Chapter 1
Malignant Mesothelioma: An Asbestos Legacy

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Abstract With the advent of the industrial age, asbestos' unique properties, including its resistance to fire, tensile strength, softness and flexibility, resulted in its widespread commercial use. Decades later, its usage was shown to have tragic medical consequences, as these fibrous minerals became causally linked to malignant mesothelioma and other debilitating diseases. Malignant mesotheliomas are aggressive tumors that arise from serous membranes, such as the pleura and the peritoneum. Mesothelioma has a dismal prognosis due to its inherent chemo- and radio-resistance as well as to the general ineffectiveness of surgical intervention. Mesotheliomas account for approximately 3200 deaths per year in the USA, with more than 450,000 deaths predicted over the next 40 years in the USA, Europe, Australia, and Japan. Legal compensation alone is projected to amount to hundreds of billions of dollars worldwide over this time span, and this already enormous figure does not include health care costs. Currently, about 125 million people worldwide are exposed to asbestos in the workplace. Given such continued exposure to asbestos fibers, there is thus great public, medical, and legal interest in this malignancy. This introduction provides a general overview of the mesothelioma burden and a brief outline about the contents of this monograph, which includes a multidisciplinary assessment of the characteristics of asbestos along with the epidemiology, cell biology, pathology, and treatment of mesothelioma. Psychological aspects and legal challenges facing mesothelioma patients and their families are also presented.

Keywords History of asbestos usage • Health effects of asbestos • Malignant mesothelioma • Mesothelioma epidemiology • Pathology and treatment • Mesothelioma cell biology and genetics • Germline and somatic mutations • Rodent models of mesothelioma • Psychological and legal issues

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1.1 Asbestos Usage Over the Years

Asbestos refers to a family of six silicate minerals that contain silicon and oxygen embodied as fibrous aggregates of long, thin crystals that can readily separate. Among its remarkably useful attributes are its resistance to fire, tensile strength, flexibility, softness, and affordability, with early usage of asbestos dating back at least two millennia. In their fascinating historical account of the ups-and-downs of asbestos' past, Alleman and Mossman alluded to the irony of the asbestos tragedy, i.e., that the medical catastrophe would never have become so severe had the industrial world not previously found the substance to be so valuable commercially (Alleman and Mossman 1997).

Over the years, asbestos has been used to weave cloaks, tablecloths, theater curtains, and flameproof suits for shielding against fires. Other everyday uses have included automobile brake shoes, air filters for military gas masks, hospital ventilators, and even cigarette filters. Mixed with rubber, asbestos permitted the development of durable steam engine components, such as steam gaskets. When melded into tar, burlap, and paper, asbestos fibers provided fire-resistant roofing material, thereby opening up a vast industry of asbestos-based construction products. Mixtures of asbestos and cement were heavily used for paneling in buildings and ships, as well as for pipes and synthetic slate roof shingles. When mixed with plastic, asbestos was used in everything from electrical boards to telephones, and vinyl-asbestos tiles became paramount in the flooring industry, including in schools. In skyscrapers, spray-on asbestos coating was used to protect steel structures against fire-induced buckling (Alleman and Mossman 1997).

1.2 Malignant Mesothelioma and Other Health Effects of Asbestos

In a seminal report published in 1960, Wagner and colleagues provided conclusive epidemiological evidence linking asbestos to malignant mesothelioma in individuals living and/or working in a crocidolite asbestos mining area of South Africa (Wagner et al. 1960). Malignant mesotheliomas are tumors derived from mesothelial cells that form the serosal membranes lining the chest and abdomen. Most mesotheliomas are highly aggressive neoplasms that have a median survival of about 9 months from the time of diagnosis. The incidence of malignant mesothelioma is several-fold higher in men than in women and is often diagnosed during the seventh and eighth decades of life, typically 20–50 years after initial exposure to asbestos. Mesothelioma currently accounts for 3200 deaths per year in the USA and about 5000 deaths in Western Europe (Henley et al. 2013; Ismail-khan et al. 2006).

In the late 1990s, it was estimated that 20% of homes and commercial buildings in the USA still contained products, e.g., shingles, cement pipes, and insulation, made from chrysotile asbestos (Alleman and Mossman 1997). Deaths due to mesothelioma

are expected to increase by 5–10% per year in most industrialized countries until about 2020, and asbestos has also been shown to cause asbestosis, pleural fibrosis/plaques, as well as lung and laryngeal cancer (Carbone et al. 2012). Notably, the incidence of mesothelioma has continued to increase despite various measures implemented in the 1970s and 1980s to reduce (U.S.) or eliminate (countries of the European Union) the use of products containing asbestos.

