

Chapter 2

Epidemiology

Lynette M. Sholl and Marina Vivero

Introduction

Malignant mesothelioma is defined by the World Health Organization (WHO) as a malignant neoplasm arising from mesothelial cells and growing in a diffuse pattern over the surfaces lining body cavities, including pleura, peritoneum, pericardium, and tunica vaginalis [1]. In approximately 90% of cases, malignant mesothelioma arises in the pleura, where it is often diagnosed at a late stage and associated with relatively rapid death [2]. A causal link between asbestos exposure and malignant mesothelioma was first drawn in studies published in the 1960s [3]; this association has since been confirmed in diverse populations across the globe in relation to both occupational exposures and naturally occurring forms of environmental asbestos. Currently, the WHO recognizes asbestos as an important occupational carcinogen and has committed to an initiative to eliminate asbestos-related diseases globally [4].

Incidence of Pleural Mesothelioma

Epidemiologic studies from the early 2000s estimated that mesothelioma is responsible for 43,000 deaths a year worldwide [5] at a mean age of 70 [6], and is more common in industrialized countries [2]. However, in light of the difficulties in diagnosing this tumor type, it has been estimated that for every four individuals diagnosed with malignant mesothelioma, another one goes undiagnosed [7]. In fact, the absence of robust disease reporting practices in countries with known asbestos consumption patterns has led some authors to speculate that approximately 39,000 cases went underreported between 1984 and 2008 in Russia and east, south, and

L. M. Sholl (✉) · M. Vivero
Department of Pathology, Brigham and Women's Hospital and Harvard Medical School,
75 Francis Street, Boston, MA 02115, USA
e-mail: lmsholl@partners.org

central Asia [7]. Analysis of the global impact of mesothelioma is complicated by several factors, including variable reporting practices in different countries, the lack of an International Classification of Diseases (ICD) code specific to malignant mesothelioma prior to 1993, and variable accuracy worldwide in diagnosing cause of death [6]. Further, in reporting periods spanning the 1990s and early 2000s, the assessment of anatomic site-specific incidence rates was confounded by the fact that nearly half of all cases were reported as arising at “unspecified sites”; however, the available data do suggest that pleural disease is about ten times more frequent than mesothelioma arising at other sites [6].

Worldwide, the incidence of malignant mesothelioma has been rising since the mid-twentieth century, with the best-documented increases in diagnoses noted in Australia and the UK. The most recent data from the UK suggest a fivefold increase in the incidence in men between 1980 and 2009, with an annual incidence of 29 per million [2]. Based on usage patterns of asbestos-containing materials in the twentieth century, peak incidence in many developed countries is expected to occur in the second and third decades of the twenty-first century [8–11]. Despite declarations from the WHO and other international organizations to halt the use of asbestos in manufacturing and construction, developing countries, especially those in Asia undergoing rapid industrialization, continue to use asbestos, and thus are expected to see further growth in the incidence of malignant mesothelioma [12].

The USA Surveillance, Epidemiology, and End Results (SEER) program data collected by the National Cancer Institute documents an incidence of 12.5 per 100,000 among US men and 2.3 per 100,000 among US women over 65 years of age. The incidence of mesothelioma increases steadily with age in men (Fig. 2.1). White non-Hispanic men are at highest risk of disease, with an overall nationwide incidence rate of 2.2 per 100,000 (irrespective of age), as compared to 0.6, 1.1, and 1.6 per 100,000 Asian/Pacific Islanders, Blacks, and Hispanics, respectively [13]. The incidence of mesothelioma varies from state to state, with the highest rates noted in Louisiana, New Jersey, and Seattle–Puget Sound in the 2005–2009 time period [13]. This regional clustering reflects the presence of local industries that have historically used asbestos, including shipbuilding, petrochemical manufacturing, and refining [2]. Likely as a result of regulatory efforts and declining use of the more carcinogenic amphibole forms of asbestos in US manufacturing practices (see below), the incidence of mesothelioma in US men that peaked in the early 1990s has declined consistently since that time [14] (Fig. 2.2).

