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A. Introduction

Malignant pericardial mesothelioma is an extremely rare but rapidly fatal cancer arising from the mesothelial surface of the pericardium, a thin serosal membrane surrounding the heart. Pericardial mesotheliomas account for less than 1% of all mesothelioma cases in most case series (Cao et al. 2017), citing Van De Water and Allen, 1967: See also International Mesothelioma Panel, 2006. In one large autopsy study, the incidence of primary pericardial mesothelioma was shown to be less than 0.0022% among 500,000 cases. (Eren et al. 2002). The mean age at presentation is approximately 46 years and the male to female ratio is approximately 2:1. (Barraso et al. 2017).

B. Incidence

The superb review article by Mezei, Chang, Mowat, Moolgavkar, 2017 provides information on the incidence of pericardial mesothelioma in the United States based upon an analysis of the U.S. Surveillance, Epidemiology and End Results Cancer Registry Data (SEER) maintained by the National Cancer Institute. According to their analysis of the SEER nine registries, the incidence in the United States is approximately 0.11 per 10 million person years for the years 2003-2013. As with the vast majority of cancers, the incidence of pericardial mesothelioma increases with age, with Mezei et al. 2017 reporting that the incidence rate among those age 50 years or above is approximately three times the rate among those below the age of 50. Id. at 351.

In a much earlier Canadian epidemiological survey, McDonald and McDonald calculated an annual incidence of 1 in 40 million for pericardial mesothelioma. McDonald, A.D. et al., "Epidemiology of Primary Malignant Mesothelial Tumors in Canada," Cancer 26:914-919, 1970. According to the International Mesothelioma Panel, the incidence of pericardial and testicular mesothelioma is less than 1% of diffuse malignant mesotheliomas.

A study on data on extrapleural malignant mesothelioma from the Italian National Mesothelioma Registry reported by Marinaccio et al. in 2010 reported a similar percentage with pleural mesotheliomas representing 92.6% of all malignant mesothelioma cases, peritoneal - 6.7%, pericardial - 0.4% and testicular - 0.3%.

A recent case series in Japan identified 105 diffuse malignant mesotheliomas diagnosed between January 2005 and December 2007 in the Rosai Group and related facilities. Among them, 94 (89.5%) originated in the pleura, 7 (6.7%) in the peritoneum, 2 (1.9%) in the pericardium, and 1 (.09%) in the tunica vaginalis testis. Fujimoto et al. 2010 at p. 1755.

In the Annual of the Pathological Autopsy cases in Japan issued by the Japanese Society of Pathology from 1958 to 1996, a total of 1,846 malignant mesothelioma cases were registered - 1,213 pleural mesotheliomas (68%), 431 peritoneal (24.1%), 108 pericardial (6.1%) and 6 tunica vaginalis testis (0.3%) and 28 "others" (1.6%). Murai, 2001. This is a significantly higher percentage than in other autopsy series. However, the annuals of the pathological autopsy cases in Japan issued by the Japanese Society of Pathology is a passive system for "the recording of autopsy reports received from individual pathologists; no confirmatory reviews are provided. Tissue slides are not sent in an archive." This may result in an over diagnosis of pericardial
mesothelioma since a significant percentage of pleural mesotheliomas spread to the pericardial surface. On the other hand, in death registries in the United States there are a significant number of mesothelioma cases which are unclassified. It's certainly possible that some of those cases are in fact pericardial mesotheliomas. A significant percentage of pleural mesotheliomas will spread to the pericardium making the task of differentiating the site of origin extremely difficult.

In an analysis of the cases of deaths worldwide from pericardial mesothelioma in the WHO database for the years 1994-2008, Delgermaa et al. identified 298 cases of pericardial mesothelioma representing .3% of deaths from malignant mesothelioma. The calculated age adjusted mortality rate was 0.03 per million for pericardial mesothelioma versus 2.3 per million and 0.3 for mesothelioma of the peritoneum.

C. State-of-the-Art

There have been scattered case reports of what is now believed to be pericardial mesothelioma throughout the 20th century. Mezei et al. (2017) indicated "the earliest report of tumors in the pericardium is attributed to Marchiafava in the mid-1870s." [citing McDonald, "Primary Endothelioma of the pericardium," Journal of Pathology Bacteriology 43:137-41 (1936). Here are some of the "highlights" as reported in the medical and scientific literature:

**Dawe et al. 1953** - The authors reported on a case of a 25 year old Marine with pericardial mesothelioma. They included a review of the literature and identified 6 epithelial, 13 spindle cell type and 5 mixed pericardial mesotheliomas from their review of the literature.

**Sylman and MacAlpin, 1971** - This is the first reference to asbestos we could identify in any of the case reports, and it was negative ("there is no association of pericardial mesothelioma with asbestosis in contra-distinction to the high correlation of asbestosis with pleural and peritoneal mesothelioma." (p. 768)

**Uys et al., 1972** - A Clinico Pathologic Conference where the participants ultimately diagnosed a 46-year old female with pericardial mesothelioma. This is the first reference to looking for asbestos bodies, and in this instance, none were found. The authors indicated that she was a "nursing sister from the UK."

**Steinberg, 1972** - This case report involved a 40-year old female pericardial mesothelioma. The author noted "there was no evidence of asbestos bodies in the lungs by routine microscopy or by examination of ashed pulmonary tissue." This is the first indication found in the medical literature where a fiber digestion was performed in a case of pericardial mesothelioma.

**Anderson and Hansen, 1974** - Anderson et al. is a review of the literature, and the authors excluded a number of cases which they believe did not meet the strict criteria for a mesothelioma of pericardial origin. They noted that "pericardial mesothelioma is a rare tumor of unknown etiology - thus there is no information of synchronous asbestosis."

**Becklake, 1976** - This is a very important state-of-the-art review article published in the American Review of Respiratory Disease in 1976 by Margaret Becklake, a professor of epidemiology at McGill University in Montreal, Quebec. It is a very influential article and it has
been cited on numerous occasions in subsequent medical and scientific literature. Table 1 contains a list of organs affected by asbestos and it includes mesothelioma of the pleura and peritoneum. For both pleural and peritoneal mesothelioma, it notes that the association with asbestos exposure is "established", but defines "established" for this purpose as "association" not "cause, established." Pericardial is not included. Dr. Becklake specifically noted at page 212 of the review that "mesothelial tumors arising in the pericardium have not been linked to asbestos."

**McDonald et al., 1977** - In 1977, Drs. J.C. and Allison McDonald published a study on the epidemiology of mesothelioma from estimated incidence in Canada and the United States, respectively. They gathered and reported on Canadian statistics on the incidence of mesothelioma from 1960 until 1972 noting that there were 312 reported mesotheliomas but only 5 were pericardial. For the United States, they had information only for the calendar year 1972 and reported that only 4 of 245 cases of mesothelioma were pericardial. The 5 Canadian cases included 1 male and 4 females whereas the U.S. cases involved 2 males and 2 females.

**Churg et al., 1978** - This was a case of pericardial mesothelioma in a 61-year old male former painter. The patient developed pericardial mesothelioma in 1972 after having undergone a pericardiopexy in 1957 for angina. "The surgical procedure consisted of opening the pericardial sac, scarifying the epicardium, and dusting 0.3 g of asbestos over the epicardial surface! (p. 419). This was no information in the history as to the type of asbestos applied, but a fiber digestion of pericardial tissue revealed the presence of anthophyllite, tremolite, and fiberglass (which was also previously applied directly on to the pericardial surface).

Amazingly, this procedure was fairly standard in the 1950s and early to mid-1960s. It was often referred to as the "Beck operation" after the surgeon who invented the procedure. See generally, Beck et al., "Operations for coronary artery disease," *JAMA* 156:1226-33 (1954).

**Antman, 1980** - Dr. Karen Antman was a very influential oncologist who at this time was affiliated with Harvard Medical School and the Sydney Farber Cancer Institute in Boston, Massachusetts. She wrote a very influential review article on malignant mesothelioma which was published in the New England Journal of Medicine in July, 1980. She included only a brief reference to pericardial mesothelioma noting that "patients with pericardial mesothelioma present with congestive heart failure, pericardial effusions, atrial arrhythmias, or cardiac tamponade. Pleural effusions are also present in approximately one-third of the cases." (p. 201). She then reported that "no association between pericardial mesothelioma and asbestos exposure has been reported." (Ibid).

