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Review Article

Asbestos-related Cancer: Exaggerated Risk Perception

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Abstract

Health risks from exposure to asbestos fibers have been evaluated based on professional histories, when fiber concentrations at workplaces were greater than today. A linear no-threshold model was used for risk estimation, although its relevance has not been proven. Asbestos fibers are often detected in lungs and pleura during autopsy, but finding evidence of fibers does not prove that a disease has been caused by asbestos. Thus, targeted detection of mesothelioma and other conditions associated with asbestos exposures has resulted in an increase in the reported incidence of mesothelioma among high-risk groups. Histological and immunochemical characteristics of malignant mesothelioma partially overlap with other cancers, which may also contribute to the overdiagnosis in exposed populations. Differences in carcinogenicity of various asbestos types are discussed here. Prohibitions of asbestos in some developed countries must be reconsidered on the basis of independent research. Lifelong bioassays are the most promising way to obtain reliable information regarding asbestos-related malignancy. It should be stressed that non-use of asbestos contributes to an increase of harm from fires, armed conflicts, and traffic accidents.

Introduction

Exposure to asbestos can cause diseases of the lungs and pleura, including mesothelioma, lung cancer (LC), asbestosis, and pleural plaques.[1,2] Malignant pleural mesothelioma (MPM) is a rare tumor that is widely believed to be caused by asbestos exposure.[3] According to a recent estimate, asbestos causes about 255,000 deaths per year worldwide, of which professional exposures are responsible for approximately 233,000 deaths.[4] Health risks associated with asbestos exposure were extrapolated from the mid 20th century and earlier times, when fiber concentrations at industrial facilities and nearby townships were much higher than today. A linear no-threshold model was used to determine risk estimation, although its relevance has not been proven.[5,6] Over the past 40–50 years, professional exposures to asbestos have decreased in the United States and other developed countries due to the use of new construction materials. As such, the vast majority of mesotheliomas are expected to be spontaneous and unrelated to asbestos after the year 2035.[6]

Both chrysotile and amphibole asbestos fibers enter the environment as a result of erosion of natural deposits, outnumbering anthropogenic fibers in many places.[7,8] Air, soil, and water are often contaminated by fibers due to industries unrelated to asbestos, such as land excavation, slope reprofiling, and tunneling.[9,10] In a study from Milan, asbestos fibers were found in 63.6% of routine post-mortem examinations, including those among children.[11] Necropsies from high risk populations have demonstrated that there is insufficient evidence to directly correlated lung and pleura pathologies with industry-related exposure or asbestos fibers.[11,12] Compared to other environmental factors, it can be reasonably assumed that there is a threshold for fiber content in the air. The maxim that "one fiber can kill" is not logical since environmental concentrations of various substances are toxic at higher doses. An increase in asbestos-related research has contributed to an elevated reported incidence of MPM and LC in populations at risk.[13] The 2014 update of the Helsinki Criteria stipulates that "even a brief or low-level exposure should be considered sufficient for mesothelioma to be designated as occupationally related."[14] This approach may lead to misclassification of spontaneous cases as occupational. As for LC, the criteria leave space for subjectivity: "Cumulative exposure, on a probability basis, should thus be considered the main criterion for the attribution of a substantial contribution by asbestos to LC risk."[14]

Asbestos and mesothelioma

The unchanging frequency of mesothelioma in industrialized countries despite asbestos prohibitions over the last 20 years has increased awareness, leading to improved diagnostic equipment, screening in high risk groups, and overdiagnosis because of imprecise demarcation for MPM compared to other cancers. The causative factors of mesothelioma include different fibers (erionite and

