Five years update on relationships between malignant pleural mesothelioma and exposure to asbestos and other elongated mineral particles

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FIVE YEARS UPDATE ON RELATIONSHIPS BETWEEN MALIGNANT PLEURAL MESOTHELIOMA AND EXPOSURE TO ASBESTOS AND OTHER ELONGATED MINERAL PARTICLES

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ABSTRACT

Despite the reduction of asbestos worldwide consumption and production due to the ban or restriction of asbestos uses in more than 50 countries since the seventies, malignant mesothelioma remains a disease of concern. Asbestos is still used, imported and exported in several countries, and the number of mesothelioma deaths may be expected to increase in the next decades in these countries. Asbestos exposure is the main risk factor for malignant pleural mesothelioma, but other types of exposures are linked to the occurrence of this cancer. Although recent treatments improve the quality of life of patients with mesothelioma, malignant pleural mesothelioma remains an aggressive disease. Recent treatments have not resulted in appreciable improvement in survival, and then the development of more efficient therapies is urgently needed. The development of novel therapeutic strategies is dependent on our level of knowledge of the physiopathological and molecular changes that mesothelial cells acquired during the neoplastic process. During the past five years, new findings have been published on the etiology, epidemiology, molecular changes and innovative treatments of malignant pleural mesothelioma. This review aims to update the results of recent researches developed on the first three topics. It will focus on the attributable risk of asbestos exposure in men and women, on co-exposure to other minerals and other elongated mineral particles or high aspect ratio nanoparticles. Recent data obtained on genomic and gene alterations, pathways deregulations, and predisposing factors are summarized.

INTRODUCTION

After the early recognition of the occurrence of lung fibrosis and cancer in workers occupationally exposed to asbestos fibers (Cooke 1924; Doll 1955; Sebastien et al. 1975; Selikoff, Churg, and Hammond 1964; Simson 1928), and the discovery of the relationship to malignant mesothelioma (Wagner, Sleggs, and Marchand 1960), numerous epidemiological and experimental studies were developed to document the relationships between asbestos exposure and human thoracic malignancies, such as lung cancer and malignant pleural mesothelioma. However, from the middle/end of the 20th century, research has shown that asbestos fibers are not the only type of mineral elongated particles responsible for lung and pleural fibrosis and cancer, in particular malignant mesothelioma. Human exposure to other natural mineral fibers has been associated to malignant mesothelioma, such as erionite, fluoro-edenite, winchite, richterite and tremolite (IARC 2012; Grosse et al. 2014; Dunning et al. 2012). Exposures to irradiation and SV40 virus as co-factor have been also implicated in the development of malignant mesothelioma (Chirieac et al. 2013; Farioli et al. 2013; Jasani and Gibbs 2012).

With the decrease in asbestos uses, some man-made mineral fibers have replaced these natural mineral fibers, especially mineral wool, glass fibers, and refractory ceramic fibers (RCFs), leading to the development of epidemiological studies in populations exposed to these fibers. IARC classified some man-made fibers (special-purpose fibers and RCFs) as carcinogenic in experimental animals, but lacking of epidemiological data; these fibers were classified in the 2B group, as possibly carcinogenic to humans. These researches were situated in the landscape of investigations developed to understand the health effects resulting from exposure to asbestos fibers and other elongated mineral particles (EMPs) (NIOSH 2011). More recently, with the development of nanotechnologies, including carbon nanotubes, the historical of asbestos diseases allowed to propose that high aspect ratio nanoparticles (HARNs) have a special cancer potential to the lungs and mesothelium, and to develop a paradigm for hazard assessment (Aschberger et al. 2010; Donaldson and Poland 2012; Tran et al. 2011).

The question of co-exposure is an important challenge to identify and define risk factors. In occupational situations, workers previously exposed to asbestos may have been exposed to

replacement fibers, and the potential effects of co-exposures also need to be investigated. Otherwise, to anticipate further issues related to exposure to other EMPs and HARNs, a better knowledge of the mechanism of action and biological signature of fibers, other EMPs and HARNs is needed for regulation and prevention purposes (NIOSH 2011). Moreover, co-exposures to asbestos and silica are also of interest as silica is not known to induce mesothelioma, but joint effects might modify the incidence.

Mesothelioma arises from the neoplastic transformation of mesothelial cells. For studying the carcinogenic effects of fibers, mesothelioma represents a specific disease, due to its relationship with exposure to mineral fibers. Mesothelioma is linked to past-asbestos exposure in about 80% of the cases. Investigation of physio-pathological changes in mesothelioma, including genomic changes, is of particular interest to link the alterations to the mechanism of action of the fibers. Other extra-thoracic cancers are associated to asbestos exposure, but the link is weaker. A link between asbestos exposure and ovarian cancer is clearly established, based on the study of several strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos, and on a meta-analysis (Bunderson-Schelvan et al. 2011; Camargo et al. 2011; IARC 2012; Reid et al. 2013). Moreover, a causal association between asbestos exposure and laryngeal cancer has been also established (IARC 2012; Menvielle et al. 2016; Offermans, Vermeulen, Burdorf, Goldbohm, Kauppinen, et al. 2014). Recently, an association between occupational asbestos exposure and pharyngeal squamous cell carcinoma in men has been also reported (Langevin et al. 2013). Finally, since the last revaluation of asbestos related cancers by IARC in 2012, associations between asbestos exposure and digestive cancers have been reported. Indeed, significant links between mortality due to stomach cancer or oesophagus cancer have been well documented (Offermans, Vermeulen, Burdorf, Goldbohm, Keszei, et al. 2014). For stomach cancer, a meta-analysis reported a meta-Standardized Mortality Ratio (SMR) = 1.15 [95% Confidence Interval (CI): 1.03-1.27] and for oesophagus cancer, the meta-SMR was 1.24 [95% CI: 1.13-1.38], with little evidences of heterogeneity (Fortunato and Rushton 2015; Li, Tang, and Wang 2015). Likewise, the role of asbestos exposure in colorectal cancers remains controversial (Bunderson-Schelvan et al. 2011; Clin et al. 2011; Fang, Le, and Band 2011; IARC 2012). A suggestive relationship for colon cancer incidence was recently found, but with less conclusive results for rectal cancer (Offermans, Vermeulen, Burdorf, Goldbohm, Keszei, et al. 2014).