**Kahn, Rohl, Barrett and Suzuki, 1980** - The authors reported on a 60-year old white male with a history of asbestos exposure while working in the shipyards during World War II, 30 years prior to his pericardial mesothelioma diagnosis. (p. 270). The authors found this case provided strong evidence for an asbestos-induced mesothelioma arising in the pericardium based on his prior exposure and the presence of ferruginous bodies in the lungs, proven to contain amosite by electron microscope analysis (pgs. 277-278). Consequently, this is the first case report where above background levels of asbestos bodies or asbestos fibers were found in the lung tissue of someone diagnosed with pericardial mesothelioma. However, the authors noted:
"An increased incidence of malignancies after exposure to asbestos has been well-established. Mesothelioma of the pleura, peritoneum, carcinoma of the lung, larynx, gastrointestinal tract and possibly of the ovary have been described, as well as cases with multiple primary tumors. On the other hand, an association of asbestos exposure with primary pericardial mesothelioma has not been reported. This paper described the first case in which such a relationship existed." (p. 270).

While the asbestos causation in this case, they also noted that "the etiology of pericardial mesothelioma is unknown." They also stated that "it remains unclear while primary pericardial mesothelioma associated with asbestos exposure has never been described. Individual factors, such as drainage, preferential lymphatic flow, and individual biological susceptibility, may play a role." (p. 280).

Mirabella, 1982 - While this is in Italian, unfortunately, there is a fairly short English summary which noted that "A review of 206 cases of primary malignant pericardial mesothelioma reported in world medical literature during the period 1875-1978 is presented. The diagnosis (always histologically proved) was made in 165 cases (80%) at autopsy and 25 cases (12.2%) by biopsy after thoracotomy; the diagnosis was described as histopathological in the remaining cases (7.8%)." Among others, the authors suggested based on their review that "pericardial mesothelioma tends to develop at a rather young age" and "possible relation between exposure to asbestos and the development of pericardial mesothelioma". (p. 215).

Vogelzang et al. 1984 - This is a review of experience at the University of Minnesota with malignant mesothelioma from 1950 to 1981. During that time they recorded 31 mesothelioma cases - 28 of which were diffuse malignant mesothelioma, and 3 which were localized. Of the 28 diffuse malignant mesothelioma, 20 were pleural, 6 were peritoneal and only 2 were pericardial. Both pericardial mesotheliomas were diagnosed in female housewives (ages 36 and 70) with "no asbestos exposure."

Fraker et al. 1984 - This is another interesting case report of someone who had undergone pericardial abrasion for relief of chest pain with sprinkling of powdered asbestos into the epicardium at age 59 in 1961. At age 81, he was diagnosed with constrictive pericarditis, which is a thickening of the pericardial tissues surrounding the heart similar to diffuse pleural thickening, thought to be the result of the asbestos implanted onto the epicardium.

Llewellyn et al. 1987 - The authors reported that "There has been no clear association between asbestos exposure and pericardial mesothelioma. This is probably because the paucity of recorded cases has not allowed an adequate epidemiological study." (p. 47)

Weg, 1998 - This is yet another case involving someone who underwent the "Beck" operations where there was installation of asbestos into the pericardial sac in an attempt to develop collateral blood flow to the heart. "This procedure attained some popularity in the 1950s and early 1960s, before coronary artery bypass attained were perfected." (p. 522).

D. Epidemiology/Case Reports

Given the rarity of pericardial mesothelioma, there are no epidemiological studies (case control or cohort). However, 200 plus case reports/case series have been published in the peer-
review medical literature. Appendix A contains a brief summary of each of these reports as well as review articles and book chapters relevant to pericardial mesothelioma. However, if the case report appeared in a foreign journal with no English translation, it was not included.

Dr. Suresh Moolgavkar and colleagues at Exponent recently published an outstanding review on the epidemiology of both mesothelioma of the pericardium and tunica vaginalis testis in the Annals of Epidemiology. Based upon their exhaustive review of all the available literature, "Of the 251 case reports identified, the authors considered potential exposure to asbestos for 109 cases with 33 (30%) of these having some potential, suspected, or confirmed exposure to asbestos, although few details were provided." (Mezei et al., 2017 at p. 351).

"Most of the case reports included patients from Europe (39%), followed by Asia (37%), and North America (22%). Of the reported cases, about two thirds (69%) were male, with a mean reported age of 47 years among males (range 20 months to 85 years) and 50 years among females. (range 19 to 76 years)." (Mezei et al., 2017 at p. 350)

E. Reviews Published in the Peer Reviewed Medical Literature

Dawe et al. 1953; Anderson and Hansen, 1974; Hillerdal, 1983; Thomason et al. 1994; Nilsson, 2009; Eren and Akar, 2002; Hassan and Alexander, 2005; Marinaccio et al., 2010; Mensi et al. 2011; Restrepo et al., 2013; Cao et al. 2016, and Mezei et al. 2017. All of these are summarized in Appendix A, and a number of them are included in the useful quotes section (G). Both Thomason et al. 1994 and Nilsson and Rasmuson, 2009 have been quite influential, having being cited frequently since their publication. Both also included a summary of case series with Thomason et al. identifying asbestos exposure in only 4 of 12 cases of pericardial mesothelioma, and Nilsson and Rasmuson identifying asbestos exposure in only 3 of 14 cases. The Cao et al. 2016 review is particularly helpful as a general review, including diagnostic issues. By far, the most exhaustive review is the more recent systematic review by Mezei, Chang, Mowat and Moolgavkar published in 2017. With the authors' permission, included as Appendix B is Table S1 which provides an excellent summary in chart form of case series and literature reviews of malignant mesothelioma of the pericardium.

F. Textbook Discussions of Pericardial Mesothelioma

There have been a number of text books which have discussed in varying detail pericardial mesothelioma. Here is a list of some of them. Summaries of the discussion and nature of these textbooks can be found in Appendix A:


Burke, A., Loire and Virmani, "Pericardial Tumours," William D. Travis, Brambilla, Muller-Hermelink and Harris, Editors World Health Organization Classification of Tumors -


Andrew Churg, Philip Cagel and Victor Roggli, AFIP Atlas of Tumor Pathology - Tumors of Serosal Membranes, p. 61 AFIP 2006


Moolgavkar, S.H., Chang, Mezei and Mowat, "Chapter 3 - Epidemiology of Mesothelioma," Joseph R. Testa, Editor, Asbestos and Mesothelioma, Springer pgs. 54-56, 2017


G. Useful Quotes to Use in Direct and Cross Examination of Experts as well as Opening and Closings

Sytman and MacAlpin, 1971

"There is no association of pericardial mesothelioma with asbestosis in contrast to the high correlation of asbestosis with pleural and peritoneal mesothelioma." (p. 768).
Fezekas et al. 1992

"In the etiology of pleural and peritoneal mesotheliomas, the role of exposure to asbestos has been demonstrated unambiguously, but the same cannot be said for the form originating from the pericardium."

Kaul et al. 1994

"Unlike pleural and peritoneal mesothelioma there has been no definite correlation between asbestos exposure and the development of pericardial mesothelioma, although most of the previous reports have shown no association between asbestos exposure and the development of pericardial mesothelioma." (p. 264).

Thomason et al. 1994

"The role of asbestos exposure as a causative factor in the development of pericardial mesothelioma is not certain, but asbestos exposure has been documented in a few patients."

Stein et al. 1995

"Primary pericardial mesothelioma is a rare malignancy, with an incidence of less than 0.0022% in major series. It is more rare than pleural mesothelioma and has no etiological connection with asbestos exposure." (p. 192).

Oreopoulos et al. 1999

"Several cases of primary peritoneal mesothelioma with previous asbestos exposure have been identified, but this relationship does not appear to be as obvious as it is for pleural or peritoneal mesothelioma." (p. 1371).

Griffin et al. 1999

"Primary malignant mesothelioma accounts for 4% of all primary cardiac tumors, and unlike pleural mesothelioma, has not been linked to asbestos exposure." (p. 421).

