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Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: www.tandfonline.com/journals/iery20

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To cite this article: Nico van Zandwijk, Glen Reid & Arthur L. Frank (2020) Asbestos-related cancers: the 'Hidden Killer' remains a global threat, Expert Review of Anticancer Therapy, 20:4, 271-278, DOI: 10.1080/14737140.2020.1745067

To link to this article: https://doi.org/10.1080/14737140.2020.1745067

Published online: 29 Mar 2020.

EXPERT REVIEW OF ANTICANCER THERAPY
2020, VOL. 20, NO. 4, 271–278
https://doi.org/10.1080/14737140.2020.1745067

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REVIEW

Asbestos-related cancers: the 'Hidden Killer' remains a global threat

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ABSTRACT

Introduction: Asbestos, the most frequent cause of occupational cancer, continues to be consumed on a massive scale, with millions of people exposed on a daily basis. This review explains why we have failed in curtailing the silent epidemic of asbestos-related disease and why the numbers of asbestos victims are likely to remain high. Emerging and developed countries have to be reminded that asbestos exposure has yet to become a problem of the past. The worldwide spread of asbestos, followed by the surge of asbestos-related cancers, resembles the lung cancer epidemic caused by smoking and stimulated by manufacturers.

Areas covered: Underreporting of malignant mesothelioma and asbestos-induced lung cancer, frequently-used arguments in the amphibole/chrysotile debate and the conclusion from bona-fide research organizations, that all forms of asbestos are carcinogenic, are reviewed. Special attention is paid to the consequences of ubiquitous environmental asbestos and the 'changing face' of malignant mesothelioma in countries with heavy asbestos use in the past.

Expert opinion: Experts in oncology, respiratory medicine, occupational and public health, and basic researchers must take responsibility and acknowledge the ongoing silent epidemic of asbestos-related diseases. The call for a world-wide asbestos ban is more urgent than ever.

ARTICLE HISTORY
Received 1 December 2019
Accepted 17 March 2020

KEYWORDS
Asbestos; chrysotile; amphibole; malignant mesothelioma; lung cancer

1. Introduction

Asbestos is often referred to as the 'Hidden Killer', as asbestos fibers are too small to see, have no warning signs like smell or tast, and cancers elicited by asbestos are diagnosed decades after first exposure. Many patients who developed asbestos cancer, especially women, were unaware that they had been exposed to a time-bomb with a very long fuse [1]. In the majority of cases of malignant mesothelioma, it is relatively straightforward to conclude on the basis of a patient's exposure history that asbestos was the cause, as mesothelioma is very seldomly elicited by other causes [2,3]. However, the long latency period between the first exposure to asbestos and the mesothelioma diagnosis can make it difficult for patients to recall their fatal exposure. It is important to note that only an experienced pathologist is able to reliably confirm the malignant mesothelioma diagnosis [4–6]. Without specific pathological expertise, the mesothelioma diagnosis becomes problematic. For example, unexpectedly low numbers of mesothelioma diagnoses in certain parts of the world may create the illusion that asbestos lacks carcinogenic potential, rather than pointing to a lack of local expertise as the likely explanation for the low incidence observed [7,8]. The recording of mesotheliomas as 'malignant pleural effusion' also reduces the reported incidence rates.

Asbestos also plays an important role in lung cancer carcinogenesis, but it is almost impossible to tease this apart from the damage caused by smoking. In an attempt to answer the difficult questions of whether asbestos was the actual cause of lung cancer and if a patient might be eligible for compensation, criteria for the causation of asbestos-induced lung cancer were established by a group of experts in Helsinki in 1997 [9,10]. However, considering the fact that asbestos and smoking are parts of a synergistic carcinogenic process [11], it is extremely difficult to accurately calculate the contribution of asbestos to lung cancers occurring in asbestos-exposed smokers. The Helsinki criteria rely on occupational history and the presence of asbestosis and fiber counts in lung tissue. These criteria received major criticism, as fiber counts in lung tissue are not considered an evidence-based diagnostic criterion [12]. Moreover, strong evidence has emerged that low levels of asbestos exposures (i.e. levels not leading to asbestosis) contribute to carcinogenesis [13].

In addition to the well-accepted association of asbestos with thoracic cancers, asbestos minerals have also been implicated as a cause of ovarian, larynx and GI tract cancers [14–19]. These latter associations are based in large part on epidemiological studies, but tissue studies in humans have documented the presence of asbestos fibers in these cancers. Establishing the causative role of asbestos in individual cases highlights the issue of general versus specific causation. Unfortunately, many of these epidemiological studies mentioned above focus primarily on asbestos and do not provide insight into other potential carcinogenic co-factors such as smoking and alcohol consumption. The recent observation that talcum powder is frequently contaminated with asbestos provides a potential new insight in the link between asbestos

