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Peritoneal Mesothelioma and Asbestos: Clarifying the Relationship by Epidemiology

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Abstract

Peritoneal mesothelioma has been recognized for over a half century, but causality with asbestos of different fiber types and the incidence of this fatal tumor in relation to asbestos exposure dose still needs clarification. In order to help bring clarity, the most important studies on peritoneal mesothelioma, including a brief history, relationship to asbestos exposures, diagnostic issues and experimental studies are reviewed including case series, case-control, occupational, and registry epidemiology studies. This review concludes that all types of asbestos, including amphiboles and chrysotile, are causative for peritoneal mesothelioma. Many cases have been found in both males and females from asbestos exposures in occupational and neighborhood settings, shown in differing epidemiology study designs. It is clear that there is a causal relationship between all types of asbestos at all dose levels for peritoneal mesothelioma and no threshold of exposure to asbestos appears safe.

Keywords: Asbestos; Mesothelioma; Peritoneal Mesothelioma; Epidemiology

Introduction

We previously updated the epidemiology of mesothelioma in relation to asbestos [1]. That review emphasized the most common type of mesothelioma, pleural. There is less clarity in the epidemiology literature concerning peritoneal mesothelioma, which we seek to rectify here.

Mesothelioma is a cancer of the mesothelium, a thin layer of cells derived from the mesoderm which lines the internal organs of the body. It is a rare tumor and is now generally considered a "sentinel" or "signal" tumor for asbestos exposure. Pleural mesotheliomas were recognized as far back as 1870 [2] and more modernly in 1931 [3] and 1943 [4]. Saccone and Coblenz [5] conducted a literature review in 1943 of the pathology of lung diseases and found 41 out of 46,000 autopsies as possible malignant mesotheliomas. Additional early case reports were published in 1935 [6] and 1952 [7]. Bonser et al. [8] in 1955 analyzed a case series of 72 asbestos worker autopsies in which asbestosis was present, and found four peritoneal tumors and two possible pleural mesotheliomas. The clear relationship between malignant mesothelioma and asbestos exposure was established by the Wagner et al. 1960 [9] report of 33 pleural cases exposed to crocidolite asbestos in northwestern portion of the Cape Province of South Africa. Thomson [10] also in South Africa, later identified seven cases of mesothelioma, four pleural and three peritoneal, all who had asbestos exposure in mines or factories; six of the seven cases also had asbestosis.

Peritoneal mesothelioma is generally considered a more rare tumor than pleural mesothelioma, accounting only for approximately 5-20% of all cases [11]. For example, in Sweden [12], the male incidence of peritoneal is ten-fold less than for pleural tumors. Swedish men have shown no increase in peritoneal mesothelioma cases since 1985. However, in women peritoneal mesothelioma has been steadily increasing and has surpassed the rate of pleural mesothelioma (0.16/100,000) [12]. Other reviewers have found that peritoneal mesothelioma accounts for 10-20% of all forms of malignant mesothelioma [13].

Some authors, after reviewing the available evidence, have concluded that chrysotile asbestos does not cause peritoneal mesothelioma [14-17]. Some have postulated a threshold [18]. Others have concluded that peritoneal is less related to asbestos than pleural [19] or occurs less in females than males [20]. Still others have stated that higher asbestos doses lead to peritoneal rather than pleural mesothelioma [21].

We review the epidemiology, including experimental data, seeking to bring clarity on asbestos fiber type and whether there is a threshold in peritoneal mesothelioma causation. In addition the occurrence in females and issues of dose are reviewed. Our goal is to use epidemiology to clarify asbestos and its' role in peritoneal mesothelioma causation to ultimately help guide efforts toward prevention.

Difficulties in diagnosis

Prior to 1999, there was no International Classification of Disease (ICD) code for mesothelioma. Thus, there was no death certificate specific code for underlying cause of death, and although the disease was discoverable histologically, mortality for both pleural and peritoneal mesothelioma was most certainly underestimated [22,23].