Both epidemiological studies and experimental work performed in vitro and in rodents have shown a strong link between mesothelioma and exposure to crocidolite asbestos, a needlelike (amphibole) form of asbestos, and erionite, a needlelike type of zeolite. Other forms of amphibole asbestos, such as tremolite, have also been associated with the development of mesothelioma, although the risk appears to be lower than for crocidolite fibers. Whether other amphibole types or the serpentine (snakelike) asbestos fiber, chrysotile, causes mesothelioma is still debated; however, the World Health Organization's International Agency for Research on Cancer (IARC) has concluded that all forms of asbestos can cause mesothelioma (IARC 2009; http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-11.pdf).

Given that asbestos is virtually an inescapable carcinogen in industrialized societies, almost everyone may have some level of exposure. Although it has been hypothesized that there is a threshold level of exposure above which risk of developing mesothelioma increases significantly, the threshold is unknown, and individual genetic susceptibility likely influences this threshold (Testa and Carbone 2016). There does not appear to be a linear dose-response relationship between asbestos exposure and development of mesothelioma, and in addition to genetic differences, tumor risk may depend on the type of mineral fiber inhaled and exposure to certain cofactors.

Interestingly, while billions of dollars per year are spent on asbestos-related litigation and asbestos abatement, progress in understanding mesothelioma pathogenesis has been hampered by limited research funding—due in part to its lower incidence than other types of cancer, such as lung and breast carcinomas, but also because of the mistaken belief by some that the disease is disappearing. In fact, the incidence of mesothelioma in the USA has remained constant since the mid-1990s. Alarmingly, in countries that produce and/or are expanding their use of asbestos, including India, China, Russia, Zambia, Colombia, and Kazakhstan, a surge in disease incidence is expected to occur in these countries (see Chap. 4 by Røe and Stella in this volume), particularly in countries such as India, where little or no precautions are being taken to prevent exposure of workers (Burki 2010). In Western countries, exposure to high levels of asbestos in the workplace has been largely abolished, but the number of workers exposed to low, but above-background, levels of asbestos has increased; furthermore, use of asbestos in some products continues in the USA (Carbone et al. 2012).

In addition to mesothelioma, asbestos was shown to act as a carcinogen in lung carcinoma, and the combination of cigarette smoking and asbestos greatly increased the risk of lung cancer (Barrett et al. 1989). Moreover, inhalation of asbestos fibers was also found to induce other occupational lung diseases, including benign pleural plaques as well as two potentially deadly diseases: asbestosis, marked by chronic

inflammation and scarring of the lungs, and a form of pneumoconiosis, a respiratory disease that restricts lung expansion. More recently, a comprehensive review by the IARC determined that there is *sufficient evidence* for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) and that exposure to asbestos can cause not only mesothelioma and lung cancer, but also cancer of the larynx (IARC 2009; http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-11.pdf). Additionally, IARC noted that positive associations have been observed between exposure to asbestos and cancers of the ovary and stomach.

Since asbestos has been shown to be the major cause of mesothelioma, with a history of asbestos exposure being documented in about 80% of individuals diagnosed with the pleural form of the tumor (Robinson and Lake 2005), and since no safe lower threshold of exposure has been identified, asbestos products have been banned in all the countries of the European Union, beginning January 1, 2005 (http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-11.pdf; EU 1999). Moreover, in addition to those exposed occupationally, family members can be at risk, e.g., as a result of washing contaminated work clothes, or simply by living in proximity to mining or asbestos cement processing factories (Magnani et al. 2001; Musti et al. 2009).

Patients with peritoneal mesothelioma, which comprise approximately 20% of all cases, tend to be younger than patients with pleural mesothelioma; moreover, a higher proportion of peritoneal mesothelioma cases, mostly women, are long-term survivors (Kindler 2013). Among patients eligible for surgery, a locoregional approach consisting of cytoreductive surgery and perioperative intraperitoneal chemotherapy—introduced over the last decade—achieved an overall 5-year survival rate of 30–60% (Mirarabshahii et al. 2012). Malignant pleural mesothelioma, on the other hand, is almost uniformly resistant to treatment. Cancer-directed surgery for malignant pleural mesothelioma is associated with a 5-year survival rate of only 15% (Wolf and Flores 2016), and chemotherapy-naive patients who were not eligible for curative surgery had a median survival of only about 12 months when treated with pemetrexed plus cisplatin, the current standard chemotherapeutic regimen (Vogelzang et al. 2003).

