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Chapter

Asbestos-Related Pleural Diseases: The Role of Gene-Environment Interactions

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Abstract

Several pleural diseases have been associated with asbestos exposure. Asbestos exposure may lead to the development of benign pleural diseases, such as pleural plaques, diffuse pleural thickening, and pleural effusion, as well as to the development of malignant mesothelioma, a highly aggressive tumour of the pleura. Asbestos exposure related to pleural diseases may be occupational or environmental. Although the causal relationship between asbestos-related pleural diseases and asbestos exposure has been well confirmed, the role of genetic factors in the development of these diseases needs to be further investigated and elucidated. The results of the studies performed so far indicate that in addition to asbestos exposure, genetic factors as well as the interactions between genetic factors and asbestos exposure may have an important impact on the risk of asbestos-related pleural diseases, especially malignant mesothelioma. This chapter aims to present how the risk of developing asbestos-related pleural diseases may be influenced by asbestos exposure, genetic factors, interactions between different genetic factors, as well as interactions between different genetic factors and asbestos exposure.

Keywords: pleural plaques, malignant mesothelioma, asbestos exposure, genetic factors

1. Introduction

Asbestos-related diseases still represent an important health problem and a huge economic burden for the society all over the world. Asbestos exposure has been associated with the development of asbestosis, pleural plaques, diffuse pleural thickening and pleural effusion, lung cancer, malignant mesothelioma of pleura and peritoneum, and several other types of cancers, like laryngeal cancer, ovarian cancer, as well as cancers of the buccal mucosa, pharynx, gastrointestinal tract, and kidney [1–13].

Asbestos-related diseases, including those of the pleura, are known to be among the most investigated occupational diseases [8–14].

2. Asbestos-related pleural diseases

Development of several pleural diseases has been associated with occupational or environmental asbestos exposure. Among them are pleural plaques, diffuse pleural thickening, pleural effusion, and malignant mesothelioma of the pleura [1–7].

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2.1 Pleural plaques

Pleural plaques are benign (nonmalignant) pleural abnormalities and among the most common asbestos-related diseases [15–17].

Pleural plaques have been defined as circumscribed, quadrangular, irregular pleural elevations with clearly demarcated edges that are often bilateral and rarely symmetrical. They may enlarge and become calcified over time. Pleural plaques commonly develop in the lower two thirds of the thorax and mostly on the outer two thirds of diaphragm. They rarely occur within less than 20 years from the first exposure to asbestos [3, 5, 15–19].

Pleural plaques are mostly asymptomatic and may cause a slight impairment of lung function when they grow in size [20].

Small pleural plaques are often difficult to discern, and standard chest radiographs are generally suboptimal for the visualisation of pleura, particularly in obese patients [3]. High-resolution CT (HRCT) scans are far superior to any other method for imaging pleural plaques as well as the diffuse pleural thickening [3, 21].

Pleural plaques have been referred predominately as a marker of asbestos exposure [2, 5, 22, 23] rather than an independent risk factor for malignant mesothelioma and lung cancer [2, 5, 24]. However, according to some authors, pleural plaques may also indicate an increased risk of asbestosis and asbestos-related cancers [18, 19]. Many studies have investigated the relationship between pleural plaques and lung cancer as well as between pleural plaques and malignant mesothelioma; however, the results of these studies are not consistent [5, 24].

Regarding the relation between pleural plaques and malignant mesothelioma, Hillerdal et al. reported that pleural plaques on the chest roentgenogram indicate an increased risk for mesothelioma [25]. In their study Karjalainen et al. presented more than five times higher risk of malignant mesothelioma in asbestos-exposed men with benign pleural disease [26]. A statistically significant association between pleural plaques and malignant mesothelioma (unadjusted), and after adjustment for the time since the first exposure and the cumulative exposure index to asbestos, was observed also in the study of Pairon et al. Based on these results, Pairon et al. concluded that the presence of pleural plaques may be an independent risk factor for pleural mesothelioma [27]. On the other hand, Reid et al. reported no increased risk of pleural malignant mesothelioma in subjects with pleural thickening after adjustment for the time since the first exposure (log years), cumulative exposure (log f/ml-years), and age at the start of the programme; however, there was an increased risk of peritoneal mesothelioma [28].