Quinn et al. 2000

"The etiology [pericardial mesothelioma] is unknown, although other extra-pleural mesotheliomas had been linked to therapeutic radiation." (p. 1927).

Vigneswaran and Stefanacci, 2000

"Although a definitive link [between pericardial mesotheliomas] and asbestos is lacking, there are some cases in which this association is reported." (p. 300).
Watanabe et al. 2000

"Unlike pleural and peritoneal mesothelioma, no definite correlation between a previous exposure to asbestos and the development of pericardial mesothelioma has been established. It is known that a mesothelioma can also be produced by therapeutic radiation exposure." (p. 387).

Eren, Akar, 2002

"Many epidemiological surveys have revealed prior exposure to asbestos in approximately 70 to 80% of all patients with pleural and peritoneal mesotheliomas. However, no definite correlation has been established between exposure to asbestos and the development of pericardial mesothelioma." (p. 370).

"The etiology of pericardial mesothelioma is unknown." (p. 369).

Val-Bernal et al. 2002

"The role of asbestos exposure as a causative factor in the development of pericardial mesothelioma is not well-established. Asbestos exposure has been documented only in 14% of the patients [citing Thomason, 1994]. This suggests that additional carcinogens may operate." (p. 184).

Fujiwara et al. 2005

"Unlike pleural or peritoneal mesotheliomas, no definite association between previous exposure to asbestos and the development of this tumor has been established." (p. 349).

Lagrotteria et al. 2005

"The etiology of primary malignant pericardial mesothelioma remains unclear. Unlike pleural or peritoneal mesothelioma, there has been no definite correlation between asbestos exposure and pericardial disease. There have been some documented cases of PMPM with a known history of asbestos exposure; however, the majority of reported cases have shown no association." (p. 187).

Papi et al. 2005

"Exposure to asbestos is correlated with the onset of pleural and peritoneal mesothelioma; however, the role of asbestos in pericardial mesothelioma is unclear." (p. 279).

Pasquotti et al. 2005

"Contrary to pleural and peritoneal mesothelioma, it is suggested that this condition does not show a clear correlation to exposure to asbestos, despite some
of the data reported in the literature; it can also be produced by therapeutic radiation exposure." (p. 755-756).

Vornicu et al. 2007

"Unlike pleural mesotheliomas, there is no clear association between asbestos exposure and the development of pericardial mesothelioma." (p. 576).

Small et al. 2008

"No definite association with asbestos exposure has been described." (p. 746).

Nilsson and Rasmuson, 2009

"No obvious relationship between asbestos exposure and the development of pericardial mesothelioma has been established." (p. 127).

Reardon et al. 2010

"Pleural and peritoneal mesothelioma development has been correlated with exposure to asbestos; however, the role of asbestos in pericardial mesothelioma is unclear." (p. 152).

Yildirim et al. 2010

"Although a relationship has been established with exposure to asbestos in pleural and peritoneal mesothelioma, the role of asbestos is not definite in malignant pericardial mesothelioma." (p. 303).

Nicolini et al. 2011

"The role of asbestos exposure [in primary mesotheliomas of the pericardium] is not clear although it has been documented in a few patients." (p. 2.).

Patel and Sheppard, 2011

"The etiology of primary malignant mesothelioma of the pericardium remains unclear. Unlike peritoneal mesothelioma and pleural mesothelioma, there has been no definite correlation between asbestos exposure and pericardial disease, as in our case." (pp. 108-109)

Sharma and Katechis, 2011

"There is a possible association with asbestos exposure, but this is seen only in cases with co-existent asbestos-related pleural disease." (p. 3).

Feng et al. 2012

"Although there is a strong association between asbestos exposure and pleural mesothelioma, this association is still controversial in pericardial mesothelioma." (p. 69).
Kayatta et al. 2013
"The association between asbestos and pericardial mesothelioma has not been well-established, partly due to the small number of reported patients." (p. 1).

Makarawate et al. 2013
"Unlike pleural mesothelioma, the relationship between asbestos and this lethal tumor is unclear." (p. 2).

Restrepo et al. 2013
"Unlike pleural mesothelioma, which has a proved association with asbestos exposure, the association of pericardial mesothelioma with asbestos is still controversial." (p. 1622).

Fernandes et al. 2014
"Although malignant mesothelioma of the pleural cavity is classically associated with asbestos exposure, no such link has been established between this exposure and PPM." (p. 4).

Gong et al. 2014
"No obvious relationship between asbestos exposure and the development of pericardial mesothelioma has been established." (p. e274).

Ramachandran et al. 2014
"Exposure to asbestosis correlated with the onset of pleural and peritoneal mesothelioma; however, the role of asbestos in pericardial mesothelioma is unclear." (p. 1).

Zatikyan et al. 2014
"The role of asbestos exposure in PPM remains unclear." (p. 1).

Isoda et al. 2015
"The cause of PPM remains unknown, unlike that of pleural mesothelioma." (p. 3).

Roggli 2015 (WHO)
"The link between pericardial mesothelioma and asbestos exposure is weak." (p. 345).

Sivirkoz et al. 2016
"The cause of this rare tumor is unknown."
Kurosawa et al. 2016

"Unlike pleural and peritoneal mesothelioma, the association between exposure to asbestos and PMPM remains controversial." (p. 553).

Lowry and Weiss, 2016

"The results of this ecologic study do not support a role for asbestos exposure in the etiologies of either pericardial or paratesticular mesotheliomas." (p. 1487).

Cao et al. 2017

"Unlike malignant pleural and peritoneal mesothelioma, the role of asbestos exposure in the pathogenesis of MPM is controversial and no clear correlation has been established." (p. 1).

Mezei, Chang, Mowat and Moolgavkar, 2017

"For pericardial mesothelioma and mTDT the available evidence is not sufficient to suggest even an association, let alone a causal relationship, between inhaled asbestos exposure and development of these diseases." (p. 355).

"In large cohorts studies of workers in varies industries with potential asbestos exposure, no pericardial mesotheliomas were reported (e.g., cohorts included in Berman and Crump, 2008; Hodgson and Darnton, 2000; Yarborough, 2006)." (p. 351).

"Overall, for both pericardial mesothelioma and mTDT, no clear differences in incidence patterns were evident by sex (relevant for pericardial mesothelioma only), ethnicity, year of diagnosis, or geographic region using SEER data, although statistical power was limited to detect any differences." (p. 355).

"In our evaluation of SEER data, the incidence trends for pericardial mesothelioma and mTDT did not correspond with sufficient latency. Taking into account trends in commercial asbestos use in the United States, which would be expected if pericardial mesothelioma or mTDT were causally associated with exposure to asbestos. For pleural mesothelioma, among males, on the other hand, the SEER data showed that trends in rates reflect trends in the commercial use of asbestos in the United States with an appropriate 30-year leg." [cites omitted]. In addition, for pericardial mesothelioma, the number of cases in the SEER registries are almost identical for males and females with similar population sizes, suggesting that occupational exposures to asbestos have played only a small role,
if at all, in the development of this malignancy. If occupational exposure to asbestos were an important determinant of risk, one would expect the incidence rate among men to be considerably higher than that among women, as is the case for pleural mesothelioma and, to a lesser extent, for peritoneal mesothelioma." (p. 355).

"In large occupational cohorts with heavy exposures to asbestos, no cases of pericardial mesothelioma or mTVT, have been reported." (p. 356).

"The lack of temporal trends in incidence of pericardial mesothelioma or mTVT that would correspond with due consideration of sufficient induction time, two historical trends of commercial asbestos use, and the lack of differences in incidence rates of pericardial mesothelioma among men and women, argue against the etiologic role of inhalation asbestos exposure in the development of these rare forms of extrapleural mesotheliomas." (p. 356).

**Moolgavkar et al., 2017**

“In conclusion, epidemiologic studies show that there is a site-specific gradient in the mesothelioma risk associated with inhalation exposure to asbestos. Pleural mesothelioma is most strongly associated with asbestos exposure. Peritoneal mesothelioma is less strongly associated with asbestos exposure, and when it is, it is associated with high exposure to amphibole asbestos. There is no evidence that mesothelioma of the pericardium and the TDT are associated with inhalation exposure to asbestos, a conclusion that is supported by a recent analysis of SEER (Lowry and Weiss, 2016).” (p. 5).

