, we prefer not to add more details in order to avoid any possible double publication, however the core information was added in the text (p 17).

Table 3: In the legend, explain Fibre-type-weighted-CEI tertiles (which are not very clearly explained in the text either)

>> The text of table 3 legend and the heading were modified. We also revised the description of exposure estimation in Material and methods (page 7-9).
Minor comments

page 4: please add explanation for abbreviation CRD (page 17)

>> It was a typing mistake. We referred to ARD (Asbestos Related Diseases)

page 6 line 148: What means "impossible age"?

>> We excluded subjects with Hiring < 13 or >70 or Retirement >70. Data were checked before exclusion to correct typing mistakes or similar errors. The information was added to the text (p 6).

page 7 line 156: "Causes were coded according to the 8th, 9th, or 10th Revisions of the International Classification of Diseases (ICD), according to the date of death." Page 12 line 335: "There was no specific code for mesothelioma of peritoneum and pleura in the 8th and 9th ICD." When was ICD10 taken in use?

>> In Italy ICD 10 was taken in use from 2003. The information was already provided in ref 38 [Pirastu et al] and it is now given also in the text of the paper (p 7).

page 8 lines 180 and 181: "interested" does not seem to be the right verb in the context

>> It was changed in ‘regarded’ or ‘affected’.

page 15 line 367: Traditional models imply an unlimited increase of MM mortality rates

>> We do not understand the comment, if any.

The text was changed in “traditional models predict an indefinite increase”.

page 16 line 387: "Moreover, mortality analyses are not very sensitive for diseases with long survival, such as laryngeal cancer in recent periods." Please, insert reference concerning the survival with laryngeal cancer.

>> A reference was added:

page 17 line 424: CRD mortality?
>> It was a typing mistake. We referred to ARD (Asbestos Related Diseases)

page 17 line 424: Cardiovascular diseases SMR was were decreased significantly lower in men
>> The text was changed in: “Mortality from cardiovascular diseases was significantly lower than expected in men,...”

Table 2: if Asbestosis is included in Pneumoconioses, for clarity this class should be renamed, e.g. All pneumoconioses
>> Table 2 was modified showing ‘Asbestosis’ and ‘Other pneumoconioses’

References (some were added in the paper)


Burki T. Health experts concerned over India's asbestos industry The Lancet. 2010;375:626-627.

Kemp M. The Other Deadly White Dust: Russia, China, India and the Campaign to Ban Asbestos. The Asia-Pacific Journal; March 29, 2010.