Despite the decrease in asbestos production, and asbestos ban in several countries, mesothelioma remains a disease of concern, because of the particularly long latency period between the time since first exposure to asbestos and the onset of the disease with an average of 40 years (30-50 years) (Robinson, Musk, and Lake 2005; Rolland et al. 2010). The World Health Organization (WHO) has estimated that mesothelioma, lung cancer, and asbestosis are responsible for about 107,000 deaths worldwide (Delgermaa et al. 2011; Kameda et al. 2014; Stayner, Welch, and Lemen 2013). Bang et al. estimated that the importance of premature mortality and loss of potentially productive years of life attributable to asbestos-related diseases were very stable between 1999 and 2010 in United States (Bang et al. 2014). This finding underlies the importance to maintain prevention efforts and to monitor surveillance of asbestos-related diseases temporal trends (Bang et al. 2014). Moreover, the outcome of patients with MPM is poor, long-term survival is rare, with the majority of patients succumbing to their disease within 2 years of diagnosis(Davidson 2015). An increase of only 3 months in overall survival with anti-VEGF and anti-folate therapy has been reported (Zalcman et al. 2015). A strong development of researches to prevent and treat this cancer is needed. In recent years, efforts have been made to improve diagnosis and prognosis, and to design treatments more adapted to the morphological and biological characteristics of the tumors (Musk et al. 2011; Robinson, Musk, and Lake 2005).

So far, the histological diagnosis of mesothelioma remains based on 3 predominant subtypes: epithelioid (50 to 60%), sarcomatoid (10 to 20%), biphasic corresponding comprising epithelioid and sarcomatoid components (25 to 35%) and a smaller percentage of desmoplastic forms (1 to 2%) (Husain et al. 2013). Well-differentiated papillary mesothelioma is an uncommon form of epithelioid mesothelioma, that is generally a non-invasive tumor with low malignant potential and that occurs mostly in women in the peritoneum, but also in pleura, pericardium, and tunica vaginalis. Some rare cases of well-differentiated papillary mesothelioma with invasive foci are now recognized as stressed in several publications (Churg et al. 2014; Galateau-Salle et al. 2004). Recent biological studies of cancers allow the identification of biomarkers, and benefit of high throughput cell biology technologies, so-called “omics researches”, that permit to characterize the genetic, metabolic and physiological changes linked to cancer. In this area of researches, new findings have been recently reported on mesothelioma.

The aim of the present work was to summarize the literature data published during the last five years, focusing on epidemiology of malignant pleural mesothelioma (MPM), with special interest to data on co-exposure to asbestos and other fibers, and to silica. Recent advances in our knowledge on the biology of mesothelioma will be summarized. They concern the genetic and epigenetic alterations of the tumor, and possible links to asbestos, and their impact in the treatment of mesothelioma. At the cell level, some new data are related to the deregulation of signaling pathways, and stemness-related features of tumor cells.

HUMAN EXPOSURE TO ASBESTOS AND OTHER EMPs AND MALIGNANT MESOTHELIOMA

In this review, asbestos refers to the natural minerals that are considered in industries and used in experimental-related studies devoted to the investigation of the pathological effects of asbestos. Asbestos is the commercial name given to a family of natural silicate mineral fibers; it refers to the 6 commercial types of asbestos (two varieties: feathery serpentines (chrysotile), and long and thin fibers of amphiboles (crocidolite, amosite, anthophyllite, tremolite and actinolite)) (Case et al. 2011). According to WHO methodology, fibers are defined as particles thinner than 3µm, longer than 5µm and of aspect-ratio >3. An EMP is an elongated mineral particle thinner than 3µm, longer than 5µm and of aspect-ratio >3, independently of its chemistry. Then asbestos fibers are also EMP. Other non-asbestiform, non-commercial amphiboles, as found in the vermiculite mines in Libby, such as winchite, richterite and tremolite, are EMP as far as their dimensions correspond to the definition. There is evidence to support the association between exposure to these fibers and the occurrence of asbestos-related diseases, especially nonmalignant pleural abnormalities, lung cancer, and malignant mesothelioma (Antao, Larson, and Horton 2012; Carlin et al. 2015).

Recent epidemiological advances linked to asbestos exposure

Mesothelioma is mainly attributable to occupational or environmental asbestos exposure. All forms of asbestos fibers are carcinogenic to human, and both pleural and peritoneal mesotheliomas are associated with asbestos exposure (IARC 2012). Despite ban of asbestos in some countries, and decline of worldwide production and use of asbestos, these minerals still represent a health problem (Stayner, Welch, and Lemen 2013). Asbestos consumption is increasing in other parts of the world such as India and much of Asia. Since recent publications have reviewed epidemiological data on asbestos exposure, we did not make a comprehensive review of the relevant literature, but instead summarized the main findings reported in these reviews. Briefly, in a worldwide literature review, all types of asbestos fibers were found to cause mesothelioma, including chrysotile (Kanarek 2011). Another review examining the patterns of asbestos exposure (production, export and use) and of asbestos-related

diseases concluded that all forms of asbestos fibers are carcinogenic to humans (Frank and Joshi 2014). The potency of the different fiber types for lung cancer risk was recently discussed, and authors have questioned the already reported and accepted potency factors for asbestos-related lung cancer, suggesting that differences might be lower (van der Bij et al. 2013). Toxicological and epidemiological studies on effects of airborne fibers were also considered for risk assessment (Lippmann 2014). This author concluded that the effects are dependent on fiber diameter, length, and biopersistence; biopersistent fibers, thinner than 0.1 μm and longer than 5 μm being the most relevant for mesothelioma (Lippmann 2014). Nevertheless, in an exhaustive review focusing on available information from peer-review publications on the size-dependent pathogenic effects of asbestos fibers reported in experimental *in vivo* and *in vitro* studies, fibers shorter than 5 μm were less pathogenic than fibers longer than 5 μm, but the cut-off of 5 μm as the limit for length is used for metrological analyses using light microscopy and is not based on scientific evidence (Boulanger et al. 2014)

Occupational exposure to asbestos

Because of their specific chemical and physical properties asbestos fibers have been used in a variety of building construction materials and in a wide range of manufactured goods (IARC 2012). Early investigations on asbestos health effects concerned workers in the production and handling of asbestos products. Over the last decades, a shift has been observed in the exposure history of MPM cases, from primary asbestos workers (handling raw asbestos material) to end-users often exposed when installing asbestos products or handling asbestos materials that are still in place (Scherpereel et al. 2010). Elevated risks of MPM were found in sheet-metal workers, plumbers, metal molders, welders, core-makers, cabinetmakers and firefighters, and in the industries of construction, shipbuilding, manufacturing of metal products, chemicals, and railroad and aircraft equipment (Pukkala et al. 2014; Rolland et al. 2010).

