Malignant Mesothelioma and Its Non-Asbestos Causes

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• ***Context.***—**Although many mesotheliomas are related to asbestos exposure, not all are, and there is increasing information on other causes of mesothelioma.**

Objective.—**To provide a review of non-asbestos causes for malignant mesothelioma.**

Data Sources.—**Review of relevant published literature via PubMed and other search engines.**

Conclusions.—**Currently, most pleural mesotheliomas (70% to 90%) in men in Europe and North America are attributable to asbestos exposure; for peritoneal mesothelioma the proportion is lower. In North America few mesotheliomas in women at any site are attributable to asbestos exposure, but in Europe the proportion is higher and varies considerably by locale. In certain geographic locations other types of mineral fibers (erionite, fluoro-edenite, and probably balangeroite) can induce mesothelioma. Therapeutic radiation for other malignancies is a well-established cause of mesothelioma, with relative risks as high as 30. Carbon nanotubes can also induce mesotheliomas in animals but there are no human epidemiologic data that shed light on this issue. Chronic pleural inflammation may be a cause of mesothelioma but the data are scanty. Although SV40 can induce mesotheliomas in animals, in humans the epidemiologic data are against a causative role. A small number of mesotheliomas (probably in the order of 1%) are caused by germline mutations/deletions of BRCA1-associated protein–1 (*BAP1*) in kindreds that also develop a variety of other cancers. All of these alternative etiologies account for a small proportion of tumors, and most mesotheliomas not clearly attributable to asbestos exposure are spontaneous (idiopathic).**

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There is a complex relationship between malignant mesothelioma and its etiologic agents. The proportion of cases attributable to asbestos varies according to sex, anatomic location, fiber type, occupation, and industry.[1–4] Whilst most pleural mesotheliomas in males are causally related to prior occupational amphibole asbestos exposure, the relationship between asbestos and mesothelioma is subject to considerable sex- and site-specific variation. For workers heavily exposed to commercial forms of amphibole asbestos, between 2% and 18% have developed pleural mesothelioma. Following occupational chrysotile exposure the incidence of pleural mesothelioma ranges from 0% to 0.47% (the latter recorded in chrysotile miners/millers).[5]

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Historically, peritoneal mesotheliomas were associated with heavy commercial amphibole asbestos exposures.[6] Such exposures are now uncommon and currently the epidemiologic evidence correlating time trends, incidence in both sexes, and asbestos exposure suggests that a much smaller fraction of tumors in men are related to asbestos, and very few tumors in women.[7] Recently, one mineralogic study[8] identified almost 50% (20 of 42) of peritoneal mesotheliomas arising in persons with fiber counts within background control values, indicating a likely alternative cause in these tumors.

Owing to the rarity of malignant pericardial and testicular mesotheliomas, analytic epidemiologic studies do not exist but an ecologic study of Surveillance, Epidemiology, and End Results (SEER) data did not support the role for asbestos in these sites.[9,10] Anecdotal case studies of pericardial, gonadal, and localized mesotheliomas report an inconstant relationship with asbestos and alone do not allow for any definite causal association with asbestos to be made.[11–13]

It is clear that not all mesotheliomas are related to asbestos exposure. In this article we review the current literature on non-asbestos–induced mesothelioma.

MINERAL FIBERS OTHER THAN ASBESTOS

Erionite

Erionite is a fibrous form of zeolite that has physical characteristics resembling the amphiboles amosite or crocidolite.[14] Erionite is a potassium aluminum silicate with variable amounts of calcium and sodium, found mostly in

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volcanic regions associated with rhyolitic tuffs. Deposits have been described in the Cappadocian region of Turkey, but some of the highest concentrations of this fiber can be found in the Intermountain West of the United States from Oregon into Mexico and the Sierra Madre Occidental region.[15–17] High amounts of airborne erionite were found in North Dakota after hundreds of miles of roads were surfaced with erionite-containing gravel.[18] More recently, erionite has also been identified in North Eastern Italy.[19]

Baris and colleagues[20] and Artvinli and Baris[21] first reported an outbreak of mesothelioma in 2 small villages in the Anatolian region of Turkey. Some of the villagers also had chronic fibrosing pleurisy. Ferruginous bodies with erionite cores were isolated from the lungs of some of these villagers.[22] The cause of the outbreak was believed to be exposure to erionite fibers used in the whitewash on the exterior of houses in the villages, although some asbestos was also identified in the region.[23] Subsequent studies demonstrated other malignancies among the villagers as well, including lung cancers.[24] With greater than 50% of mesotheliomas in Turkish villagers being caused by erionite, a genetic predisposition to fiber-induced carcinogenesis was proposed by some researchers, although the same was challenged by others.[25,26]

In consideration of the high concentration of erionite fibers in North America as noted above, perhaps it is not surprising that a high incidence of lung cancer and malignant mesothelioma has been identified in 1 rural area with erionite contamination.[27] Kliment et al[28] reported a case of a 47-year-old Mexican emigrant to the United States who was diagnosed with malignant pleural mesothelioma and pleural plaques. He had lived the first 20 to 25 years of his life in Central Mexico, and fiber burden analysis demonstrated considerable quantities of high-aspect ratio erionite fibers in the patient's lung tissue. Oczypok et al[29] reported an additional case of a 53-year-old Mexican emigrant to the United States who was diagnosed with malignant pleural mesothelioma. He moved to the United States as a young adult, and analysis of his lung tissue samples revealed elevated quantities of high-aspect ratio erionite fibers. Similar fibers were identified in rhyolitic tuff material and soil on the family farm where the patient grew up.

Experimental animal studies have confirmed the high carcinogenic potential of erionite, including the production of malignant mesotheliomas.[30–32] Early changes including pleural fibrosis, mesothelial hyperplasia, and mesothelial dysplasia have also been reported.[33,34] Although the exact mechanisms of carcinogenesis are unknown, it is of interest that like asbestos, erionite primes and activates the NLRP3 inflammasome, which in turn triggers an autocrine feedback loop in mesothelial cells. This feedback loop is modulated by the interleukin-1 receptor.[35] Based on the foregoing, more cases of erionite-induced mesothelioma are likely to be identified in regions of the world where this fiber is prevalent and exposures to humans occur.