Considering lung cancer, Fletcher reported two times higher risk of developing this malignoma in shipyard workers with pleural plaques compared to those without plaques [29]. Hillerdal et al. suggested that the risk for bronchial carcinoma may be increased in subjects with pleural plaques observed on the chest roentgenogram [25]. A slightly elevated risk of lung cancer was found in the asbestos-exposed men with benign pleural disease also in the study of Karjalainen et al. [26]. In the study of Cullen et al., asbestos-exposed smokers with pleural plaques or other asbestos-related pleural changes had a 44% higher risk of lung cancer than the unexposed heavy smokers [30]. Lung cancer mortality was significantly associated with pleural plaques when unadjusted and also after adjustment for smoking and asbestos cumulative exposure index in the follow-up study of Pairon et al. They concluded that pleural plaques may be an independent risk factor for lung cancer death in asbestos-exposed workers and could be used as an additional criterion in the definition of high-risk populations eligible for CT screening [27]. On the contrary, the study of Partanen et al. showed no increased risk of lung cancer in subjects with pleural plaques [31].

Nevertheless, although pleural plaques may be the endpoint and the development of pleural plaques may be an entirely independent process from the development of malignant mesothelioma and lung cancer, it is likely there is a link between pleural plaques and the aforementioned malignant diseases [5].

2.2 Diffuse pleural thickening

Diffuse pleural thickening that affects visceral pleural surface is not sharply demarcated and is often associated with fibrous strands extending into the parenchyma. There are frequent adhesions between the visceral and parietal pleurae, leading to obliteration of the pleural space. It can be extensive and cover the whole lobe or even the whole lung. The thickness ranges from less than 1 mm up to 1 cm or more. Diffuse pleural thickening is a less frequent manifestation of asbestos exposure than pleural plaques [15, 32–34].

Diffuse pleural thickening may lead to significant respiratory disability. In subjects with diffuse pleural thickening, forced vital capacity and single breath diffusing capacity are considered to be lower in comparison to subjects without this disorder [35–37].

From the diagnostic point of view, a chest radiograph is used as a standard method for detecting diffuse pleural thickenings; however, also in this case, HRCT scans are far superior to any other method [20, 37, 38].

Similar to pleural plaques, the diffuse pleural thickenings may be also associated with malignant diseases [20].

2.3 Pleural effusion

Asbestos-related changes of pleura include also benign asbestos pleural effusion, which is a nonmalignant pleural disease [39]. It has been first described in 1964, and it is also known as asbestos pleurisy [39, 40].

Diagnostic criteria for asbestos pleural effusion include previous asbestos exposure, determination of pleural effusion by chest radiograph, HRCT or thoracocentesis, and the absence of other causes of effusion [39]. In the vast majority of undiagnosed unilateral pleural effusions, the fluid is sent for cytological analysis. However, there still remains an uncertainty about the sensitivity to diagnose malignant pleural effusion. It is important to know that in patients presenting with clinical suspicion of malignant mesothelioma, cytological sensitivity is low [41].

Nevertheless, unexplained pleural effusion and pleural pain in subjects exposed to asbestos should always raise the suspicion of pleural malignant mesothelioma [42]. Sneddon et al. reported that more than 70% of patients with malignant mesothelioma develop pleural effusions, which contain tumour cells, representing a readily accessible source of malignant cells for genetic analysis [43].

2.4 Malignant mesothelioma

Malignant mesothelioma is a rare but highly aggressive and fatal cancer of serosal surfaces with poor prognosis, related to occupational and/or environmental (nonoccupational) asbestos exposure. It arises most commonly from mesothelium of the pleural surface. Rarely, it may occur also in other serosal membranes of the human body that are also coated with mesothelium, such as peritoneum, pericardium, and tunica vaginalis [44–46].

The major cause and carcinogen for the development of malignant mesothelioma is asbestos. In the study of McDonald et al., asbestos exposure was proved in almost 80% of patients with malignant mesothelioma [47]. Additionally in

the study of Franko et al., asbestos exposure was confirmed in 86% of patients with malignant mesothelioma, but it could not be confirmed with certainty in the remainder of the patients [48].

The latency period between the first exposure to asbestos and the development of malignant mesothelioma is long and can range from 15 to 60 years or even more [48–50].

Considering clinical features, in the vast majority of patients, the onset of symptoms is insidious and nonspecific, with chest pain and breathlessness being the most common features [51]. These symptoms are usually mild at the onset of the disease and are often attributed to other causes, which delays the diagnosis. The chest pain is often described as a sensation of heaviness or coldness in one side of chest or abdomen and can be caused by the effusion or the tumour [51–53]. The referral of this unspecified pain to the upper abdomen or shoulders, probably as a result of involvement of the diaphragmatic pleura, may lead to the inappropriate investigation and consequently delays the diagnosis. Breathlessness may be manifested as the new onset of dyspnoea or the deterioration of the symptoms of other respiratory diseases such as chronic obstructive pulmonary disease. The latter results in further diagnostic delays [51, 54]. Another feature during the course of this cancer is a dry cough, which is rarely troublesome in the early stages and is seen in about 10% of patients [51, 55]. Other relatively common features are weight loss, fatigue, anorexia, sweats, malaise, lassitude, and intermittent low-grade fever [51, 56]. Malignant mesothelioma is occasionally found incidentally during radiological investigation of some other health problems. Another rather rare presentation of this malignoma is pneumothorax [51].

