Author's response to reviews

Title: Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional study

Authors:

Christophe Paris (christophe.paris@nancy.inserm.fr)
Aurelie Martin (aurelie.martin@gmail.com)
Marc Letourneux (letourneux-m@chu-caen.fr)
Pascal Wild (pascal.wild@inrs.fr)

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

MS : ID 5767519471657033

Please find hereafter the answers to the reviewers’ comments concerning our manuscript
“Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed
populations for screening and follow-up: a cross-sectional study.”

Reviewer's report

Title: Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-
exposed populations for screening and follow-up: a cross-sectional study

Version: 1 Date: 15 November 2007
Reviewer: Paul De Vuyst
Reviewer's report:
The paper could be interesting because of the large number (over 1000) of asbestos-
exposed subjects who underwent CT and for whom information about the individual
cumulative exposure is also available. The authors have a large expertise in CT
evaluation of asbestos workers. About the half of subjects have pleural plaques and 6
% asbestosis. The presence of these lesions is associated with the time since first
exposure and the cumulative exposure. The screening methods do not address the
malignant asbestos-related diseases. The authors should emphasize what they really
consider as new and original in their study.
The statistical part is incomprehensible for the mean and even “upper” reader,
and not only the appendix.
The paper should be shortened, especially the discussion part
The text should be more precise and straightforward

Major Comments
1. What is the hypothesis tested by the study? What is the message for clinicians or
radiologists who have probably no access to precise evaluation of exposure?

We agree with the reviewer and propose to modify the initial text in order to better precise
both main hypothesis and key messages.
We added at the end of introduction the following sentence:
« The aim was to determine which exposure parameters are most useful to the clinicians
in the selection of asbestos-exposed subjects to be submitted to a CT-Scan as part of a
screening exercise ». 

We also rewrote and simplified our results section as well as the beginning of the
discussion part in order to indicate the main messages of our paper from a clinical point of
view as following:
“Overall, TSFE was the key variable for both pleural plaques and asbestosis, and
duration of exposure was not found to be predictive, adjusted on TSFE. High exposure
concentration to asbestos appears also to be a significant variable with a less significant
effect than TSFE. Regarding these results, clinicians should mainly consider these two
variables before including exposed subjects in a CT-scan screening. According to our
modelling of incidence, a useful periodicity of survey of pleural plaques by CT-scan may range between 5 to 10 years"

We also addressed a new discussion point relative to the availability of dose estimates of asbestos exposure for clinicians in the discussion section as following:

A second point is the availability of dose exposure assessment and accordingly the usefulness of our results for clinicians. Atmospheric measurements, as in our study, are rarely available and retrospective assessment of asbestos exposure is usually based on job-specific questionnaires and job exposures matrices [24]. None of these two methods is clearly the better [25]. However, some combinations of the two may provide sufficiently accurate estimates of asbestos exposure [26] and may be used in actual clinical practice.

2. Why were the subjects with known diseases and/or involved in previous CT screening campaigns excluded from the study, if correct evaluation of exposure was available?

There were two reasons for this selection. The first is a practical one as the National Health Insurance supported the cost of the screening only in absence of known asbestos-related diseases. Indeed, in case of occupational diseases, the legislation and the funding are totally different. The second one is to avoid bias linked to the knowledge of asbestos-related diseases at inclusion, which is a condition for the fitting of incidence (see discussion)

3. The CT methodology changed over time (incremental and then helical) depending on the date of inclusion

Our study is clearly between two generation of CT-Scan, incremental and then helical. In order to minimize the difference between CT-Scan, only incremental CT-Scan with joined centimetric slices of complete thorax were kept. However, in both cases, all examinations included HRCT slices. The two generation of CT-Scan differed by the number of HR slices as the first kind included 6 slices (five of which were equally spaced between the carina of trachea and the bottom part of costophrenic angles) and the helical CT a complete exploration of thorax. The difference in the numbers of slices is thought to have little effect on asbestosis prevalence as discussed in the paper and in Paris et al. SJWEH 2004. We clarified these points in the corresponding method section “Diagnosis of pleural plaques and asbestosis from imaging”

4. Statistics: the statistical part should be rewritten and made much easier to understand. Paragraph on page 9, presenting Table 2 is particularly unclear. The regression formulae are not given. The abbreviations OR, CI, P are not explained.

We gave more details on the logistic regression model and how they were obtained in the methods section; we rewrote the paragraph which the referee found unclear and hope that it is clearer now. The abbreviations are now explained in the footnotes of the tables.