Fluoro-edenite

Fluoro-edenite is a non-asbestos mineral fiber with similar morphology and composition to the actinolite-tremolite series. It was originally characterized in 1997 from rock deposits taken near the city of Biancavilla (Catania, Eastern Sicily, Italy). The mineral ore was extracted from quarries in Monte Calvario, southeast of Biancavilla and subsequently commercially used as a building material for road paving, and residential and commercial plaster and mortar construction. A 10-fold increase in pleural neoplasms was reported in exposed subjects in a mortality study.[36] Pleural plaques have also been identified in Biancavilla construction workers exposed to fluoro-edenite.[37]

Animal experimental studies show mesothelioma induction following fluoro-edenite implantation in rat peritoneal cavities.[38] In vitro studies show that fluoro-edenite is an inducer of DNA damage and reactive oxygen species production, with overall decreased cell viability.[39] The International Agency for Research on Cancer has subsequently classified fibrous fluoro-edenite as carcinogenic to humans (group 1).[40]

Balangeroite

This gageite-like mineral is a fibrous iron-rich magnesium silicate with a complex structure often intergrown with chrysotile deposits. It comprises around 0.2% to 0.5% contamination of the chrysotile from the San Vittore mine in Balangero, Italy. The fibrous mineral has similarities in morphology but lower biodurability than commercial amphiboles.[41–43] The role of this fibrous amphibolic mineral in the induction of mesothelioma in Balangero, Italy, is controversial with some authors attributing mesotheliomas to it and others questioning its precise role.[44–46] The controversy is complicated by the fact that the Balangero mine occasionally milled imported commercial amphibole from South Africa; this conclusion is supported by the fact that some Balangero chrysotile miners have identifiable commercial amphiboles (crocidolite, amosite) as well as noncommercial amphibole tremolite in lung tissue on mineral analysis.[47,48]

Carbon Nanotubes

Carbon nanotubes have a number of wide applications in industry. They are formed from varying high-aspect ratio graphene cylinders, which can assume a fibrous habit. There has been concern that their close physical similarities to asbestos may pose a health risk.[49] It is recognized that both in vitro and in vivo studies do not necessarily transfer any significance to human populations. Nonetheless, there exist in vitro studies that show carbon nanotube cytotoxicity, and in vivo studies have shown the development of mesothelioma in both genetically modified cancer-sensitized mice and Fischer 344 rats exposed to carbon nanotubes via peritoneal and intrascrotal inoculation, respectively.[50,51] Pleural inflammation has been correlated with fiber length.[52,53] Presently it is not practicable to evaluate at an epidemiologic level whether there exists any association between carbon nanotube exposure and human disease.

Other Minerals

A variety of man-made vitreous fibers have been studied to evaluate their potential to induce mesothelioma in humans. These include rock wool, slag wool, glass fiber, and glass filament. Systematic reviews of synthetic vitreous fibers have concluded that the combined evidence based on epidemiologic and toxicologic data provides little support of any increased risk of mesothelioma following exposure.[54,55] Such man-made fibers have low biopersistence in tissue systems. In contrast, in vivo high-dose chronic inhalational experiments to more biopersistent refractory ceramic fibers

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have been associated with the induction of mesothelioma in Syrian golden hamsters.[56]

Anecdotal case reports linking mesothelioma to metals beryllium and nickel,[57,58] and crystalline silica in sugar cane,[59] have never been supported by analytic epidemiologic studies. At present, the weight of evidence does not support that these minerals are causes of malignant mesothelioma in humans.

RADIATION

Radiation is a recognized pancarcinogen. The evidence linking radiation with malignant mesothelioma in humans has come from 3 sources: first, case reports, case series, and retrospective cohort studies of patients previously receiving therapeutic irradiation for tumors; second, from reported mesothelioma cases following radioactive thorium dioxide contrast medium "Thorotrast" and; third, from studies of atomic energy/nuclear industry workers exposed to prolonged lower levels of irradiation.

Pleural, peritoneal, and pericardial mesotheliomas have all been reported after radiotherapy to treat childhood and adolescent tumors, most notably with Hodgkin and non-Hodgkin lymphoma, germ cell neoplasms, Wilms tumor of the kidney, and breast cancer.[60–66] The latent period has been reported to be between 5 to more than 50 years with radiation-induced mesotheliomas showing an equal male to female ratio.[67,68]

A variety of tumors including pleural and peritoneal mesothelioma, hepatocellular carcinoma, hemangioendothelioma, and cholangiocarcinoma have been reported after intravenous Thorotrast administration.[69–71] The radioactive $^{232}ThO_2$ is insoluble and following injection, deposits in organs and is associated with slow decay and prolonged alpha-ray emission.

Mesotheliomas have also been reported in an occupational setting in radiation technologists exposed to external gamma-ray emission and internal radionuclides.[72] The risk of mesothelioma was also elevated among British Atomic Energy workers employed between 1946 and 1990 and at the Idaho National Engineering and Environmental Laboratory where nuclear processing and demolition occurred, emphasizing the significance of external scatter radiation at lower doses.[73,74]

Animal experiments with ^{239}plutonium dioxide have shown epithelial tumors, sarcomas, and mesotheliomas in around 30% of rats after intraperitoneal injection.[75] Inhalation and intrapleural injection studies showed much lower rates of mesothelioma formation (0.2% and 3.7%, respectively).[76] Aerosolized ^{144}cerium dioxide was found to induce mesothelioma in 0.7% of 566 rats.[77]

A recent review of SEER data found that post external beam radiation mesothelioma risk increased with longer latency and showed a stronger association with peritoneal mesothelioma.[78] A recent genetic profiling study of radiation-induced mesotheliomas showed some copy number gains outnumbering deletions, whereas deletions of 6q, 14q, 17p, and 22q were more frequently seen in those asbestos-associated mesotheliomas tested, signifying potential different molecular mechanisms of induction.[79]

Overall there is consistency of evidence that shows radiation is a risk factor for malignant mesothelioma in directly irradiated tissues and to a lesser extent in tissue remote from the target area.