An English case-control study estimates lifetime risks for British-born male in the 1940s with ≥10 years of asbestos exposure before the age of 30 years-old. Lifetime risks were estimated at 5.9% for carpenters, 2% for electricians, plumbers and painters, 0.8% for other construction workers, 1.8% for other recognized high-risk occupations and 0.6% in other industries where asbestos may be encountered (Rake et al. 2009). Otherwise, a British cohort study did not find

sufficient evidence that greater intensity asbestos exposures would lead to shorter mesothelioma latencies (Frost 2013).

Environmental exposure to asbestos

MPM is also linked to environmental exposure to asbestos, either in areas of the world where asbestos (generally tremolite) exists as a geological component of the soil (Corsica in France, Cyprus, Turkey, and New Caledonia) or to neighborhood exposures in people living close to asbestos mines or factories, such as the residents of Wittenoom, an Australian town near a crocidolite mine, or in Casale Monferrato, an Italian town next to an asbestos cement factory (Baumann et al. 2011; Ferrante et al. 2015; Hillerdal 1999). Residential distances from industrial sources of asbestos and wind conditions have an impact on the risk of developing environmental mesothelioma (Kurumatani and Kumagai 2008; Tarres et al. 2013). Domestic cases are described in households of asbestos workers, mainly because of asbestos exposure via clothes used at work and washed at home (Lacourt et al. 2014).

Attributable risk of asbestos exposure for MPM

Few studies estimated the attributable risk (AR) of asbestos exposure for MPM (Agudo et al. 2000; Aguilar-Madrid et al. 2010; Lacourt et al. 2014; Rake et al. 2009; Spirtas et al. 1994). While for men, AR of occupational asbestos exposure ranged from 83.1% [99% IC: 74.5-91.5] in France to 85% in the United Kingdom (Lacourt et al. 2014; Rake et al. 2009), it was systematically lower in women from 22.5% [95% CI: 3.2-71.7] in the United States to 41.7% [99% CI: 25.3-58.0] in France (Lacourt et al. 2014; Spirtas et al. 1994). Two studies estimated an AR of occupational asbestos exposure without stratifying by sex; it was 62.0% [99% CI: 48.4-75.6] including all probabilities of exposure to asbestos in Spain and 44% in Mexico (Agudo et al. 2000; Aguilar-Madrid et al. 2010).

Besides occupational asbestos exposure, the French and UK studies estimated the AR of non-occupational asbestos exposure among subjects never occupationally exposed to asbestos. A difference between men and women still persisted, but the AR was higher in women than in men: in France, the AR among men was 20.0% [99% CI: 33.5-73.5] against 38.7% [99% CI: 8.4-69.0]

in women and in United Kingdom, the AR among men was 1.3% against 16% in women (Rake et al. 2009). In total, from 86.4% to 87.3% of male cases and from 38.1% to 64.8% of female cases were attributed to any source of asbestos exposure (Lacourt et al. 2014; Rake et al. 2009). Thus, these recent data highlight that in women, the AR of asbestos exposure for MPM is enhanced when considering only occupational exposure to asbestos, in comparison with both occupational and non-occupational exposures (38.1% vs 64.8%), whereas this AR remains relatively stable in men (86.4% and 87.3%, respectively) (Lacourt et al. 2014). Nevertheless, an unexplained part of AR for MPM in women (about a third) still persists due to weak asbestos exposure, very remote in time of exposure or other still unknown etiological factors.

In an exhaustive study of 318 female MPM cases in the French National Mesothelioma Surveillance Program between 1998 and 2009, 4 clusters were identified: occupational exposure to asbestos and man-made vitreous fibers (MMVF) (7.9%); radiation exposure during radiotherapy (12.9%); any asbestos exposure (19.8%); and "non-exposure" characteristics (59.4%) (Camiade et al. 2013).

Co-exposures to asbestos and MMVF or silica particles

This part of the review of the literature focuses on the joint effect of asbestos and other EMPs, namely, MMVF. Workers previously exposed to asbestos may have been further exposed to other particles. The question of co-exposure is an important challenge to identify and define risk factors. Co-exposures to asbestos replacement fibers are emerging. Co-exposures to silica are also of interest as silica is not known to induce MM but joint effects might modify the incidence of MPM. Then, these associations are also considered here. From cohort studies of workers, the joint effect of asbestos and other particles has not been studied likely due to the small number of observed mesothelioma cases and the availability of exposure data for both asbestos and other mineral particles.

From case-control studies, only 3 population-based studies (Germany, Canada and France) attempted to study the joint effect of occupational asbestos exposure and other mineral particles (Lacourt et al. 2013; Lacourt et al. 2014; Pintos et al. 2009; Rodelsperger et al. 2001). In the three studies, all cases were incident and histologically confirmed male cases. Whereas occupational

asbestos exposure and MMVF exposure were retrospectively assessed by expertise in the German and Canadian study, job-exposure matrices were used in the French study.

The German study included 125 cases and 125 controls recruited from Hamburg between 1988 and 1991 (Rodelsperger et al. 2001). Whereas odds ratios (ORs) for subjects only exposed to asbestos and for subjects only exposed to MMVF were 19.8 [95% CI: 4.7-83] and 15.1 [95% CI: 1.05-218], respectively, OR increased by a factor of four when subjects were exposed to both asbestos and MMVF (OR=61.3 [95% CI: 12.9-292]). The Canadian study included 35 cases and 1,965 control subjects recruited from Montreal between 1979 to 1986 or 1996 to 2001 (Pintos et al. 2009). OR was increased for subjects ever exposed to both asbestos and MMVF (OR=8.0 [95% CI: 3.4–18.9]) compared to those only exposed to asbestos (OR=1.2 [95% CI: 0.3-4.3]). While both studies reported a potential synergistic joint effect of asbestos and MMVF, it should be noted that 95% CI were wide and overlapped each other. Besides, the joint effect of asbestos and MMVF was studied using an ever vs never exposed indicator for both exposures. Thus, the increased OR observed for subjects exposed to both asbestos and MMVF may be due to confounding by asbestos exposure. The cumulative asbestos exposure may be higher in subjects exposed to both asbestos and MMVF compared to subjects only exposed to asbestos leading to an artificially increased OR. In the Canadian study, authors further adjusted for the duration of asbestos exposure in their models but results were unchanged.

