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Chapter 8

Gene-Environment Interactions: The Case of Asbestosis

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Abstract

It is becoming evident that both environmental/lifestyle and genetic factors may influence the development of many diseases. This chapter highlights the importance of considering gene-environment interactions, which is shown on the example of our studies into asbestosis, one of the most frequent asbestos-related diseases. Asbestos fibres induce generation of reactive oxygen and nitric species (ROS and RNS), and it is generally accepted that ROS and RNS are involved in the pathogenesis of asbestos-related diseases. Human tissues contain specific enzymes that metabolise ROS and RNS, such as superoxide dismutases (SODs), catalase (CAT), glutathione-S-transferases (GSTs) and inducible nitric oxide synthase (iNOS). As these enzymes are encoded by polymorphic genes, genetic variability in an individual's capacity to detoxify these reactive species may modify the risk for disease. Our previous studies into asbestosis showed that the associations between the risk of asbestosis and *MnSOD* Ala-9Val polymorphism and between asbestosis and *iNOS* genotypes were modified by *CAT* −262C>T polymorphism. A strong interaction was also found between smoking (lifestyle factor) and *GSTM1*-null polymorphism, between smoking and *iNOS* $(CCTTT)_n$ polymorphism and between cumulative asbestos exposure (environmental factor) and *iNOS* $(CCTTT)_n$ polymorphism. The findings of our studies and other studies indicate that in addition to environmental and/or occupational exposure to different hazards and lifestyle factors, genetic factors as well as the interactions between different genotypes, between genotypes and lifestyle factors and between genotypes and environmental/occupational exposure to hazards may also have an important role on the development of diseases and should be further investigated.

Keywords: asbestosis, exposure, gene-environment interactions, gene-gene interactions

1. Introduction

It is becoming evident that both environmental and genetic factors may influence the development of many diseases [1–7]. It is therefore important to consider gene-environment interactions when studying diseases related to exposure to different hazards and lifestyle factors.

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, from phenotypic characteristics (e.g. metabolic capacity) or, most importantly, from an analysis of deoxyribonucleic acid (DNA) sequence [8].

The research into gene-environment interactions requires the information on both environmental/lifestyle and genetic factors [7, 8]. Primary candidates for gene-environment interaction studies have been mostly genes coding for xenobiotic-metabolising enzymes [3]. Genetic variability in these genes may lead to interindividual differences in the capacity for xenobiotic metabolism, thus modifying an individual's susceptibility to the development of disease [3].

The approach to the analysis of gene-environment interactions is presented using the example of our study into asbestosis, which is one of the most frequent asbestos-related diseases. According to the model of causation, asbestos exposure, genetic factors and possibly also unknown causes have a crucial role in the occurrence of asbestosis [9]. Although asbestos-related diseases are among the most extensively studied occupational diseases, and the causal relationship between asbestos exposure and asbestosis has been well proved [10–14], relatively little has been known about the genetic factors that might modify an individual's susceptibility to the development of this disease [6, 15–17].

2. Asbestos exposure

Asbestos is a commercial name for a group of fibrous silicates with certain toxic properties, such as the ability to produce inflammation, fibrous scarring and cancer [18–20]. Based on their physical and chemical structures, asbestos fibres can be classified into two major groups: chrysotile and amphiboles [20–25].

Occupational exposure to asbestos occurs in asbestos mining, production and milling of asbestos fibres; in asbestos cement industry; in construction; in machine and insulation product industry; in ship building or repair; in car industry; in production of brakes and clutches; in car, bus, lorry, railway carriage and aeroplane repair; in asphalt mixing; in disposal of asbestos waste and materials; in brickworks; in textile industry and in other industries and activities [20, 22, 26–28].

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Local population can be exposed to asbestos mostly in the neighbourhood of factories where asbestos is produced or used (exposure to polluted air, water and food). The source of environmental asbestos exposure may also be asbestos cement sheets, asbestos insulators and other asbestos-containing products. Asbestos fibres may also be found in water which flows through asbestos cement pipes, especially if they have been damaged. Workers exposed to asbestos may bring asbestos home to the family members on clothing or hair [26–28].

3. Asbestos-related diseases

Asbestos exposure has been associated with the development of asbestosis; pleural diseases, such as pleural plaques, diffuse pleural thickening and pleural effusion and several types of cancer: lung cancer, diffuse malignant mesothelioma of the pleura and peritoneum, cancer of the larynx, cancer of the ovary as well as the cancers of the buccal mucosa, the pharynx, the gastrointestinal tract and the kidney [11, 12, 16, 25, 29–41].