CHRONIC INFLAMMATION

Anecdotal reports of malignant mesothelioma of the pleura and peritoneum have been reported following chronic serosal inflammatory conditions.[80–85] In the pleura, malignant mesothelioma has occurred after therapeutic plombage post tuberculosis and in individuals with long-standing chronic empyema. Diffuse malignant mesothelioma of the peritoneum has similarly been reported in persons with recurrent peritonitis consequent to relapsing diverticulitis and in individuals with Crohn disease.[86] In young patients, peritoneal mesothelioma has been observed following ventriculoperitoneal shunts for hydrocephaly. Peritoneal mesothelioma has also developed in several individuals with recurrent peritonitis resulting from familial Mediterranean fever.[87]

The mechanisms by which chronic serosal inflammation contributes to the pathogenesis of mesothelioma are not known although it has been suggested that they may be mediated via chronic interleukin-6 production, a regulatory cytokine in acute phase reactions.[88]

SIMIAN VIRUS 40

There has been considerable interest in the possible role of simian virus 40 (SV40) as an etiologic agent for human mesothelioma. SV40 is a DNA polyomavirus that commonly infects Asian macaque monkeys. In naturally immunocompetent hosts the virus generally produces inapparent infection. However, the SV40 virus has been shown to produce pathologic effects in either immunocompromised hosts and/or in nonhost species. SV40 is a transforming virus with tumorigenic effects observed in in vitro studies and following intrapleural or intracardiac injection studies in rodents.[89] Human exposure to SV40 is believed to have largely occurred after administration of contaminated live and attenuated poliovirus vaccines, prepared from infected monkey kidney tissue culture cell lines.[90] It is estimated that between 1954 and 1963, hundreds of millions of people worldwide were likely exposed to SV40 via this route.

The viral genome encodes several oncogenic proteins, most notably large T-antigen (Tag), which inactivate the tumor suppressor activity of p53 and p-retinoblastoma family proteins. Multiple researchers have demonstrated in archived samples the presence of either SV40 Tag DNA segments by polymerase chain reaction methodology or SV40 Tag protein by immunohistochemistry in a proportion of mesotheliomas.[91,92] However, the detection rates of SV40 and human mesothelioma show considerable variability, with a number of laboratories not being able to confirm the presence of SV40 Tag protein or SV40 DNA in their mesothelioma cases.[93,94] Additionally, there have been inconsistencies in the ability of different laboratories to detect SV40 sequences in the same specimens.[95]

Irrespective of discussions regarding the consistency of the viral detection data, the presence of SV40 DNA and protein in mesothelioma does not allow for any causal relationship between the virus and the tumor to be drawn. In humans SV40 may be a passenger virus in the mesothelial cells without causing pathology or tumorigenesis.

Numerous epidemiologic studies have not demonstrated any association between mesothelioma incidence and polio vaccine administration.[96–98]

Overall the role of SV40 as an etiologic agent in human mesotheliomas is unconvincing.

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BAP-1 CANCER-PREDISPOSITION SYNDROME

There has been much recent interest in the role of *BAP-1* (BRCA1-associated protein–1) in mesothelioma. BAP-1 is a nuclear localizing deubiquitinating hydrolase enzyme.[99] The *BAP-1* gene is located on chromosome band 3p21. BAP-1 protein regulates genes concerned with cell cycle progression, DNA damage repair, and cellular differentiation. BAP-1 expression may be lost in tumors by deletion of the gene or by a variety of mutations that prevent deubiquitinating activity and nuclear localization. These findings have led to the suggestion that *BAP-1* is a tumor suppressor gene and this idea is supported by the finding of an increase in spontaneous development of ovarian, lung, and breast carcinomas, and a few mesotheliomas ex asbestos in about half of mice with genetically engineered *BAP-1* mutations that match those found in BAP-1 cancer syndrome families.[100]

Germline *BAP-1* mutations have been implicated in the induction of mesothelioma. Germline *BAP-1* mutations are inherited in an autosomal dominant manner and confer a high risk of mesothelioma in individuals and in affected families. Recently, a BAP-1 hereditary cancer predisposition syndrome has been described,[101] which includes in affected patients/families uveal and cutaneous melanomas, renal clear cell carcinomas, atypical spitzoid nevi (so-called melanocytic BAP-1–mutated atypical intradermal tumors), and probably other neoplasms including basal cell carcinoma and intrahepatic cholangiocarcinoma.[102]

The incidence of *BAP-1* germline mutations is not well defined. Testa et al[101] reported that 7.7% (2 of 26) of spontaneous mesotheliomas carried *BAP-1* germline mutations; however, 3 subsequent series totalling approximately 300 apparently sporadic cases examined with targeted deep sequencing revealed only 1 patient with a germline mutation,[103–105] suggesting that germline BAP-1 cancer syndrome cases account for at most a very small percentage of all mesotheliomas. Carbone et al[106] reported a BAP-1 cancer syndrome kindred of around 80 000 individuals, with the kindred traceable back 9 generations to a couple that immigrated to the United States in the 1700s. This observation raises the possibility that germline *BAP-1* mutations actually only occur in a few kindreds.

Because individuals carrying *BAP-1* germline mutations are believed to start with only 1 abnormal allele, it has been proposed that germline *BAP-1*–associated mesotheliomas may reflect relatively low-level asbestos-induced mutations of the second allele in genetically susceptible hosts.[107] There is some support for this idea from animal models. Xu et al[108] generated *BAP-1*$^{+/-}$ mice and reported that these mice developed mesothelioma at twice the rate of wild-type mice after intraperitoneal injection of crocidolite asbestos; the tumors also occurred earlier in the *BAP-1*$^{+/-}$ mice. No mesotheliomas were found in *BAP-1*$^{+/-}$ mice not exposed to asbestos. Napolitano et al[109] observed that *BAP-1*$^{+/-}$ mice had a significantly higher incidence of mesothelioma after intraperitoneal injection of crocidolite at a dose that rarely induced mesothelioma in wild-type mice. However, other animal studies have yielded conflicting results, with Kadariya et al[100] observing mesothelioma formation without asbestos exposure in *BAP-1* knockout mice.

The only study that, to our knowledge, has attempted to look at mesothelioma incidence in germline mutation and control groups is that of Ohar et al,[107] who reported germline *BAP-1* mutations in 9 of 150 patients with mesothelioma and a family history of cancer (6%) as compared to none in series of asbestos-exposed control case individuals without a family history of cancer. The authors concluded that these findings support a role for low-level asbestos exposure in the genesis of mesotheliomas. Unfortunately, the study design is flawed, since no details of the asbestos exposures were provided. Because of the vastly different potencies of chrysotile versus commercial amphibole exposure in producing mesothelioma and the importance of dose, latency, and tumor site, one would need groups properly matched for these features in order to determine whether *BAP-1* germline mutations actually do increase the mesothelioma risk from asbestos exposure.