1.3 Outline of Monograph Contents

To understand how clinical outcomes may be improved in the future, it is necessary to better comprehend the biology of the disease. In recognition of the continuing global use of asbestos and its deadly legacy, this volume includes reviews on the various forms of asbestos and their relative carcinogenic potential, the epidemiology and biology of mesothelioma, and the current therapeutic options for this aggressive, therapy-resistant malignancy. In Chap. 2, Wylie describes the physical and chemical attributes of a group of very narrow fibrils that form bundles of parallel fibers characteristic of the “asbestiform habit.” Included in this chapter are

numerous photographs of the various types of asbestiform amphiboles, such as crocidolite, as well as the serpentine group of minerals that include chrysotile, the most widely used type of asbestos. Erionite, a fibrous zeolite, is also discussed.

Chapters 3, 4, and 5 discuss various aspects of the epidemiology of malignant mesothelioma, particularly in connection with exposure to asbestos or erionite. In addition to asbestos and other carcinogenic mineral fibers, Moolgavkar and coworkers point out that there is evidence for idiopathic mesotheliomas, i.e., those that arise spontaneously or from an obscure or unknown cause, as well as for other contributing factors, including germline and acquired, age-related gene mutations. Other risk factors, such as ionizing radiation, and the impact of non-occupational low levels of fiber exposure are also reviewed. Røe and Stella review the history of asbestos usage and its connection with mesothelioma causation as well as current unresolved questions and controversies regarding the epidemiology and biology of this dreaded disease. Additionally, these authors review recent studies indicating that man-made carbon nanofibers could pose dangers similar to those of asbestos in the coming years, and thus they urge regulatory bodies to be proactive in ensuring thorough evaluation of novel substances before commercial use. Emmett and Cakouros describe a diverse group of communities that have a high incidence of malignant mesothelioma and other asbestos-related diseases. They highlight lessons from communities where there is an elevated risk of mesothelioma due to asbestos mining, processing, and manufacturing as well as regions such as Cappadocia, Turkey, where asbestiform erionite occurs naturally in the local environment. They also describe a wide assortment of issues, including shortcomings in the regulatory definition of asbestos, diffuse administrative responsibilities, diverse community attitudes about disease risk and prevention, as well as difficulties in quantifying exposures and justifying remediation actions.

In Chap. 6, Pavlisko et al. describe in detail the gross pathology of mesothelioma arising from pleura, peritoneum, pericardium, and the tunica vaginalis. The authors provide an overview of the histomorphologic growth patterns, ranging from epithelioid to sarcomatoid, and discuss the importance of immunohistochemical stains in helping to assure the diagnosis of malignant mesothelioma. They also review the value of BAP1 immunohistochemistry together with fluorescence in situ hybridization for detection of homozygous loss of the gene encoding p16INK4A in distinguishing benign/reactive from malignant mesothelial proliferations.

Chapters 7, 8, 9, 10, and 11 present overviews of various biological processes important in the development and progression of malignant mesothelioma. Thompson and Shukla review the role of asbestos-induced inflammation in mesothelioma, fibrosis, and other lung diseases. They discuss the possibility that early inflammatory gene "signatures" might be exploited as novel predictive biomarkers and therapeutic targets to aid in early diagnosis and treatment of mesothelioma, respectively. Cheung and colleagues highlight our current understanding of the role of both germline and acquired (somatic) mutations in human malignant mesothelioma, as well as lessons learned from experimental studies of asbestos-exposed rodent models of mesothelioma. The authors review the body of literature about relevant genes, particularly the tumor suppressor genes *BAP1*, *CDKN2A* and *NF2*,

which are frequently mutated somatically in human mesotheliomas and may serve as "drivers" of this lethal disease. They also explore recent research about familial risk of mesothelioma due to germline mutation of *BAP1* and potentially other genetic factors that may play a role in tumor predisposition (Testa et al. 2011). Evidence for gene–environment interaction, i.e., the convergence of germline *BAP1* mutation and exposure to asbestos fibers in the same individual, is also highlighted. De Rienzo et al. discuss recent efforts to discover gene signatures that might hold promise for personalized therapeutic decisions, with the goal of improving clinical outcome in patients with mesothelioma. They summarize findings using several different technologies such as sequencing, expression, and methylation arrays, and they discuss current challenges, including the need for large-scale validation before gene signatures can be implemented into the clinic. Mossman provides an overview of cell signaling and epigenetic mechanisms critically involved in the transformation of a mesothelial cell into a malignant mesothelioma. She reviews integrated genomic and proteomic analyses of mesothelioma, which have uncovered recurrent activation of multiple cell signaling cascades and transcription factors, as well as epigenetic mechanisms, with an emphasis on research that links such changes to key cell survival and proliferative pathways in tumor formation. Broaddus and coworkers discuss the value of three-dimensional, multicellular spheroid models for investigating mechanisms of cell survival in mesothelioma. They highlight areas in which in vitro multicellular spheroids and ex vivo tumor fragment spheroids have advanced the understanding of mesothelioma cell survival and other processes. As compared to conventional two-dimensional (monolayer) cultures, their findings with spheroid models appear to more closely mimic the therapeutic response in the actual tumor and could offer novel insights that can be subsequently tested in the clinic.