The most common form of spread of malignant mesothelioma in addition to the worsening of the presenting symptoms is dysphagia due to esophageal compression, sympathetic nerve involvement of the arm, neurological syndromes such as Horners's syndrome, recurrent laryngeal nerve palsy, paraplegia as a result of spinal canal invasion, severe pain in the chest wall as a consequence of tumour invasion and nerve root involvement, malignant pericardial invasion and effusion, obstruction of superior venal cava, and occurrence of intermittent hypoglycemia [51, 53].

A rapid and accurate diagnosis of malignant mesothelioma is very important for therapeutic reasons [44]. Pleural pain and unexplained pleural effusion in subjects exposed to asbestos should raise the suspicion of pleural malignant mesothelioma. Chest radiography, which is a simple and easily available tool, is usually the first investigation performed. The typical findings are pleural effusion, occasionally nodular pleural thickening, irregular fissural thickening, or a localised mass lesion [57]. Important imaging modality is HRCT scanning, which at the diagnosis often shows pleural effusion at disease site, pleural thickening, as well as involvement of the interlobar fissure and invasion of the chest wall. As for MRI, it has superior soft tissue contrast over CT. Diffusion-weighted MRI is considered to be a promising strategy for evaluating tumour extension and response to treatment [57]. Another method is PET-CT, which combines HRCT scanning with injection of 18-fluoro-deoxy-glucose; however, also this scan has several limitations as it cannot differentiate between pleural malignant mesothelioma and metastatic pleural malignancy [57].

Invasive procedures are needed for prompt and accurate diagnosis of pleural malignant mesothelioma. Cytological samples are obtained by thoracentesis and biological tissue by ultrasound-/or radiological-guided biopsy or thoracoscopy [57]. Based on histopathology, malignant mesotheliomas can be classified into epithelioid, biphasic, and sarcomatoid subtypes [45]. However, this aggressive cancer remains difficult to diagnose in the early phases of the disease. Therefore, potential serum markers that could facilitate an early diagnosis and help to evaluate response to treatment have been extensively investigated. Among them are mesothelin [48, 58–60], fibulin-3

[61, 62], osteopontin [51], survivin [63], and others. However, the results of the studies on tumour markers are not consistent; therefore further research is needed.

Pleural malignant mesothelioma is treated by surgery, also used in combination with chemotherapy and/or radiotherapy, which attempts to eradicate the malignant tissue and is an essential option to help the patient to reduce the pain and control pleural effusions [46, 53]. Radiotherapy is relatively common treatment for pleural malignant mesothelioma. Although several studies have indicated that radiotherapy is unable to cure this cancer, it has been shown that radiotherapy administrated pre- or postoperatively alone or in combination with other treatments, is useful to limit tumour spreading, controls pain, and improves the 2-year rate of overall survival from 20 to 34% [46, 64]. However, the systemic cytotoxic chemotherapy remains one of the few therapeutic options that has been shown to improve survival in patients with malignant pleural mesothelioma even in advance stage, when patients are not candidates for aggressive surgery [46, 65]. The most commonly used is the combination of pemetrexed with cisplatin and gemcitabine with cisplatin or another platinum compound. It was reported that the combination of cisplatin and pemetrexed gave a 3-month survival benefit over cisplatin alone, improving median survival from 9.3 to 12.1 months [66]. Comparable results were obtained for gemcitabine/cisplatin doublet [67–70]. Furthermore, the introduction of chemotherapy, in particular treatment with low-dose gemcitabine in prolonged infusion and cisplatin significantly improved survival of Slovenian malignant mesothelioma patients with median overall survival being increased from 5.6 to 14.5 months [68].

3. Asbestos exposure and pleural diseases

Asbestos is a commercial collective name for a group of naturally occurring fibrous hydrated silicates that share similar physical and chemical properties [13, 71–75]. According to their fibre morphology, asbestos fibres have been sub-classified into two main groups, serpentine and amphibole. Serpentine asbestos includes chrysotile, which is also known as white asbestos. The vast category of amphiboles includes commercial asbestos crocidolite (also named blue asbestos), amosite (also called brown asbestos), anthophyllite, as well as the noncommercial types of asbestos like actinolite and tremolite asbestos [13, 75–80].

These fibres have been greatly valued for their tensile strength, thermal resistance, durability, and flexibility. However, on the other hand, asbestos fibres are known to cause inflammation, fibrotic changes in the lung, and malignant diseases [71, 72, 75].