The interpretation of the human data is muddied by a lack of detail about putative asbestos exposures. Baumann et al[110] reported that none of their 23 patients with germline mutations had occupational asbestos exposure and commented that these tumors either were caused by low-level environmental exposure to asbestos or were not caused by fiber carcinogenesis at all. However, the female preponderance and the fact that half of the tumors were peritoneal argue against low-level asbestos carcinogenesis, since most asbestos-induced mesotheliomas are pleural, and one would expect that asbestos carcinogenesis augmented by a genetic predisposition should maintain this ratio; indeed, if the presumption is that these patients had low-level inhalational exposures, it is hard to explain how they could develop more peritoneal than pleural mesotheliomas, since that kind of ratio has only been observed in a few worker cohorts with very high exposure to commercial amphibole (amosite or crocidolite) exposure.

Germline *BAP-1* mutations may have implications in relation to prognosis. Baumann et al[110] reported survival data on 23 patients with germline *BAP-1* mutations and concluded that germline *BAP-1*–mutated mesotheliomas are associated with longer survival than the usual sporadic mesotheliomas. The male to female ratio was 9:14, and half of the patients were younger than 55 years. Of note, 10 of the tumors were peritoneal, 10 pleural, and 3 recorded as originating from both sites. The median survival for the pleural tumors was 2 years and for the peritoneal tumors, 10 years. The authors concluded that germline *BAP-1*–mutated mesotheliomas are associated with a longer survival than the usual sporadic mesothelioma. This idea must be viewed in light of the fact that 13 of the 23 subjects (56%) had a second malignancy, so the apparent longer survivals may reflect a lead time bias for subjects undergoing frequent medical surveillance. However, studies on mesotheliomas with somatic *BAP-1* mutations (eg, Leblay et al[111]) have also found that such tumors are associated with longer survival, so loss of BAP-1 may in fact confer a better prognosis.

SPONTANEOUS (IDIOPATHIC) MESOTHELIOMAS

All of the etiologies discussed above account for a small proportion of mesotheliomas. After excluding tumors caused by asbestos exposure, the next largest fraction is spontaneous (idiopathic) mesothelioma.

The scientific evidence for a background rate of spontaneous mesotheliomas arising in unrelated fashion to asbestos comes from the following sources: first, no temporal relation between malignant mesothelioma in women and historic use of commercial forms of asbestos—the age-adjusted mesothelioma incidence in US women from 1973 to 2008 has been stable[3,112]; second, the

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Mesotheliomas Attributable to Asbestos		
Author, y, Source	**Country**	**Mesotheliomas Attributable to Asbestos**
Spirtas et al,[1] 1994, US Cancer Registries, Veteran Administration Hospital	United States	88% pleural mesotheliomas – men 58% peritoneal mesotheliomas – men 23% pleural + peritoneal mesothelioma – women
Rake et al,[2] 2009, UK Cancer Registry and physician records	United Kingdom	86% mesotheliomas – men 38% mesotheliomas – women
Price and Ware,[3] 2009, SEER	United States	78% mesotheliomas – men <10% mesotheliomas – women
Offermans et al,[116] 2014, Netherlands Cohort Study	the Netherlands	32%–34% all cases
Lacourt et al,[117] 2014, population case-control study	France	87% mesotheliomas – men 65% mesotheliomas – women
Gennaro et al,[118] 2005, Liguria Mesothelioma Registry	Italy	85% mesotheliomas – men 42.5% mesotheliomas – women
Gorini et al,[119] 2002, Tuscany Registry	Italy	85% mesotheliomas – men 26% mesotheliomas – women
Marinaccio et al,[120] 2012, Italian Mesothelioma Registry	Italy	86% pleural mesothelioma – men 63% pleural mesothelioma – women

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

occurrence of malignant mesotheliomas in children aged below the lowest recorded latent period for occupational asbestos-associated mesotheliomas[113]; third, cases of malignant mesothelioma in persons with no history of asbestos exposure despite extensive investigation and/or with detectable fibers on mineral analysis[114]; fourth, the spontaneous occurrence of various tumors including malignant mesothelioma in laboratory animals.[115]

One approach to determining the proportion of mesotheliomas that are spontaneous is to examine the fraction reported as being caused by asbestos exposure. Various reports on this topic exist in the literature (see the Table).[1–3,116–120] However, the exact proportion of such spontaneous mesotheliomas as a fraction of all mesotheliomas is difficult to ascertain in a coherent fashion across studies because of varying study designs, different patient selection schemes, different views of what occupations entail significant asbestos exposure, as well as differences in the historic use of amphibole versus chrysotile asbestos between countries.

From the Table it is clear that there is a definite and sometimes quite substantial fraction of mesotheliomas that have no identifiable external cause, and that, not surprisingly, this fraction is greater in women than men (for the simple reason that more men than women had occupational levels of asbestos exposure) and the fraction is greater in the peritoneum than pleura. The fraction with no identifiable external cause also is reported as higher in the United States as compared with European data sources.

Henley et al[112] recently combined data from the National Program for Cancer Registries and SEER for mesotheliomas diagnosed between 2003 and 2008 and showed that overall female mesothelioma rates were flat, whereas male rates continue to decline. The results noted that the anatomic site of mesothelioma differed between men and women at different ages. Below 45 years of age, irrespective of anatomic site, mesothelioma was more common in women than men and peritoneal disease predominates, observed in 51% of cases. This observed age-, sex-, and site-specific demographic, as discussed earlier, argues against a fiber-induced carcinogenesis in which male sex and pleural disease predominate.

Historically, peritoneal mesotheliomas have been typically observed following heavy cumulative commercial amphibole asbestos exposures and nowadays such cases are increasingly uncommon. Recent updated trend analysis shows that the incidence of peritoneal mesotheliomas among both men and women shows little or no association with commercial asbestos use trends in the United States.[7] Trends in some European countries also show that a large fraction of peritoneal mesothelioma is unrelated to asbestos with flat age-adjusted incidence rates in men and women.[121,122] However, there is observed geographic variations in the attributable fraction to asbestos. Marinaccio et al,[123] analyzing the Italian National Mesothelioma Register, concluded in their analysis that 76% (of 188) of male and 34% (of 50) of female peritoneal mesotheliomas had occupational asbestos exposure.

Recent studies have shown that many mesotheliomas harbor somatic mutations of *BAP-1*, *NF2*, and to a lesser extent, *SETD2*, *TP53*, *DDX3X*, *ULK2*, *RYR2*, *CPAF45*, *SETDB1*, and *DDX51*.[124] Deletions of the 9p21 region containing $p16^{INK4A}$, *p15*, *p14*, and *MTAP* are common in mesotheliomas. There also appear to be molecular differences between pleural and peritoneal mesothelioma cells in genomic copy number losses and gains, indicating that different genetic pathways may be implicated at the different site.[79,125] However, there are no data thus far that would suggest specific etiologies associated with 1 or any combination of these mutations/deletions.