The review by Mesaros et al. (Chap. 12) focuses on recent advances in the identification of biomarkers of response to asbestos exposure, with the ultimate goal being to promote early diagnosis and timely clinical intervention. They evaluate various potential biomarkers of response to asbestos exposure, including the High Mobility Group Box 1 (HMGB1) protein, which has a regulatory role in inflammatory immune responses. Preliminary work has revealed that increased nonacetylated HMGB1 in serum may serve as a biomarker of asbestos exposure, whereas acetylated serum HMBG1 was associated with progression to mesothelioma. The potential merit of combined use of a multiplexed serum lipid biomarker panel with serum protein biomarkers is also discussed.

Chapters 13, 14, 15, and 16 contain comprehensive overviews of state-of-the-art therapies for mesothelioma. Wolf and Flores describe current surgical approaches for mesothelioma. They point out that although the role of surgical resection in malignant pleural mesothelioma is controversial, surgery has yielded long-term survivors, with a 15% 5-year survival in eligible patients. The authors summarize preoperative, perioperative, and postoperative management of mesothelioma patients as well as results of studies evaluating the two operations developed for surgical resection, extrapleural pneumonectomy and radical or extended pleurectomy/decortication (P/D), with the authors advocating the better tolerated P/D procedure for

most pleural mesothelioma patients. Simone et al. discuss the role of both technologically sophisticated ionizing radiotherapy and non-ionizing radiotherapy (photodynamic therapy—a procedure that combines a photosensitizer, light, and oxygen) in both the palliative and definitive treatment of pleural mesothelioma, particularly in providing durable local control. The authors outline the mechanistic and logistical basics of radio- and photodynamic therapies and their use in the multidisciplinary care of mesothelioma patients. They also discuss the potential for future improvements in the use of these therapies. Zauderer summarizes standard chemotherapeutic approaches as well as clinical trials of novel molecularly targeted agents for malignant mesothelioma. She reviews challenges in conducting large randomized clinical trials in mesothelioma, including the scarcity and geographic distribution of patients, the intrinsic chemoresistance of the malignancy, as well as the limited interest and modest financial support from pharmaceutical companies and various funding agencies. Despite these drawbacks, standard cytotoxic chemotherapeutic regimens have been established, and clinical trials with multiple novel agents are ongoing. Thomas et al. review immunotherapeutic strategies to inhibit immune checkpoints and their ligands in mesothelioma. Furthest along currently are clinical investigations of the tumor differentiation antigen mesothelin, with immunotherapies developed that include immunotoxin, tumor vaccine, chimeric antigen receptor T cell, and antibody-based approaches. The authors also describe current work aimed at understanding the antitumor responses to immune-based approaches and ways to identify prospectively those patients most likely to respond to immunotherapy.

In addition to understanding the etiology, biology, and treatment of mesothelioma from a scientific and medical perspective, understanding the disease from the vantage point of the patient is critical. Thus, the final section of this volume focuses on the patient experience. Mesothelioma patients face enormous medical, stress-related, and financial challenges as emphasized in Chaps. 17 and 18. Hartley and Hesdorffer present an overview of medical and legal aspects of the disease, in particular lawsuits intended to seek compensation for patients who develop a mesothelioma potentially caused by exposure to asbestos fibers. Factors to consider when seeking legal advice—and the qualifications of prospective law firms—are presented. Pretrial discovery processes are discussed in detail, including possible requests for genetic testing to determine if an underlying heritable factor may have contributed to development of the disease. The authors also summarize new developments at the intersections between medicine and law, i.e., the possible use of molecular biomarkers, as well as genetic and epigenetic signatures, as potential indicators of asbestos exposure. Buchholz provides a compassionate overview of the complex experience of the mesothelioma patient. He delves into the psychological, sociological, and communicative elements of the individual patient's experience, with the aim being to help medical caregivers comprehend and better respond to that experience. Through interesting case studies, the author illustrates that mesothelioma patients are under great stress that is often unrecognized, but which may be alleviated, at least in part, when the nature of suffering is identified and integrated into a comprehensive treatment strategy.

Finally, the Editor thanks all of the chapter authors for their invaluable contributions to this volume on asbestos and mesothelioma. In the interest of transparency, the publisher has requested that all authors include a brief conflict of interest statement, because a diagnosis of mesothelioma often results in litigation, and many investigators are consulted about matters concerning disease causation—often with very different perspectives on such issues. In any case, the views and opinions expressed by authors of individual chapters do not necessarily reflect those of the Editor.

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