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Review

Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases

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ABSTRACT

Exposure to asbestos fibers is a major risk factor for malignant pleural mesothelioma (MPM), lung cancer, and other non-neoplastic conditions, such as asbestosis and pleural plaques. However, in the last decade many studies have shown that polymorphism in the genes involved in xenobiotic and oxidative metabolism or in DNA repair processes may play an important role in the etiology and pathogenesis of these diseases. To evaluate the association between diseases linked to asbestos and genetic variability we performed a review of studies on this topic included in the PubMed database. One hundred fifty-nine citations were retrieved; 24 of them met the inclusion criteria and were evaluated in the review. The most commonly studied *GSTM1* polymorphism showed for all asbestos-linked diseases an increased risk in association with the null genotype, possibly linked to its role in the conjugation of reactive oxygen species. Studies focused on *GSTT1* null and *SOD2 Ala16Val* polymorphisms gave conflicting results, while promising results came from studies on α1-antitrypsin in asbestosis and *MPO* in lung cancer. Among genetic polymorphisms associated to the risk of MPM, the *GSTM1* null genotype and two variant alleles of *XRCC1* and *XRCC3* showed increased risks in a subset of studies. Results for the NAT2 acetylator status, *SOD2* polymorphism and EPHX activity were conflicting. Major limitations in the study design, including the small size of study groups, affected the reliability of these studies. Technical improvements such as the use of high-throughput techniques will help to identify molecular pathways regulated by candidate genes.

Contents

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1. Introduction

Exposure to asbestos fibers is a well-known risk factor for malignant pleural mesothelioma (MPM), lung cancer, and other non-neoplastic conditions, such as asbestosis and pleural plaques.

Different mechanisms of damage caused by asbestos fibers have been identified or hypothesized. Inhaled asbestos fibers penetrate the lung epithelium and irritate the pleural cell lining, causing repeated cycles of damage, repair and local inflammation. This repeated scratching may lead to the formation of plaques or to mesothelioma. Another possible mechanism could occur when asbestos fibers interfere with the mitosis. The damages caused to the mitotic spindle could potentially lead to aneuploidy or induce the other typical chromosome anomalies often found in mesothelioma [1].

Asbestos toxicity and carcinogenicity may be mediated by reactive oxygen or nitrogen species (ROS/RNS). This mechanism, activated by the interaction of asbestos fibers with the mesothelial cells and from the prolonged phagocytic activity of inflammatory cells, is probably the most circumstantiated one [1,2]. The free radicals generated by these processes may cause cellular toxicity and carcinogenicity by inducing lipid peroxidation, altering signal transduction pathways, and damaging the DNA directly [3]. Consequences of oxidative damage include single strand breaks and DNA base modification [4]. Furthermore, asbestos-induced DNA damage has been demonstrated to activate tyrosine kinase (TK) both in lung epithelium and in mesothelial cells [5]. In addition, asbestos fibers induce phosphorylation of the mitogen-activated protein kinases and extra cellular signal-regulated kinases 1 and 2 and elevate expression of early response proto-oncogenes (*FOS* or *JUN* or activator protein 1 family members) [6–9].

In the last decade the role of genetic polymorphism in the pathogenesis of cancer and other diseases has been the object of intensive research. Many studies have focused on polymorphic genes active in various steps of xenobiotic and oxidative metabolism, or in DNA repair processes.

Even though mesothelioma has been considered for many years the paradigm of environmentally determined cancers, the presence of a genetic component in the etiology of this disease has been hypothesized, mostly based on the evidence that only a minority of asbestos exposed subjects develop MPM (5–17% of individuals heavily exposed). This consideration, together with the frequent reports of MPM familial clustering [10,11], suggested a role of genetic susceptibility also in this disease. Similar arguments have been carried out also for other asbestos-mediated diseases, both neoplastic, like lung cancer, and non-neoplastic (e.g., asbestosis, pleural plaques).

In this paper, we will review published studies addressing the association between diseases linked to asbestos and genetic polymorphisms. The relevance of genetic factors in explaining the pathogenesis of these diseases will be discussed, with a special focus on MPM.

2. Bibliographic search

The search for papers was performed using the PubMed database (National Library of Medicine, National Institutes of Health, Bethesda, MD, USA—http://www.ncbi.nlm.nih.gov/PubMed) and it was updated up to January 31, 2008. Specific keywords (Mesh terms[mesh]) and free texts terms (words in title or abstract field[tiab]) were used as a search strategy. The first group of terms referred to main concepts related to genetic polymorphisms (polymorphism, genetic[mesh] OR genotype[mesh] as keywords, and polymorphism[tiab] OR polymorphisms[tiab] OR polymorphic[tiab] OR SNP[tiab] OR "single nucleotide polymorphism" as free text in title and in abstract field). The second group referred to main pathologies associated to asbestos exposure (Mesothelioma[mesh] OR (asbestos[mesh] AND (lung neoplasms[mesh] OR pleural neoplasms[mesh] OR pleural diseases[mesh] OR pleura[tiab] OR pleural[tiab])) OR asbestosis[mesh] OR mesothelioma[tiab] OR asbestos[tiab] OR asbestosis[tiab]).

2.1. Inclusion/exclusion criteria

One hundred fifty-nine citations were retrieved through Medline search. All potentially interesting articles were obtained and manually reviewed. Only papers specifically providing a quantitative estimate of the association between genetic polymorphisms and diseases linked to asbestos exposure were further considered. Studies including less than 10 subjects in each study group and studies on animals or *in vitro* were excluded from the analysis. Five potentially interesting articles in Russian and in Chinese could not be translated and were discarded. Twenty-four papers, describing 19 studies, met the inclusion criteria and were reported in the review.

3. Genetic polymorphism and non-neoplastic diseases associated to asbestos exposure

Eight studies evaluated the role of genetic polymorphisms in non-neoplastic diseases associated to asbestos exposure (Table 1). All these studies were conducted in the framework of occupationally exposed subjects (maximum number of subjects: 639 [12,13]). The most common disease was asbestosis, but pleural abnormalities have been investigated as well. Polymorphic genes were genotyped by PCR and restriction enzyme-based methods.