Asbestos exposure related to asbestos-related pleural diseases, as well as to other asbestos-related diseases, may be occupational or/and environmental.

Workers may be occupationally exposed to asbestos in many working sectors, including disposal of asbestos waste and materials; construction; asbestos-cement industry; brickworks; asphalt mixing; machine and insulation products industry; production of clutches and brakes; bus, lorry, railway carriage, car, and airplane repair; ship repair and building; textile industry; asbestos mining, production and milling of asbestos fibres; textile industry; and other sectors [73–75, 77, 81–83].

Environmental (nonoccupational) exposure to asbestos (in the neighbourhood or household) occurs in the vicinity of the factories and other working sectors where asbestos is used. In these areas inhabitants are exposed to asbestos with polluted air, water, and food. Nonoccupational exposure to asbestos may also occur due to the use and improper removal of asbestos-cement roofing, asbestos insulation, and other products containing asbestos. Asbestos fibres can be found in water that runs on asbestos-cement tubes, especially if they do not have lining or if they are

damaged. Family members of workers who work with asbestos and bring asbestos home with clothes, shoes, and hair can also be exposed to asbestos [13, 81–83].

Although the causal relationship between asbestos-related pleural diseases and asbestos exposure has been well confirmed, the role of genetic factors in the development of these diseases needs to be further investigated and elucidated.

3.1 Molecular mechanisms linking asbestos exposure and pleural diseases

Recent studies have led to a better understanding of molecular mechanisms underlying the pathogenesis of asbestos-related diseases, including malignant mesothelioma. Although it has been shown that asbestos fibres deposited in lungs and translocated to pleura may have direct genotoxic effects on epithelial and mesothelial cells, the main molecular mechanism linking asbestos exposure with fibroplasia and neoplasia is related to the generation of reactive oxygen and nitric species thus leading to oxidative stress and inflammation [84].

Reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical (OH•), and reactive nitrogen species (RNS) can be generated directly by the asbestos fibres as they contain redox-active iron (Fe^{2+}, Fe^{3+}) that may catalyse the formation of hydroxyl radical through Fenton reaction [85]. Secondly, ROS may be generated also indirectly by inflammatory cells such as macrophages during the frustrated phagocytosis of asbestos fibres. This process also leads to the release of proinflammatory cytokines that further potentiate the asbestos-related inflammatory response [86].

Another recently described molecular mechanism by which asbestos may contribute to inflammation is the activation of the so-called pattern recognition receptors that sense pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs, respectively) and trigger cellular responses. One class of these receptors, the nucleotide binding and oligomerization domain (NOD)-like receptors (NLRs), has been shown to be directly activated by asbestos fibres [87]. NLRP3 inflammasomes may be activated also indirectly by the released ROS and proinflammatory cytokines such as high-mobility group box 1 protein (HMGB1) [88]. Activation of NLR triggers assembly and activation of a multiprotein complex composed of the NLRP3 scaffold protein, CARD containing adaptor protein, and caspase-1. The subsequent cleavage and activation of caspase-1 lead to the downstream cleavage of pro-interleukin-1β (pro-IL-1β) and release of mature proinflammatory cytokine IL-1β that triggers the early inflammatory response following asbestos exposure [89]. IL-1β release then leads to activation and enhanced expression of other cytokines, among them tumour necrosis factor (TNF) and transforming growth factor beta-1 (TGFB1) [90, 91]. Furthermore, TGFB1 may downregulate collagen degradation through matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). Several MMPs and TIMPs play an essential role in tissue repair and remodelling. Among them, MMP1, MMP9, MMP12, and TIMP2 have been proposed to contribute to the development of pulmonary fibrosis [92].

Asbestos fibres and ROS may also activate other receptors and signalling pathways such as epidermal growth factor receptor (EGFR) and the downstream protein kinases AKT and ERK, leading to the activation of c-Fos and c-Jun proto-oncogenes and dysregulation of mitogenic signalling, promoting fibrosis and malignant transformation [93]. Because of the long-term persistence of asbestos fibres, the inflammation becomes chronic and is accompanied by gradual progression from mesothelial hyperplasia to mesothelioma after a latency period of several decades. In vitro and in vivo evidence implicate oxidative stress, chronic inflammation, genetic and epigenetic alterations, as well as direct cellular toxicity and genotoxicity

as the main mechanisms in the asbestos-related development of fibrosis and in malignant mesothelial cell transformation [94].