4. Clinical presentation of asbestosis

Asbestosis is an interstitial pulmonary process that develops into diffuse pulmonary fibrosis after a long latency period [42, 43]. The disease continues to progress even after the cessation of exposure, and the process is irreversible. One of the earliest symptoms may be dyspnoea, which is manifested at first only after strenuous exertion, but subsequently with less and less exertion, and eventually it appears even at rest. Another non-specific symptom and usually late manifestation of the disease is irritating and dry, usually non-productive cough, sometimes associated with chest pain [42, 44]. Pulmonary function changes are characterised mostly by a restrictive impairment [27, 28, 42–44]. Later, obstructive airway impairment may also occur [27, 28]. On chest radiographs, small irregular opacities appear initially in the lower lung fields that may enlarge with more advanced disease and involve also middle lung fields [27, 42–44]. Characteristic features of asbestosis on high-resolution computed tomography (HRCT) include fibrotic intralobular interstitial thickening and interlobular septal thickening, subpleural lines and opacities, parenchymal bands, ground-glass opacities and, in more severe disease, variable honeycombing [27].

5. Reactive oxygen and nitric species: the link between asbestos exposure and the development of asbestosis

The pathogenesis of asbestosis is still poorly understood. The findings of studies on cell cultures and animal models indicate that reactive oxygen and nitric species (ROS and RNS) are involved in the pathogenesis of this disease [23, 30, 45–55]. The most important reactive metabolites in the pathogenesis of asbestos-related lung diseases are superoxide anion (O_2^-),

hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$) and nitric oxide (NO) [46, 48, 56, 57]. Asbestos may stimulate the production of ROS in two different ways. The first mechanism involves redox-active iron (Fe^{2+}, Fe^{3+}) in asbestos that catalyses the formation of $OH^{\cdot}$, whereas the second mechanism involves the production of ROS by alveolar macrophages during the phagocytosis of asbestos fibres [58–60]. Reactive oxygen species in lungs may lead to the production of cytotoxic and potentially genotoxic electrophilic compounds [46].

It has also been suggested that asbestos fibres may upregulate the activity of inducible nitric oxide synthase (iNOS), thus inducing the production of NO by alveolar macrophages and pulmonary epithelial cells [51, 61–64]. Because NO is a free radical, it reacts readily with other reactive oxygen metabolites (as, for instance, O_2^-), leading to the formation of toxic metabolites, most importantly peroxynitrite [65–69]. Nitric oxide may play a role in the initiation and progression of asbestosis [51, 64, 70, 71]. However, the data presented by Dörger et al. [72] indicate that iNOS-derived NO plays a dual role in acute asbestos-induced lung injury and that although iNOS deficiency resulted in an exacerbated inflammatory response, it improved oxidant-promoted lung tissue damage.

Reactive oxygen species and RNS can damage all types of biomolecule, including lipids, proteins and deoxyribonucleic acid (DNA). Complex defence mechanisms, including enzymes, proteins and antioxidants, are involved in the prevention of cell damage [73, 74].

6. Enzymes involved in the detoxification of reactive oxygen and nitric species

Human tissues contain specific enzyme systems to detoxify ROS and RNS. Superoxide dismutases (SODs) and catalase (CAT) together with glutathione peroxidases represent an important line of the primary antioxidant enzyme defence system against ROS. Superoxide dismutases catalyse the dismutation of O_2^- to H_2O_2 and oxygen (O_2), whereas CAT subsequently catalyses the conversion of H_2O_2 to water (H_2O) and O_2 [48, 75–82]. Three distinct SOD isoenzymes have been identified in mammals: a cytosolic copper-zinc SOD (CuZnSOD or SOD1) localised in cytoplasmic compartment with cooper (Cu) and zinc (Zn) in the catalytic centre, manganese SOD (MnSOD or SOD2) that is localised in mitochondria and uses manganese (Mn) as a cofactor and extracellular SOD (ECSOD or SOD3) that also contains Cu and Zn in the catalytic centre and is located in the extracellular space [74, 82, 83].