**Muta et al., 2017**

"Regarding the etiology of malignant mesothelioma, exposure to asbestos is associated with pleural and peritoneal mesothelioma. However, the link between pericardial mesothelioma and asbestos exposure is obscure." (p. 3)

**H. Diagnosis of Pericardial Mesothelioma**

Pericardial mesothelioma is a diagnostic challenge, particularly prior to death. It is estimated that only approximately 30% of cases are diagnosed prior to death. Cao et al. 2016 [citing Vigneswaran et al. 2000] The symptoms are not specific, and include shortness of breath, chest pain, pericardial effusion (fluid in the pericardial space), constrictive pericarditis (fibrotic thickening of the pericardium usually caused by chronic inflammation, but in this case, by the neoplasm), potentially leading to congestive heart failure, atrial or ventricular arrhythmias and cardiac tamponade (compression of the heart caused by pericardial effusions and thickening). See generally Pavlisko et al. 2017; Griffin et al. 1999.

One of the major diagnostic challenges is the rarity of pericardial mesothelioma. Only a few clinicians will see a case of malignant pericardial mesothelioma in their careers. (Cao, 2017). Moreover, only a small fraction of constrictive pericarditis cases represent a primary pericardial mesothelioma. For instance, in a case series in Great Britain of 25 patients with
constrictive pericarditis, the etiology was determined to be: 10 patients - idiopathic; 5 post-viral; 3- tuberculosis; 2-renal failure; 1-malignancy; 1-radiotherapy; and 3-post surgery. (Marshall et al. 2006). Cao, 2017 summed up the difficulties of the differential diagnosis as follows:

"Pericardium involvement can occur in three conditions. Firstly, malignancies can originate in the pericardium. In addition, malignant tumors can infiltrate the pericardium by direct extension, either via a primary site or regional nodes. Finally, the pericardium can be the hematogenous metastasis site, of which the most common are breast, melanoma, and lung cancer. MPM can be misdiagnosed as tuberculous pericarditis, coronary artery disease, cardiomyopathy, pericardial metastatic tumors, and adenocarcinoma. [citing Gong, 2014]. Reasons leading to misdiagnosis are: 1) it is so rare that not enough attention is paid to it and only a few doctors will see a case in the careers; 2) the non-specific manifestations and non-contributory radiological findings make it easily misdiagnosed as other diseases; 3) symptoms can be relieved by cardiac therapy, diuretics, and pericardiocentesis, which may mask the real condition of the disease; 4) pericardial biopsy is relatively hard to achieve and pericardial effusion cytology has a low positive rate." Cao, 2017 at p. 4

Fincher in a review of the medical literature from 1935 to 1991, identified 90 cases of malignant pericardial effusion as the initial complication of cancer. The locations of the underlying malignancies giving rise to these effusions were in descending order or incidence: lung, gastrointestinal tract, unknown origin, breast, kidney, lymphoma, and leukemia. Fincher et al. 1993. In a series of 8 patients who underwent pericardiectomy for constrictive pericarditis that developed secondary to neoplastic disease, 5 (62.5%) were diagnosed with lung cancer, 2 (25%) with malignant pleural mesothelioma and 1 (12.5%) with Hodgkin's lymphoma. (Buyukbayrak et al. 2014).

It can also be difficult to distinguish a primary pleural mesothelioma from a primary pericardial mesothelioma as pleural mesotheliomas can extend into the pericardium and cause symptoms identical to those caused by pericardial mesothelioma. Assessment of the entire clinical picture as well as pathology is essential in distinguishing primary pleural from pericardial mesotheliomas. Among 33 patients who had been exposed to asbestos in one study, 15 (45.5%) had pericardial involvement seen on echocardiography:

"Pathological involvement of the heart commonly occurs in patients with malignant pleural mesothelioma. Pericardial thickening is one of the most common forms of cardiac involvement." (Ozer et al. 2000 at p. 335).

Regarding the pathological diagnosis of pericardial mesothelioma, it is rarely diagnosed on cytology, as cytology is often negative. Nilsson et al. found only 4 of 17 cases (23%) cases of pericardial mesothelioma undergoing cytological examination were found to be malignant. (Nilsson et al. 2009).

As in the case of pleural and peritoneal mesothelioma, malignant pericardial mesothelioma can be classified into three major types: "epithelial, sarcomatoid, and biphasic." Some authors believe epithelial is the most commonly seen but others describe biphasic as the
most common feature. As in the case of pleural mesothelioma, immunohistochemistry plays an essential role after a diagnosis, and the immuno markers utilized in the diagnosis of pleural mesothelioma are the same as those for pericardial mesothelioma. See generally Roggli, 2015 and Cao, 2017. After confirming you are dealing with a malignancy, the main differential diagnosis is metastatic carcinoma, particularly, lung adenocarcinoma, although both angiosarcomas and synovial carcinomas may mimic pericardial mesothelioma as well. (Roggli, 2015).

It may be impossible to distinguish the two if there is extensive metabolic activity via PET scan in both the pleura and pericardium. However, if the symptoms largely consist of constrictive pericarditis, pericardial effusion and there is little or no evidence of malignancy in the pleura, it is much more likely to be a primary pericardial then pleural mesothelioma.

I. Constrictive Pericarditis Associated with Asbestos Exposure/History

The non-malignant condition of constrictive pericarditis potentially associated with asbestos exposure is beyond the scope of this outline. However, that literature may be relied upon by plaintiffs' expert in arguing that asbestos must make its way to the pericardium even in the absence of positive asbestos body or asbestos fiber identification. See Section O for a brief discussion of defense response. The following articles identify constrictive pericarditis and its possible association with asbestos exposure. There is a summary of each of these articles in Appendix A: Al Jarad, 1993; Fischbein et al., 1988; Pope et al., 1989; Davies et al., 1991; Cordioli, 1994; Trogrlic et al., 1997; Roggeri et al., 2003; Lin et al., 2012; Khatri, 2012.

J. Unusual Variants of Primary Pericardial Mesothelioma

There are case reports of several extremely rare and unusual variants of pericardial mesothelioma, including deciduoid mesothelioma of the pericardium (Reis-Filho, 2002) (asbestos not an etiologic factor), localized epithelial mesothelioma of the pericardium (Shimazaki, 2000); Akamoto et al. 2008; Yang et al. 2009; Cao et al. 2017. There have also been at least two case reports of pericardial multicystic mesothelioma. See generally Drut, 1999 (pericardial multicystic mesothelioma in a 7-year old boy with Down's syndrome); Morita et al. 2011 (63-year old male with multicystic mesothelioma of the pericardium extending into the pleura). These cases are quite unusual since multicystic mesothelioma is such a rare variant, and is usually localized to the pelvic peritoneal surface with female predominance. See generally Churg, Cagle and Roggli, 2006.

K. Fiber Burden Analysis

Several studies have included an evaluation of either asbestos fiber or asbestos body content in the lungs and/or pericardium. However, the only study reporting the presence of asbestos fibers in the pericardium was the Churg et al. 1978 case report where asbestos fibers where applied directly to the pericardium 15 years before the diagnosis of pericardial mesothelioma in an attempt to resolve intractable angina after heart surgery.

1) The following studies reported either no asbestos bodies or within background asbestos/asbestos fiber content from examination of lung tissue:
Hirano et al. 2002 (no asbestos bodies found in lung tissue)

Steinberg, 1972 (44-year old male - "There was no evidence of asbestos bodies in the lungs by routine microscopy or by examination of ashed pulmonary tissue." p. 819.

Uys et al. 1972 (A case presentation at clinical pathological conference - 46 year old female - looked for asbestos bodies and found none in the lungs)

Feng et al. 2012 (An electrician who denied asbestos exposure - lung asbestos body digestion performed - showed high normal amount of asbestos bodies in dissected lung tissue).