The landmark Selikoff et al. [24] study of 17,800 asbestos insulators found that in the first 175 deaths from mesothelioma, 64% were from peritoneal and 36% were from pleural. In their continued study of the insulators Selikoff and Seidman [25] found there was great discordance between the underlying cause of death on the death certificates and more detailed clinical and histopathological evidence (called "Best

Evidence"), especially for peritoneal mesothelioma. In fact, 60.5% of the 458 cases of pleural and peritoneal mesothelioma combined would have been missed if just the death certificate was available. In the 2271 deaths recorded among the 17,800 asbestos insulation workers observed from Jan 1 1967-Dec 31 1976, only 24 were listed as peritoneal mesothelioma on the Death Certificate as compared to 112 which were found using "Best Evidence"[26].

Peritoneal mesotheliomas are often difficult to differentiate in pathologic diagnosis from ovarian, colon and other abdominal cancers [27]. Pathology reports can more definitively establish the diagnosis by using immunochemistry for mesothelioma and adenocarcinoma markers [28], or a panel of staining approaches [29,30]. There are different subtypes of peritoneal mesotheliomas, including low-grade tubulopapillary, with or without deep tissue invasion, high-grade epitheloid type with deep invasion and high-grade sarcomatoid type. Most peritoneal mesotheliomas are epithelial and are histologically similar to pleural mesothelioma; peritoneal mesotheliomas have a tubulopapillary pattern and are stromal malignant [27]. As characterized by Shih CA et al. [31] in describing a case in a 54 old male construction worker "…diffuse malignant peritoneal mesothelioma is a rare disease characterized by a difficult diagnosis, different presentations, variable course, and poor prognosis." In a study of 25 female patients [32], survival prognosis was found to be from 1 month to 15 years, often less than one year. Kindler [33] in a review of peritoneal mesothelioma emphasized the difficulty of diagnosis, that cytology is rarely helpful, and thus the experience of a pathologist with the help of several immunohistochemical tests is essential. Kindler [33] differentiated three major pathologic subtypes: epithelial, sarcomatoid, and biphasic, and stated that women have a higher proportion of peritoneal vs. pleural (44% vs. 19%), that most cases are epithelial, and patients with peritoneal are significantly younger than pleural (mean age 63.3 vs 70.8 years). Peritoneal has a shorter median survival than pleural, and women live longer than men (13 vs. 6 months) [33].

Occupational cohorts

Suzuki [34] reviewed 1517 mesothelioma cases from the Selikoff et al. [24,35] epidemiology studies of insulation workers in the U.S. and Canada. The site of the mesothelioma was known in 1496 of the 1517 cases. The preponderance of pleural as compared to peritoneal is often cited in reviews of occupational cohorts [19]. However, the ratio was reversed in this asbestos insulation worker cohort. That ratio was 1: 2.6 between pleural and peritoneal in the asbestos insulation workers [24,35]. Ribak et al. [36] described 356 mesothelioma deaths in this cohort as of 1987. Out of these cases, 222 were peritoneal (60%). Enticknap [37] and Newhouse and Berry [38] also reported more peritoneal than pleural in their cases.

Dement et al. [39] conducted a retrospective cohort study of 1261 white male chrysotile asbestos textile workers in South Carolina employed for one or more months between 1940 and 1975. One peritoneal mesothelioma was observed among this cohort (diagnosis confirmed by autopsy). The interval between initial employment and death was 34 years. The authors noted there were several other death certificates which mentioned 'cancer of the abdomen' however, no autopsy or other confirmatory data were available. Further description and follow-up of this South Carolina chrysotile asbestos textile worker cohort [40] expanded the numbers of workers to 3072 and found three cases of mesothelioma including the specification that the one peritoneal case was a female case.