Risk Factors for Malignant Pleural Mesothelioma

Malignant pleural mesothelioma is highly associated with asbestos exposure. A study examining populations derived from Los Angeles, New York State, and Veterans Administration Hospitals nationwide estimated that the attributable risk for exposure to asbestos among men with pleural mesothelioma was 88% [15]. The risk of pleural mesothelioma following exposure to asbestos is dose dependent, as clearly documented in the Wittenoom cohort of crocidolite miners and millers

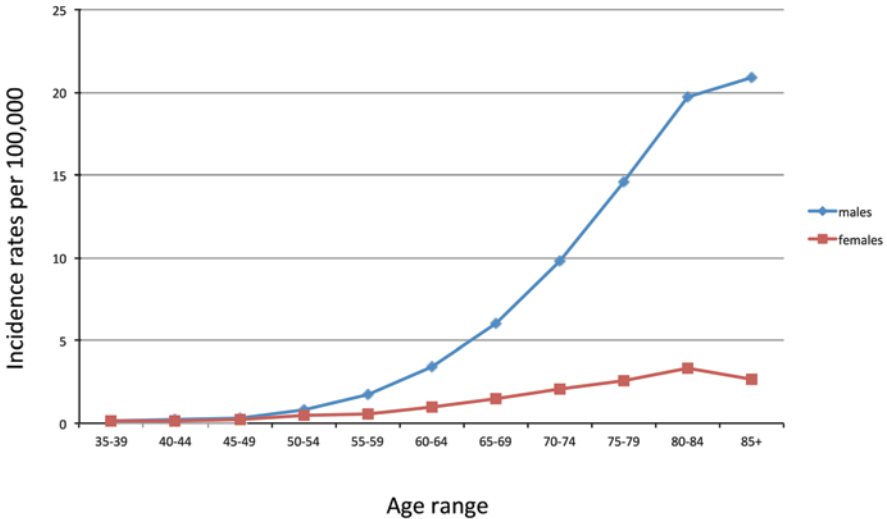


Fig. 2.1 Age-adjusted rates of malignant mesothelioma in the USA according to gender. (Adapted from SEER data)

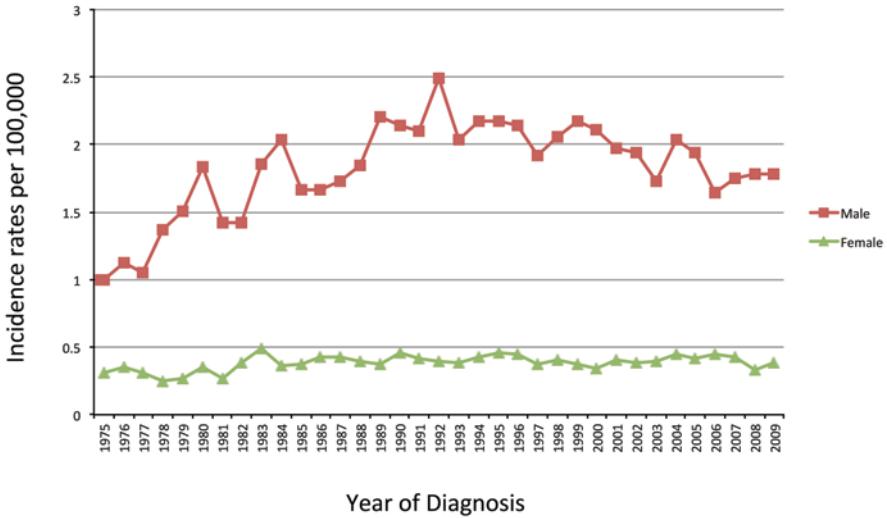


Fig. 2.2 Age-adjusted SEER incidence rates of mesothelioma from 1975–2009 according to gender

from Western Australia [16]. Risk increases in a linear or supralinear fashion over time, even after exposure cessation [17]. The clinical presentation of mesothelioma lags behind the time of first exposure by about 30 years (latency period). Thus, the increasing incidence of pleural mesothelioma in the 1970s reflected a surge in asbestos usage in war-related manufacturing during World War II, and the peak in-

cidence of pleural mesothelioma in the USA in the early 1990s reflects the peak use of amphiboles in US manufacturing practice in the 1960s [18]. Worldwide, men are three- to fourfold more likely to die of malignant pleural mesothelioma than women [6]. This observation reflects higher likelihood of more intense asbestos exposure among men than women in post-World War II industrial practice. Studies of women engaged in the manufacture of crocidolite-containing gas masks in England during World War II showed that they too were at significantly increased risk of death from lung and pleural tumors as compared to other malignancies [19].