Another important family of enzymes involved in the detoxification of xenobiotics and electrophiles produced by ROS and RNS is glutathione S-transferases (GSTs) [84–87]. They catalyse the conjugation of reduced glutathione to different electrophiles [88]. These conjugation reactions mostly result in less reactive products [89]; however, in some cases, the products are more reactive and consequently more harmful than the parent compound [90, 91]. Seven classes of cytosolic GST isoenzymes have been recognised in mammals (Alpha, Mu, Pi, Sigma, Theta, Omega, Zeta) [84–86, 91, 92]. The major GST enzyme in the human lung is GSTP1, which belongs to the Pi class [90, 91, 93], while GSTM1 (Mu class) and GSTT1 (Theta class) were most frequently investigated [90, 91].

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7. Genetic variability of metabolic enzymes

Genetic polymorphisms are the most common cause for genetic variability of detoxification and antioxidative enzymes [15–17, 80, 91, 94–99].

The most common functional single nucleotide polymorphism (SNP) of the *MnSOD* gene is C to T substitution (c.201C>T, rs4880), which results in alanine (Ala) to valine (Val) amino acid change at position −9 of the mitochondrial targeting sequence (MnSOD p.Ala-9Val) [96, 97, 100]. It has been suggested that this SNP alters the secondary structure of the protein and hence may affect the efficiency of transport of the MnSOD into the mitochondria, where it would be biologically available [96, 97].

ECSOD is secreted into extracellular space where it binds lung matrix components and inhibits their fragmentation in response to oxidative stress [101, 102]. In the *ECSOD* gene, a C to G substitution (c.896C>G, rs1799895) leads to amino acid change from arginine (Arg) to glycine (Gly) at position 213 (p.Arg213Gly) [89, 100, 103–105]. This polymorphism causes an 8- to 15-fold increase in the concentration of plasma ECSOD levels due to impaired binding to the extracellular matrix [103, 104].

The most common functional SNP of the catalase gene (*CAT*) consists of a C to T substitution at position −262 in the promoter region (*CAT* c.−262C>T) and has a substantial impact on the basal expression as well as the CAT levels in red blood cell [80]. The findings of later studies indicated lower CAT activity in subjects with the −262TT genotype than those with the CT and CC genotypes [106–111].

Regarding GSTs, the most common polymorphism of the *GSTM1* and *GSTT1* genes in most of the populations is null polymorphism due to homozygous deletion (null genotype) of these genes, which result in the absence of the GSTM1 and GSTT1 enzyme activity [17, 91]. *GSTM1*-null genotype has been associated with an increased risk of asbestosis in some studies [16, 86], while this association has not been proved in the others [15, 17]. No association has been found between *GSTT1* deletion polymorphism and asbestosis in the studies published so far [17, 86]. As for the *GSTP1* gene, two common single nucleotide polymorphisms in the coding sequence were reported to result in amino acid substitution that may lead to reduced conjugating activity of the enzyme [91, 98, 112, 113]. The first polymorphism is characterised by adenine (A) to guanine (G) transition of nucleotide 313 in exon 5 (c.A313G), which causes an isoleucine (Ile) to valine (Val) substitution at position 105 of the GSTP1 enzyme (p.Ile105Val), resulting in three possible genotypes: 105 Ile/Ile, 105 Ile/Val or 105 Val/Val. The second polymorphism involves the cytosine (C) to thymine (T) transition at nucleotide 341 in exon 6 (c.C341T), which results in alanine (Ala) to Val substitution at position 114 of the GSTP1 enzyme (p.Ala114Val). Regarding codon 114, three genotypes are also possible: 114 Ala/Ala, 114 Ala/Val or 114 Val/Val [91, 98]. Based on the presence of the polymorphisms in both codons 105 and 114, *GSTP1* genotypes can be combined into groups with a presumed high, intermediate or low conjugation capacity of the enzyme.

The human *iNOS* gene is also known to be polymorphic. Several types of polymorphisms have been identified in the promoter region of the *iNOS* gene [99, 114]. The CCTTT pentanucleotide

tandem repeat polymorphisms have been associated with the transcriptional promoter activity, which has been shown to increase with the CCTTT repeat number. Based on that, alleles with 11 or fewer CCTTT repeats are usually defined as short alleles (S) and the ones with 12 or more repeats as long alleles (L). Accordingly, the subjects can have SS, SL or LL genotype [115].