2) The following studies found either no asbestos bodies, or asbestos fibers or within background levels of asbestos or asbestos fibers in the lung and pericardium:

Tateishi et al. 2013 (61-year old woman who denied asbestos exposure - "no pleural or pericardial plaques or asbestos bodies were observed.")

Ashinuma et al. 2015 (no asbestos bodies observed).

Horie et al. 2010 (85-year old male retired school teacher without asbestos exposure history - asbestos bodies not observed).

Watanabe et al. 1999 (27-year old male with no asbestos exposure - asbestos bodies were not detected in the lung, the pleura, or the pericardium even with careful examination of multiple sections. p. 659).

Morita et al. 2011 ("No asbestos body was found with iron staining in the lungs, pleura, peritoneum and other organs." p. 321).

Kurowawa et al. 2016 (37-year old female without a history of asbestos exposure - no evidence of the presence of asbestos bodies on histological examination at autopsy”).

Saisho et al. 2016 (67-year old Japanese male with no asbestos exposure history - "no asbestos bodies were evident in tissue samples of the pericardium and pleural nodule”).

3) There have been a few studies which have reported positive findings for asbestos bodies/elevated asbestos levels in lung tissue:

Rizzardi et al. 2010 (patient lived in a Monfalcone, a shipbuilding town in northeast Italy, and had a history of asbestos exposure).

Fujiwara et al. 2005 (patient sharpened talc pencils in the factory for 28 years - no asbestos found in tumor tissue but mildly elevated number of asbestos bodies (2000 ab/gm dry tissue - observed in lung parenchyma).

Kahn et al. 1980 (asbestos bodies as well as amosite asbestos found in lungs of a 60-year old male who previously worked in a shipyard during World War II).
Morinaga et al. 1989 reported on 23 mesothelioma cases certified by the Osaka Mesothelioma Panel - 21 pleural, 1 pericardial and 1 peritoneal. They reported that TEM analysis with EDXA detected asbestos in 19 of the 23 confirmed mesotheliomas, but they do not indicate whether the single pericardial mesothelioma was included in the group with positive findings.

4) Finally, there are two articles which either provide no evidence for an assertion that asbestos fibers or bodies have been found in pericardial tissue (other than the case where asbestos was directly applied to the pericardium) or misstate the evidence.

In Maruyama et al. 2006, the authors reported on a case of pericardial mesothelioma in a 47 year male with no history of asbestos exposure. They also noted that "occupational asbestos exposure has been reported, and in a prospective study was found to be definite in 3 out of 15 cases (20%) and possible in 4 out of 15 cases (27%). In further support of this association, asbestos bodies have occasionally been identified within MPM." (at p. 247). The authors provide no cite whatsoever for the study or the occasional finding of asbestos within peritoneal mesothelioma.

In Burke, AFIP, Fasicle, 1996, Burke reported that asbestos bodies may be identified within pericardial mesothelioma, supporting an association with asbestos exposure, citing Eck, 1978. However, Churg, 1978 was a unique case involving a 61-year old male who had previously had asbestos instilled on to his epicardial surface to treat angina. Eck, 1978 is a German article and the English translation of the abstract provides no reference whatsoever to finding asbestos bodies in pericardial tissue.

L. Other Potential Risk Factors for Pericardial Mesothelioma

1) Radiation Therapy and Pericardial Mesothelioma.

There have been a number of case reports of individuals previously receiving therapeutic radiation for treatment of breast cancer, Hodgkin's Lymphoma and non-Hodgkin's Lymphomas subsequently developing pericardial mesotheliomas following a latency period of 14-27 years:

a. Velissaris et al. 2001 (45 year old female who received mantel field radiotherapy for Hodgkin's Lymphoma 24 years prior to pericardial mesothelioma diagnosis)

b. Small et al. 2008 (62-year old female who received radiotherapy for breast cancer 10 years previously)

c. Yildirim et al. 2010 (40-year old male treated with radiotherapy for non-Hodgkin's lymphoma 27 years previously)

d. Bendek et al. 2010 (39-year old male with history of radiotherapy for Hodgkin's lymphoma 23 years previously)
e. Sardar et al. 2012 (72-year old female who received radiation therapy 25 years previously)

2) Other Potential Risk Factors.

"Suspected risk factors for pleural mesothelioma, such as genetic predisposition, infections, and dietary factors [citing Schiffman et al. 1988] are also mentioned as potentially related to pericardial cases [citing Rizzardi et al. 2010 and Murai, 2001] as are inflammation and healing associated with prior heart surgery (e.g., [citing Rizzardi et al. 2010]). Many of the cases reported in the literature described prior history of heart disease, such as pericarditis, tamponade or heart defect, although the relationship between these conditions and a later diagnosis of pericardial mesothelioma is tenuous at best and may represent early symptoms of pericardial mesothelioma (cites omitted)." Mezei et al. 2017 at 351.

3) Germline BAP1/Pericardial Mesothelioma

Thus far, no cases of pericardial mesothelioma in individuals with a germline BAP1 mutation have been identified and published in the medical literature.

M. Reasons Why Asbestos Exposure is not a Significant Cause of Pericardial Mesothelioma

1) There are no epidemiological studies (case-control or cohort) studies of pericardial mesothelioma and therefore no epidemiological support for a causal association between asbestos exposure and pericardial mesothelioma

2) In the absence of epidemiological studies there have been a number of case reports and case series of patients with pericardial mesothelioma. Of the 251 case reports identified by Mezei et al. 2017, the authors addressed potential exposure to asbestos in only 109 cases, with approximately 67% of these having no history of asbestos exposure. In the two most cited case series and reviews to date on asbestos and pericardial mesothelioma, Nilsson, and Rasmuson and Thomason, 1994, a large percentage of cases had no known asbestos exposure:

<table>
<thead>
<tr>
<th></th>
<th>Exposure</th>
<th>No Known Exposure</th>
<th>Not Mentioned</th>
</tr>
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<tbody>
<tr>
<td>Nilsson &amp; Rasmuson</td>
<td>3/14 (21%)</td>
<td>11/14 (77%)</td>
<td>16/30 (53%)</td>
</tr>
<tr>
<td>Thomason</td>
<td>4/12 (33%)</td>
<td>8/12 (67%)</td>
<td>16/28 (57%)</td>
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</table>

3) No pericardial mesotheliomas have been reported in several of the largest asbestos cohorts with heavy exposure to asbestos. (Chrysotile only; mixed; and amphibole only).
Mezei et al. 2017 analyzed all of the epidemiological studies identified in Hodgson and Darnton, "The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure," Annals of Occupational Hygiene 44:565-601(2000), Yarborough, C.M., 2006, as well as Berman and Crump, "Update of Potency Factors for Asbestos-Related Lung Cancer and Mesothelioma," Critical Reviews in Toxicology 38(S1):1-47 (2008) and identified no case of pericardial mesothelioma. These cohorts include the Quebec Chrysotile Miner and Miller Cohort filed by McDonald and McDonald, the Selikoff insulator cohort, the cohort of crocidolite miners/millers in Australia, crocidolite and amosite and chrysotile miners/millers in South Africa, among others. If asbestos was a significant factor in the development of pericardial mesothelioma, one would expect to see at least some pericardial mesotheliomas in the largest cohorts with heaviest exposure to asbestos, particularly amphibole asbestos. There are no reports of even a single case of pericardial mesothelioma in these cohorts.

4) The male/female ratio is significantly different for pericardial mesothelioma then for pleural mesothelioma.

In many of the case series and reviews published in the medical literature, the male/female ratio for pericardial mesothelioma has been approximately 2 or 3 to 1 compared to a male/female ratio of pleura mesothelioma ranging as high as 8:1 and the Mezei, et al 2017 analysis of the incidence of malignant mesothelioma of the pericardium in the NCI SEER nine cancer registries from 1973 to 2013, a total of 16 cases of pericardial mesothelioma were identified in males while 19 cases were identified in females. This represents a male/female ratio of 1:1.2. Since there is a general consensus that the fairly high male to female ratio for pleural mesothelioma is accounted for by the much greater percentage of males being occupationally exposed to asbestos, a 1:1.2 male/female ratio would be consistent with a very large percentage of pericardial mesotheliomas being unrelated to asbestos. According to Mezei, et al., "The number of cases in the SEER Registries is "almost identical for males and females with similar population sizes, suggesting that occupational exposures to asbestos have played only a small role, if at all, in the development of this malignancy." (Id at p. 355).