Environmental exposure to asbestos poses an increased, albeit generally lower risk as compared to occupational exposure, with family members of asbestos workers and those who live in proximity to asbestos industries showing an increased risk for pleural mesothelioma as compared to other geographic cohorts [20]. Remarkably, high frequencies of pleural mesothelioma have been documented in rural populations where asbestos is present in surface soil and residents have long-standing environmental exposure to the fibers. One cohort study of the rural Dayao community in southwestern China, where crocidolite is prevalent in the soil, estimated an annual mesothelioma mortality rate of up to 365 per million, with mesothelioma accounting for 22 % of cancer deaths [21]. Studies from southeastern Turkey have documented a two- to fivefold increased incidence of malignant pleural mesothelioma among inhabitants of villages where soil-containing tremolite and chrysotile have been used for whitewashing and other household purposes, as compared to villages where asbestos-containing minerals have not been detected [22, 23]. Even in the absence of direct exposure to asbestos-containing soil related to farming or household practices, proximity to sources of naturally occurring asbestos, such as serpentinite and other ultramafic rocks in California, is associated with an increased risk of malignant mesothelioma [24].

Prognosis of Malignant Pleural Mesothelioma

As of the mid-2000s, survival in US populations for all comers with mesothelioma was 40.9 % at 1 year, 12.2 % at 3 years, and 3.9 % at 5 years [13]. More recent population data from European cohorts have described similar survival outcomes, with adverse prognostic features including older age, male sex, and sarcomatoid histology [25, 26]. Current use of multimodality therapy, including surgery, radiation, intracavitary chemotherapy, and systemic chemotherapy, has led to some improvement in survival, but these approaches are rarely curative and are controversial [27]. Retrospective analysis of population-based data derived from the SEER dataset of patients diagnosed with malignant mesothelioma demonstrated no significant improvement in overall outcomes over the past four decades, with a median survival of 7.2 months for patients diagnosed in the 1970s versus 7.1 months in the 2000s [13] (Fig. 2.3). There has been a statistically significant improvement in survival among patients with distant disease (5.5 months in 1970s versus 7.0 months in 2000s, $p=0.001$); however, this improvement is marginal in clinical terms [28].

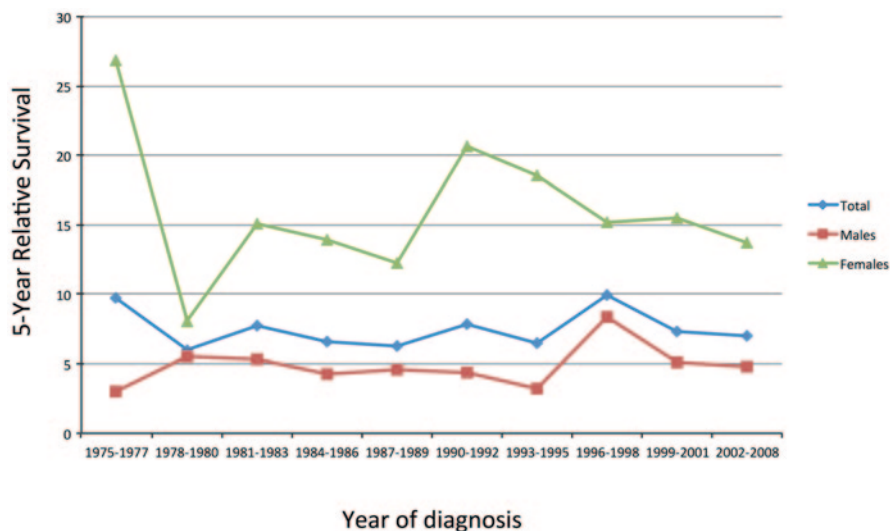


Fig. 2.3 A 5-year relative survival of patients with mesothelioma by gender and year of diagnosis

In patients undergoing chemoradiotherapy and/or surgery, features associated with adverse survival include male gender, sarcomatoid histology, and advanced pathologic stage according to the American Joint Committee on Cancer staging system [29, 30].