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Article highlights

- Global asbestos consumption has continued to surge for decades after solid evidence showed that these minerals are carcinogenic.
- The long latency between exposure to asbestos and the occurrence of malignant mesothelioma and lung cancer frequently obscures their causal relationship.
- Continued research is needed to more firmly establish the association between asbestos exposure and cancers of the larynx, the ovary and the GI tract.
- Diagnosing malignant mesothelioma remains a considerable challenge for pathologists.
- Unexpectedly low numbers of cases of malignant mesothelioma reported in emerging countries reflect a lack of local pathological expertise rather than the lack of carcinogenic potency of asbestos.
- The criteria established for the diagnosis of asbestos-related lung cancer have been heavily criticized and contribute to an underestimation of asbestos as the cause of lung cancer.
- Differences in the carcinogenic potency of chrysotile and amphibole asbestos — a major focus of studies, sponsored by the pro-asbestos lobby – have been exploited to support the assertion that chrysotile can be safely used.
- The deadly asbestos experience of countries that were among the first to embrace the 'miracle' product, is insufficiently or misunderstood by the authorities of emerging (Asian) countries, allowing the pro-asbestos lobby to defend unrestricted use of asbestos.
- Occupational asbestos exposure deserves our continued attention and preventive action, especially in emerging countries.
- Recent studies underline the dangers of exposure to environmental asbestos. Considering the millions of tons asbestos still consumed annually that become part of 'our' environment, it is time to invest in better diagnostics, advanced strategies for prevention, and more effective novel treatments.

and cancer of the ovary and a series of case reports revealing mesothelioma in people with frequent talcum powder use appears to underline the carcinogenic potential of this form of asbestos [20,21].

In this article we draw attention to the future consequences of the rapid worldwide surge of asbestos consumption during the previous century and the ongoing unrestricted use of asbestos in emerging countries, especially in Asia. By presenting a concise review including data from recent epidemiological and carcinogenesis studies we aim to raise the awareness of health authorities and governmental representatives around the world about the underappreciated problems caused by the spread of millions of tons of carcinogenic asbestos around the world.

2. The carcinogenicity of asbestos

The term Asbestos describes a group of naturally occurring silicate minerals and is considered the most frequent cause of occupational cancer. Two forms of asbestos are recognized. One is characterized by straight, needle-like fibers (amphiboles) and the other by snake-like, curly (serpentine) fibers. Chrysotile (white asbestos) is the single serpentine form and constitutes 90–95% of all asbestos fibers utilized worldwide. The amphibole group is subdivided into amosite (brown asbestos), crocidolite (blue asbestos), tremolite, anthophyllite and actinolite. Although serpentines and amphiboles are both listed as a Group 1 carcinogen [22], there is a legitimate ongoing discussion about the difference in carcinogenic potency of these two forms of asbestos. The consensus among scientists is that both amphibole and chrysotile fibers cause cancer and that even limited/low asbestos exposure is associated with increased cancer risk. Conversely, there remains a group of chrysotile proponents, who argue that the cancer risk of this form of asbestos is almost negligible, and that chrysotile can be safely used. These pro-chrysotile lobbyists are notably present in countries where chrysotile is mined and exported and a link with the asbestos industry is often visible. Pro-asbestos lobby groups with an active internet presence include the International Chrysotile Association [23], Uralasbest [24], the Chrysotile Information Center [25], the Fiber Cement Products Manufacturers Association in India [26] and the Vietnam Roofsheet Association [27]. The obvious influence of these lobby organizations on the public debate is considerable. A more dangerous result of their activities is that the scientific debate has also been affected, exemplified by the fact that the International Agency for Research on Cancer (IARC) sent a delegate to a conference organized by the pro-asbestos lobby [28]. The asbestos industry has also been active in financing research projects [29], with the ultimate aim of highlighting the differences between amphiboles and chrysotile and promoting the 'favourable' toxicity profile of chrysotile [30]. Unsurprisingly, these projects have been used to cast doubt about the 'real' dangers of asbestos [31]. These recent activities took a more sinister turn when one pro-asbestos group financed an undercover operation in the UK [32] to obtain information from the asbestos ban movement in order to dominate the debate on the continuation of asbestos use in emerging countries.

The asbestos 'debate', also known as the amphibole or chrysotile debate, concentrates on a supposed lack of carcinogenic potency of chrysotile asbestos and uses the following arguments: 1. Differences in the composition and shape of asbestos fibers explain the difference in carcinogenic potency between amphiboles and chrysotile [33,34]. 2. Chrysotile is almost always contaminated by amphiboles and the contaminating amphiboles are responsible for carcinogenicity of 'chrysotile' [35,36]. 3. The accumulation of amphiboles in the lungs of experimental animals and the rapid clearance of chrysotile from the lungs of the same animals support the conclusion that chrysotile lacks carcinogenic potency [37]. The counter arguments used are: 1. Persistence of asbestos fibers in lung parenchyma cannot be used as a surrogate for mesothelioma carcinogenesis; mesothelioma originates in the (parietal) pleura and the kinetics of asbestos fibers in the pleura have not been studied in detail [38]. 2. In addition to the association between chrysotile exposure and mesothelioma, epidemiological studies have confirmed that there is also a strong link between occupational chrysotile exposure and the occurrence of lung cancer [39–41]. These observations undermine the theory that rapid chrysotile clearance (as observed in the lungs of experimental animals) is able prevent the induction of lung cancer or mesothelioma. 3. A critical review concluded that not any type of asbestos fiber can be excluded from having the potency to induce disease (cancer) [42], and prominent pulmonary retention of chrysotile fibers was noted in repeated biopsies from 12 German Mesothelioma Registry cases [43], both contradicting the rapid chrysotile clearance theory that was based on animal experiments only.