Delgermaa, 2011 summarized the WHO database on the number of mesothelioma deaths reported to the WHO between 1994 and 2008. It contains the largest series of mesothelioma deaths reported to date. Among 92,253 mesothelioma deaths, 298 cases of pericardial mesothelioma were reported with a male/female ratio of 1.8:1 versus pleural 3.7:1 and peritoneal 1.6:1.

5) There is strong evidence that pericardial mesotheliomas occur spontaneously in the absence of any contribution from asbestos exposure.

a. There are numerous case reports of pericardial mesothelioma in young children without asbestos exposure:

Burr et al. 1964 (20-month old infant)

Sytman, 1971 (17-year old boy)

Yilling et al. 1982 (17-year old boy)
Eker et al. 1989 (9-year old boy with no history of asbestos exposure)

Nambiar et al. 1992 (12-year old boy with no asbestos exposure diagnosed with malignant localized fibrous pericardial mesothelioma)

Tjeerdsama and Van Veldhuisen, 1998 (19-year old male)

Suman et al. 2004 (19-year old male with no evidence of asbestos exposure)

Garcia et al. 2004 (two infants - both less than 1 year old)

Ost et al. 2008 (19-year old female)

Kayatta et al. 2013 (19-year old male)

b. There are numerous case reports in the medical literature of a variety of animals without asbestos exposure developing pericardial mesothelioma.

**Dogs**

Ikede et al. 1980 (Basset hound); McDonough et al. 1992 (three dogs); Stepien et al. 2000 (idiopathic pericardial effusions in 17 dogs); Balli et al. 2003 (11-year old dog); Gallach and Mai, 2013 (8-year old Pit Bull Terrier)

**Horses**

Carnine et al. 1977

**Monkeys**

Chandra and Mansfield, 1991 (spontaneous pericardial mesothelioma in an 18-year old Rhesus monkey that served as an untreated control in a chronic study)

**Calves**

Takasu et al. 2006 (neonatal calf)

**Bengel Tiger**

Wiedner et al. 2008 (circus Bengel tiger "with no known asbestos exposure")

**Rats**

Nash and Kaliner, 1984 (spontaneous PPM in a 17-year old Wistar rat used as an untreated control); Peano et al. 1998 (spontaneous PPM in male Sprague Dawley rat) Langner et al. 1998 (Fischer 344 rat)
6) The incidence trend over time is inconsistent with asbestos being a significant causal factor in pericardial mesothelioma.

In Mezei et al. 2017's analysis of the SEER database (i.e. SEER nine registries), the incidence of pericardial mesothelioma decreased from 0.78 per million person years in 1973-1982 to 0.19 per 10 million person years in the years 2003-2013:

The absolute incidence rates were not materially different between males and females. Id. at 351.

The authors of this review concluded:

"In our evaluation of SEER data, the incidence trends for pericardial mesothelioma and MTDT did not correspond with sufficient latency. Taken into account, to trends in commercial asbestos use in the United States, which would be expected of pericardial mesothelioma or MTDT were causally associated with exposure to asbestos. For pleural mesothelioma among males, on the other hand, the SEER data showed that trends in rates reflect trends in the commercial use of asbestos in the United States with an approximately 30-year leg [citing Moolgavkar, 2009; Price and Ware, 2004.

Similar trends were reported in Denmark by Skammeritz et al. 2013. Data from the Danish Cancer Registry were analyzed for cases of malignant mesothelioma of the pleura, peritoneum and pericardium occurring in the 1943-2009 period. The authors identified a total of 3,394 cases of diffuse malignant mesothelioma. Men comprised the vast majority of cases (76%) and as expected, pleural mesothelioma comprised 87% of all cases of diffuse malignant mesothelioma. Importantly, the increase in incidence over the timeframe 1943 to 2009 was attributable to the drastic increase in pleural mesothelioma whereas the incidence of malignant mesothelioma of the pericardium "was very low for both sexes throughout the period." (Id. at p. 2).
Figure 1 set out below "depicts national incidence rates for men and women:
Skammeritz, Ellen, Hansen and Johanson, "Regional Differences in Incidence of Malignant Mesothelioma in Denmark," Danish Medical J 2013;60(3):A4592

7) **Analysis of geographic distribution of incidence of pericardial mesotheliomas in the United States is consistent with asbestos exposure not being a significant factor in pericardial mesothelioma.**

Lowry and Weiss, 2016 utilized age-adjusted incidence data from the SEER data base for the period 1973-2011. They compared the incidence of mesothelioma among men greater than 50 years of age in the San Francisco-Oakland and Seattle-Puget Sound areas compared to other regions in the SEER data base. Whereas the rate of pleural mesothelioma was twice as high in the San Francisco and Seattle-Puget Regions compared to other areas, in contrast, the rate of pericardial mesothelioma was not elevated in either compared to other regions. The authors "hypothesized that the regional patterns in incidence of paratesticular and pericardial mesotheliomas would parallel those of pleural mesotheliomas if in fact occupational asbestos exposures causes those rarer types as well." (p. 1487). The authors limited their study population to men aged greater than or equal to 50 years at diagnosis "because most occupational exposure to asbestos has historically occurred in men." (Id. at 1488). On the basis of their analysis showing distinctly different trends between pleural and pericardial (as well as paratesticular) mesothelioma, the authors concluded:
"The results of this ecologic study do not support a role for asbestos exposure in the etiologies of either pericardial or paratesticular mesotheliomas; however, this study was limited by small number and was unable to directly ascertain asbestos exposure."  Id. at 1487.

8) The failure to identify asbestos in pericardial tissue weighs heavily against a significant role for asbestos in the causation of pericardial mesothelioma.

Accept in the extremely unusual and artificial circumstances of direct application of asbestos to the pericardium is treatment for angina utilizing the "Beck" procedure,[in the 1950s and early to mid-1960s] Asbestos fibers or bodies have a not been identified in pericardial tissue. There is a general consensus among plaintiff experts that asbestos has to make its way to the target organ in order to contribute to the development of cancer (in this case pericardial mesothelioma). The apparent inability of asbestos fibers to do so weighs against a significant role of asbestos in the causation of pericardial mesothelioma. As was summarized by Mezei et al. 2017:

"Some considerations of anatomy and embryonic development may also be used to support the apparent lack of a causal relationship between inhalation [of] asbestos exposure and pericardial mesothelioma. The fibrous layer of the pericardium represents a natural barrier that the asbestos fibers need to penetrate. Typically, lymph travels from the pericardium to the mediastinal lymph nodes and then connects to the thoracic duct (cites omitted). Lymph from the lung tissue drains to the bronchomediastinal lymph nodes then travels to the thoracic duct in order for fibers from the lung to reach the pericardium, they would need to follow the flow of lymph from the lungs to the thorax and then they would need to travel retrograde against the typical flow of lymph down the thoracic duct, and through the mediastinal lymph nodes, to reach the pericardium. (cites omitted)."  Id. at 356.

9) The younger average age of individuals with pericardial mesothelioma versus pleural mesotheliomas weighs against a significant role of asbestos in the causation of pericardial mesothelioma.

The median age in the case series of Nilsson and Rasmuson, 2009 was 46 years. This compares to the review by Thomason et al. 1994 in which over half of the patients were diagnosed between the fifth and seventh decade. In their review of the WHO data base from 1994 to 2011, Delgermaa et al. 2011 reported the mean age at death for pleural versus peritoneal versus pericardial mesothelioma respectively was 70.1 years, 66 years, and 61 years. The significant difference in mean age at diagnosis or death from pericardial versus pleural mesothelioma weighs against asbestos having the same role in the development of pericardial mesothelioma as it does in pleural mesothelioma.