To account for confounding by asbestos exposure, the French study conducted analysis looking at the dose response relationship between occupational asbestos exposure and MPM in the presence or absence of additional exposure to mineral wool, crystalline silica or refractory ceramic fibers (Lacourt et al. 2013; Lacourt et al. 2014). This study included 1,199 cases and 2,379 controls recruited from several districts of France between 1987-1996 and 1998-2006. Authors systematically reported that the effect of occupational asbestos exposure was increased in presence of a co-exposure. When considering the entire dataset, for subjects occupationally exposed only to asbestos between 1 to 10 fibers/ml.yrs, the OR was 3.7 [95% CI: 2.4-5.6] compared to subjects not exposed to asbestos, mineral wool and silica. However, it increased to 7.1 [95% CI: 5.0-10.1], 8.9 [95% CI: 4.5-17.6] and 10.3 [95% CI: 7.0-15.0] when subjects were additionally exposed to mineral wool, silica or to the three mineral particles respectively (Lacourt et al. 2013). When restricting the dataset to subjects ever exposed to asbestos (988 cases and 1,125 controls), the OR for subjects occupationally exposed only to asbestos at 50 fibers/ml-

yrs was 1.9 [95% CI: 1.4-2.5] and was 12.8 [95% CI: 4.7-35.1] when subjects were additionally exposed to refractory ceramic fibers (Lacourt et al. 2014). While the issue of the joint effect of asbestos and other mineral particles should be further explored, from the actual literature, the hypothesis of a synergistic joint effect should be considered.

Association between pleural plaques and MPM or lung cancer

Pleural plaques are benign fibrotic lesions thickening parietal or diaphragmatic pleura, composed of avascular and acellular collagen connective tissue. Pleural plaques are mostly linked to past asbestos exposure. Recently, a follow-up study from the French Asbestos-Related Diseases Cohort (ARDCO), based on a screening Program for Asbestos-Related Diseases in asbestos-exposed male subjects (n = 5,287), reported a strong association between the occurrence of MPM and pleural plaques detected by CT scan (unadjusted hazard ratio (HR) = 8.9 [95% CI: 3.0-26.5]; adjusted HR = 6.8 [95% CI: 2.2-21.4] after adjustment for time since first exposure and cumulative exposure index to asbestos). The results of this study suggest that pleural plaques are an independent risk factor of MPM (Pairon et al. 2013). More recently, a significant association between pleural plaques and lung cancer mortality was reported after adjustment for smoking status and asbestos exposure in this same cohort among 1,118 subjects (20.7%) with pleural plaques after 6-year follow-up (Pairon et al. 2014).

Human exposure to other EMPs and MPM

Amphiboles, other than asbestos

Asbestos is not the only EMP associated to an enhanced risk of mesothelioma development. Other amphiboles (winchite and richterite, so-called “Libby amphiboles”) found in vermiculite mines in Montana (USA) induce mesothelioma in human, and show biological actions, in animals and cultured cells, similar to asbestos fibers (Cyphert et al. 2012; Dunning et al. 2012; Hillegass et al. 2013; Kodavanti et al. 2014). In a recent publication, an elevated percentage of mesothelioma in women, and individuals younger than 55 years, was reported in Southern Nevada, as due to environmental exposure to amphiboles (Baumann, Buck, et al. 2015). In these areas, several types of amphiboles were found, as in Libby (winchite, richterite and tremolite), as

well as actinolite) (Baumann, Buck, et al. 2015). Elsewhere, an excess of mesothelioma has been observed in iron ore miners in Northeastern Minnesota, where mining and processing of taconite iron ore generate non-asbestos EMP of undefined type (Lambert et al 2016). Fluoro-edenite is an endemic natural amphibole fiber present in Biancavilla soil in Sicilia (Italy) and also present in the major quarry from which building materials have been extensively extracted. The risk estimated of incidence of MPM in Biancavilla town is higher than in the Sicilian region (Biggeri et al. 2004; Bruno et al. 2014; Comba, Gianfagna, and Paoletti 2003). Recently, a probable link between the presence of pleural plaques and exposure to fluoro-edenite fibers in subjects not exposed to asbestos has been reported through residing in Biancavilla and through their occupation (Rapisarda et al. 2015). IARC classified fibrous amphibole fluoro-edenite as carcinogenic to humans (Group 1) (Grosse et al. 2014).

Erionite

Erionite belongs to another group of natural minerals, the zeolite group. It is endemic in Turkey and western United States, also strongly associated with the risk of development of mesothelioma (Carbone et al. 2011; Jasani and Gibbs 2012). Recently, erionite has been also localized in Central Mexico and associated to a high risk of mesothelioma and lung cancer (Ortega-Guerrero et al. 2015).

Synthetic vitreous fibers

Synthetic vitreous fibers (SVF) are subdivided into glass wool, rock wool, slag wool, refractory ceramic fibers and other special-purpose fibers. The IARC classification of SVF was based on chronic inhalation and intra-tracheal instillation studies of special-purpose glass fibers resulted in significant increases of MPM in rats and hamsters. Insulation glass wool, continuous glass filament, rock (stone) wool and slag wool are not classifiable as to their carcinogenicity to humans (Group 3) (IARC 2002). Recently, the existence of little epidemiologic and toxicological evidence concerning a potential link between SVF exposure and risk of mesothelioma occurrence was reported (Boffetta et al. 2014). RCFs have a carcinogenic potency in animals, causing lung cancer and mesothelioma (IARC 2002). In epidemiological studies, a significant association has

been previously reported, with the occurrence of pleural plaques detected on chest X-ray, but no significant link was established between MPM and RCF exposure in humans (Lockey et al. 1996; Lockey et al. 2002). According to our knowledge, no new epidemiological data is available. Presently, the link between respiratory cancers occurrence and SVF exposure is still unclear, but some fibers may have characteristics able to induce pathogenic effects (Greim et al. 2014; Lippmann 2014).