Alerted by the ongoing debate about the carcinogenicity of chrysotile and the use of arguments derived from studies financed by the pro-asbestos lobby [30] the Joint Policy

Committee of Epidemiology Societies published the following statement in June 2012: *'A rigorous review of the epidemiologic evidence confirms that all types of asbestos fibers are causally implicated in the development of various diseases and premature death. Numerous well-respected international and national scientific organizations, through an impartial and rigorous process of deliberation and evaluation, have concluded that all forms of asbestos are capable of inducing mesothelioma, lung cancer, asbestosis and other diseases. These conclusions are based on the full body of evidence, including the epidemiology, toxicology, industrial hygiene, biology, pathology, and other related literature published to the time of respective evaluations'* [44].

3. The surge of asbestos consumption

Asbestos is lightweight, resistant to heat, humidity and chemical degradation, does not conduct electricity, and at the same time shows high tensile strength. These characteristics made asbestos a 'miracle material' and significantly contributed to the rapid rise in the popularity of this group of minerals in the 20th century. By the 1920s asbestos had become the material of choice for brake linings, but it was also used for gaskets, asbestos cement pipes and sheets, flooring and roofing products, electrical and thermal insulating materials, coatings and heat shields. In the U.S., flat pack homes, offices, schools, farm buildings and even small railway stations complete with seats were made entirely from asbestos cement. Asbestos also became the insulation/fireproofing standard for war and commercial ships, while soundproof asbestos tiles were increasingly used in the music and film industries. Moreover, farming communities near asbestos mines/factories used asbestos tailings to neutralize soil acids as well as a 'clean' material to pave roads. In WW II asbestos became a critical war material (fire retardant/gasmasks) and the dramatic rise of asbestos consumption in the developed world continued long after the association with thoracic cancers was first noted [45]. There were some 3000 recorded uses of asbestos from 'fireproof' textiles to cigarette filters and fake snow to decorate Christmas trees [46]. In a response to the newly discovered health risks of smoking, Kent cigarettes began producing Micronite filtered cigarettes in 1952. These filters consisted of 30% crocidolite and within 4 years 13 billion Micronite filtered cigarettes were sold. Thirty years later it was found that of the 33 people who had worked in the filter factory, 15 had died from cancer (including 8 lung cancer cases and 5 mesotheliomas; relative risk 8.2; 95% Confidence Interval: 4.6–13.4) and 5 from asbestosis [47]. The development of mesothelioma following smoking of asbestos-filtered cigarettes has also been documented [48].

For much of the previous century Canada was the leading producer of asbestos (chrysotile). Today the quantities mined in Canada, where the mines have been closed, are dwarfed by the amounts of asbestos produced by Russia, China and Kazakhstan. At the same time that the developed world agreed to ban or constrict the use of asbestos after noticing its deadly consequences, emerging countries continued to increase their asbestos consumption [49]. In many of these countries occupational and environmental regulations were/are not in place and arguments derived from the 'doubt studies' organized by the asbestos industry [31] are used to promote unrestricted use of chrysotile. In other words, the discussion about differences in carcinogenic potency between chrysotile and amphiboles is used to support the unfounded assumption that chrysotile can be used safely.

Over the past four decades the scientific community has been consistent in warning of the dangers of asbestos carcinogenicity. In 1980, Lemen et al reviewed all the studies on asbestos exposure and cancer attributed to this exposure and he was among the first to underline that all forms of asbestos are carcinogenic [50]. The Collegium Ramazzini, recognizing the dangers of ongoing chrysotile consumption, called for an universal ban on the mining, manufacture, and use of asbestos in 1999 [51]. In 2007, (historical) asbestos consumption data were combined with age-adjusted mortality rates, revealing an evident association between the mortality from malignant mesothelioma and the asbestos consumption in the world [52]. In 2010 and 2011, the Collegium Ramazzini repeated its calls for an universal asbestos ban [53]. Very recently, the important etiological role of chrysotile for mesothelioma was once more confirmed by a follow -up study in Italian chrysotile miners. The risk of both pleural an peritoneal cancer mortality and of mesothelioma incidence increased with increasing cumulative exposure, duration and latency. Similar trends were seen in lung cancer [54].

In the beginning of the 1980s, many years after the deadly consequences of exposure to asbestos had been noted, Western European countries and Australia began to implement asbestos bans [45]. In Sweden, where asbestos consumption had already slowed in the second half of the 1970s, a reduction in the mesothelioma incidence (the surrogate for asbestos exposure) was noted at the time of the ban [55]. Japan and Korea, who started consuming asbestos on a broad scale in the 1960s (a much later date than Europe and Australia), were confronted with the first clusters of mesothelioma deaths in the beginning of the 2000s [56,57]. The ensuing public discussion resulted in a complete asbestos ban in both countries [58].

