Does the Amount of Asbestos Exposure Influence Prognosis?

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Two recent papers in the Journal of Thoracic Oncology propose two opposite hypotheses: that the amount of asbestos in the lungs may directly correlate with shorter survival in patients with mesothelioma and, on the opposite, that the amount of asbestos in the lungs does not influence survival.

Most pleural mesotheliomas continue to occur in patients who have been exposed to asbestos. “Asbestos” is a collective commercial and legal name given for regulatory purposes to six of approximately 400 mineral fibers present in nature. These six fiber types were used by different industries, exposing millions of individuals worldwide to the risk of developing mesothelioma. Many mineral fibers are potentially carcinogenic, but only asbestos fibers are regulated: their use has been strictly reduced and regulated or entirely prohibited in the 80s and 90s in most of the Western world. Asbestos is inhaled and is trapped in the lungs where, by means of the lymphatic vessels, may reach the pleura. Asbestos causes inflammation in the lungs of patients exposed to high amounts of fibers, ensuing in diffuse bilateral lung fibrosis (asbestosis). In the pleura, asbestos-induced inflammation that results in scar tissue radiologically visible, the so-called pleural plaques. These markers of asbestos exposure are present in approximately 90% of patients with mesothelioma who were exposed to levels of asbestos above the background. In patients exposed to high amounts of asbestos, the fibers may also reach, by means of the lymphatic vessels, the abdominal lymph nodes, mesentery, and omentum, where they can cause peritoneal mesothelioma.

Thanks to the restrictions and regulatory measures taken since the 80s and 90s to reduce asbestos exposure, presently, heavy exposures are found almost exclusively among members of the older cohorts of patients with mesothelioma. Accordingly, presently, peritoneal mesothelioma is rarely linked to asbestos exposure.

Although imaging is helpful to identify asbestos exposure, lung content analyses are considered the most reliable test to measure exposure to asbestos and other carcinogenic mineral fibers. Moreover, this technique allows for identifying the types of fibers to which an individual has been exposed (Fig. 1). Nevertheless, because fibers have different biopersistence, lung content analyses underestimate exposure to chrysotile, a type of asbestos fiber that is rapidly degraded in tissues.

Asbestos fibers cause mesothelial cell death. The paradox of how a fiber that kills mesothelial cells could cause mesothelioma was addressed by the discovery that asbestos triggers the translocation of HMGB1 from the nucleus to the cytoplasm, where NFκB activation and autophagy are induced. These two prosurvival mechanisms allow mesothelial cells to escape asbestos-induced cell death, and eventually over time genetically damaged mesothelial cells may become malignant. In parallel, asbestos-dependent cell necrosis causes the release of HMGB1 in the extracellular space, where HMGB1 kickstarts the inflammatory process that results in the production of mutagenic oxygen radicals and drives the growth of malignant cells. Moreover, chronic inflammation activates several cellular pathways...
that support malignant growth.\(^{19-22}\) Several therapeutic approaches have been and are being designed targeting these and other pathways activated on asbestos exposure.\(^{23-26}\) Although effective in mice, their efficacy in preventing or reducing the growth of mesothelioma in humans remains to be revealed.\(^{27-28}\)

In synthesis, it is well established that asbestos exposure causes mesothelioma and key mechanisms by which asbestos causes mesothelioma have been elucidated.\(^{29}\)

Can the amount of asbestos present in the lungs influence tumor prognosis? If so, how? The two papers by Laaksonen et al.\(^{1}\) and Barbieri et al.\(^{2}\) tried to address this question, but they reached opposite conclusions. Similarly, older studies discussed by the two publications reported conflicting results. The papers by Laaksonen et al.\(^{1}\) and Barbieri et al.\(^{2}\) were submitted at about the same time, and they went through a strict peer-review process. Let us analyze some possible causes of these discordances.

In both publications, germline mutations of BAP1 (or of other genes) were not included as selection criteria for patients’ analysis. It has been reported that in carriers of germline BAP1 or other pathogenic gene mutations, the risk of developing mesothelioma is increased.\(^{30}\) At the same time, these patients have a marked improved prognosis compared with the prognosis of patients affected by the more common and aggressive mesotheliomas caused by asbestos.\(^{31-33}\)

Therefore, the authors of both papers raise the hypothesis that the presence/absence and the number of patients carrying these mutations in their cohorts might have influenced the results.\(^{1,2}\) This hypothesis is reasonable because several members of the same family carrying germline mutations are usually affected by mesothelioma, resulting in an aggregation of these patients in the same hospital.