Numerous chromosomal abnormalities and genetic and epigenetic alterations were identified in human mesothelioma tissues in asbestos-exposed workers [94]. Asbestos-induced mutagenicity is also mediated through direct or indirect pathways. Asbestos fibres may induce mutagenicity and genotoxicity directly through physical interaction with the mitotic machinery of dividing cells after being phagocytized by the target cells. Longer asbestos fibres in particular, may cause DNA double-strand breaks or interact with the mitotic spindle thus leading to aneuploidy [94]. The indirect genotoxic and mutagenic effects occur due to asbestos-generated ROS and RNS that may produce a variety of DNA and chromosomal damages, such as 8-hydroxydeoxyguanosine (8-OHdG), DNA single-strand breaks, and chromosome fragmentation. Other frequently observed genomic alteration includes homozygous deletion or change of methylation pattern of tumour suppressor and p16INK4a and p14ARF at the 9p21 locus in humans. p16INK4a/p14ARF homozygous deletion has been reported to occur at a frequency of 50–70% of MM tissues and primary MM cells, whereas in stable MM cell lines, the frequency is as high as 90%. The loss of p16INK4a/p14ARF leads to the inactivation of another two important tumour suppressors, pRB and p53. The loss of neurofibromatosis type 2 (NF2) gene leads to the deficiency of its product Merlin and the consequent loss of inhibition of Merlin's downstream target YAP, a proto-oncogene and transcriptional coactivator that promotes cell proliferation. Copy number amplification of proto-oncogenes such as JUN, MYC, and YAP was also reported [94].

Homozygous deletion of another tumour suppressor gene, BAP1, was recently reported in familial malignant mesothelioma. BAP1 is part of a multiprotein complex that is involved in DNA damage response and regulation of gene transcription [95].

3.2 The role of genetic factors in the development of asbestos-related pleural diseases

Recent studies have shown that in addition to asbestos exposure, genetic factors may have an important role in the occurrence, progression, and response to treatment of asbestos-related diseases. Most studies have focused on genetic variability, in particular genetic polymorphisms in genes involved in the pathways related to molecular mechanisms linking asbestos exposure and pleural diseases as potential candidate genes that may influence individual susceptibility to asbestos-associated disorders. Most of the studies focused on asbestosis and malignant mesothelioma as the most common respective nonmalignant and malignant diseases related to asbestos exposure, while only a small number of studies included patients with pleural thickening and pleural plaques. This chapter is leaving asbestosis-related studies aside, as they are related to interstitial and not pleural lung disease.

3.2.1 Genetic variability in antioxidative defence genes

The defence mechanism against ROS is complex and involves several enzymes. Superoxide dismutases (SODs), catalase (CAT), and glutathione peroxidases (GPX) constitute the first line of the antioxidant enzyme defence system against ROS, while glutathione S-transferases (GSTs) play an important role in the detoxification of cytotoxic secondary metabolites of ROS. The major GST enzyme in the human lung is GSTP1, which belongs to the Pi class. Two other important polymorphic GSTs are GSTM1 (Mu class) and GSTT1 (Theta class) [96]. Another Phase 2 enzyme studied in asbestos-related diseases is *N*-acetyltransferase 2 (NAT2), involved in the metabolism of various xenobiotics including the aromatic and

heterocyclic amines present in tobacco smoke and the diet [97]. The genes coding for all these enzymes are known to be polymorphic. Some of these polymorphisms alter gene expression or enzymatic activity and may modify the ability for the elimination of ROS or their products [98–100].

Manganese SOD (SOD2) was found to be highly expressed in malignant mesothelioma; however, *SOD2* rs1799725 (Val16Ala) polymorphism was not found to be associated with either malignant or nonmalignant asbestos-related diseases in a group of 124 Finnish asbestos insulators, among which 20 workers developed malignant mesothelioma, 41 had nonmalignant pulmonary disorders such as asbestosis and/or pleural plaques, while 63 had no pulmonary disorders [98]. On the other hand, homozygotes for *SOD2* 16Ala/Ala genotype were found to have a threefold increased risk for malignant mesothelioma when genotype distributions were compared among 90 Italian patients with malignant mesothelioma and 395 controls [100]. In this cohort, increased risk for malignant mesothelioma was also observed in carriers of homozygous *GSTM1* deletion (*GSTM1* null genotype), while no association was observed for polymorphisms in other *GST* genes [100].

Kukkonen et al. [101] investigated nine polymorphisms in six genes (*EPHX1*, *GSTM1*, *GSTM3*, *GSTP1*, *GSTT1*, and *NAT2*) related to metabolism of oxidative species in a cohort of 1008 Finnish asbestos-exposed workers. Only a trend of association was observed between *GSTM1* null genotype and the extent of pleural plaques as well as between *GSTP1* Ile105Val polymorphism and the calcification of pleural plaques. However, when pleural plaques were stratified according to the severity of radiological changes, *GSTT1* null genotype was significantly associated with the greatest thickness of the pleural plaques [101].