Clin et al. [41] conducted a retrospective morbidity study of 2024 subjects who worked in an asbestos reprocessing plant located in Calvados area of Normandy, France. Asbestos was used in this plant to product friction linings and textiles. All surviving subjects in 2004 who had worked in the period 1978-2004 for at least one year in the plant (2024 individuals) were studied (1604 men-79.2% and 420 women-20.75%). An exposure matrix was created based on the company's own job exposure data which was derived from dust accumulation measurements. The Calvados digestive cancer registry was used for case identification. All cases of peritoneal mesothelioma were validated by an expert pathologist. Three peritoneal mesotheliomas were observed among men, and five among women. The authors calculated Standard Incidence Ratios (SIR) comparing rates in the cohort with the general population of the area. For the entire cohort in men the peritoneal SIR was 15.93 (CI 3.2-46.55) and in women 61.3 (CI 19.76-143.06). For men in the asbestos cohort with cumulative asbestos exposures over 80 fibres/mL x years, the SIR was 97.66 (CI 31.47-227.91) and for women 22.63 (CI 4.55-66.13). "The presence of eight cases of peritoneal mesothelioma in the study population (SIR=25.04 (CI 10.78-49.33) confirmed the significantly elevated incidence of these cancers for both genders" [41]. The results agree with an American study [42,43] which compiled all cases peritoneal mesothelioma from 1973 to 1984 and in which the percentage of cases in women was higher than in men. This finding is contrary to other studies that claim a lesser causal relationship between asbestos exposure and peritoneal mesothelioma in women as compared to men [20]. There have been other reports of peritoneal mesotheliomas in occupational groups exposed to chrysotile asbestos from all over the world including China [44,45] Italy [46,47] Australia [48] and Canada [42,49].

Case series and case-control studies

Welch et al. conducted a case-control study of 40 cases of primary peritoneal mesothelioma cases compared to controls with appendicular cancer. Twelve of the cases had asbestos exposure as compared to eight of the controls and eight had done brake lining work as compared to six controls [50].

Manzini examined fifteen patients with malignant peritoneal mesothelioma for asbestos exposure and many other factors including listed cause of death, survival time and others. Twelve of the cases were men and three were women. They found a history of asbestos exposure in all twelve men and it was absent in the three women. Manzini reiterated the findings of many other investigators that the diagnosis of peritoneal mesothelioma is very difficult [51].

Cocco and Dosemeci conducted a case control study of peritoneal mesotheliomas collected from death certificates from 24 U.S. states 1984-1992 (657 deaths) and compared them with 6570 (10 to 1 match for region, gender, race and 5 year age group) controls who died of non-cancer diseases. The goals of the study were to assess occupational risk and to test a new job-exposure matrix technique for occupational epidemiology studies. The matrix found 17 male control cases and three controls in the high probability category of exposure to asbestos. For men, the risk of peritoneal mesothelioma increased significantly by intensity and probability of exposure to asbestos. The authors acknowledge the large possibilities of occupational exposure misclassification and the problem of diagnosis of both peritoneal and pleural mesothelioma especially in the era before there was an ICD code for the disease as the underlying cause of death. For women, the lack of spousal occupation was an important missing piece of data. For

men, they calculated an odds ratio of 1.8 (95% CI 1.3-2.4) of asbestos exposure for the peritoneal mesothelioma cases [52].

Spirtas et al. [53] conducted a case-control study of mesothelioma from two U.S. cancer registries and 39 Veterans Administration hospitals. Of the 208 cases, 183 (162 men, 21 women) were classified as pleural or peritoneal and 25 (21 men, 4 women) were peritoneal only. Controls had died of other causes excluding cancer, respiratory disease, suicide or violence. For men with peritoneal cancer, the attributable risk asbestos exposure was 58% (95% CI 20-89%) and for women with both pleural and peritoneal combined 23% (95% CI 3-72%). The authors' possible explanations for the discrepancy between men and women, was greater misclassification of exposure in women, a lower background incidence rate, or lower asbestos exposures.

Registry studies

Burdorf et al. [20] explored peritoneal mesotheliomas from the Swedish and Netherlands Cancer Registers (1989-2003) aiming to investigate the role of asbestos. One clear finding was a downward shift in rates, especially in Sweden, around the 1999-2000 period, probably due to a change in the International Classification of Diseases (ICD) code to version 10. It is presumed that previous to the year 2000 many peritoneal tumors in females were misclassified as ovarian and vice versa. The Netherlands did not have such a time shift presumably due to a long time tradition there of pathological review of all mesotheliomas. The authors found no evidence for a time trend in peritoneal mesothelioma in both sexes except for the change in Sweden in females, and concluded that this may be evidence for a more limited role of occupational exposure to asbestos in the etiology of peritoneal mesothelioma among women.