For pericardial and tunica vaginalis testis mesothelioma no analytic case-control epidemiologic studies exist to evaluate the relation between these tumors and asbestos. Ecologic studies using SEER data show trends in the incidence of pericardial and tunica vaginalis testis mesotheliomas that do not match those of pleural mesothelioma,[9,10] and meta-analytic studies of large occupational cohorts with heavy asbestos exposures report no cases of pericardial or tunica vaginalis testis mesothelioma.[4] For pericardial and tunica vaginalis testis mesothelioma the available evidence suggests most cases are spontaneous (idiopathic) mesotheliomas.

CONCLUSIONS

Mesothelioma has an evolving relationship with its varied causes. This is because first, the total number of cases attributable to asbestos is continuously diminishing in line with diminishing historic exposures. The scientific literature indicates that there is a definite and sometimes substantial fraction of mesotheliomas that have no history of asbestos

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exposure. This fraction is greater in the United States than in European countries, more in women than men, and greater in peritoneal than pleural mesotheliomas. In approximate terms, some 60% to 90% of mesotheliomas in US women (pleural and peritoneal sites, respectively), and a substantial proportion of peritoneal mesotheliomas in men are likely unrelated to asbestos.[1,3,7,8,121,122] This is particularly so in younger patients (younger than 45 years). Second, there is an increasing awareness of alternative biopersistent mineral fibers that can induce mesothelioma in certain geographic locations. For a minority of patients with mesothelioma (for whom there is no history of asbestos exposure) there will be some discernible and specific carcinogenic agent (either a biopersistent mineral fiber or radiation exposure) that has induced the tumor. Third, and most significantly, there has been considerable expansion in the understanding of molecular genetics in mesothelioma.

As a cancer, mesothelioma is a genetic disease. In substantially less than 1% of patients with mesothelioma (when there is no external agent exposure), the mesothelioma will be induced by a specific inherited genetic mutation; scientific evidence presently favors the role of *BAP-1*. These genetically inherited mesotheliomas arise at a younger age, show no sex or clear anatomic site predilection with some involving multiple serosal sites. The presence of other concomitant cancers, in particular ocular, or cutaneous melanomas, and renal cell carcinomas, should prompt clear consideration of an inherited cancer predisposition syndrome and *BAP-1* mutational status should be evaluated. The role of mutated BAP-1 in mesothelioma and its interaction with carcinogens is an evolving area. The available scientific literature is conflicting in animal studies. At present, the limited human data would favor the proposition that germline *BAP-1* mutation can induce mesothelioma ex asbestos.

References

1. Spirtas R, Heineman EF, Bernstein L, et al. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med*. 1994;51(12):804–811.

2. Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer*. 2009;100(7):1175–1183.

3. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. *Crit Rev Toxicol*. 2009;39(7):576–588.

4. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*. 2000;44(8):565–601.

5. Gibbs GW, Berry G. Epidemiology and risk assessment. In: Craighead JE, Gibbs AR, eds. *Asbestos and Its Diseases*. Oxford, United Kingdom: Oxford University Press; 2008:94–119.

6. Browne K, Smither W J. Asbestos-related mesothelioma: factors discriminating between pleural and peritoneal sites. *Br J Ind Med*. 1983;40(2):145–152.

7. Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005. *Cancer Causes Control*. 2009; 20(6):935–944.

8. de Ridder GG, Kraynie A, Pavlisko EN, et al. Asbestos content of lung tissue in patients with malignant peritoneal mesothelioma: a study of 42 cases. *Ultrastruct Pathol*. 2016;40(3):134–141.

9. Mezei G, Chang ET, Mowat FS, Moolgavkar SH. Epidemiology of mesothelioma of the pericardium and tunica vaginalis testis. *Ann Epidemiol*. 2017;27(5):348–359.

10. Lowry SJ, Weiss NS. Geographic distribution of incidence of pericardial and paratesticular mesotheliomas in the USA. *Cancer Causes Control*. 2016; 27(12):1487–1489.

11. Patel J, Sheppard MN. Primary malignant mesothelioma of the pericardium. *Cardiovasc Pathol*. 2011;20(2):107–109.

12. Attanoos RL, Gibbs AR. Primary malignant gonadal mesotheliomas and asbestos. *Histopathology*. 2000;37(2):150–159.

13. Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. *Am J Surg Pathol*. 2005;29(7):866–873.

14. Dogan AU, Dogan M, Hoskins JA. Erionite series minerals: mineralogical and carcinogenic properties. *Environ Geochem Health*. 2008;30(4):367–381.

15. Baris YI, Grandjean P. Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite. *J Natl Cancer Inst*. 2006;98(6): 414–417.

16. Ortega-Guerrero MA, Carrasco-Núñez G. Environmental occurrence, origin, physical and geochemical properties, and carcinogenic potential of erionite near San Miguel de Allende, Mexico. *Environ Geochem Health*. 2014; 36(3):517–529.

17. Sheppard R. *Occurrences of Erionite in Sedimentary Rocks of the Western United States*. Denver, CO: US Department of the Interior, US Geological Survey; 1996. Open file report 96-108.

18. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A*. 2011;108(33): 13618–13623.

19. Giordani M, Mattioli M, Ballirano P, et al Geological occurrence, mineralogical characterization, and risk assessment of potentially carcinogenic erionite in Italy. *J Toxicol Environ Health B Crit Rev*. 2017;20(2):81–103.

20. Baris YI, Sahin AA, Ozesmi M, et al. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgup in Anatolia. *Thorax*. 1978;33(2):181–192.

21. Artvinli M, Baris YI. Malignant mesotheliomas in a small village in the Anatolian region of Turkey: an epidemiologic study. *J Natl Cancer Inst*. 1979; 63(1):17–22.

22. Sebastien P, Gaudichet A, Bignon J, Baris YI. Zeolite bodies in human lungs from Turkey. *Lab Invest*. 1981;44(5):420–425.

23. Rohl AN, Langer AM, Moncure G, Selikoff IJ, Fischbein A. Endemic pleural disease associated with exposure to mixed fibrous dust in Turkey. *Science*. 1982;216(4545):518–520.

24. Baris B, Demir AU, Shehu V, Karakoca Y, Kisacik G, Baris YI. Environmental fibrous zeolite (erionite) exposure and malignant tumors other than mesothelioma. *J Environ Pathol Toxicol Oncol*. 1996;15(2–4):183–189.