Despite the consensus among scientists, the recommendations from leading health organizations and the asbestos bans implemented in several developed countries [30,59,60] lobby groups continue to be highly active. Funded and controlled by asbestos interests in Russia, Canada, Kazakhstan, Brazil, India, Mexico and Zimbabwe, and closely aligned with national representatives of these countries, these groups successfully opposed the listing of chrysotile as a hazardous material under the United Nations Rotterdam ACT for more than twenty years [61,62]. The voice of health authorities in emerging countries was either seldomly heard or effectively silenced by the pro-asbestos lobby. Only the increasing activities of grassroots organizations ensured that the clear and urgent message from scientists, concerned about the devastating consequences of exposure to asbestos, was well understood [63,64]. Tireless campaigning of activists, changing political momentum and high court decisions resulted in asbestos

bans in Canada and Brazil. Columbia, another country with an active asbestos mine, followed Brazil in 2019. In the meantime, asbestos consumption in Asia remained high, effectively planting the time-bombs that will explode in the decades to come [45,49,65,66].

While more than sixty countries have banned asbestos, the U.S. continues to allow the importation and restricted use of asbestos. The recent actions taken under the Toxic Substances Control Act, which are expected to lead to loosening of asbestos policies by Environmental Protection Agency (EPA), reflect a similar mind-set to those in emerging countries. In this context it is important to note that the pro-asbestos lobby (Uralasbest, Russia) has used its Facebook page to lavish praise on the US president and the EPA for the decision to 'no longer deal with the negative effects potentially derived from products containing asbestos'. The contrast between evidence-based public health measures and irresponsible trade practices in the largest economy of the world has never been so sharp [67]. One can only hope that a new bill, including a complete asbestos ban, as supported by the Asbestos Diseases Awareness Organization (ADAO), will pass in the U.S. congress.

4. The changing face of malignant mesothelioma and the consequences of living in a polluted environment

Lawyers involved in asbestos litigation in Australia, a country with one the world's highest per-capita asbestos consumption rates in the past, were the first to realize that the profile of their clients had changed over the years. Initial clients diagnosed with malignant mesothelioma were miners and workers in the asbestos industry (first wave), but later carpenters, plumbers, electricians, car mechanics and others who had been working with and around asbestos containing materials followed (second wave). These cases predominantly affected males, but more recently, both males and females from diverse backgrounds, who were exposed to asbestos present in the environment, were diagnosed with mesothelioma (third wave). In this context it is important to note that exposure to asbestos-contaminated work clothes had already been recognized as a cause for mesothelioma in housewives via so-called 'para-occupational' asbestos exposure [68]. A fourth wave may follow if the current phase of asbestos removal is not done properly.

Data from the Australian Mesothelioma Registry reveal that in 2017, more than fifty years after the rapid surge of asbestos consumption and thirty years after introducing restrictions, the incidence of mesothelioma was not yet declining [69]. More than 20% of the newly registered male and more than 90% of the female mesothelioma cases reported asbestos exposure in non-occupational-only settings. It is therefore highly likely that the role of environmental asbestos exposure is significantly underestimated [70]. In other words, despite the introduction of preventive measures three decades ago the asbestos-contaminated environment (an estimated one in three Australian houses is assumed to contain some form of asbestos in building materials) is expected to significantly contribute to the incidence of asbestos-related cancers in Australia.

In other countries the ultimate consequences of living in an asbestos- contaminated environment have also been noted. Simply living near the Eternit asbestos factory in Casale Monferrato (Italy) was sufficient to cause mesothelioma in local residents [71]. Similar observations have been made around asbestos industries in another part of Italy [72] and elsewhere in the world (Japan, Finland etc). In the Netherlands roads and garden paths paved with tailings of another (Eternit) asbestos factory in the municipality of Goor also led to multiple mesothelioma cases [73]. The carcinogenic potency of environmental asbestos is highlighted by the results of a long-term (> 60 yr) follow-up of more than 12,000 former school pupils in a register-based cohort study in Denmark [74]. Attending primary school near an asbestos cement plant lead to a highly significant increase in mesothelioma incidence in later life. Moreover, loose-fill asbestos insulation present in a considerable number of houses in and near Canberra (Australia) also turned out to be associated with a significantly increased cancer risk, particularly mesothelioma, later in life [75]. There is no doubt that living in an asbestos-polluted environment greatly increases the risk of developing mesothelioma.

It is likely that a similar cause-and-effect relationship exists for lung cancer. However, due to the confounding effect of smoking and a lack of specific histological or molecular markers for asbestos-induced lung cancer [76,77] this relationship has remained obscure. In this respect it is worth considering the remarkably high lung cancer incidence rates in Eastern European countries and the former USSR [78]. While these countries are known for their high rates of smoking, high asbestos consumption was also prevalent. It is certainly worth investigating whether the ubiquitously present asbestos might have made a contribution to the high lung cancer incidence reported in these countries.