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Abbreviations: LC, lung cancer; Mg, magnesium; MPM, malignant pleural mesothelioma; SV40, simian virus 40.
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carbon nanotubes), radiation, simian virus 40 (SV40), inflammatory and hereditary conditions.[15–25] There is evidence that SV40 has contributed to the global spread of MPM despite asbestos bans.[26] SV40-like DNA sequences are often detected in malignant mesotheliomas but not in surrounding non-cancerous cells.[26–28] The number of reports on SV40 DNA sequences in mesotheliomas has outnumbered that of other tumors.[29] SV40 can replicate in human mesothelial cells that remain infected and release viral progeny over a long period of time. One study showed that more than 50% of hamsters injected with SV40 in the peritoneal cavity or cardiac chambers developed mesotheliomas, and almost all of the hamsters developed mesothelial tumors following SV40 injections into the pleural cavities.[30] The increased incidence of MPM in the 1960's and thereafter coincided with human exposure (1955–1963 and later in some countries) to the viable SV40 in poliomyelitis vaccines.[26] Presumably, endoscopic and other manipulations applied at increased rates in high risk groups contributed to virus spread. For example, in Russia bronchoscopy was used in patients with asbestos-related bronchitis and in those suspected of having dust diseases, pneumonia, and other conditions, sometimes with questionable indications.[31–36]

Mesothelioma is not sharply demarcated as an entity; many MPMs are histologically similar to other cancers. The absence of pathognomonic markers can make differential diagnosis difficult, especially for sarcomatoid MPM,[37] and immunochemical methods are not always helpful for diagnosis.[22,38,39] Reportedly, about 1 in 10 malignant mesotheliomas in the United States has been misdiagnosed.[40] According to one report, the initial histopathological diagnosis of MPM remained unchanged in 67% of cases, was revised in 13%, and left questionable in the rest after re-examination.[41] The molecular basis of mesothelioma remains largely unknown.[42] Although numerous markers have been proposed (mesothelin, osteopontin, fibulin-3), no one marker has been reliably specific.[43–45] Mesothelin showed promise as a marker, but its sensitivity turned out to be suboptimal.[43,45,46] Mesothelin expression is prominent in various cancers,[47] but it is not expressed in sarcomatoid tumors and is expressed in only approximately 50% of epithelioid MPMs.[48,49] According to a recent meta-analysis, fibulin-3 had the highest diagnostic value for MPM; however, further research was not supportive of its diagnostic reliabilty.[45] MicroRNA down-regulation has been extensively studied,[50,51] but its diagnostic value turned out to be limited because microRNA can also be abnormally expressed in other cancers.[51–54] Chromosomal aberrations in malignant mesothelioma are diverse,[24,55–58] thus, cytological diagnosis of mesothelioma is notoriously difficult.[46,59] The Helsinki Criteria made no specific recommendations regarding the use of biomarkers for screening and diagnosing mesothelioma.[14,44] Considering the heterogeneity of MPM, no single marker can provide sufficient sensitivity and specificity.[45] As a result, there is a general tendency to overestimate the validity of immunohistochemical and molecular markers for diagnosing MPM.[60] Moreover, MPM often exhibits intra-tumoral heterogeneity and subclones.[61] Unlike many cancers, driver mutations have not been firmly established for MPM.[57] The sensitivity of fluid cytology is low,[46] and the non-specificity causes difficulties for MPM diagnosis.[62] A neoplasm classified as mesothelioma using available methods and marker combinations is not necessarily different from other tumors. The imprecise demarcation of MPM from other malignancies enhances the screening effect and diagnostic yield in exposed populations, thus contributing to an overestimation of asbestos-related risks. In populations exposed to asbestos, experts purposefully check for MPM. As a result, MPMs are detected at above average rates, and overdiagnosis in questionable and borderline cases may occur. Conversely, in the general population MPM is easily missed and is misdiagnosed as other cancers due to its rarity and lack of specific features.[45]