25. Dogan AU, Baris YI, Dogan M, et al. Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey. *Cancer Res*. 2006; 66(10):5063–5068.

26. Metintas M, Hillerdal G, Metintas S. Malignant mesothelioma due to environmental exposure to erionite: follow-up of a Turkish emigrant cohort. *Eur Resp J*. 1999;13(3):523–526.

27. Ortega-Guerrero MA, Carrasco-Nunez G, Barragan-Campos H, Ortega MR. High incidence of lung cancer and malignant mesothelioma linked to erionite fibre exposure in a rural community in Central Mexico. *Occup Environ Med*. 2015;72(3):216–218.

28. Kliment CR, Clemens K, Oury TD. North American erionite-associated mesothelioma with pleural plaques and pulmonary fibrosis: a case report. *Int J Clin Exp Pathol*. 2009;2(4):407–410.

29. Oczypok EA, Sanchez MS, van Orden DR, et al. Erionite-associated malignant pleural mesothelioma in Mexico. *Int J Clin Exp Pathol*. 2016;9(5): 5722–5732.

30. Maltoni C, Minardi F, Morisi L. Pleural mesotheliomas in Sprague-Dawley rats by erionite: first experimental evidence. *Environ Res*. 1982;29(1):238–244.

31. Suzuki Y, Kohyama N. Malignant mesothelioma induced by asbestos and zeolite in the mouse peritoneal cavity. *Environ Res*. 1984;35(1):277–292.

32. Ozesmi M, Patiroglu TE, Hillerdal G, Ozesmi C. Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. *Br J Ind Med*. 1985; 42(11):746–749.

33. Hill RJ, Edwards RE, Carthew P. Early changes in the pleural mesothelium following intrapleural inoculation of the mineral fibre erionite and the subsequent development of mesothelioma. *J Exp Pathol*. 1990;71(1):105–118.

34. Fraire AE, Greenberg SD, Spjut HJ, et al. Effect of erionite on the pleural mesothelium of the Fischer 344 rat. *Chest*. 1997;111(5):1375–1380.

35. Hillegass JM, Miller JM, MacPherson MB, et al. Asbestos and erionite prime and activate the NLRP3 inflammasome that stimulates autocrine cytokine release in human mesothelial cells. *Part Fibre Toxicol*. 2013;10:39–52.

36. Paoletti L, Batisti D, Bruno C, et al. Unusually high incidence of malignant pleural mesothelioma in a town of eastern Sicily: an epidemiological and environmental study. *Arch Environ Heath*. 2000;55(6):392–398.

37. Rapisarda V, Ledda C, Ricceri V, et al. Detection of pleural plaques in workers exposed to inhalation of natural fluoro-edenite fibres. *Oncol Lett*. 2015; 9(5):2046–2052.

38. Soffritti M, Minardi F, Bua L, et al. First experimental evidence of peritoneal and pleural mesotheliomas induced by fluoro-edenite fibres present in Etnean volcanic material from Biancavilla (Sicly, Italy). *Eur J Oncol*. 2004;9(3): 169–175.

39. Cardile V, Renis M, Scifo C, et al. Behaviour of the new asbestos amphibole fluor-edenite in different lung cell systems. *Int J Biochem Cell Biol*. 2004;36(5):849–860.

40. Grosse Y, Loomis D, Guyton KZ, et al; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes. *Lancet Oncol*. 2014;15(13): 1427–1428.

41. Groppo C, Tomatis M, Turci F, et al. Potential toxicity of nonregulated asbestiform minerals: balangeroite from the western Alps, part 1: identification and characterization. *J Toxicol Environ Health A*. 2005;68(1):1–19.

42. Turci F, Tomatis M, Gazzano E, et al. Potential toxicity of nonregulated asbestiform minerals: balangeroite from the western Alps, part 2: oxidant activity of the fibers. *J Toxicol Environ Health A*. 2005;68(1):21–39.

Downloaded from http://meridian.allenpress.com/doi/pdf/10.5858/arpa.2017-0365-RA by guest on 30 March 2023

43. Gazzano E, Riganti C, Tomatis M, et al. Potential toxicity of nonregulated asbestiform minerals: balangeroite from the western Alps, part 3: depletion of antioxidant defences. *J Toxicol Environ Health A*. 2005;68(1):41–49.

44. Piolatto G, Negri E, La Vecchia C, et al. An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. *Br J Ind Med*. 1990;47(12):810–814.

45. Turci F, Tomatis M, Compagnoni R, et al. Role of associated mineral fibres in chrysotile asbestos health effects: the case of balangeroite. *Ann Occup Hyg*. 2009;53(5):491–417.

46. Pira E, Pelucchi C, Piolatto PG. Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. *Occup Environ Med*. 2009; 66(12):805–809.

47. Browne K. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure [author reply in *Ann Occup Hyg*. 2001;45(4):336–338]. *Ann Occup Hyg*. 2001;45(4):327–329.

48. Pooley FD. Investigation of the importance of tremolite in the production of asbestos related disease and its relevance as a long term indicator of chrysotile exposure. Report prepared for the Health and Safety Executive, United Kingdom; 1990.

49. Donaldson K, Poland CA, Murphy FA, et al. Pulmonary toxicity of carbon nanotubes and asbestos: similarities and differences. *Adv Drug Deliv Rev*. 2013; 65(15):2078–2086.

50. Sakamoto Y, Nakae D, Fukumori N, et al. Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male fischer 344 rats. *J Toxicol Sci*. 2009;34(1):65–76.

51. Takagi A, Hirose A, Nishimura T, et al. Induction of mesothelioma in p53 +/- mouse by intraperitoneal application of multi-wall carbon nanotube. *J Toxicol Sci*. 2008;33(1):105–116.

52. Poland CA, Duffin R, Kinloch I, et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol*. 2008;3(7):423–428.

53. Donaldson K, Murphy FA, Duffin R, et al. Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. *Part Fibre Toxicol*. 2010;7:5. doi:10.1186/1743-8977-7-5.

54. Marsh GM, Gula MJ, Youk AO, et al. Historical cohort study of US man-made vitreous fiber production workers: II, mortality from mesothelioma. *J Occup Environ Med*. 2001;43(9):757–766.

55. Boffetta P, Donaldson K, Moolgavkar S, et al. A systematic review of occupational exposure to synthetic vitreous fibers and mesothelioma. *Crit Rev Toxicol*. 2014;44(5):436–449.