5. Susceptibility factors, smoking and asbestos, long-term consequences of a contaminated environment and the failure to register all asbestos victims in emerging countries

The pathophysiology of mesothelioma is gradually becoming unraveled. Taking clinical and experimental evidence together, it is assumed that inhaled asbestos fibers will end up in the pleura inducing a chronic inflammatory reaction including 'frustrated phagocytosis', leading to the loss of tumor-suppressive mechanisms [79]. Cyclin-dependent kinase inhibitor 2A *(CDNK2A)*, neurofibromatosis type 2 *(NF2)* and BRCA1-associated protein *(BAP1)* are the most frequently mutated tumor-suppressor genes found in mesothelioma. An increasing number of reports suggest that there is a genetic basis for being more susceptible to asbestos carcinogenesis [80,81]. Carriers of *BAP1* mutations were found to have a high incidence of malignancies (a cancer syndrome including mesothelioma) in contrast to unaffected family members [82]. As almost no cases of sporadic MM showed germline BAP1 mutation [83], it is hoped that additional gene-disease correlation studies will help defining the place of susceptibility factors. Where lung cancer carcinogenesis is concerned it is assumed that the inflammatory reactions elicited by inhaled

asbestos will occur in the respiratory epithelium and lung parenchyma. In comparison with mesothelioma there is limited data on the molecular changes induced by inhaled asbestos and the genetic abnormalities seen in lung cancer are considered to be dominated by effects of smoking [84].

Long-term epidemiological studies in chrysotile miners and chrysotile textile workers in China have provided better insight into the increased lung cancer risk caused by asbestos exposure and the synergy between asbestos and cigarette smoke exposures [40,85]. Specific asbestos-associated DNA methylation changes have recently emerged as potential markers of asbestos carcinogenesis in lung cancer [86]. However additional validation studies are needed before these markers can be added to our armentarium. Thus, conclusive data on the association between asbestos in the environment and lung cancer incidence are not yet available. As such there remains a great need for epidemiological studies using molecular markers to provide a fuller picture of all the harm induced by asbestos.

The practice in emerging countries to use asbestos without restriction and a failure to safely dispose of huge quantities of asbestos waste have created an environmental problem of an unprecedented size. Even the most optimistic scenario (i.e. the introduction of a ban for all forms of asbestos) will not affect the millions of tons of asbestos that have already contaminated the environment in places such as South Africa, India and Canada; it is illusionary to think that every polluted site can be reliably located. Moreover, it is highly unlikely that emerging countries will have the financial resources needed to remediate asbestos present in their environment. Unfortunately, the most likely scenario will be an unrecognized asbestos time-bomb that will continue to 'silently' explode.

The absence of pathology services with sufficient expertise in emerging countries, combined with a lack of accurate disease markers, means that the true extent of the relationship between asbestos and cancer remains significantly underestimated. Death due to mesothelioma and lung cancer, usually occurring at advanced age (after a long latency), will remain unnoticed as few resources exist to ascertain the cause of death of elderly people living in the rural communities. Vital statistics are frequently incomplete or lacking altogether, allowing the asbestos industry and its corrupted companions [87,88] to argue that no asbestos-related deaths have been recorded and that their products can be safely used. In India, a country consuming more than 300,000 metric tons of asbestos each year, governmental representatives claim that they cannot deny the poor a cheap asbestos roof above their head and argue that this is more important than curtailing the environmental asbestos disaster that is currently unfolding. Poor people will be the first bear the brunt of the tragic consequences: 1.25 million asbestos-related cancer patients are expected in India, which already has a major lack of palliative care facilities [89]. Every year on the beaches of India, Pakistan and Bangladesh, hundreds of large ocean ships are dismantled with no or lax environmental regulations. The ships are driven right up to the shoreline and then attacked by hammer and blowtorch resulting in the contamination of workers and the environment with massive amounts of asbestos and other hazardous waste [90].

6. Expert opinion

Despite numerous scientific reports, urgent calls from multiple scientific and health organizations and the tireless campaigning of grassroots organizations, the corrupt forces promoting the 'safe' use of asbestos have succeeded in driving an unparalleled surge of asbestos consumption in emerging countries during the last three decades. This sinister lobby closely resembles that of the tobacco industry, which targeted emerging countries, when the deadly impact of smoking became public in the developed world [91].

With this in mind it is vital that the facts about the devastating consequences associated with continued asbestos exposure – as summarized in this article – are conveyed to medical specialists, healthcare workers and politicians around the world. If no action is undertaken the 'silent killer' will continue to affect the lives of a rapidly increasing number of people and generations thereafter.

Researchers, epidemiologists, oncologists, respiratory, occupational and public health physicians must continue to take responsibility to reinforce the fact that the world is facing an asbestos disaster of unprecedented size. Only by acting now will we be able to prevent this future impact on global health from worsening. Despite being a mostly preventable man-made cancer, vested interests in the asbestos industry are responsible for the continued rise in the number of asbestos victims. We must combine preventive measures with investment in research into improved diagnostic techniques, and research into novel therapies if we are to meet the global threat that millions of people will face in the future [92,93].

Acknowledgments

We thank Anna Fife and Elaine Tam (University of Sydney) for careful proofreading and editing of the manuscript.

Funding

This paper received no funding.