5. France has adopted a surveillance program for asbestos-exposed workers, who may benefit from social advantages, such as compensation and early retirement, including for pleural plaques. This type of screening programs for benign and
limited lesions (not necessarily “diseases” as mentioned in the abstract) is of scientific interest, but the medical and/or social impact may be not relevant in other countries.

We totally agree with the reviewer to the limited (null ?) medical impact on such screening of pleural pulmonary lesions in absence of treatment. The relation between pleural plaques and lung cancer is controversial and the benefit of lung cancer screening is hotly discussed to date. However as mentioned in the introduction some countries have already installed funds to compensate asbestos related diseases (France) or currently debate on this particular point as the American Senate. Finally, an increasing number of papers reported the use of HRCT scan in asbestos exposed subjects (we provided some recent references in the introduction) and this question seemed relevant to us.

6. Some references are not classical peer-reviewed papers: 3, 4, 15, 17.

We deleted these references

Minor Comments
7. Abstract. How do the authors define asbestosis on CT? This probably means “interstitial changes compatible with asbestosis”

We agree, done

Finally, we shortened in several parts the discussion, particularly the § on relation between pleural plaques and lung cancer as we have no data on this specific topic, as well as the statistical discussion
Reviewer's report
Title: Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional study

Version: 1 Date: 6 December 2007
Reviewer: Muzaffer Metintas

Reviewer's report:
In general
1. A different methodology has been adopted in collecting the study data; the study is not prospective or retrospective, nor is entirely a cross-sectional study. The data source is made up of two irrelevant groups: the retirees and working people over 50 years of age. The study was carried out by combining the two groups. This created difficulties in determining the standards of the study. It took 4-5 years to scan all the retirees and the working people, and this compels the study standards.

We apologize for the confusion introduced by our presentation of the population. We included in the study subjects over 50 years, whatever the working status (retirees or not) from specific plants well known to have past heavy use of asbestos. The design of the study is cross-sectional, the survey of patients beginning by the most exposed subjects (as a consequence the older ones) with the same clinical and radiological procedure. In particular, all patients underwent an HRCT (see reviewer 1, comment 3). We modified the description of our population in the first paragraph of the methods section in order to be more precise and to answer to the reviewer:

“A screening program for asbestos-related diseases was instated in 1991 in Normandy (France). We included in this study volunteers subjects over 50 years, including retirees whatever their ages, from specific plants well known to have past heavy use of asbestos, mainly asbestos textile and friction materials fabrication, insulation and energy production The program began by the most exposed workers (as a result the older ones), and was then progressively extended to the more recently exposed subjects.”

2- A key issue was the reason why the cases of diffuse pleural fibrosis developed due to asbestos were not included in the study and assessment. Diffuse pleural fibrosis is different pathological condition than pleural plaque. The fact that it is not treated in the study is a shortfall. How were these cases determined during the study received or under which heading were these included?

Again we apologize for the confusion. Patients with diffuse pleural fibrosis were kept in the population studied but no relationships analyses were performed regarding the small number of cases. We changed the corresponding sentences in the methods section “Diagnosis of pleural plaques and asbestosis from imaging” as following:

“Radiological abnormalities namely interstitial changes compatible with asbestosis, pleural plaques and diffuse pleural thickening, were independently rated…”

“Only certain pleural plaques and interstitial changes compatible with asbestosis were considered for statistical analyses due to the small number of cases of pleural diffuse thickening.”
Minor comments:
As chapters
Abstract:
3. The objective of the study was not specified.

Done (last sentence of the background):
“The aim was to determine which exposure parameters are most useful to the clinicians in the selection of asbestos-exposed subjects to be submitted to a CT-Scan as part of a screening exercise.

4. The definition of asbestos exposed volunteers and the characteristics of the groups included in the study were unable to reconcile.

See comment (reviewer 2, comment 1) on the new precisions of the definition of our population (Methods section, Eligibility criteria)

5. The result does not provide an answer to the question behind the study.

The synthesis of our results at the beginning of the discussion section in now in agreement with the aim of the study (see also reviewer 1, comment 1)

6. Introduction:
The references from 7 to 10 to justify the fact explained at the end of the first paragraph dates back to years 1985 to 1998.

We deleted the reference dated of 1985

8. The objective of the study must have clearly been expressed right before the last paragraph.

Done, see also comment 1 to the reviewer 1

8. Population and methods:
It was mentioned that the retiree group was reached via e-mail correspondence or meetings. But, what was the total number of people? How many of them were contacted? It is rather ambiguous. What is the upper age limit of the retiree group?

It is difficult to assess precisely the number of subjects in all plants as the information was given by occupational physicians for some of them. We added a sentence in the “limits section” of the study in order to precise this point. We also precised the definition of retirees concerning the age in methods section.