Serpentine and amphibole asbestos

There is a widely accepted opinion that amphibole (actinolite, amosite, anthophyllite, crocidolite, tremolite) asbestos is more carcinogenic than chrysotile (serpentine) asbestos. The latter, however, is not harmless.[63–65] There are discrepancies between human (epidemiological) and experimental data. In some experiments, serpentine and amphiboles were demonstrated to exert approximately the same level of carcinogenicity both for mesothelioma and LC.[66–73] In one experiment using rats, chrysotile exposure resulted in more pulmonary fibrosis and neoplasms than amphiboles.[67] Based on rat inhalation studies, the asbestos expert J. Christopher Wagner wrote: "There was no evidence of either less carcinogenicity or less asbestosis in the groups exposed to chrysotile than those exposed to the amphiboles."[66] In rats, chrysotile produced inflammation and cancer after a shorter latency than crocidolite,[74] and chrysotile produced precancerous chromosomal abnormalities *in vitro*.[70,75] Asbestos produced in Russia is predominantly chrysotile, which has relatively low carcinogenic potential.[76] Nevertheless, the carcino-, fibro-, and mutagenicity of chrysotile has been established both in experimental and human research.[77–81] The consensus is that, if adequate measures are taken, contemporary methods applied in the asbestos industry are acceptably safe.[81,82]

In humans, the ratio of LC risk for chrysotile compared to amosite and crocidolite has been reported to be between 1:10 and 1:50. For mesothelioma, the ratio was 1:100 and 1:500 respectively.[5,83] In a later study, ratios of 1:5 and 1:10, respectively, were reported.[84] The same experts noted that it is difficult to explain the difference between experimental and epidemiological data.[5] This is potentially explained by the hypothesis that long chrysotile fibers remain in pulmonary tissues for 1–2 years, which may be sufficient to cause tumors in rats but not in humans.[85] Experiments with larger animals (primates) could clarify these discrepancies. Of note, chrysotile clearance from the lungs may partly result from fiber splitting and relocation to the pleura. Chrysotile is the prevailing asbestos fiber found in post-mortem pleura, including plaques.[86–89] Considering the above, the following statement by David Bernstein is surprising: "Longer chrysotile fibers rapidly clear from the lung and are not observed in the pleural cavity."[90] Note that asbestos fibers are usually looked for in tissues but not in the cavity. Mesothelioma is more frequent in the parietal rather than visceral pleural layer.[91] Experiments using Gamble's solution that simulates interstitial fluid (discussed below) demonstrated that only a very small amount of silicon is dissolved from chrysotile but a larger amount of magnesium (Mg) is released.[92] Silicon is mainly responsible for fiber strength, but washing out of Mg from surfaces of fibrils might contribute to longitudinal splitting. As a consequence, the total quantity of thin fibers may increase, leading to carcinogenic effects.[68,93–100]

The carcinogenic effect of fibers depends on dose, dimension, and durability, commonly known as the three "D's".[19,101–103] If the biopersistence of carcinogenic is equal, differences in toxicity depend on the fiber dimensions.[104] Long chrysotile fibers are believed to be more toxic as they are less efficiently removed by phagocytizing cells.[105,106] However, according to another study, short thin chrysotile fibers prevailed in the lung and pleura of individuals with MPM, suggesting that short and thin fibers contribute

to MPM development.[107] Differences in carcinogenicity between short and long fibers are not entirely clear, and more independent research is needed. Furthermore, tremolite admixtures in commercial chrysotile can reinforce carcinogenicity.[108] In one study, the difference in mesothelioma risk from human exposures to pure chrysotile and its mixtures with amphiboles was insignificant.[109]

The carcinogenicity of different asbestos types was compared in a meta-analysis of 19 human studies assessing the influence of research quality on the slopes of exposure-response relationships for LC. The difference between chrysotile and amphiboles was difficult to confirm when the meta-analysis was restricted to studies of higher quality.[83] After accounting for quality, there appeared to be little difference in the exposure-response slopes for cumulative exposure to chrysotile compared to amphiboles.[83,110] According to a systematic review, the pooled risk estimates for LC were higher after exposures to amphiboles (1.74) than to chrysotile (0.99). However, the overall risk was greater in lower compared to higher quality studies: 1.86 vs. 1.21.[111] Differences between results of high- and low-quality research might underlie the contradicting findings because it is apparently easier to find support for preconceived ideas in poor-quality and manipulated studies rather than in high-quality research.