No association was also found between *SOD2* and *CAT* polymorphisms and the malignant mesothelioma risk in a study that included 159 Slovenian malignant mesothelioma patients and 122 controls. All the controls were occupationally exposed to asbestos in the asbestos-cement manufacturing plant but did not develop any disease associated with asbestos exposure [102]. However, this study reported an association between NAD(P)H quinone dehydrogenase 1 (*NQO1*) rs1800566 (p.Pro187Ser) SNP and malignant mesothelioma risk. NQO1 catalyses the reduction of quinones to hydroquinones, thus preventing the formation of free radicals. The carriers of at least one polymorphic *NQO1* allele (CT and TT genotypes) had an increased risk of malignant mesothelioma compared to carriers of homozygous wild-type CC genotype [102].

In a Finnish cohort, an association was reported between the *NAT2* slow-acetylator genotype and increased risk for both malignant (mesothelioma) and nonmalignant (asbestosis and pleural plaques) pulmonary disorders among asbestos-exposed workers [103, 104]. On the contrary, the *NAT2* slow-acetylator genotypes were associated with decreased risk of mesothelioma in the Italian study population [105]. Conflicting results were reported also regarding the impact of microsomal epoxide hydrolase (EPHX1), a metabolising enzyme that plays a dual role in the activation and detoxification of exogenous chemicals, such as epoxides and PAHs [106]. *EPHX1* low-activity genotypes were positively associated with malignant mesothelioma in the Italian study population, while in the Finnish study population, the association was negative [105].

3.2.2 Genetic variability in NLRP3 inflammasome

Two polymorphic genes leading to enhanced innate immune response and increased production of inflammatory cytokines were investigated in asbestos-related pleural diseases. *NLRP3* rs35829419 (p.Gln705Lys; C > A) is a gain-of-function polymorphism that leads to increased NLRP3 activation after stimulation.

On the other hand, *CARD8* rs2043211 (p.Cys10Ter, A > T) is a loss of function SNP that results in nonfunctional protein so that the CARD-8 inhibition of caspase-1 is lost. Therefore, both SNPs are associated with proinflammatory phenotype [107, 108]. Both SNPs were analysed in a large Finnish study that investigated 16 polymorphisms from nine genes (NLRP3, CARD8, TNF, TGFB1, GC, MMP1, MMP9, MMP12, and TIMP2) involved in innate immunity and intracellular matrix remodelling in 951 Finnish asbestos-exposed workers. Among the two investigated *NLRP3* SNPs, only rs35829419 was associated with interstitial lung fibrosis but showed no association with fibrotic changes of pleura. Among the three investigated *CARD8* SNPs, rs2043211 (p.Cys10Ter, A > T) was associated with the greatest thickness of pleural plaques [107].

3.2.3 Genetic variability in signalling and inflammatory pathways

Asbestos-related activation of inflammation also leads to increased TNF and TGFB1 production. *TNF* promoter polymorphism rs1800629 (−308G > A) was reported to lead to higher constitutive and inducible transcriptional TNFa levels [109]. Genotype and allele frequencies of TNF promoter polymorphism rs1800629 (−308G > A) were associated with radiographic pleural changes among German workers occupationally exposed to asbestos. Compared with the healthy nonexposed control group, carriers of at least one polymorphic TNF −308 A allele had at higher risk for hyaline pleural plaques, while no association was observed for calcified pleural plaques [91].

TGFB1 is a multifunctional cytokine that regulates the proliferation and differentiation of cells [110] and was reported to promote the pathogenesis of lung fibrosis and act as a tumour suppressor in normal cells. Two *TGFB1* polymorphisms in codons 10 (Leu10Pro) and 25 (Arg25Pro) affecting TGFB1 protein production were associated with a higher risk for fibrotic lung diseases but a lower risk for lung cancer in a German cohort that included 591 patients with pulmonary fibrosis, 147 patients with bronchial carcinoma, and 83 healthy control subjects [90].

Kukkonen et al. investigated common polymorphisms in *TNF* and *TGFB1* genes; however, only *TGFB1* showed associations with visceral pleural fibrosis among 951 Finnish Caucasian asbestos-exposed workers. In stratified analysis carriers of at least one *TGFB1* rs2241718 variant allele were protected against visceral pleural fibrosis. On the other hand, *TGFB1* haplotype analysis showed an association with pleural plaque calcification. In particular, *TGFB1* rs1800469-rs1800470 GC and AT haplotypes conferred increased risks for pleural plaque calcification when compared with the most common haplotype, GT [107].

3.2.4 Genes involved in matrix remodelling

In the above-mentioned study, Kukkonen et al. also investigated common polymorphisms of several metalloproteinases and their inhibitors (*MMP*1 rs1799750, *MMP9* rs3918242, *MMP12* rs652438, and *TIMP2* rs2277698) involved in matrix remodelling. The study reported an association between the *TIMP2* rs2277698 SNP and pleural thickenings, and the variant allele was found to predispose to a high degree of pleural plaque calcification [107].