10) Since low dose chrysotile does not increase the risk for pleural mesothelioma, it certainly would not be expected to increase the risk for pericardial mesothelioma.
There is absolutely no reason to believe that even if there was a risk of pericardial mesothelioma from asbestos exposure that it would be any greater than the risk of pleural mesothelioma from asbestos exposure. To the contrary, there is every reason to believe, as summarized above, that the risks of pleural versus peritoneal mesothelioma are materially different. Accordingly, all of the epidemiology that supports no increased risk for low dose chrysotile (such as the numerous case control studies showing no increased risk of pleural mesothelioma among vehicle mechanics performing brake work it strongly applies that such exposures do not increase the risk of pericardial mesothelioma).

N. The defense response to plaintiffs' key argument/literature on chrysotile/pericardial mesothelioma.


The Marinaccio et al. analysis of data from the Italian National Register reported that 62% of pericardial mesothelioma cases (23 men and 13 women) diagnosed between 1993 and 2004 were classified as having definite, probable or possible asbestos exposure versus 81% of pleural mesothelioma cases. Plaintiffs' counsel attempt to use Marinaccio in support of their claim that a significant percentage of pericardial mesotheliomas are asbestos related.

Defense Response:

a. As emphasized in Mezei et al. 2017, "The registry study of Marinaccio et al. provides no direct evidence that pericardial [MTDT mesotheliomas] are associated with inhaled asbestos exposure. Id. at 356.

b. The Marinaccio study does not have any controls and therefore does not calculate any risk ratio.

c. A significantly small percentage of pericardial mesothelioma cases were deemed to have asbestos exposure then pleural mesothelioma (81.3% versus 62%) and even less than peritoneal mesothelioma (69.7%).

d. Most importantly, table 3 provides the number of cases of mesothelioma of the peritoneum, pericardium, tunica vaginalis by industry shipbuilding), there were no cases of pericardial mesothelioma in the asbestos cement industry and none in shipbuilding. Thus, "there are no cases in the highest risk industries (i.e., industries in which asbestos exposure is significant and in which the highest rates of pleural mesothelioma are seen). . . . Therefore there is no correlation between the risk of peritoneal mesothelioma and the risk of pericardial or TDT mesotheliomas in Marinaccio et al., suggesting that inhaled asbestos is not associated with pericardial and TDT mesotheliomas." Mezei 2017 at 356. Marinaccio et al. in fact remark, "The absence of exposure in the shipbuilding, railway, and asbestos-cement industries (the sectors traditionally involved in asbestos exposure for pleural MM) for all the 67 pericardial and testicular cases is noteworthy but not easy to interpret and these findings need to be confirmed in a larger sample." Marinaccio et al. 2010 at 764.

The authors note that pericardial mesothelioma accounts for 0.7% of all malignant mesotheliomas. The aim of this study as described by the authors was to identify the characteristics of pericardial mesotheliomas occurring in Lombardy, a highly industrialized region of northern Italy. They selected cases of pericardial mesothelioma registered in the Lombardie mesothelioma registry between 2000 and 2009. They identified 8 cases (6 men and 2 women) with a median age at diagnosis 55.5 years and stated that occupation exposure to asbestos was documented in 5 of the 7 cases for which they obtained an interview. They argued that their findings supported the role for asbestos and the pathogenesis for pericardial mesothelioma.

**Defense Response:**

a. The abstract in fact noted that "although asbestos exposure is a recognized etiological factor pleural and peritoneal mesotheliomas, its role in the development of pericardial mesothelioma is controversial." Id. at 276.

b. As in the cases identified by Marinaccio in 2010, none of the jobs with possible asbestos exposure identified for the cases of pericardial mesothelioma were in the highest risks industries such as shipbuilding and asbestos cement.

c. There was no information on whether any of the cases had asbestos bodies or fibers in lung tissue.

3) **Plaintiffs rely on a number of cases reports of constrictive pericarditis in individuals with a history of asbestos exposure to support their contention that it is likely pericardial mesotheliomas are asbestos-related as well.**

There are several case reports in the medical literature of constrictive pericarditis occurring in individuals with an asbestos exposure history. Plaintiffs rely on those case reports to argue that if asbestos can cause constrictive pericarditis, there is no reason to believe that asbestos exposure could not cause pericardial mesothelioma as well. Constrictive pericarditis results in chronic fibrous thickening of the pericardium. If the thickening is extensive enough, it can impair the heart by restricting the filling of all the cardiac chambers.

**Defense Response:**

While there have been several reports, including Fischbein, 1988, Pope et al., 1989 and Roggeri et al., 2003 of constrictive pericarditis in individuals with a history of asbestos exposure, it is generally accepted that the majority of constrictive pericarditis cases are in fact idiopathic or post-cardiac surgery as well as post-radiation therapy in etiology. See generally, Bertog et al., 2004; and Cameron et al., 1987. In a Chinese study published in 2012, of 33 patients with constrictive pericarditis who underwent surgery from January 2005 to December 2010 in a major university hospital in Shanghai, China, 33 (65%) had tuberculous constrictive pericarditis, 13 (25%) had idiopathic pericarditis, 3 (6%) had previous cardiac surgery and 1
(2%) had connective tissue disease. Lin et al., 2012 at p. 1235. Because of a much lower incidence of tuberculosis in the United States, one would not expect a higher rate of idiopathic constrictive pericarditis and a lower rate from tuberculosis in the United States.

As one investigator who published a case report ("An unusual case of constrictive pericarditis"), in a 61-year old retired clerical worker whose previous chest x-rays had shown bilateral pleural thickening and plaque formation suggestive of prior asbestos exposure required while working for 13 years in a foundry stated:

"Although the medical literature has linked asbestos exposure with constrictive pericarditis, major pieces of the puzzle have not been elucidated. It is unknown whether constrictive pericarditis patients with prior asbestos exposure possess unique signs or symptoms that differentiate them from the majority of patients with constrictive pericarditis. A more extensive case series could be conducted for clarification." Khatri, 2012.

There is no reason to believe that idiopathic constrictive pericarditis could not occur in individuals who had a prior history of asbestos exposure. Moreover, none of the case reports of constrictive pericarditis in asbestos-exposed individuals reports finding asbestos fibers or bodies in the pericardial tissue, nor did any of them have a control population to compared to.


The authors reviewed records for 6,030 cases of death due to malignant mesothelioma between 2003 and 2008. Of all these cases, a clinical diagnosis of malignant mesothelioma was confirmed for 928-794 pleural (85.5%), 123 peritoneal (12.2%), 7 pericardial (0.8%) and 5 testicular tunica vaginalis testis (0.5%). Id. at 483. While pleural plaques were identified on chest x-rays in 280 of 818 cases (34.2%), but only one of the 7 pericardial mesothelioma cases (14.3%). This compares with 242 of 703 cases of pleural mesothelioma (34.4%) and 36 of 106 cases of peritoneal mesothelioma (33.9%).

Examination of lung tissue for asbestos "particles" was determined in 103 malignant mesothelioma cases (92 of the pleural and 11 of the peritoneum), but in none of the pericardial mesotheliomas.

Table 4 provides information on occupation by site of mesothelioma. For five pericardial mesotheliomas (apparently 2 had no occupation with potential asbestos exposure), there was one case each in the occupations of construction, shipbuilding, and plumbing, one in manufacturing and one in the category "others".

Defense Response

a. Rather than demonstrating the high percentage of pericardial mesotheliomas are associated with asbestos exposure, the study proves the opposite: Only one
of the 7 cases had pleural plaques (14.3%) compared to 34.4% of the pleural mesotheliomas and 33.9% of the peritoneal mesotheliomas.

b. The assessment of accuracy of diagnosis was less than satisfactory. It was based entirely upon a review of medical records, x-rays, and CT images rather than an independent pathological review of the pathology specimens. Mesothelioma is a pathological diagnosis and distinguishing pleural from pericardial mesothelioma pathologically can be quite challenging. While the authors provide numbers and percentages for the method of pathological diagnosis for mesotheliomas of the pleura and peritoneum, they provide no such information for pericardial mesothelioma, other than stating that two cases of malignant mesothelioma of the pericardium were diagnosed on the basis of examination of pericardial fluid only.


The study provided data about non-occupational exposed malignant mesothelioma cases currently available in the National Register of Mesotheliomas, a surveillance of mesothelioma incidence, which has been active since 2002 in Italy. In the period between 1993 and 2008, the authors claim they identified one case of pericardial mesothelioma in a female (0.1% of mesothelioma collected by the registry in this timeframe.) Non-occupational exposure included a familial, environmental and leisure activity exposure.