Asbestos and Malignant Mesothelioma

A substantial body of literature is dedicated to the physical and chemical features of asbestos fibers that contribute to carcinogenesis. The results of these studies have resulted in a widely accepted “fiber pathogenicity paradigm” encompassing the characteristics of a pathogenic fiber and the general process by which it leads to tumor formation. In general, a fiber must (a) be inhaled, (b) travel through the upper respiratory tract and be deposited in the lower respiratory tract, (c) persist within the body for a significant amount of time, (d) travel to the parietal pleura, and (e) possess pro-inflammatory and genotoxic physical and chemical properties. In vitro, in vivo, and human epidemiologic studies of asbestos and other fibers have suggested that fibers with high-aspect (length-to-diameter) ratios of $>3:1$, small diameters ($0.25\text{--}0.4\text{ }\mu\text{M}$), and longer fibers with a minimum length of $5\text{ }\mu\text{M}$ (ideally, lengths of $>10\text{ }\mu\text{M}$) produce the greatest pathogenic effects [31–36]. Fibers possessing these qualities are present in significant quantities in many widely used types of asbestos and asbestiform materials, and are thought to account for the majority of fiber-related malignant pleural mesotheliomas [35, 37]. While the physical properties of fibers are thought to mediate most of their carcinogenic effects, the chemical

Table 2.1 Asbestos fiber types, carcinogenic potency, and commercial uses

Fiber	Mineralogic group	Potency	Commercial use
Chrysotile (serpentine)	Chrysotile	Low	Cement, textiles, friction products
Crocidolite (Riebeckite)	Amphibole	High	Pipe production, gas masks, cigarette filters ^a
Amosite (Cum-mingtonite/Grunerite)	Amphibole	Intermediate	Cement, textiles, insulation ^a
Anthophyllite	Amphibole	Limited data	Construction, insulation Contaminant of talc
Tremolite	Amphibole	Limited data	Contaminant of chrysotile, talc, vermiculite, diamond mines
Actinolite	Amphibole, chemically similar to tremolite	Limited data	Gemstones (jade, cat's eye); co-contaminant with tremolite

^a Historical uses only in most industrialized countries

composition of a pathogenic fiber is also contributory inasmuch as it affects fiber structure, ability to generate oxidative damage, and biopersistence.

The principal types of commercial asbestos are chrysotile, amosite, and crocidolite, also known as white, brown, and blue asbestos, respectively, based on their physical coloration (Table 2.1). Amosite and crocidolite are amphiboles, according to their mineralogic properties. Industries in which workers are most likely to be exposed to one of these forms of asbestos include mines, textile industries, and manufacturing of cement, insulation, and brakes (Table 2.2). Of these three fiber types, crocidolite is associated with the highest risk of mesothelioma development; risk of death from mesothelioma following crocidolite exposures is up to one order of magnitude higher than following amosite exposure and two orders of magnitude higher than with chrysotile exposure [38].

Chrysotile is the most commonly employed asbestos fiber, historically accounting for ~95% of total asbestos use [39]. The pathogenicity of chrysotile fibers in development of mesothelioma has been up for debate. Studies of lung tissue from Quebec miners and millers with mesothelioma have demonstrated that very-high-fiber loads of chrysotile can be oncogenic in the absence of significant concentrations of amosite or crocidolite. However, in many cases, chrysotile is accompanied by high levels of tremolite, particularly in mining and textile industries, thus the actual etiologic agent is unclear [40]. Indeed, chrysotile fibers, unlike the amphiboles, are not readily retained in the lung. Chrysotile is relatively fragile and fragments easily, permitting phagocytosis by pulmonary macrophages, and may actually dissolve in lung tissue due to leaching of magnesium out of the fiber. In contrast, amphiboles (which include tremolite) have a straight and broad structure and do not fragment readily, thus they are less susceptible to phagocytosis, and are chemically stable in a biologic environment [41].

Table 2.2 Occupations associated with pleural and peritoneal mesothelioma

Anatomic site	Occupation ^a
<i>Pleural</i>	Insulation
	Asbestos production and manufacture
	Plumbing
	Vehicle body building
	Shipbuilding/shipyard/ship repair
	Construction
	Furnace/boiler installation and repair
	Brake lining work
	Building demolition
	Production of paper products
<i>Peritoneal</i>	Insulation
	Asbestos production and manufacture
	Vehicle body building
	Construction
	Plumbing
	Cement workers
	Mining