Other elongated nanoparticles (Carbon nanotubes, carbon nanofibers, tubular clays)

The health effects of other types of HARNs, carbon nanotubes (CNTs), carbon nanofibers (CNFs) and nanotubular clays are a present subject of researches (Genaidy et al. 2009; Jaurand 2015; Kayat et al. 2011; Lecouvet 2015). Numerous studies were recently performed to investigate the health effects of CNTs. CNTs are new technological material receiving a large range of industrial and biomedical applications due to their particular electronic and mechanical properties (Kayat et al. 2011; Aschberger et al. 2010; Shvedova et al. 2009; Tran, Zhang, and Webster 2009; Upadhyayula et al. 2009). Industrial and economic development of nanotechnology requires the political and scientific communities to consider issues relating to safety of these materials (Fatkhutdinova, Khaliullin, and Shvedova 2015; Jaurand and Jean 2016). CNTs belong to the category of HARNs, with diameters less than or equal to 100 nanometers, and length that may reach several dozen of micrometers. There are several classes of CNTs, single-walled, double-walled and multi-walled carbon nanotubes. The main route of human occupational exposure is suggested to be inhalation and dermal contact, but environmental exposure could occur regarding the uses of CNTs (Aschberger et al. 2010; Tran, Zhang, and Webster 2009). The ecotoxicological impact of CNTs is also of concern (Upadhyayula et al. 2009). Presently, there is no epidemiological data on the effects of CNTs on human health. Experimental studies are available, showing that some CNTs may have biological effects similar to asbestos (cellular damage, pulmonary inflammation, genotoxicity) (Genaidy et al. 2009; Jaurand 2015; Kayat et al. 2011). A recent IARC monograph reviewed the literature on the toxicological effects of CNTs. One type of multi-walled CNTs (MWCNT-7) was classified as possibly carcinogenic to humans (Group 2B), and single-walled CNTs and multi-walled CNTs

excluding MWCNT-7 as not classifiable as to their carcinogenicity to humans (Group 3) (Grosse et al. 2014).

Other naturally occurring minerals of nanotubular structure, such as the natural clay minerals, halloysite and imogolite, are used in many industrial applications (Vahedi and Pasbakhsh 2015). Halloysite forms multi-layered hollow cylinders and imogolite forms single walled tubes. Halloysite has been used commercially in ceramics and potteries, and as reinforcing agents. Due to their properties, these aluminosilicate nanotubes have potential applications in catalysis, molecular separation, and as loading agents in polymers. Both have potential applications in the area of drug delivery systems and nanobiomedicine (Abdullayev and Lvov 2011; Rapisarda et al. 2015). They can be used as unmodified or surface-modified depending on their uses. A few studies have investigated the toxicity of naturally occurring clays. So far, halloysite nanotubes do not appear to exert a cytotoxic effect while some imogolite nanotubes may be cytotoxic and genotoxic. However, due to the insufficient number of studies and wide diversity of the nanotubes it is not possible to draw conclusions on their potential impact on human health (Jaurand In press; Maisanaba et al. 2015).

RECENT ADVANCES IN OUR KNOWLEDGE ON THE MOLECULAR BIOLOGY OF MALIGNANT MESOTHELIOMA

Genomic alterations in MPM

The genes with the highest frequency of genetic alteration in MPM are *CDKN2A* (cyclin-dependent kinase 2A), *NF2* (neurofibromin type 2) and *BAP1* (BRCA1 (breast cancer 1)-associated protein 1) tumor suppressor genes (COSMIC v2, http://cancer.sanger.ac.uk/cosmic) (Forbes et al. 2015).

The first two are known for a long time, but recurrent somatic mutations in *BAP1* gene were more recently identified (Bott et al. 2011). *BAP1* is a tumor suppressor gene located on 3p21, a chromosome region frequently lost in mesothelioma (Jean et al. 2012). The percentage of *BAP1* mutations in sporadic MPM reported in the literature depended on the method of analysis; most of sequencing methods did not allow detection of large deletion in tumor samples due to the presence of normal contaminated cells. The percentage of mutations in tumor samples was 20-23%, as determined by Sanger sequencing (Testa et al. 2011; Zauderer et al. 2013). Bott et al.

found 42% *BAP1* loss or mutation in primary mesothelioma by integrated genomic analysis and FISH (Fluorescence In Situ Hybridization) (Bott et al. 2011). Higher rate (61%) was reported in DNA isolated from cultures of mesothelioma tumors, in a Japanese study using Sanger sequencing, array CGH (Comparative Genomic Hybridization) and real-time polymerase chain reaction (PCR) (Yoshikawa et al. 2012). A similar rate was reported in 22 frozen biopsies of US patients (Nasu et al. 2015). Sanger sequencing detected mutations in DNA in 27% of the cases and a total of 60% was found with further MLPA analysis (Multiplex Ligation-dependent Probe Amplification). These results point out that an integrated approach is required to determine the frequency of *BAP1* genetic alterations in mesothelioma.

Inactivation of *CDKN2A, NF2* or *BAP1* genes in mice enhance the frequency of mesothelioma after exposure to asbestos, showing that they are driver genes of mesothelial carcinogenesis (Altomare et al. 2011; Fleury-Feith et al. 2003; Xu et al. 2014). *CDKN2A* gene encodes two cell cycle regulators $p16^{INK4A}$ and $p14^{ARF}$. This gene is located on a locus in 9p21, frequently lost by homozygous deletion in MPM, which also contains the *CDKN2B* gene explaining also the frequent alterations to this later gene (Jean et al. 2011). *NF2* gene encodes the merlin multifunctional protein that plays a role in cell adhesion and regulates many signaling pathways involved in cell proliferation including Hippo pathway. *BAP1* gene encodes a nuclear deubiquitinase particularly involved in transcription regulation and remodeling of chromatin whose functions are not fully known. Other tumor suppressor genes are mutated at lower frequencies in MPM as the well-known *TP53* gene involved in the carcinogenesis of several cancers (COSMIC v2) (Forbes et al. 2015) or the *LATS2* gene (Bott et al. 2011; Murakami et al. 2011). *LATS2* gene encodes a serine-threonine kinase that is a member of the Hippo pathway as merlin (*NF2*). Members of other signaling pathways have mutation in MPM, such as the hedgehog pathway, but at a lower frequency than Hippo pathway (Lim et al. 2013).

In contrast to tumor suppressor genes, oncogene mutations are infrequent in MPM. Mutations in *KRAS*, *BRAF*, *EGFR* and *PIK3CA* genes have been described earlier in the literature and the low frequency rate of mutation was confirmed by recent studies (Mezzapelle et al. 2013; Schildgen et al. 2015; Shukuya et al. 2014). Oncogenic recurrent mutations in the *TERT* promoter were also identified at a low frequency, but are strongly associated with sarcomatoid MPM. These mutations are involved in the overexpression of the gene encoding the catalytic subunit of telomerase (Tallet et al. 2014).