Another confounding factor, possibly contributing to the opposite results of the two publications, is the clinical setting of the patients before their death, when lung biopsy specimens taken during the autopsy were subjected to fiber content analysis. In both publications,\(^{1,2}\) no data are provided about therapy. The most common therapy for mesotheliomas consists of a combination of cisplatin–pemetrexed,\(^{32}\) at times in combination with other drugs, surgery, and radiation. The median survival benefit of 2 to 3 months with the addition of chemotherapy (alone or as trimodality therapy together with surgical resection and radiation) is well established.\(^{1}\) Nevertheless, patients with sarcomatoid mesothelioma are resistant to therapy; therefore, many of them are treated only with supportive therapy. Very ill patients who cannot tolerate surgery or other types of aggressive therapies may also receive only supportive care. The type of therapy and the proportions of treated patients in these two papers,\(^{1,2}\) although unknown, may vary. Moreover, recently, several immune-based approaches have been attempted in mouse models\(^{33}\) and patients with mesothelioma. Immunotherapy may benefit some patients with sarcomatoid mesothelioma, although the data are not conclusive.\(^{1,25,26}\) We do not know whether any of the patients in these two studies,\(^{1,2}\) were treated with immunotherapy.

In summary, because the conclusions drawn by both conflicting papers\(^{1,2}\) are based on survival/all-cause mortality, possible differences in therapy might have influenced survival.

The additional problem about a possible association between asbestos load and prognosis, as noted by both Laaksonen et al.\(^{1}\) and Barbieri et al.\(^{2}\) is the issue of the apparent lack of plausibility, which is one of the criteria used in cancer research to distinguish a mere association from a causative effect.\(^{34}\) There are no known mechanisms by which the amount of asbestos in tissues might influence tumor aggressiveness per se, as noted by the authors.\(^{1,2}\)

Nevertheless, it seems possible that the deleterious effects on survival that Laaksonen et al.\(^{1}\) observed might have been caused by a higher percentage of patients in their cohort with severe bilateral lung fibrosis.
Asbestos Exposure Influences on Prognosis

August 2022

Michele Carbone, Haining Yang, Giovanni Gaudino: Writing and original draft preparation.
Fabrizio Bardelli: Contributing figure.
Haining Yang, Giovanni Gaudino, Fabrizio Bardelli, and Michele Carbone: Reviewing and editing.

References

(asbestosis) that often develops among those exposed to high amounts of asbestos. Asbestosis compromises gas exchanges and causes right ventricular hypertrophy, which in turn leads to right ventricular failure. Some of the patients with asbestosis may develop mesothelioma. These patients, owing to the compromised cardiopulmonary function caused by asbestosis, are often ineligible for surgery and other aggressive therapies, thus having shorter survival. In other words, the differences among the results observed by Laaksonen et al.1 and Barbieri et al.2 might be related to a higher number of patients with severe asbestosis in the cohort studied by the former article.1 An additional hypothesis is that mesothelioma, because of the field effects of asbestos, often occurs as a polyclonal malignancy.35 Maybe exposure to a certain type of fibers or to a higher number of asbestos fibers may cause the development of more malignant clones, and this could affect prognosis. Nevertheless, no experimental evidence is available to support this hypothesis.

A recent article by Visona et al.,36 using a methodology similar to the one used by Laaksonen et al.1 and Barbieri et al.,2 did not find any association between the amount of asbestos in the lungs and latency or survival; however, this article also lacks the clinical information and their cases were not screened for the possible presence of germline mutations.

In summary, the missing clinical information in these two papers1,2 prevents a conclusive assessment of the possible correlation between fiber burden and prognosis in mesothelioma. These two papers1,2 have both determined with accuracy the fiber content in the lung of biopsy specimens from sizable cohorts of patients deceased with mesothelioma (590 and 185 biopsies, respectively), by using appropriate and sensitive methods (scanning transmission electron microscopy and transmission electron microscopy combined with radiograph spectroscopy, respectively). Nevertheless, the possible connection between fiber load and prognosis in pleural and peritoneal mesothelioma is probably influenced by a complex and multifactorial combination of factors. These factors, in addition to fiber exposure, may include germline mutations, the type of therapy, and the percentage of patients in each cohort with asbestosis with the consequent compromised cardiopulmonary function, which in turn will make them ineligible for several therapies. All these components should be considered in future studies that may try to address this issue.

CRediT Authorship Contribution Statement
Michele Carbone: Conceptualization, Writing and original draft preparation.