^a Occupations are listed in order of approximate highest to lowest risk

Anthophyllite, actinolite, and tremolite are less commonly used in industrial practices in the USA, although these have been mined and used for commercial purposes in other countries and are known contaminants of other industrial minerals including talc and vermiculite. Studies in animal models have suggested that anthophyllite is carcinogenic and contributes to the development of malignant mesothelioma [42]; however, confirmed human cases of anthophyllite-attributable mesothelioma are very rare [43]. Tremolite is a contaminant of other mineral deposits, including chrysotile (see above) and vermiculite, which is used as a form of insulation and a gardening material. In addition to the epidemiologic evidence linking environmental exposure to tremolite in Turkish villages to malignant mesothelioma (see above), occupational exposure to tremolite is linked to development of disease as well. Cohort studies from Libby, Montana, the location of a large tremolite-contaminated vermiculite mine, have shown that miners, millers, and processors of vermiculite were significantly more likely to die of asbestos-related diseases, including mesothelioma, than the general population [44]. Actinolite is chemically similar to tremolite and may be found in combination with tremolite deposits, but is less common [45].

Irrespective of these different chemical and biologic properties, all of these fibers are classified together for the purposes of defining workplace regulations under the Occupational Safety and Health Administration (OSHA) [46] and are regulated under the Environmental Protection Agency’s Clean Air Act [47]. The Toxic Substances Control Act banned manufacture and importation of asbestos-containing paper products and flooring felt, as well as any nonhistorical, “new uses” of asbestos.

The Clean Air Act and Consumer Product Safety Act have banned the use of materials containing > 1 % asbestos that are sprayed on and asbestos-containing wall-patching compounds [48].

In the USA, asbestos-containing products persist in construction, clothing, and car manufacture and repair [47]. Chrysotile was used in automotive brakes until its use was banned by the Environmental Protection Agency (EPA) in the 1980s. Although OSHA cites an unspecified risk of mesothelioma among automotive mechanics, epidemiologic studies to date have failed to demonstrate an increased incidence among this group relative to background [49]. Similarly, chrysotile was ubiquitous in industrial and residential drywall products until the late 1970s; despite some reports of asbestos-related disease among individuals who used drywall-patching compounds, subsequent epidemiologic studies failed to confirm any health risks associated with using these products. A recent study of Chinese chrysotile-textile plant workers demonstrated an excess risk of lung cancer and respiratory diseases, although the small number of individuals included in the study precluded drawing any conclusions with regard to risk of mesothelioma [50].

Mesothelioma and Non-Asbestos Fibers

Almost all studies concerning non-asbestos fibers as etiologic agents in malignant pleural mesothelioma are based on the assumption that any natural or man-made fiber that fits the “fiber pathogenicity paradigm” (see above) has carcinogenic potential in humans (Table 2.3).

Biogenic Silicates in Plant Fibers

The presence of silica and silicates in asbestiform fibers and the observation of increased lung cancer and mesothelioma risk in Louisiana and Indian sugarcane farmers with no known asbestos exposure led to an investigation of silica fibers in sugarcane [51, 52]. Certain plants have been shown to absorb and accumulate environmental silica, yielding, according to Newman et al., needle-shaped biogenic crystals of approximately 0.85 μm in diameter and 10–300 μm in length [51]. Although additional epidemiologic studies of farming-related fiber exposure have not been performed, the theoretical risk of mesothelioma associated with biogenic silica crystals has been proposed based on their physical similarity to asbestos fibers.

Erionite

Erionite is a naturally occurring non-asbestos fiber. Records of mesothelioma “epidemics” in small villages of central Anatolia in Turkey, where mesothelioma

Table 2.3 Strength of evidence for increased risk of mesothelioma in non-asbestos exposures

Agent	Mode of exposure	Strength of evidence
Radiation	Iatrogenic	Strong
SV40 Infection	Contaminated polio vaccines	Insufficient
Natural fibres		
Erionite	Environmental/building material	Strong
Fluoro-edenite	Environmental	Limited
Plant-derived silicates	Occupational	Insufficient
Man-made fibres		
Glass wool ^a	Insulation	Insufficient
Continuous glass filaments ^a	Textiles, plastics	Insufficient
Rock and slag wool ^a	Thermal and acoustic insulation	Insufficient
Refractory ceramic fibers ^a	High-temperature insulation	Insufficient
P-aramids	Insulation, automotive products	Insufficient
Carbon nanotubes	Occupational	None