There are only few NGS (Next Generation Sequencing) data for MPM. Recently, the *CUL1* gene, a component of an ubiquitin ligase, was suggested as a driver gene for mesothelial carcinogenesis, as the frequency of damaging *CUL1* mutations was greater than the significance threshold expected for driver mutations in an exome sequencing study of 22 MPM (Guo et al. 2015). Genetic alterations of member genes of the mSWI/SNF chromatin remodeling complex and of the Hippo pathway, others than *NF2* and *LATS2* genes, were found in another NGS studies of 8 and 16 MPM, respectively (Miyanaga et al. 2015; Yoshikawa et al. 2012). The largest NGS study including 123 formalin-fixed, paraffin-embedded (FFPE) biopsies showed a complex landscape view of the somatic genomic alterations in MPM (Lo Iacono et al. 2015). The pattern of MPM mutation would be clarified with the expected release of TCGA (The Cancer Genome Atlas, https://tcga-data.nci.nih.gov) exome data, which included 87 MPM.

Genomics of MPM

Several omics studies have been conducted on MPM to identify chromosomal alterations, epigenetic modifications and gene expression deregulations.

Analyzes of chromosomal alterations in mesothelioma, performed by various techniques, such as cytogenetic analysis of standard karyotype, classical CGH or SNP (single nucleotide polymorphism) arrays, showed that numerous chromosomal abnormalities are associated with MPM. They also resulted in a fairly reliable mapping of the recurrent altered regions (Jean et al. 2012; Melaiu et al. 2013). Recently, studies using high-resolution oligonucleotide microarrays allowed to define smaller chromosome regions with biallelic deletion, which are potentially informative about the presence of tumor suppressor genes (Klorin et al. 2013). Spectral karyotyping (SKY) and RNA sequencing identified more precisely chromosome translocations in MPM, whose recurrence remains to be determined (Klorin et al. 2013; Panagopoulos et al. 2013).

Methylome analyses by micro-array demonstrated that MPM are characterized by alterations of the global epigenetic profile and show specific patterns of gene methylation as compared to normal pleura or other tumors (Christensen et al. 2009; Goto et al. 2009). Specific DNA methylation profile of MPM could be used as diagnostic and prognostic biomarker (Christensen et al. 2009; Goto et al. 2009), but no precise epigenetic signature was defined since these two initial publications (Vandermeers et al. 2013). However, recent data support the role of an

epigenetic mechanism in mesothelial carcinogenesis by identifying new genes or miRNAs acting as tumor suppressors, which are downregulated by DNA methylation (Cheng et al. 2013; Cioce et al. 2014).

Transcriptome microarray studies on MPM are quite numerous, more than twenty before 2011. They were carried out either on cultured cell lines either on tumor samples, and generally include few tumor cases, three studies exceeding thirty cases (Gordon et al. 2003; Gordon et al. 2005; Holloway et al. 2006) and one study approaching one hundred cases (Lopez-Rios et al. 2006). These studies mainly focused on the comparison between MPM and normal pleura or mesothelial cells, between histological subtypes of MPM or between MPM and other invasive or metastasizing tumors in the pleura, mainly lung adenocarcinoma. The identified biomarkers were listed in recent reviews (Jean et al. 2012; Melaiu et al. 2012). Given the inconsistency between results of transcriptome studies, large independent series of MPM will be needed to validate specific MPM biomarkers. Recently, expression deregulation of 59 of 119 biomarkers, selected from data mining study combined with a literature review of transcriptomic studies, were validated by RT-qPCR in an independent series of 22 MPM and 20 normal pleura (Melaiu et al. 2015). Transcriptomic approaches have a diagnostic interest as demonstrated by gene expression ratio analysis (De Rienzo et al. 2013) and a prognostic interest as shown by older studies, which defined predictors of survival based on gene expression (Gordon et al. 2009; Gordon et al. 2003; Gordon et al. 2005; Lopez-Rios et al. 2006; Pass et al. 2004). These studies also allow to clarify the molecular inter-tumor heterogeneity of MPM. Two older studies classified MPM into subgroups, which correlated with histological types (Gordon et al. 2005; Hoang et al. 2004). Recently, a classification of MPM in three molecular subtypes based on differences in gene expression of 53 tumor samples was proposed with no correlation with clinical or histological characteristics of the tumors (Suraokar et al. 2014). A classification in two molecular subtypes was also defined from 38 cultured MPM primary cell lines and validated using 108 MPM tumor samples. This classification is of interest as it is related partly to histological subtypes and allows to separate epitheloid MPM in two subgroups of different survival outcome (de Reynies et al. 2014).

In the same way as for the transcriptomic studies, miRNome analyses focused mainly on the differences between MPM and normal tissues or other types of cancer. These studies lead to the identification of several potential MPM diagnosis biomarkers, which were summarized in a

recent review (Reid 2015). The differences of miRNA expression between MPM histological subtypes were also considered. MiRNA expression levels may be also good biomarkers for predicting the prognosis as first mentioned in 2010 (Pass et al. 2010) and as investigated in several recent studies (Andersen et al. 2014; Kirschner et al. 2015; Matsumoto et al. 2014). These studies lead to the identification of individual miRNA, which expression is linked to prognosis such as miR-29c-5p, miR-193b or miR-31 or the establishment of predictive signature composed of several miRNAs. However, prognosis value validation of these miRNAs predictors is needed in larger independent MPM cohorts. Interestingly, the use of miRNAs as therapeutic targets is an emerging field in MPM even if the effectiveness of this strategy has been shown for the moment only in preclinical models (Reid et al. 2013; Ueno et al. 2014). There is a clinical trial in progress using miRNA-loaded nanocells, which derived from genetically-modified bacteria, for the delivery of miRNA in mesothelioma (Kao et al. 2015).