The authors identified a total of 15,845 cases of malignant mesothelioma in the period between 1993 and 2008, with the pleural site reported in 93% (14,736 cases), the peritoneal cases in 6.4% (1,017 cases) and pericardial and testicular cases account for 0.3% (41 and 51 cases, respectively).

Defense Response

a. The male/female ratio was 2.6 among pleural cases, but only 1.4 and 1.9 among peritoneal and pericardial cases, respectively.

b. Diagnostic coding criteria had three classes of decreasing level of certainty: certain, probable and possible malignant mesothelioma. While the authors provide a breakout by the total number for the category of certain v. probable/possible malignant mesothelioma or possible, they do not provide any information by site of mesothelioma. Consequently, we have no idea whether the one female case of pericardial mesothelioma with familial, environmental or leisure activity exposure was in the "certain", "probable" or "possible" category.

c. We also have no idea what the nature of the alleged non-occupational exposure to asbestos was in the case of the single pericardial mesothelioma. Table 2 provides information on the modalities of exposure for malignant mesothelioma cases, but it is not broken out by site, and therefore it is impossible to know which of the cases in the various categories were pleural, peritoneal, pericardial or tunica vaginalis.
d. It is telling that the authors cite one of the numerous Italian cohort studies of Casale Monferrato asbestos cement factory workers who had shown a large excess of pleural mesothelioma (Ferrante, 2007), none of those cases were pericardial.
O. Pericardial Mesothelioma References


73. Selivanenko, V.T., Panasenko, V.I., [Rare case of rheumatic heart valve disease combined with pericardial mesothelioma in a 28 year old patient – Abstract Only – Article in Russian], Grudn Khir 3:93, 1985.


Appendix A

Summaries of all Pericardial Mesothelioma Literature
(Will be available online)
### Appendix B

Table S1 "Case Series and Literature Review of Malignant Mesothelioma of the Pericardium," from Mezei, G., Chang, Mowat and Moolgavkar, "Epidemiology of Mesothelioma of the Pericardium and Tunica Vaginalis Testis," Annals of Epidemiology 27:348-359, 2017

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Data Source</th>
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<tbody>
<tr>
<td>Dozer et al., 1953 [1]</td>
<td>Literature review</td>
<td>Published literature on mesothelioma of the pericardium</td>
<td>1914–1953</td>
<td>25</td>
<td>Women 46.7 (22–79) Men 36.4 (18–58)</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Anderson and Hansen, 1974 [2]</td>
<td>Literature review</td>
<td>Published literature on primary pericardial mesothelioma (included cases with no asbestos, other than to lymph nodes, and cases with complete autopsy in case of death)</td>
<td>up to 1972</td>
<td>31</td>
<td>Women 43.9 (2–78) Men 45.5 (1–78)</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Hildreth, 1983 [3]</td>
<td>Literature review</td>
<td>Patients treated with mesothelioma at University of Minnesota</td>
<td>up to 1981</td>
<td>33</td>
<td>Women (36 and 75)</td>
<td>No</td>
<td>Discussed but no numbers provided</td>
</tr>
<tr>
<td>Armitan et al., 1984 [5]</td>
<td>Case series</td>
<td>Mesothelioma cases among Italian railway workers and family members, various sources (not clearly specified)</td>
<td>1965–1985</td>
<td>5</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not presented separately for pericardial mesothelioma</td>
</tr>
<tr>
<td>Maltoni et al., 1991 [6]</td>
<td>Case series</td>
<td>English literature on primary pericardial mesothelioma</td>
<td>1993 (death)</td>
<td>1</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Exposed to asbestos (mostly chrysotile) in boiler, driver, cafe</td>
</tr>
<tr>
<td>Thomassen et al., 1994 [7]</td>
<td>Literature review</td>
<td>English literature on primary pericardial mesothelioma</td>
<td>1972–1992</td>
<td>28</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Exposure 4/12 (33.3%)</td>
</tr>
<tr>
<td>Yates et al., 1997 [8]</td>
<td>Case series</td>
<td>All deaths from malignant mesothelioma in 1987 in South East England</td>
<td>1987 (year of death)</td>
<td>1</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not presented separately for pericardial mesothelioma</td>
</tr>
<tr>
<td>Neumann et al., 2004 [10]</td>
<td>Patient registry</td>
<td>German mesothelioma register English literature on primary pericardial mesothelioma</td>
<td>1987–2000</td>
<td>1</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Exposure 3/14 (21.4%)</td>
</tr>
<tr>
<td>Fujimoto et al., 2009 [12]</td>
<td>Case series</td>
<td>WHO-mortality database Retrospective investigation of deaths, records medical records</td>
<td>2005–2007</td>
<td>2</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Both pericardial cases were exposure to asbestos (office workers)</td>
</tr>
<tr>
<td>Delgerma et al., 2011 [13]</td>
<td>Case series</td>
<td>Mesothelioma cases among Italian railway workers and family members, various sources (not clearly specified)</td>
<td>1994–2008</td>
<td>7</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not specifically addressed</td>
</tr>
<tr>
<td>Gennia et al., 2011 [14]</td>
<td>Case series</td>
<td>Retrospective investigation of deaths, records medical records</td>
<td>2005–2008</td>
<td>6</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Pleural plaques (17/433) of pericardial MM</td>
</tr>
<tr>
<td>Maltoni et al., 1995 [15]</td>
<td>Case series</td>
<td>Mesothelioma cases among Italian railway workers and family members, various sources (not clearly specified)</td>
<td>1981 (death)</td>
<td>1</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Exposed to asbestos (mostly chrysotile) in boiler, driver, cafe</td>
</tr>
<tr>
<td>Marinaccio et al., 2009 [16]</td>
<td>Patient registry</td>
<td>Italian National Mesothelioma Registry (ReMa) (RPSI, National Institute for Occupational Safety and Prevention - regional centers - 85% of Italian population)</td>
<td>1997</td>
<td>3</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not specified for pericardial mesothelioma cases</td>
</tr>
</tbody>
</table>

(continued on next page)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Data Source</th>
<th>Time Period Reviewed</th>
<th>No. of Cases</th>
<th>Mean Age, Years (Range)</th>
<th>Asbestos Exposure Considered?</th>
<th>% Exposed (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinaccio et al., 2009 [17]</td>
<td>Patient registry</td>
<td>Italian National Mesothelioma Registry (ReMa) (RPSI, National Institute for Occupational Safety and Prevention - regional centers - 85% of Italian population)</td>
<td>1993–2001</td>
<td>15</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not specified for pericardial mesothelioma cases</td>
</tr>
<tr>
<td>Marinaccio et al., 2007 [18]</td>
<td>Patient registry</td>
<td>Italian National Mesothelioma Registry (ReMa) (RPSI, National Institute for Occupational Safety and Prevention - regional centers - 85% of Italian population)</td>
<td>1993–2001</td>
<td>3</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Not specified for pericardial mesothelioma cases</td>
</tr>
<tr>
<td>Marinaccio et al., 2010 [19]</td>
<td>Patient registry</td>
<td>Italian National Mesothelioma Registry (ReMa) (RPSI, National Institute for Occupational Safety and Prevention - regional centers - 85% of Italian population)</td>
<td>1993–2001</td>
<td>36</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>Asbestos exposure is 60.8% of pericardial mesothelioma cases</td>
</tr>
<tr>
<td>Menz et al., 2011 [20]</td>
<td>Patient registry</td>
<td>Lombardy Mesothelioma Registry</td>
<td>2000–2009</td>
<td>8</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>5 of 7 cases with interview were exposed</td>
</tr>
<tr>
<td>Current literature review*</td>
<td>Literature review (case reports)</td>
<td>1947–2013</td>
<td>292</td>
<td>Women (36 and 75)</td>
<td>Yes</td>
<td>24/112 (20.9%)</td>
<td></td>
</tr>
</tbody>
</table>

* Case reports of malignant mesothelioma of the pericardium are summarized in this row [1,2,7,11,21–23].

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