9. In this group in which the death rate is high, it is observed that the dead cases were not comprehended. Death certificates were not utilized as data source. Thus, because the deaths caused by the asbestos exposure were not obtained, it is out of question to possess an actual prevalence rate from the study.

The standard definition of a prevalence is as the proportion of people who have the disease at a specific instant (e.g. Rothman and Greenland Modern Epidemiology).
Deceased subjects are therefore not relevant. It would have been even more interesting to obtain CT-scans repeatedly with the corresponding mortality in order to be able to estimate directly the incidence but as this is a cross-sectional study only the prevalence can be directly obtained. As presented in this paper, prevalence data can be used to estimate the incidence if one is willing to make certain assumptions.

9. **It is not clear whether the working individuals over 50 years of age were comprehended as the group younger than the retiree group and with a continuing asbestos exposure.**

This point is now presented in more detail in the methods paragraph presenting the study population

10. **It is not suitable to obtain the incidence data and develop a mathematical model from a cross-sectional study ground.**

We do agree only partially with the reviewer for this point. Without further assumptions, it is indeed impossible to obtain estimates of the incidence based only on prevalence data. If these assumptions are fulfilled however, then it is possible. This was shown in the paper by Jarvholm cited in our paper and whose model we have extended by incorporating the mean exposure concentration. In our data, as discussed in the part of the discussion on the limitations of our study, we found that the assumptions are reasonable for pleural plaques but probably not for asbestosis.

12. **Since the beginning dates of pathologies due to asbestos observed in the initial scans of which the study was grounded were not specified, there exists a bias in the temporal dimension in finding the incidence data.**

We agree with the reviewer but have already discussed this point in the discussion (first limit)

13. **It was stated that the CT-scans utilized to assess the pleural plaques were different. The error created by the image difference would affect the outcome of the research.**

See response to the reviewer 1 (comment 3) and corresponding modifications in the methods section.

14. **Only the retired subjects seemed to have been scanned by HRCT. How was the other group differentiated in terms of asbestosis without HRCT? In this case â## without the use of HRCT â## how were the other parenchyma diseases eliminated?**

All patients underwent an HRCT. See the reformulated sentences on CT scan definition in methods section
15. The references provided for pleural plaque and asbestosis definitions are insufficient. In the publication, the diagnosis steps of pleural plaque and asbestosis should be described and more recent and sufficient reference information should be provided.

We used previously published references for the definition of radiological abnormalities and in particular the work of Gevenoix that is often cited in such articles including by Metintas et al. (ERJ 2005). Accordingly we precised our radiological abnormalities particularly the pleural plaques definition as following:

“In particular, pleural plaques were defined as discrete, dense, pleural linear structures, which may have a smooth or nodular inner surface, calcified or not, and with a width of at least 2mm”

Results:
16. While, in Table 1, the addition of individuals in accordance with their smoking characteristics must produce a rate of 100%, it gives the rate of 100.1%. It would be appropriate to put Â± sign before the standard deviation.

This is not a mistake but an effect of rounding. Changing any of the partial figures would be a worse mistake. We inserted the ± sign before the standard deviations.

17. The fact that whether there was a difference between the characteristics that were contained in Table 1 and treated in the text were not tested. We do not know if the differences were significant or not.

Table 1 is a descriptive table and as such does not require tests of hypotheses. Any p-value for a comparison between these three groups would be more or less meaningless. A test for smoking would for instance correspond to the test of the hypothesis that smoking causes pleural plaques or asbestosis which makes no real sense. For the exposure variables the situation is again different. As these exposure variables are quite correlated, any difference in exposure between the disease groups would show in all the variables. The only substantively significant differences are thus the adjusted differences as presented in the subsequent tables.

17. Non-existence of diffuse pleural fibrosis also appears to be an issue here.

See the comment 2 of this section and the corresponding changes in the methods section “Diagnosis of pleural plaques and asbestosis from imaging”.

Discussion:
18. This section will be rearranged following the implementation of other suggestions. I recommend the use of the below-mentioned literature during that arrangement.

We simplified the discussion section in several parts, see also response to reviewer 1

References:
19. Standards have not been complied with concerning the spelling rules of literature.

Some useful literature

We deleted references not complied with rules literature (French references). We thank the reviewer for providing some references and we included some of these in our references list. We also simplified the discussion (see also comments to the reviewer 1)

We hope that our answers to Referee's comments as well as the improvements made in the manuscript will address all your questions, and allow this article to be published in your journal.

Sincerely yours.

Ch Paris, MD, PhD