Declaration of Interest

Arthur L Frank regularly testifies in asbestos-related matters, primarily for plaintiffs. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Linton A, Vardy J, Clarke S, et al. The ticking time-bomb of asbestos: its insidious role in the development of malignant mesothelioma. Crit Rev Oncol Hematol. 2012;84(2):200–212.
2. Peterson JT Jr., Greenberg SD, Buffler PA. Non-asbestos-related malignant mesothelioma. A review. Cancer. 1984;54(5):951–960.
3. Farioli A, Ottone M, Morganti AG, et al. Radiation-induced mesothelioma among long-term solid cancer survivors: a longitudinal analysis of SEER database. Cancer Med. 2016;5(5):950–959.
4. Guo Z, Carbone M, Zhang X, et al. Improving the accuracy of mesothelioma diagnosis in China. J Thorac Oncol. 2017;12(4):714–723.
5. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of malignant mesothelioma: part 2. Malignant mesothelioma subtypes, pleural synovial sarcoma, molecular and prognostic aspects of mesothelioma, BAP1, aquaporin-1 and microRNA. J Clin Pathol. 2013;66(10):854–861.
6. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of mesothelioma: part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol. 2013;66(10):847–853.
7. Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. Environ Health Perspect. 2011;119(4):514–518.
8. Soeberg MJ, Luong MA, Tran VT, et al. Estimating the incidence of malignant mesothelioma in Vietnam: a pilot descriptive cancer registration study. Int J Occup Environ Health. 2016;22(2):167–172.
9. Henderson DW, Rodelsperger K, Woitowitz HJ, et al. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. Pathology. 2004;36(6):517–550.
10. Tossavainen A. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health. 1997;23(4):311–316.
11. Klebe S, Leigh J, Henderson DW, et al. Asbestos, smoking and lung cancer: an update. Int J Environ Res Public Health. 2019;17:1.
12. Landrigan PJ, Collegium R. Comments on the 2014 helsinki consensus report on asbestos. Ann Glob Health. 2016;82(1):217–220.
13. van der Bij S, Koffijberg H, Lenters V, et al. Lung cancer risk at low cumulative asbestos exposure: meta-regression of the exposure-response relationship. Cancer Causes Control. 2013;24(1):1–12.
14. Ferrante D, Chellini E, Merler E, et al. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. Occup Environ Med. 2017;74(12):887–898.
15. Offermans NSM, Vermeulen R, Burdorf A, et al. Occupational asbestos exposure and risk of esophageal, gastric and colorectal cancer in the prospective Netherlands cohort study. Int J Cancer. 2014;135(8):1970–1977.
16. Luberto F, Ferrante D, Silvestri S, et al. Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy. Environ Health. 2019;18(1):71.
17. Awan KH, Hegde R, Cheever VJ, et al. Oral and pharyngeal cancer risk associated with occupational carcinogenic substances: systematic review. Head Neck. 2018;40(12):2724–2732.
18. Bounin A, Charbotel B, Fervers B, et al. Professional risk factors associated with the cancer of the ovary. Literature review. Bull Cancer. 2014;101(12):1089–1108.
19. Reid A, de Klerk N, Musk AW. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2011;20(7):1287–1295.
20. Moline J, Bevilacqua K, Alexandri M, et al. Mesothelioma associated with the use of cosmetic talc. J Occup Environ Med. 2020;62(1):11–17.
21. Fitzgerald S, Harty E, Joshi TK, et al. Asbestos in commercial indian talc. Am J Ind Med. 2019;62(5):385–392.
22. Arsenic, Metals, Fibres and Dusts, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No.100C, IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Lyon (FR): International Agency for Research on Cancer; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK304375/
23. International Chrysotile Association. [cited 2020 Mar 20]. Available from: https://chrysotileassociation.com/
24. Uralasbest. Available from: www.uralasbest.ru
25. Chrysotile Information Center. Available from: http://www.chrysotile-asia.com/
26. Fibre Cement Products Manufacturers Association. Available from: https://fcpma.in/
27. Chrysotile Vietnam. Available from: https://chrysotile.vn.
28. Holmes D. IARC in the dock over ties with asbestos industry. Lancet. 2013;381(9864):359–361.
29. McCulloch J. Saving the asbestos industry, 1960 to 2006. 433021. 2006;121(5):609–614.
30. Baur X, Soskolne CL, Lemen RA, et al. How conflicted authors undermine the World Health Organization (WHO) campaign to stop all use of asbestos: spotlight on studies showing that chrysotile is carcinogenic and facilitates other non-cancer asbestos-related diseases. Int J Occup Environ Health. 2015;21(2):176–179.
31. Michaels D. Doubt is their product: how industry's assault on science threatens your health. New York (NY): Oxford University Press; 2008.
32. Hazards 144. 2018. Available from: http://www.hazards.org/haz144/index.htm
33. Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol. 2008;38(Suppl 1):49–73.
34. Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol. 2008;38(Suppl 1):1–47.
35. McDonald JC, McDonald AD, Hughes JM. Chrysotile, tremolite and fibrogenicity. Ann Occup Hyg. 1999;43(7):439–442.
36. McDonald JC, McDonald AD. Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg. 1997;41(6):699–705.
37. Bernstein D, Rogers R, Smith P. The biopersistence of Canadian chrysotile asbestos following inhalation: final results through 1 year after cessation of exposure. Inhal Toxicol. 2005;17(1):1–14.
38. Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. Am J Public Health. 1996;86(2):179–186.
39. Wang X, Courtice MN, Lin S. Mortality in chrysotile asbestos workers in China. Curr Opin Pulm Med. 2013;19(2):169–173.
40. Wang X, Yano E, Qiu H, et al. A 37-year observation of mortality in Chinese chrysotile asbestos workers. Thorax. 2012;67(2):106–110.
41. Stayner L, Smith R, Bailer J, et al. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. Occup Environ Med. 1997;54(9):646–652.
42. Dodson RF, Atkinson MA, Levin JL. Asbestos fiber length as related to potential pathogenicity: a critical review. Am J Ind Med. 2003;44(3):291–297.
43. Feder IS, Tischoff I, Theile A, et al. The asbestos fibre burden in human lungs: new insights into the chrysotile debate. Eur Respir J. 2017;49:6.
44. Joint Policy Committee of Epidemiology Societies. Position statement on asbestos; 2012. Available from: https://epidemiologyinpolicy.org/documents/01.JPC-SE-Position_Statement_on_Asbestos-June_4_2012-Summary_and_Appendix_A_English.pdf
45. Stayner L, Welch LS, Lemen R. The worldwide pandemic of asbestos-related diseases. Annu Rev Public Health. 2013;34:205–216.
46. Hadley B, Rennell T. Asbestos - the Future Risk. 1st ed. London, UK: Iskaboo Publishing Ltd; 2013 March 1; p. 157.