56. Mast RW, Hesterberg TW, Glass LR, et al. Chronic inhalation and biopersistence of refractory ceramin fibers in rats and hamsters. *Environ Health Perspect*. 1994;102(suppl 5):207–209.

57. Gold C. A primary mesothelioma involving the rectovaginal septum and associated with beryllium. *J Pathol Bacteriol*. 1967;93(2):435–442.

58. Hueper WC. Experimental studies in metal carcinogenesis, I: nickel cancers in rats. *Tex Rep Biol Med*. 1952;10(1):167–186.

59. Newman RH. Fine biogenic particulate silica fibers in sugarcane: a possible hazard. *Ann Occup Hyg*. 1986:30(3):365–370.

60. Austin MB, Fechner RE, Roggli VL. Pleural malignant mesothelioma following Wilms' tumor. *Am J Clin Pathol*. 1986;86(2):227–230.

61. Shannon VR, Nesbitt JC, Libshitz HI. Malignant pleural mesothelioma after radiation therapy for breast cancer: a report of two additional patients. *Cancer*. 1995;76(3):437–441.

62. Small GR, Nicolson M, Buchan K, et al. Pericardial malignant mesothelioma: a latent complication of radiotherapy? *Eur J Cardiothorac Surg*. 2008;33(4):745–747.

63. Teta MJ, Lau E, Sceurman BK, et al. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. *Cancer*. 2007;109(7):1432–1438.

64. Li X, Brownlee NA, Sporn TA, Mahar A, Roggli VL. Malignant (diffuse) mesothelioma in patients with hematologic malignancies: a clinicopathologic study of 45 cases. *Arch Pathol Lab Med*. 2015;139(9):1129–1136.

65. Antman KH, Corson JM, Li FP, et al. Malignant mesothelioma following radiation exposure. *J Clin Oncol*. 1983;1(11):695–700.

66. Anderson KA, Hurley WC, Hurley BT, et al. Malignant pleural mesothelioma following radiotherapy in a 16-year-old boy. *Cancer*. 1985;56(2): 273–276.

67. Crew KD, Neugut AI, Antman KH. Malignant mesothelioma following radiation: advances in pathogenesis, diagnosis and translational therapies. In: Pass HI, Vogelzang NJ, Carbone M, eds. *Malignant Mesothelioma*. New York, NY: Springer; 2005:350–363.

68. Roggli VL, Oury TD, Moffatt EJ. Malignant mesothelioma in women. In: Rosen PP, Fechner RE, eds. *Anatomic Pathology*. Vol 2. Chicago, IL: ASCP Press; 1998:147–163.

69. Travis LB, Hauptmann M, Gaul LK, et al. Site-specific cancer incidence and mortality after cerebral angiography with radioactive thorotrast. *Radiat Res*. 2003;160(6):691–706.

70. Maurer R, Egloff B. Malignant peritoneal mesothelioma after cholangiography with thorotrast. *Cancer*. 1975;36(4):1381–1385.

71. Stey C, Landolt-Weber U, Vetter W, et al. Malignant peritoneal mesothelioma after Thorotrast exposure. *Am J Clin Oncol*. 1995;18(4):313–331.

72. Horie A, Hiraoka K, Yamamoto O, et al. An autopsy case of peritoneal malignant mesothelioma in a radiation technologist. *Acta Pathol Jpn*. 1990;40(1): 57–62.

73. Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. *Cancer Causes Control*. 2009;20(8):1237–1254.

74. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res*. 2015;183(6):620–631.

75. Sanders CL, Jackson TA. Induction of mesotheliomas and sarcomas from 'hot spots' of $^{239}PuO_2$ activity. *Health Phys*. 1972;22(6):755–759.

76. Sanders CL. Pleural mesotheliomas in the rat following exposure to $^{239}PuO_2$. *Health Phys*. 1992;63(6):695–697.

77. Hahn FF, Lundgren DL. Pulmonary neoplasms in rats that inhaled cerium–144 dioxide. *Toxicol Pathol*. 1992;20(2):169–178.

78. Farioli A, Ottone M, Morganti AG, et al. Radiation-induced mesothelioma among long-term solid cancer survivors: a longitudinal analysis of SEER database. *Cancer Med*. 2016;5(5):950–959.

79. Borczuk AC, Pei J, Taub RN, et al. Genome-wide analysis of abdominal and pleural malignant mesothelioma with DNA arrays reveals both common and distinct regions of copy number alteration. *Cancer Biol Ther*. 2016;17(3):328–335.

80. Hillerdal G, Berg J. Malignant mesothelioma secondary to chronic inflammation and old scars: two new cases and review of the literature. *Cancer*. 1985;55(9):1968–1972.

81. Kodama Y, Hoshi S, Minami M, et al. Malignant mesothelioma associated with chronic empyema with elevation of serum CYFRA19: a case report. *Biosci Trends*. 2008;2(6):250–254.

82. Roviaro GC, Sartori F, Calabro F, Varoli F. The association of pleural mesothelioma and tuberculosis. *Am Rev Respir Dis*. 1982;126(3):569–571.

83. Roggli VL, McGavran MH, Subach JA, Sybers HD, Greenberg SD. Pulmonary asbestos body counts and electron probe analysis of asbestos body cores in patients with mesothelioma: a study of 25 cases. *Cancer*. 1982;50(11): 2423–2432.

84. Gentiloni N, Febbraro S, Barone C, et al. Peritoneal mesothelioma in recurrent familial peritonitis. *J Clin Gastroenterol*. 1997;24(4):276–279.

85. Riddell RH, Goodman MJ, Moossa AR. Peritoneal malignant mesothelioma in a patient with recurrent peritonitis. *Cancer*. 1981;48(1):134–139.

86. Butnor KJ, Pavlisko EN, Sporn TA, et al. Malignant peritoneal mesothelioma and Crohn disease. *J Clin Pathol*. 2017;70(3):228–232.

87. Livneh A, Langevitz P, Pras M. Pulmonary associations in familial Mediterranean fever. *Curr Opin Pulm Med*. 1999;5(5):326–331.

88. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science*. 2008;320(5876):674–677.

89. Cicala C, Pompetti F, Carbone M. SV40 induces mesotheliomas in hamsters. *Am J Pathol*. 1993;142(5):1524–1533.

90. Rizzo P, Di Resta I, Powers A, et al. Unique strains of SV40 in commercial polio vaccines from 1955 not readily identifiable with current testing for SV40 infection. *Cancer Res*. 1999;59(24):6103–6108.