Hemminki and Li [12] studied peritoneal mesothelioma cases from 1961-1998 from the Swedish Family-Database. Niney-six male and 113 female cases were found. The incidence in both men and women increased until 1985, but in men leveled off, whereas it continued to increase in women. Twenty-nine percent of the men had typical asbestos related jobs, with bricklayers and plumbers being the highest. Only one of the women had a typical asbestos job. The authors speculate that the increasing trend in women must be a result of asbestos exposure from asbestos in place in homes and workplaces, whereas the male cases were mostly from workers using asbestos containing products.

A study of cases 1993-2001 on the Italian mesothelioma registry [54] included 2544 cases with asbestos exposure history [55]. Of the 2165 male cases, 83 (3.8%) were confirmed as peritoneal and of the 360 female cases, 19 (5%) were peritoneal. Given all the cases had an asbestos exposure history, the mean latency for males was 41.9 (+/-9.9) and for females 36.8 (+/-10.2) years. Latency was getting shorter through the time period 1993-2001, and occupationally exposed cases had a shorter latent period than environmental or household asbestos exposure [55].

Hassan and Alexander [27] conducted a review of non-pleural mesotheliomas using United States Surveillance, Epidemiology and End Results (SEER) data. They estimated that U.S. mesothelioma numbers are about 2500 per year, with peritoneal being about 10-20%. Overall mesothelioma rates were higher in men than women, but women had higher peritoneal rates. Peritoneal accounted for 17% of mesotheliomas in women and 7% in men [27].

Price and Ware [18] studied the mesothelioma incidence data also using the SEER data for included areas of the U.S. for 1973-2000 in order to project possible future trends. They projected approximately 71,000 mesothelioma cases 2003-2054. They assumed females were excluded from potential occupational exposures to asbestos and even excluded all female peritoneal mesotheliomas from their analysis. Thus, their projection of a possible decline in female mesothelioma rates in the future due to female asbestos exposures falling below a "threshold" of exposure is not sufficiently justified in the paper. In contrast to Price and Ware [18], Teta et al. [56] attributed rates among females at older ages due to past occupational exposures. Teta et al. [56] also used the SEER data, using the years 1973 to 2002. Of the 6078 mesotheliomas, 83% (5073) were pleural and 11% (647) were peritoneal. In males 87% of the cases were pleural. Women had higher percentage of peritoneal cases (22%) than men (8%).

Moolgavkar et al. [57] analyzed mesothelioma incidence in the SEER database for 1973-2005. It appeared that after adjustment for temporal trends that the age-specific incidence rates of both pleural and peritoneal mesotheliomas were close to identical in both women and men. Age adjusted rates for peritoneal mesothelioma in both sexes (1.2 per million person-years in men, 0.8 per million person-years in women) showed no temporal trends over the study years. It was estimated that 94,000 cases of pleural and 15,000 cases of peritoneal mesothelioma would occur in the U.S. over the years 2005-2050.

Henley et al. [58] studied mesothelioma incidence from the U.S. SEER Program and the National Program for Cancer Registries for the years 2003-2008. Of the total of 19,011 mesotheliomas, 15,615 were pleural (82.1%) and 1754 (09.2%) peritoneal. The authors conducted a correlational analysis by site by location and found a Pearson correlation of 0.70, $p<0.0001$ for males and 0.78 $p<0.0001$ for females, which supported the hypothesis that pleural and peritoneal mesothelioma share a common cause, exposure to asbestos. This correlation is similar to those reported in Italy [55] and other places internationally [19].

Delgermaa et al. [59] reported on malignant mesothelioma worldwide using the WHO database 1994-2008. They report 92,253 deaths from malignant mesothelioma in 83 countries during that period. Park et al. [60] suggest one case is missed for every 4 or 5 reported; thus, the number of deaths could be underestimated. Delgermaa et al. [59] reported that many countries reported a temporal increase, and that pleural and peritoneal were on the rise in both sexes through the time period studied. Of the 92,253 deaths from malignant mesothelioma 72,000 were male and 20,252 female. Of the 38,121 pleural deaths, the male to female ratio was 3.7 to 1, and of the 4116 peritoneum deaths the male to female ratio was 1.6 to 1. The burden of mesothelioma is slowly shifting to countries that have used more asbestos recently such as India [59].