^a Based on conclusions made by the International Agency for Research on Cancer (IARC) Monographs Working Groups in 2001

accounts for up to 50% of mortality, began to surface in 1975 and 1978. Examination of rock and dust samples from the area in 1979 demonstrated the presence of erionite fibers <0.25 μM in diameter and up to 5 μM in length, and spurred continued study of the natural fibers and epidemiology of mesothelioma in the region. Baris et al. conducted a survey of the Anatolian villages of Karain, Karlik, and Sarihidir in 1987, demonstrating that respirable erionite fibers composed 20–80% of dust clouds in the village streets and that higher levels of exposure correlated with increased mortality from mesothelioma [53]. In vitro and in vivo inhalational studies in rodents have confirmed the potent carcinogenicity of erionite, which has been listed as a group I known human carcinogen by the International Agency for Research on Cancer (IARC) working group [54–56]. Environmental studies in the USA have identified naturally occurring erionite in North Dakota, South Dakota, Nevada, Oregon, and other areas of the western USA, and have demonstrated physical similarities between the erionite fibers present in those locations and those known to cause mesothelioma in Turkey [56, 57]. One small published series demonstrated radiologic changes in erionite-exposed North Dakota residents similar to those seen in asbestos-exposed individuals [57], and a single case report of erionite-associated mesothelioma in the USA [58]; however, more epidemiologic studies will be necessary to determine the erionite-associated cancer burden in the USA.

Other Natural Fibers

Exposure to fluoro-edenite, another natural fibrous amphibole first detected in eastern Sicily, has been shown to correlate with the risk of mesothelioma in patients with no known asbestos exposure in one small case series [59].

Synthetic Fibers

Synthetic organic and inorganic fibers have been produced in greater quantities worldwide as a response to increased regulation of asbestos, and are used in a variety of industrial and domestic products. Inhalational studies in animals have revealed sufficient evidence to suggest that special-purpose glass fibers and refractory ceramic fibers have significant carcinogenic potential, but only limited evidence of carcinogenicity pertaining to other inorganic fibers [60]. There is some evidence of dose-dependent radiographic pleural and interstitial changes in populations exposed to inorganic synthetic fibers, usually occurring 15–20 years after exposure, but these results are frequently confounded by asbestos and smoking exposure, and limited by small numbers of patients. Overall, epidemiologic studies of workers exposed to inorganic man-made fibers have not shown significant increases in mortality due to pleural malignancy in comparison with unexposed populations [60–62].

P-aramids, a type of organic man-made fiber used in heat-resistant fabrics, ropes, cables, brake pads, and other products, have been studied in animals and shown to have mild pro-inflammatory, pro-fibrotic, and proliferative effects on the pleura, but have not been shown to cause mesothelioma [37]. No human cases of malignant or nonmalignant disease have been documented as a result of p-aramid exposure.

Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical or bundle-like man-made carbon structures with properties that potentially fit the fiber pathogenicity paradigm [35, 36]. Animal studies have demonstrated that intraperitoneal, intratracheal, and inhalational exposure to CNTs results in increased inflammation and fibrosis [35, 63, 64]. Consistent with the fiber pathogenicity paradigm, long CNTs appear to be more pathogenic than short CNTs. Mesothelioma has been reported in *Trp53* heterozygous mice and in wild-type mice following peritoneal and scrotal injection with CNTs [64], but additional studies will be necessary to draw definitive conclusions about the risk of mesothelioma in CNT-exposed animals and humans. No documented cases of mesothelioma in humans exposed to CNTs currently exist.

Malignant Pleural Mesothelioma and Simian Virus 40

Simian virus 40 (SV40) is a virus of Asian macaques generally thought not to be infective in humans unless artificially introduced. Large-scale human exposure to SV40 occurred between 1956 and 1966 in areas of Europe, Great Britain, and the USA as a result of widely-distributed contaminated polio vaccines grown in monkey renal-cell cultures. Approximately 10–15% of selected populations who were not exposed to the contaminated vaccine are reported to be seropositive for SV40,

<http://www.springer.com/978-1-4939-2373-1>

Diffuse Malignant Mesothelioma

Allen, T.C. (Ed.)

2015, XI, 142 p. 56 illus., 46 illus. in color., Hardcover

ISBN: 978-1-4939-2373-1