91. Pass H, Donington P, Wu P, et al. Human mesotheliomas contain the simian virus 40 regulatory region and large tumor antigen DNA sequences. *J Thorac Cardiovasc Surg*. 1998;116(5):854–859.

92. Shivapurkar N, Wiethege I, Wistuba E, et al. Presence of simian virus 40 sequences in malignant mesotheliomas and mesothelial cell proliferations. *J Cell Biochem*. 1999;76(2):181–188.

93. Manfredi JJ, Doug J, Liu WJ, et al. Evidence against a role for SV40 in human mesothelioma. *Cancer Res*. 2005;65(7):2602–2609.

94. Lundstig A, Dejmek A, Eklund C, Filinic I, Dillner J. No detection of SV40 DNA in mesothelioma tissues from a high incidence area in Sweden. *Anticancer Res*. 2007;27(6B):4159–4161.

95. Strickler HD. A multicenter evaluation of assays for detection of SV40 DNA and results in masked mesothelioma specimens. *Cancer Epidemiol Biomarkers Prev*. 2001;10(5):523–532.

96. Strickler HD, Goedert JJ, Devesa SS, Lajey J, Fraumeni JF, Rosenberg PS. Trend in U.S. pleural mesothelioma incidence rates following simian virus 40 contamination of early poliovirus vaccines. *J Natl Cancer Inst*. 2003;95(1):38–45.

97. Engles EA, Katki HA, Nielsen NM, et al. Cancer incidence in Denmark following exposure to poliovirus vaccine contaminated with simian virus 40. *J Natl Cancer Inst*. 2003;95(7):532–539.

98. Stratton K, Almario DA, McCormick M. *Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer*. Washington, DC: The National Academy of Sciences; 2002.

99. Wang A, Papneja A, Hyrcza M, et al. Gene of the month: BAP1. *J Clin Pathol*. 2016;69(9):750–753.

100. Kadariya Y, Cheung M, Xu J, et al. BAP-1 is a bona fide tumor suppressor: genetic evidence from mouse models carrying heterozygous germline BAP-1 mutations. *Cancer Res*. 2016;76(9):2836–2844.

101. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43(10):1022–1025.

102. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. *J Transl Med*. 2012;10:179.

103. Sneddon S, Leon JS, Dick IM, et al. Absence of germline mutations in BAP1 in sporadic cases of malignant mesothelioma. *Gene*. 2015;563(1):103–105.

104. Rusch A, Ziltener G, Nackaerts K, Weder W, Stahel RA, Felley-Bosco E. Prevalence of BRCA-1 associated protein 1 germline mutation in sporadic malignant pleural mesothelioma cases. *Lung Cancer*. 2015;87(1):77–79.

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105. Betti M, Casalone E, Ferrante D, et al. Inference on germline BAP1 mutations and asbestos exposure from the analysis of familial and sporadic mesothelioma in a high-risk area. *Genes Chromosomes Cancer*. 2015;54(1):51–62.

106. Carbone M, Flores EG, Emi M, et al. Combined genetic and genealogic studies uncover a large BAP1 cancer syndrome kindred tracing back nine generations to a common ancestor from the 1700s. *PLoS Genet*. 2015;11(12): e1005633.

107. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. *Cancer Res*. 2016;76(2):206–215.

108. Xu J, Kadariya Y, Cheung M, et al. Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma. *Cancer Res*. 2014; 74(16):4388–4397.

109. Napolitano A, Pellegrini L, Dey A, et al. Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma. *Oncogene*. 2016;35(15):1996–2002.

110. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis*. 2015;36(1):76–81.

111. Leblay N, Leprêtre F, Le Stang N, et al. BAP1 is altered by copy number loss, mutation, and/or loss of protein expression in more than 70% of malignant peritoneal sesotheliomas. *J Thorac Oncol*. 2017;12(4):724–733.

112. Henley SJ, Larson TC, Wu M, et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003–2008. *Int J Occup Environ Health*. 2013;19(1):1–10.

113. Fraire AE, Cooper S, Greenberg SD, et al. Mesothelioma of childhood. *Cancer*. 1988;62(4):838–847.

114. Kraynie A, de Ridder GG, Sporn TA. Malignant mesothelioma not related to asbestos exposure: analytical scanning electron microscopic analysis of 83 cases and comparison with 442 asbestos-related cases. *Ultrastruct Pathol*. 2016; 40(3):142–146.

115. Maekawa A, Odashima S. Spontaneous tumors in ACI/N rats. *J Natl Cancer Inst*. 1975;55(6):1437–1445.

116. Offermans NS, Vermeulen R, Burdorf A, et al. Occupational asbestos exposure and risk of pleuralmesothelioma, lung cancer, and laryngeal cancer in the prospective Netherlands cohort study. *J Occup Environ Med*. 2014;56(1):6–19.

117. Lacourt A, Gramond C, Rolland P, et al. Occupational and non-occupational attributable risk ofasbestos exposure for malignant pleural mesothelioma. *Thorax*. 2014;69(6):532–539.

118. Gennaro V, Ugolini D, Viarengo P, et al. Incidence of pleural mesothelioma in Liguria Region, Italy (1996-2002). *Eur J Cancer*. 2005;41(17): 2709–2714.

119. Gorini G, Silvestri S, Merler E, et al. Tuscany mesothelioma registry (1988-2000): evaluation of asbestos exposure. *Med Lav*. 2002;93(6):507–518.

120. Marinaccio A, Binazzi A, Marzio DD, et al; ReNaM Working Group. Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. *Int J Cancer*. 2012 ;130(9):2146–2154.

121. Hemminki, K, Li X. Time trends and occupational risk factors for peritoneal mesothelioma in Sweden. *J Occup Environ Med*. 2003;45(4):451–455.

122. Burdorf, A, Jarvholm B, Siesling S. Asbestos exposure and differences in occurrence of peritoneal mesothelioma between men and women across countries. *Occup Environ Med*. 2007;64(12):839–842.

123. Marinaccio A, Binazzi A, Di Marzio D, et al. Incidence of extrapleural malignant mesothelioma and asbestos exposure, from the Italian national register. *Occup Environ Med*. 2010;67(11):760–765.

124. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016;48(4):407–416.

125. Takeda M, Kasai T, Enomoto Y, et al. Comparison of genomic abnormality in malignant mesothelioma by the site of origin. *J Clin Pathol*. 2014;67(12):1038–1043.

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