Boffetta [19] used data from selected European cancer registries and the SEER registries to estimate age standardized incidence rates for peritoneal mesothelioma, which among men range from 0.5 to 3 cases per million in the population. Higher rates were reported in smaller areas with higher past use of asbestos, such as Genoa, Italy, which had an age standardized rate in 1995 of 5.5 per million. Rates among women were generally lower than men, in the range of 0.2 to 2 cases per million. Although in some countries, such as Sweden, the males and females rates were similar.

Chrysotile asbestos and peritoneal mesothelioma

There are many cases of peritoneal mesothelioma in cohorts of chrysotile exposed populations with a significant excess of mesothelioma, and peritoneal mesotheliomas have been well documented in chrysotile exposed populations [1].

Borow et al. [61] described 72 cases of mesothelioma from a hospital in New Jersey nearby an asbestos mill. 21 of the cases (29%) were peritoneal. Chrysotile was the main asbestos used in the mill, with some crocidolite having been present in some of the processes. Only chrysotile was used in the textile division, and all the cases were only exposed to chrysotile as far as can be determined. Godwin and Jagatic [62] described peritoneal mesothelioma in a 43-year-old woman who wove brake linings made from chrysotile. Exposure was three years as a young adult, with death from peritoneal mesothelioma at age 43. Heller et al. [63] studied the tissues of seven peritoneal malignant mesotheliomas in women, with no recorded asbestos exposure history by transmission electron microscopy (TEM) energy-dispersive spectroscopy, and electron diffraction. Asbestos fiber burdens were found in six of the cases. Two showed crocidolite, two showed chrysotile, one showed both chrysotile and amosite, and one showed chrysotile and tremolite. Fiber burdens were large, from 56,738 to 1,963,250 fibers per gram wet weight tissue. All fibers were between one and five microns.

An important case was that of the "black swan" peritoneal mesothelioma [64]. This case report was of a case of peritoneal mesothelioma in a 62 year old who had worked for many years in a Canadian mine and mill whose only asbestos exposure was to tremolite free chrysotile. It had been postulated by some [65] even when chrysotile was the predominant asbestos exposure to a mesothelioma, that the real cause was an amphibole contaminant called tremolite. This "black swan" case should have put that theory to rest [64]. Robinson et al. [66] summarizes that issue: "The association of chrysotile with malignant mesothelioma was once thought to be due to contamination of chrysotile with the amphibole tremolite: however current evidence, particularly from electron microscope studies, supports the view that chrysotile itself can cause malignant mesothelioma…." [66 p: 1592].

Experimental data

Experimental data in animals shows that peritoneal injection of asbestos causes mesothelioma. Intra-pleural and intra-peritoneal inoculation of asbestos into a variety of animals, especially rats and hamsters, has been the most frequently used technique for assessment of mesothelioma induction. Details of animal testing were reviewed in the most recent International Agency for Research on Cancer (IARC) monograph on the carcinogenicity of asbestos [67]. Peritoneal injections were used in a series of studies by Davis et al. [68]. In these studies [68], intraperitoneal injections with asbestos of differing types: amosite, chrysotile (including chrysotile from different geologic sources), crocidolite and zeolite, all resulted in a high incidence of peritoneal mesothelioma, demonstrating that if asbestos reaches the peritoneal surface it is capable of inducing mesothelioma.

Maltonia and Minardi [69] injected Sprague Dawley rats intraperitoneally with 25 mg of asbestos of different types. Peritoneal mesotheliomas were found with crocidolite in 95% of male and 100% of female rats, and with Canadian chrysotile in 90% of male and 70% of female rats; other fiber types showed similar results. There was increasing peritoneal tumor response with increasing dose [69]. Frank et al. [70] showed that the UICC Reference chrysotile used in these experiments was free of tremolite. Therefore chrysotile asbestos itself appeared to be the responsible carcinogen.