47. Talcott JA, Thurber WA, Kantor AF, et al. Asbestos-associated diseases in a cohort of cigarette-filter workers. N Engl J Med. 1989;321 (18):1220–1223.
48. Dodson RF, Hammar SP. Pleural mesothelioma in a woman whose documented past exposure to asbestos was from smoking asbestos-containing filtered cigarettes: the comparative value of analytical transmission electron microscopic analysis of lung and lymph-node tissue. Inhal Toxicol. 2006;18(9):679–684.
49. Frank AL, Joshi TK. The global spread of asbestos. Ann Glob Health. 2014;80(4):257–262.
50. Lemen RA, Dement JM, Wagoner JK. Epidemiology of asbestos-related diseases. Environ Health Perspect. 1980;34 (Feb):1–11.
- **The first review of over 100 epidemiological studies dating back to one of the first reported cases of asbestos-related disease.**
51. Ramazzini C. Call for an international ban on asbestos. J Occup Environ Med. 1999;41(10):830–832.
- **The first call for an international ban on asbestos by a distinguished group of scientists, clearly stating that all forms of asbestos should be banned.**
52. Lin RT, Takahashi K, Karjalainen A, et al. Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis. Lancet. 2007;369 (9564):844–849.
53. Ramazzini C. Asbestos is still with us: repeat call for a universal ban. J Occup Environ Med. 2010;52(5):469–472.
54. Ferrante D, Mirabelli D, Silvestri S, et al. Mortality and mesothelioma incidence among chrysotile asbestos miners in Balangero, Italy: a cohort study. Am J Ind Med. 2020;63 (2):135–145.
55. Westerholm P, Remaeus B, Svartengren M. The Tale of Asbestos in Sweden 1972–1986-The Pathway to a Near-Total Ban. Int J Environ Res Public Health. 2017;14:11.
56. Gemba K, Fujimoto N, Kato K, et al. National survey of malignant mesothelioma and asbestos exposure in Japan. Cancer Sci. 2012;103(3):483–490.
57. Yoon Y-R, Kwak KM, Choi Y, et al. The asbestos ban in Korea from a grassroots perspective: why did it occur? Int J Environ Res Public Health. 2018;15(2):198.
58. Furuya S, Takahashi K. Experience of Japan in achieving a total ban on asbestos. Int J Environ Res Public Health. 2017;14:10.
59. Vincenten J, George F, Martuzzi M, et al. Barriers and facilitators to the elimination of asbestos related diseases-stakeholders' perspectives. Int J Environ Res Public Health. 2017;14(10):1269.
60. Collegium R. The 18th Collegium Ramazzini statement: the global health dimensions of asbestos and asbestos-related diseases. Scand J Work Environ Health. 2016;42(1):86–90.
61. Ruff K. UN scientific agency collaborating with scientists involved in sabotaging UN rotterdam convention. Int J Occup Environ Health. 2013;19(3):160–162.
62. Kazan-Allen L. The asbestos war. Int J Occup Environ Health. 2003;9 (3):173–193.
63. Ruff K. How Canada changed from exporting asbestos to banning asbestos: the challenges that had to be overcome. Int J Environ Res Public Health. 2017;14:10.
64. Kazan-Allen L. The debate on banning asbestos. CMAJ. 2001;165(9): 1189. author reply 91-3.
65. Kazan-Allen L. Ban asbestos phenomenon: the winds of change. New Solut. 2011;21(4):629–636.
66. Leong SL, Zainudin R, Kazan-Allen L, et al. Asbestos in Asia. Respirology. 2015;20(4):548–555.
67. Lemen RA, Landrigan PJ. Toward an asbestos ban in the United States. Int J Environ Res Public Health. 2017;14:11.
68. Noonan CW. Environmental asbestos exposure and risk of mesothelioma. Ann Transl Med. 2017;5(11):234.
69. Australian Institute of Health and Welfare. Mesothelioma in Australia 2018. Australia; 2019. Available from: https://www.aihw.gov.au/reports/can/130/mesothelioma-in-australia-2018/contents/table-of-contents
70. Soeberg MJ, Leigh J, van Zandwijk N. Malignant mesothelioma in Australia 2015: current incidence and asbestos exposure trends. J Toxicol Environ Health B Crit Rev. 2016;19 (5–6):173–189.
71. Ferrante D, Mirabelli D, Tunesi S, et al. Pleural mesothelioma and asbestos exposure: a case-control study with quantitative risk assessment. Occup Environ Med. 2016;73(3):147–153.