Integrated multi-omics studies on the same MPM cases should allow to better characterize the molecular features of MPM and to clarify the different pathways of mesothelial carcinogenesis. Unfortunately, integrated multi-omics studies are rare in MPM and incomplete. To our knowledge, only one study combined SNP and methylome arrays to analyze contributions of chromosomic and epigenetic alterations in MPM and revealed a strong association between global gene copy number alterations and global epigenetic dysregulation in MPM, rather than a discrete, local coordination of gene inactivation (Christensen et al. 2010), and two studies linked omic data to the mutation profile of the tumors. Lopez-Rios *et al.* analyzed genetic alterations of the *CDKN2A* gene and performed a transcriptomic study using the same samples, but did not really integrate the result (Lopez-Rios et al. 2006). De Reynies *et al.* compared the distribution of the mutations in the main genes involved in mesothelial carcinogenesis (*CDKN2A*, *NF2*, *BAP1* and *TP53*) in the two transcriptomic MPM subgroups they defined, showing a higher frequency of *BAP1* mutation in the subgroup with the best prognosis (de Reynies et al. 2014). The analysis of TCGA (The Cancer Genome Atlas, https://tcga-data.nci.nih.gov) data, which include exome, SNP, methylation, mRNA and miRNA analysis on the same 87 MPM cases, would be a first step toward integrated approaches in MPM. Taking into account genetic and genomic data and also clinical, histological and epidemiological data will open important diagnostic and prognostic prospects and lead to the development of personalized medicine for patients.

Pathways deregulation

During the past ten years, genetic and epigenetic studies have increased our understanding of the molecular pathogenesis of MPM. The results demonstrated that multiple signaling pathways are altered in mesothelioma. Alterations in cell cycle regulation were first detected by the deletion of genes at the *INK4* locus (Xio et al. 1995). The Hippo pathway was further identified due to the inactivation of *NF2* gene (Sekido 2010). Alterations of other regulators of Hippo pathway, *LATS1* and *LATS2* and *SAV1*, and the overexpression of the transcription cofactor YAP have been reported in some MPM (Jaurand and Jean 2016). Deregulation of this pathway can also occur via the inhibition of merlin phosphatase, MYPT1-PP1δ, by protein kinase C-potentiated phosphatase inhibitor (CPI-17), which is frequently overexpressed in MPM, leaving merlin in a phosphorylated inactive form (Petrilli and Fernandez-Valle 2015; Thurneysen et al. 2009). Loss of merlin could also lead to activate the E3 ubiquitin ligase, CRL4(DCAF1), which is inhibited by its binding to the active, growth-inhibitory form of merlin in the nucleus (Petrilli and Fernandez-Valle 2015).

Further studies have documented changes in the regulation of other pathways, from mutations in key members and/or their differential expression in comparison to normal mesothelial cells. A number of studies have emphasized the role of receptor tyrosine kinases (RTKs), which activation leads to constitutive upregulation of two major downstream cell signaling cascades involved in many regulations, including cell growth and survival i.e. Raf/MEK-extracellular signal-regulated kinase and phosphoinositide-3 kinase (PI3K/AKT), and the mTOR downstream signaling (Jaurand and Jean 2016; Jean et al. 2012; Sekido 2013). Our knowledge on the deregulated pathways is increasing. Hedgehog pathway seems activated in MPM, possibly due to mutations in members, receptors or regulators of the pathway such as PTCH1, SMO an SFU, and its activation is associated with the worst clinical outcome (Felley-Bosco and Stahel 2014). Several members of the WNT pathway have been reported as deregulated in MPM relative to mesothelial cells, by the overexpression of agonists (WNTs, Dvl) or down regulation of antagonists (SFRP4, WIF-1, Dvl) providing evidence for altered expression of a number of Wnt/Fzd signaling molecules in MPM (de Assis, Locatelli, and Isoldi 2014; Fox et al. 2013; Jaurand and Jean 2016; Pohl et al. 2015).

Stem cells

Using side-population isolation or selection of tumor initiating cells, some studies have identified populations of mesothelioma cells that express several putative cancer stem cell (CSC) markers such as CD9, CD24, and CD26, ABCG2, OCT4/POU5F1 and nestin (Ghani et al. 2011; Pasdar et al. 2015; Thies et al. 2015). These cells have interest as targets for pharmacological novel anti-tumor drugs (Favoni et al. 2012). Further researches will likely be developed to better define the characteristics of the cell types present in the tumor; more particularly their stemness characteristics.

Recently, one study suggested that MPM originate as polyclonal tumors based on the methylation status of the polymorphic human androgen receptor (*HUMARA*) locus (Comertpay et al. 2014). Future studies including deep whole genome sequencing will precise the natural history of the MPM and the clonal origin of MPM.

Predisposing factors

The role of factors that influence susceptibility to mineral fiber-induced diseases has been recently reviewed, including age, gender and disease status, genetics, and nutrition as previously reviewed (Below et al. 2011; Toumpanakis and Theocharis 2011). Several studies investigated on polymorphism analyses of genes involved in xenobiotic and oxidative metabolism and DNA repair systems such as, *GSTT1*, *GSTM1*, *NAT2*, *CYP1A1*, *EPHX*, *XRCC1*, *XRCC3, RAD50*, *RAD54L* and *RAD21*, but no reproductive and clear-cut result was evidenced (Below et al. 2011; Toumpanakis and Theocharis 2011). According to our knowledge no new findings have been more recently published. However, the knowledge of single nucleotide polymorphism in genes of the DNA repair system is of interest to account for the response to chemotherapy and identification of biomarkers (Frischknecht et al. 2015; Panou et al. 2015; Peters et al. 2014).

The familial occurrence of mesothelioma has been observed since the 80's (Dawson et al. 1992). More recently, *BAP1* was shown frequently mutated in several hereditary cancers, uveal melanoma, cutaneous melanomas, basal cell carcinoma and renal cell carcinoma (Murali, Wiesner, and Scolyer 2013). It has been suggested that *BAP1* mutations is implicated in an hereditary cancer predisposition in a small subset of families with uveal melanoma and other cancers, including mesothelioma (Abdel-Rahman et al. 2011). The discovery of *BAP1* germline

mutations in two families with a high incidence of mesothelioma was first reported in 2011 (Testa et al. 2011). Further DNA sequencing in 26 sporadic MPM demonstrated 2 cases with germline mutations in *BAP1*, previously diagnosed for uveal melanoma. The *BAP1* mutational status was studied in five multiplex families that showed malignant tumor predisposition, including mesothelioma (Betti et al. 2015). Only one family carried a truncating germline mutation suggesting that other genes may be involved in familial MPM predisposition syndrome (Betti et al. 2015). In this study, all patients have been exposed to asbestos, most frequently by household exposure, reported as low, due to occupational exposure of parents (Betti et al. 2015).