In humans, a number of studies documented transport of asbestos fibers from the lung to the peritoneum. Dodson et al. [71] reported on asbestos bodies found in mesentery and omentum among 20 individuals in whom mesothelioma was diagnosed. Asbestos bodies were found in the lungs of eighteen, in mesentery samples from five and omentum samples from two individuals; seventeen had uncoated asbestos fibers in at least one extrapulmonary site. Heller [63] found asbestos fiber burdens ranging from 56,738 to 1,963,250 fibers per gram wet weight tissue in the tumor tissue among six of seven women with peritoneal mesothelioma. Kohyama et al. [72] looked for asbestos fibers and ferruginous bodies (iron coated asbestos fibers) in lung parenchyma, lung cancer tissues, pleural plaques, and pleural and peritoneal mesothelioma tissues from thirteen North American insulation workers; fibers were found in extrapulmonary sites. Amosite fibers were fewer in number in both pleural plaques and pleural and peritoneal mesothelioma tissues than in lung tissue, whereas chrysotile fibers were seen in similar numbers as in the lungs. The authors also reported that the likelihood of translocation was strongly related to the thinness of the fiber [72]. Asbestos fibers have been found in mesenteric lymph nodes in autopsies of individuals with asbestos exposure [73], supporting the hypothesis that lymph drainage is an important translocation mechanism for asbestos in the human body [73,74)]. Kurimoto et al. [75] reported this in a case of peritoneal mesothelioma asbestos fibers at concentrations >10,000 fibers/g dry tissue, which were found in all samples of intra-abdominal tissue examined (except in the small intestine.)

Is there a threshold for asbestos exposure and peritoneal mesothelioma?

Most mortality studies of asbestos exposed populations have reported both pleural and peritoneal mesotheliomas when the study design allowed the differentiation. These studies have shown different proportions of pleural/peritoneal ratios in known exposed asbestos populations. The review by Boffetta [19] presented the epidemiologic studies relevant to threshold. The review discussed 20 asbestos cohort studies, which reported specifically on peritoneal mesothelioma. Boffetta [19] concluded there was a strong correlation between pleural and peritoneal deaths, although there was limited information on dose response specifically for peritoneal mesothelioma. Even though Selikoff [35] found that peritoneal mesothelioma occurred as a higher proportion of all mesotheliomas in the highly exposed 17,800-person cohort of asbestos insulators from the U.S. and Canada, low-dose exposure can also cause the disease [50,65]. The report from Browne and Smither [76], often cited to support the conclusion that peritoneal mesothelioma is associated with longer and heavier exposure, had six cases of peritoneal mesothelioma with six months or fewer of exposure, and three cases with two or fewer months.

Studies have shown different proportions of pleural/peritoneal ratios of sites in known low dose exposed asbestos populations. In the study of mesothelioma by Newhouse and Thompson [77] 27 of the 83 patients of confirmed mesothelioma patients studied from London hospitals had peritoneal. This study is noteworthy for its detailed occupational and residential histories as well as pointing out the importance of neighborhood and residential exposures to asbestos, not just occupational asbestos exposure, in mesothelioma causation. Fifteen of the 27 peritoneal mesotheliomas were female cases. Of these

27 male and female cases, fifteen had asbestos factory history (five male, ten female) two males were asbestos laggers or insulators, two females had asbestos exposure from relatives, and four female and three males had no history of asbestos exposure. The authors document that a significant percentage ($p<0.01$) of the mesotheliomas in their study had no documented asbestos occupational or exposure from a relative or household member, but had lived within a half mile of an asbestos factory, and thus presumed significant environmental asbestos exposure [77]. Vianna and Polan [78] provided evidence of an increased risk following non-occupational exposure to asbestos. In addition, a case series from China found that 80% of women, with peritoneal mesothelioma had asbestos exposure including non-occupational exposure [79].

Strauchen [80] studied 2025 autopsies at Mt. Sinai performed 1883-1910, before the widespread use of commercial asbestos and found no cases of mesothelioma. Wojcik et al. [81] studied the New Jersey Cancer Registry and death certificate data for methodological considerations and ICD code changes over time in the last century as applied to attributing mesothelioma as a cause of death. Wojcik et al. [81] systematically showed how a large proportion of mesotheliomas have been missed. Therefore, all our incidence estimates from the last century were likely large underestimates. In a review, Hillerdal [82] concluded that there is no threshold for asbestos exposure for both pleural and peritoneal mesothelioma.