Strbac et al. investigated 10 different SNPs in three *MMP* genes (*MMP2*, *MMP9*, and *MMP14*) in a group of 236 Slovenian patients with malignant mesothelioma and 161 healthy blood donors as the control group. The study reported a decreased risk for malignant mesothelioma in carriers of at least one polymorphic *MMP2* rs243865 allele, and this association was even more pronounced in patients with known asbestos exposure. None of the other tested polymorphisms showed

association with the risk of malignant pleural mesothelioma [111]. Furthermore, a study including 199 Slovenian malignant mesothelioma patients suggested that *MMP* polymorphisms may have a role as prognostic biomarkers in malignant mesothelioma, as carriers of polymorphic *MMP9* rs2250889 allele had shorter time to progression and shorter overall survival compared to noncarriers. In contrast, carriers of at least one polymorphic *MMP9* rs20544 allele had longer time to progression and longer OS (overall survival than noncarriers [112].

3.2.5 Genes involved in DNA repair mechanisms

It has been suggested that genetic variability of proteins involved in DNA repair mechanisms may affect the risk of malignant mesothelioma. Based on the mechanisms of either oxidative stress related or direct DNA damage discussed above, polymorphic genes in DNA repair pathways such as base excision repair (BER), nucleotide excision repair (NER), as well as homologous recombination may play a role in susceptibility to asbestos-related malignant diseases [93]. However, so far only a few studies investigated the influence of the genetic variability of proteins involved in DNA repair mechanisms on the development of malignant mesothelioma. In particular, polymorphisms in genes coding for excision repair cross-complementing group 1 protein (ERCC1) involved in NER and X-ray repair cross-complementing protein 1 (XRCC1) involved in BER were most frequently investigated in asbestos-related malignant diseases [113, 114].

Dianzani et al. investigated seven SNPs in four DNA repair genes (*XRCC1*, *XRCC3*, *XPD,* and *OGG1*) in a population-based case-control study that included 81 patients and 110 age and sex-matched controls from Casale Monferrato, an Italian town known for high levels of asbestos pollution. Two of the investigated polymorphisms were significantly associated with increased malignant mesothelioma risk in both homozygous and heterozygous carriers when compared to noncarriers: *XRCC1* rs25487 (399Q) and *XRCC3* rs861539 (241T). Homozygous and heterozygous carriers of *OGG1* rs1052133 −326C allele were also at increased risk for malignant mesothelioma; but this association did not reach statistical significance. Also, the association with malignant mesothelioma risk was not significant when *XRCC1* and *XRCC3* haplotypes were considered [113].

A follow-up study included 220 malignant mesothelioma patients and 296 controls from two Italian towns, Casale and Turin, and investigated 35 SNPs in 15 genes possibly related to asbestos carcinogenicity. Among them, 14 SNPs in 10 genes involved in DNA repair were studied; however, only three SNPs were found to be associated with malignant mesothelioma. When only asbestos-exposed patients were considered in the analysis, the risk for malignant mesothelioma was found to increase with the number of *XRCC1* rs25487 (399Q) polymorphic alleles and *XRCC1* −77T alleles. Increased risk for malignant mesothelioma was also observed in *XRCC1* haplotype analysis. *ERCC1* rs11615 (N118N) polymorphism was also found to be associated with increased malignant mesothelioma risk in the dominant genetic model, both in the entire study group and when considering only asbestos-exposed patients [114].

Betti et al. also investigated one functional SNP in *hOGG* (rs1052133 p.Ser326Cys) involved in the repair of 8-oxoguanine that may result from ROS damage; however no association was found with the risk for malignant mesothelioma [114]. Similarly, no association between this polymorphism and the risk for malignant mesothelioma was observed in a Slovenian study cohort of 150 malignant mesothelioma patients and 122 controls, who were occupationally exposed to asbestos but did not develop any asbestos-related diseases [102].

Recently, a larger number of 273 malignant mesothelioma patients and 193 controls from the same Slovenian cohort were analysed for four SNPs in two DNA

repair genes (*ERCC1* rs11615, rs3212986, and *XRCC1* rs1799782, rs25487), but only *ERCC1* rs3212986 was found to be significantly associated with the risk for malignant mesothelioma. However, this polymorphism was found to have a protective effect as carriers of *ERCC1* rs3212986 heterozygous GT or homozygous TT genotypes had a decreased risk of malignant mesothelioma [115].

4. Gene-environment interactions in asbestos-related pleural diseases

It has become increasingly obvious that both environmental and genetic factors may influence the development of many diseases [116–119], including asbestos-related pleural diseases.