- **Important update of the consequences of asbestos exposre in the occupational and the environmental setting in Casale Monferrato (asbestos cement plant), a very well-executed case-control study.**
72. Consonni D, De Matteis S, Dallari B, et al. Impact of an asbestos cement factory on mesothelioma incidence in a community in Italy. Environ Res. 2019;108968. DOI:10.1016/j.envres.2019.108968
73. Sinninghe Damsté HEJ, Siesling S, Burdorf A. Environmental exposure to asbestos in the area around Goor has been established as the cause of pleural mesothelioma in women. Ned Tijdschr Geneeskd. 2007;151(44):2453–2459.
74. Dalsgaard SB, Würtz ET, Hansen J, et al. Environmental asbestos exposure in childhood and risk of mesothelioma later in life: a long-term follow-up register-based cohort study. Occup Environ Med. 2019;76(6):407–413.
- **Excellent long–term follow–up study showing the devastating consequences of asbestos exposure during childhood.**
75. Korda RJ, Clements MS, Armstrong BK, et al., Risk of cancer associated with residential exposure to asbestos insulation: a whole-population cohort study. Lancet Public Health. 2017;2(11):e522–e8.
- **Carefully executed epidemiological study estimating the consequences of residential asbestos exposure in Australia.**
76. Nielsen LS, Bælum J, Rasmussen J, et al. Occupational asbestos exposure and lung cancer–a systematic review of the literature. Arch Environ Occup Health. 2014;69(4):191–206.
77. Olsson AC, Vermeulen R, Schüz J, et al. Exposure-response analyses of asbestos and lung cancer subtypes in a pooled analysis of case-control studies. Epidemiology. 2017;28(2):288–299.
78. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–1403.
79. van Zandwijk N, Reid G. Asbestos and the pathophysiology of mesothelioma. In: Ceresoli G, Bombardieri E, D'Incalci M, editors. Mesothelioma. Cham: Springer; 2019;19–33.
80. Cheung M, Testa JR. BAP1, a tumor suppressor gene driving malignant mesothelioma. Transl Lung Cancer Res. 2017;6(3):270–278.
81. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. Cancer Res. 2016;76(2):206–215.
82. Ascoli V, Cozzi I, Vatrano S, et al. Mesothelioma families without inheritance of a BAP1 predisposing mutation. Cancer Genet. 2016;209(9):381–387.
83. Betti M, Aspesi A, Sculco M, et al. Genetic predisposition for malignant mesothelioma: A concise review. Mutat Res. 2019;781:1–10.
84. Malhotra J, Malvezzi M, Negri E, et al. Risk factors for lung cancer worldwide. Eur Respir J. 2016;48(3):889–902.
85. Yano E, Wang X, Wang M, et al. Lung cancer mortality from exposure to chrysotile asbestos and smoking: a case-control study within a cohort in China. Occup Environ Med. 2010;67(12):867–871.
86. Kettunen E, Hernandez-Vargas H, Cros M-P, et al. Asbestos-associated genome-wide DNA methylation changes in lung cancer. Int J Cancer. 2017;141(10):2014–2029.
87. Egilman D, Bird T, Lee C. Dust diseases and the legacy of corporate manipulation of science and law. Int J Occup Environ Health. 2014;20(2):115–125.
88. Castleman B. Criminality and asbestos in industry. New Solut. 2017;26(4):557–580.
89. Jadhav AV, Gawde NC. Current asbestos exposure and future need for palliative care in India. Indian J Palliat Care. 2019;25(4):587–591.

90. Singh R, Cherrie J, Rao B, et al. Assessment of the future mesothelioma disease burden from past exposure to asbestos in ship recycling yards in India. Int J Hyg Environ Health. 2020;225:113478;In print.
91. Gilmore AB, Fooks G, Drope J, et al. Exposing and addressing tobacco industry conduct in low-income and middle-income countries. Lancet. 2015;385(9972):1029–1043.
92. Fan X, McLaughlin C, Robinson C, et al. Zeolites ameliorate asbestos toxicity in a transgenic model of malignant mesothelioma. FASEB Bioadv. 2019;1(9):550–560.
93. Reid G, Johnson T, van Zandwijk N. Manipulating microRNAs for the treatment of malignant pleural mesothelioma: past, present and future. Front Oncol. 2020;10. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2020.00105/full