Are peritoneal mesotheliomas in women attributable to asbestos?

There are multiple studies in which women were exposed to amphibole and/or chrysotile asbestos and developed peritoneal mesothelioma [41,43,51-53,57,58,73,79-87] There are additional studies of female peritoneal mesothelioma. Keal [88] reported eight female cases of peritoneal cancers on an examination of records from London hospital records and specimens (four of which were probably from the ovary and four from the peritoneum) who all had asbestosis. In an extension of the Keal [88] study, Hourihane [89] reported thirteen certain and four probable peritoneal mesotheliomas with asbestos fibers or asbestos bodies in their lung tissue specimens. Of the thirteen certain cases, eight were in females; of the uncertain four probable cases, three were in females. Eleven of the certain cases had lung tissue available for examination for asbestos bodies. Seven of the eleven had asbestos bodies, two of which were females, two with not only asbestos bodies, but also fibrosis of the lungs. Enticknap [37] discovered eleven cases of peritoneal mesothelioma among asbestosis cases in England 1948-1953. Eight were male and three female and they were between the ages of 38 and 78 years with a latent period of 20-46 years and asbestos exposures between 10 months and 32 years duration.

Dawson et al. also explored malignant mesothelioma in women. Of the 175 cases reviewed, 29 were peritoneal. Five of the 29 had a direct report of occupational asbestos exposure history. Transmission electron microscopy (TEM) was performed on lung tissue, and 98% of all the mesotheliomas studied showed amphibole asbestos burdens higher than controls, indicating to the authors that asbestos is causal in mesothelioma, including peritoneal, in women [85].

Other factors

Boffetta [19] reviewed other potential causes of peritoneal mesothelioma besides asbestos including simian virus 40 (SV40) and genetics. There is no credible evidence for either as a cause of peritoneal mesothelioma. The animal experimental studies and the epidemiology studies all point to asbestos fibers of all types as the cause of peritoneal mesothelioma. Camargo et al. [90] reviewed occupational exposure to asbestos and ovarian cancer and supported a causative association. They reiterated the diagnostic difficulty of differentiating ovarian cancer from peritoneal mesothelioma in females. The Camargo et al. [90] meta-analysis found asbestos causative for ovarian cancer. Since asbestos causes both peritoneal mesothelioma and ovarian cancer, the epidemiology picture of causation is not as difficult as the differential diagnosis between these diseases in females.

Conclusion

Peritoneal mesothelioma has been documented for over a half century. Historically, and even currently, it is difficult to diagnose. Despite improvements in the last decade, there certainly have been many missed cases over the years, especially in females, often mistakenly labeled as ovarian cancer. It is clear from the epidemiology studies that many types of occupational exposures to all types of asbestos fibers, in many different exposures settings, including mining, making materials out of asbestos and working with asbestos in place, have contributed to peritoneal mesothelioma causation. In addition asbestos neighborhood exposures have been documented to be causally associated. It is clear that both amphibole and chrysotile asbestos exposed people of both sexes in many countries of the world have died from peritoneal mesothelioma. The registry studies predict that peritoneal mesothelioma cases will be substantial for at least the next 35 years due to past and current exposures. The dose-response for peritoneal mesothelioma from asbestos has not been established, and thus to be precautionary, all exposures to asbestos at any dose must be considered potentially causative. The use of asbestos is continuing in many countries of the world, particularly in India and others where worker protections are often lax, and thus the issues reviewed here are of public health importance to prevent future peritoneal mesotheliomas. Post-occupational health surveillance of asbestos workers is necessary for early detection and treatment of cancer in future victims of work that led to asbestos exposures [91].

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Competing interests

Professor Kanarek has served as a consultant to government and international agencies on asbestos health effects, and has been a consultant and witness on plaintiff's litigation concerning asbestos and disease.

Authors contributions

MSK conceived of the work and drafted the manuscript. MKK reviewed the studies cited and edited and helped rewrite the manuscript. Both MSK and MKK read and approved the final manuscript.

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