Therefore it is important to consider gene-environment interactions when studying diseases related to exposure to different hazards, such as asbestos. Environmental and lifestyle factors have been investigated in many epidemiological studies using self-reported information obtained by questionnaires, interviews, records, or measurements of exposure. However, very few epidemiological studies included the information on genetic risk factors. Similarly, many studies investigating genetic factors obtained little information on environmental factors and lifestyle. Genetic predisposition can be presumed from family history, phenotypic characteristics (e.g., metabolic capacity), or, most importantly, the analysis of DNA sequence. The research into gene-environment interactions requires the information on both environmental and genetic factors [116–118]. Primary candidates for the gene-environment interaction studies have been mostly genes coding for xenobiotic metabolising enzymes. Genetic variability in these genes may lead to interindividual differences in capacity for xenobiotics metabolism, thus modifying an individual's susceptibility to the development of diseases [116]. Furthermore, genetic factors usually do not act independently but may also interact or modify each other. This applies also to asbestos-related pleural diseases [102].

The results of the studies performed so far indicate that in addition to asbestos exposure, the genetic factors, as well as the interactions between genetic factors and asbestos exposure, may have an important impact on the risk of asbestos-related pleural diseases, in particular on malignant mesothelioma [102, 115, 120, 121].

Regarding asbestos-related pleural diseases, the interactions between genetic factors and asbestos exposure have been studied in the case of malignant mesothelioma [102, 115, 120, 121].

The case-control study of Franko et al. investigated the influence of functional polymorphisms of *NQO1*, *CAT, SOD2*, and *hOGG1* genes, gene-gene interactions, and gene-environment interactions on malignant mesothelioma risk. The authors reported that although there was no independent association between either *CAT* rs1001179 or *hOGG1* rs1052133 polymorphism and malignant mesothelioma, the interaction between both polymorphisms showed a protective effect. However, no interaction was found between investigated genetic polymorphisms and asbestos exposure [102].

The case-control study of Levpuscek et al. that investigated the influence of functional polymorphisms in *ERCC1* and *XRCC1* genes, the interactions between these polymorphisms, as well as the interactions between these polymorphisms and asbestos exposure on malignant mesothelioma risk found that interaction between *ERCC1* rs11615 polymorphism and asbestos exposure significantly influenced the risk of this cancer. Carriers of polymorphic *ERCC1* rs11615 allele who were exposed to the low level of asbestos had a decreased risk of malignant mesothelioma. Based on these findings, it has been suggested that the genetic variability of DNA repair mechanisms could contribute to the risk of developing of this aggressive cancer [115].

The possible impact of gene-environment interactions on pleural malignant mesothelioma risk was investigated also in the study of Tunesi et al., who conducted a gene-environment interaction analysis including asbestos exposure and 15 single nucleotide polymorphisms (SNPs) previously identified through a genome-wide association study on Italian subjects. Positive deviation from additivity was found for six SNPs (rs1508805, rs2501618, rs4701085, rs4290865, rs10519201, and rs763271), and four of them (rs1508805, rs2501618, rs4701085, and rs10519201) deviated also from multiplicative models. Generalised multifactor dimensionality reduction analysis showed a strong malignant pleural mesothelioma risk due to asbestos exposure and suggested a possible synergistic effect between asbestos exposure and rs1508805, rs2501618, and rs5756444. The results of the presented study also suggested that gene-asbestos interaction may play an additional role in malignant pleural mesothelioma susceptibility [120].

According to our knowledge and the available literature, the influence of gene-environment interactions on the risk of developing other asbestos-related diseases (pleural plaques, diffuse pleural thickening) has not been studied so far.

5. Conclusions

Given that asbestos is still present in the working and living environment all over the world and that pleural asbestos-related diseases, in particular malignant mesothelioma, represent an important health problem worldwide, further research is needed to identify new serum and genetic and epigenetic markers of risk for developing these diseases, for early diagnosis, and for prediction of disease progression and response to treatment. The increasing incidence and poor prognosis of pleural malignant mesothelioma calls for new more effective detection methods, including the identification of novel biomarkers for early and reliable detection of this aggressive cancer, especially in high-risk populations with a known history of asbestos exposure. The influence of gene-environment interactions on the risk of these diseases may be particularly important and should be further investigated. These findings may serve as a basis for the development of new methods for an earlier diagnosis of asbestos-related pleural diseases and may also be used to identify new targets for a more effective treatment, especially of malignant mesothelioma. Furthermore, they could add to our understanding of pathogenesis of asbestos-related pleural diseases and enable their prevention. In this way, they could significantly contribute to the improvement of the quality of life as well as to prolonging lifespan and ageing of subjects exposed to asbestos.

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