Publications by David Bernstein have commented on this connection: "Bernstein and colleagues completely ignored the human lung burden studies that refute their conclusion about the short biopersistence of chrysotile."[93] However, it has been noted that, by failing to cite and discuss contradicting data, Bernstein *et al*. did not provide a balanced analysis, having created a document to support the interests of chrysotile producers.[93,112] As an example: "Following short-term exposure the longer chrysotile fibers rapidly clear from the lung."[90] Considering the possibility of fiber migration to the pleura (discussed above), it is insufficient to assess the asbestos contents only in the lung. Conclusions by Bernstein *et al*. about low durability of chrysotile were supported by their own experiments.[90,113] However, their results can be explained by pretreatment of fibers with acids, inducing hydration, fragility, and breaking.[112] "Bernstein's study protocol induces a very short fiber half-life, from which he concludes weak chrysotile carcinogenicity. Bernstein's findings contradict results obtained by independent scientists. Bernstein's results can only be explained by an aggressive pre-treatment of fibers, inducing many faults and fragility in the fibers' structure, leading to rapid hydration and breaking of long fibers in the lungs."[112] The solubility of fibers in neutral and acidic environments differs considerably.[114] For comparison, the solubility of different fibers was tested with Gamble's solution.[92] The solubility of both chrysotile and crocidolite was very low, as a few nanograms of dissolved silicon per cm^2 of the fiber surface was comparable to several thousands of ng/cm^2 for glass wool. Carbon fibers were almost insoluble in the Gamble's solution.[92] Admittedly, the dissolution of chrysotile may be more efficient in acidic lysosome vacuoles. Amphiboles are probably more carcinogenic than chrysotile, but further independent research is needed to quantify the difference.

Future prospect

There is sufficient evidence and literature to support asbestos as a carcinogen.[115] A majority of the scientific community and leading authorities support the concept that all asbestos forms are pathogenic and increase the risk of malignancy.[116] However, some epidemiological studies appear to be biased in their conclusions due to overdiagnosis in high risk groups, imprecise exposure histories, and conflicts of interest.[117] The number of publications focused on asbestos is growing, making it difficult to determine which sources are reliable and which are biased. There was a suggestion that "grassroots organizations intimidated governments into approving more restrictive regulations."[118] Some "grassroots" and Green activists may serve certain companies or governments, specifically with regards to nuclear energy and pushing up fossil fuel prices.[119] Asbestos is prohibited in some countries while others continue its production and sales.[120] Different fiber types are sometimes intermixed in the international trade.[121] Carbon nanotubes and artificial fibers are also associated with health risks. However, compared to asbestos, the carcinogenicity of these substitutes is largely dependent on fiber biopersistence, diameter, and length.[25,122,123] Thus, lifelong bioassays are needed to fully understand the carcinogenicity of these asbestos substitutes. Experiments with fiber inhalations, comparable to professional exposures, do not require invasive methods for diagnosis and have become ethically acceptable. It should be noted, though, that bioassays with "exposure concentrations that were orders of magnitude greater than those reported for worker exposure"[124] are of limited conclusiveness.

Asbestos has been used in industry and construction for many years due to its high thermal, electrical, and chemical resistance.[125] Different asbestos forms have their advantages and preferred application areas. Amphiboles are acid-resistant, thermo-stabile, and durable.[126] This is an additional reason in support of the "All Fibers Equal"[127] concept in regard to asbestos and some other fibers.

Conclusions

Considering industrial interests in support of chrysotile,[128–130] and newly synthesized artificial fibers, any deviations from the "All Fibers Equal" approach must be based on high-quality, independent research. It should be stressed that non-use of asbestos would enhance damage from fires, traffic accidents, and armed conflicts, which is of importance in view of the current international tensions.

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Author contributions

JSV contributed to the study, and drafting and critical revision of the manuscript.

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