Recently, germinal DNA sequencing was carried out in sporadic MPM for *BAP1* mutations. All but one DNA showed a wild type sequence in 78 sporadic MPM, by Sanger sequencing (Rusch et al. 2015), and all germline DNAs were wild-type in 22 mesothelioma samples (Nasu et al. 2015). Sanger sequencing and MLPA analyses found no germinal mutation in 103 MPM samples. In an analysis of PubMed databases identifying families studies with germline *BAP1* mutations in mesothelioma (both pleural and peritoneal), and comparing to sporadic cases recorded in the United States Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2010, patients with germline *BAP1* mutations in mesothelioma had a longer survival than without *BAP1* mutation (Baumann, Flores, et al. 2015). Using tissue microarray analyses a prolonged survival was also reported in mesothelioma with *BAP1* loss (Arzt et al. 2014; Farzin et al. 2015)

These studies demonstrate that the risk of mesothelioma is influenced by *BAP1* germline alterations, and mesothelioma can develop as a familial cancer syndrome (Sekido 2013). Importantly, the presence of germline *BAP1* mutations in sporadic MPM is very low; showing that mesothelioma induction in asbestos-exposed patients is not a consequence of germline mutation.

Immunohistochemistry (IHC) is an accessible method to determine protein expression, useful to diagnosis and prognosis. The results reported in two publications suggest that IHC may be a reliable method to identify *BAP1* mutations as they found a correlation between BAP1 expression and mutations (Andrici et al. 2015; Nasu et al. 2015). Loss of BAP1 determined by IHC is proposed as useful to support the diagnosis of mesothelioma. Loss of BAP1 and/or $p16^{INK4A}$ by IHC in well-identified mesothelial cells was recently considered as useful for cytological diagnosis of mesothelioma, regarding the good correlation between the protein status in a series

of 15 pairs biopsies/cytology samples (Hwang et al. 2015). However, further researches with a greater number of cases are necessary to validate these results

CONCLUSIONS

The relationship between asbestos exposure and the development of MPM is well established, and all epidemiological data have demonstrated that asbestos exposure is found in a large percentage of MPM cases, with a higher risk for men than for women. The calculations of AR show that the risk is much higher for men compared to women, for occupational exposure, while it is the opposite for non-occupational exposures. However, when both types of exposures were associated, the risk in women becomes closer that of men. Additional risk factors (other types of fibers, irradiation) or cofactors (SV40) have emerged. MMVF now appear potential cofactors to increase the risk of MPM. Epidemiological studies should be developed to investigate the risk of multi-exposures associated with asbestos, including low doses, and to other new particles, especially HARNs.

Many progresses have been made in our understanding of the biology of MPM and the molecular changes occurring in MPM cells. From recent data, a role of *BAP1* in familial mesothelioma was found, but germline mutations in *BAP1* are infrequent in sporadic mesothelioma. Except an activating mutation in the promoter of *TERT*, somatic mutations have been found in tumor suppressor genes. Overall, the number of genes with recurrent mutations is limited. In contrast, there is a high rate of chromosome aberrations, mainly deletion of chromosome regions, leading to gene copy number alterations; These genomic characteristics may be associated to the mechanism of action of asbestos. Up to now, there is no signature of asbestos in MPM, but more frequent losses in chromosomal 14q11 region were reported in exposed patients (Borczuk et al. 2016; Jean et al. 2011). NGS studies should allow to precise the genetic and genomic landscape of MPM mutations. Characterization of the genetic changes in MPM from asbestos-exposed patients would be of interest to better understand the mechanism of action of asbestos and would be useful to study the effects of other EMPs.

The integration of “omics” studies should permit to develop a molecular pathophysiological classification of MPM, which in addition to histological classification and clinical criteria should improve diagnosis and therapeutic strategy. Unfortunately, MPM remains an incurable disease.

Recent strategies focused on targeted therapies, but the molecular characteristics of the tumors were not tested to determine the relevance of the drug on the basis of the molecular specificities of the tumors and exposure. In the future, this knowledge should improve these new therapeutic options, towards a therapy of precision for MPM.

Epidemiological studies have demonstrated that asbestos fibers are not the only carcinogenic natural fibers and that the carcinogenic potency is not limited to amphibole fibers, either asbestos, or non-asbestos. Our knowledge on exposure situations in workers demonstrated that the hypothesis of a synergistic joint effect should be taken into consideration. Co-exposures to asbestos and to some man-made fibers or to silica enhance the risk of mesothelioma. This should be further investigated to better define the risk of mixed exposures that occur both in workers and in the general population. Epidemiological data have also demonstrated that exposure to asbestos and to other amphiboles or to erionite is not limited to occupational situations, but environmental exposures have been linked to the occurrence of mesothelioma. Domestic exposures have been early reported. In these situations, the level of exposure is lower than in workers' exposures. A recent study found a consistent elevated risk of mesothelioma in the domestically exposed populations. Simulations of low-level of chrysotile-exposed workers indicate asbestos levels commensurate with background concentrations in those exposed domestically (Goswami et al. 2013).

On the basis of the mechanisms of carcinogenicity of asbestos, the biological effects of other particles sharing some dimensional features with asbestos have been considered. Man-made fibers and more recently EMPs are the subject of numerous studies. The current researches benefited of the works on asbestos and led to consider the effects of CNTs. Although the weight of evidence is insufficient, due to the variety of CNTs and limited number of studies for several toxicity endpoints, it was found that some CNTs might pose danger for human health. The development of researches on the molecular characteristics of MPM has a paramount interest for a better classification of MPM, and definition of the different physio-pathological changes specific of the tumors. This identification will permit to develop therapeutic strategies absolutely needed for this orphan disease.

Note

During the review process of the manuscript, several relevant papers have been published. Frequent *SETDB1* mutations have been found in MPM (Kang et al. 2016). Otherwise, the genetic landscape of MPM has been specified by reporting recurrent mutations, gene fusions and splicing alterations in a large series of tumor samples (Bueno et al. 2016). A recent trial associating anti-VEGF and anti-folate therapy has increased by three months the overall survival of patients with MPM (Zalcman et al. 2015). Concerning the effects of CNTs, aberrant changes in mRNA and ncRNA (non-coding RNA) expression profiles in the blood of workers, exposed or not exposed to MWCNTs, have been reported (Shvedova et al. 2016).

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