8. Gene-environment interactions and asbestosis

We are presenting the example of an approach to gene-environment interaction research by summarising and building on the results of our studies that aimed to investigate the influence of interactions between different genotypes (*MnSOD*, *ECSOD*, *CAT*, *GSTM1*, *GSTT1*, *GSTP*, *iNOS*), between genotypes and smoking and between genotypes and cumulative asbestos exposure on the risk of developing asbestosis [6, 14, 116–119].

A nested case-control study included 262 cases with asbestosis and 265 controls with no asbestos-related disease. All the subjects included in the study were employed in the asbestos cement manufacturing plant of Salonit Anhovo, Slovenia, and occupationally exposed to asbestos. Data on smoking were obtained from all subjects using a standardised questionnaire [25, 120] and checked during the interview. The data on the cumulative asbestos exposure, expressed in fibres/cm^3-years [intensity in fibres per cm^3 of air multiplied by time of exposure expressed in years], were available for all the subjects from the previous study [25]. The diagnosis of asbestosis or 'no asbestos-related disease' was based on the Helsinki Criteria for Diagnosis and Attribution of Asbestos Diseases [121] and on the American Thoracic Society recommendations [122]. Each case was confirmed by an interdisciplinary group of experts (consisting of an occupational physician, a radiologist and a pulmonologist) of the State Board for Recognition of Occupational Asbestos Diseases at the Clinical Institute of Occupational Medicine. Capillary blood samples from the finger tips of all cases and controls have been collected on FTA Mini Cards (Whatman Bioscience) for the isolation of deoxyribonucleic acid (DNA) and genotyping. All the genetic analyses were performed using PCR-based approaches as previously described [6, 14, 116–119].

Before testing interactions, the associations between outcome [in our case asbestosis] and individual variables were assessed using univariate logistic regression analysis. As expected, asbestosis was associated with cumulative asbestos exposure, whereas no association was found with smoking (OR = 0.98, 95%; CI = 0.69–1.39 for ever versus never smoking) [14]. Analysing the association between asbestosis and individual genotypes, an important association was observed between asbestosis and *MnSOD* genotype (OR = 1.50, 95% CI = 1.01–2.24 for -9Ala/Ala versus combined Ala/Val and Val/Val genotypes) [118]. Only non-significantly elevated risk of asbestosis was observed for the *ECSOD* and *CAT* genotypes (OR = 1.63, 95% CI = 0.62–4.27 for *ECSOD* 213Arg/Gly versus the Arg/Arg genotype and OR = 1.36, 95% CI = 0.70–2.62 for *CAT* −262 TT compared to combined CT and CC genotypes, respectively) [117, 118]. Regarding GSTs, no association was found between asbestosis and *GSTM1*-null genotype (OR = 1.01, 95% CI = 0.71–1.43), while the presence of *GSTT1*-null genotype showed

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a protective effect for this disease (OR = 0.61, 95% CI = 0.40–0.94) [14]. On the other hand, *GSTP1* genotype coding for an enzyme with a high conjugation capacity versus genotypes resulting in an intermediate or low enzyme activity significantly increases the risk of developing asbestosis (OR = 1.49, 95% CI 1.06–2.10) [116]. A slightly elevated risk of asbestosis was also found for the *iNOS* LL genotype compared to the combined SL and SS genotypes (OR = 1.20, 95% CI = 0.85–1.69) [119]. Based on the above-mentioned results, it could be suggested that the genotypes may increase, decrease or have no effect on the risk of disease, in our case asbestosis.

Univariate modelling was followed by multivariate analysis and interactions as the genes usually do not act independently, but may interact. To test the interactions, simple categorical models based on stratification were constructed first, followed by logistic regression models using dummy variables. The analysis showed that the association between asbestosis and *MnSOD* Ala-9Val genotypes was modified strongly by *CAT* −262 C>T genotypes. An increased risk of developing asbestosis was observed for the combined *MnSOD* -9Ala/Val and Val/Val genotypes compared to the Ala/Ala genotype only among those subjects who also had *CAT* −262TT genotype, suggesting an interaction, which was further confirmed by logistic regression analysis using dummy variables (OR = 4.49, 95% CI = 1.08–18.61) [6]. Considering that both MnSOD and CAT constitute a part of the primary defence system against ROS and catalyse the consecutive reactions in the detoxification of ROS [48, 74, 80, 82], this interaction could be considered as logical and biologically plausible. Similarly, the association between asbestosis and *iNOS* $(CCTTT)_n$ genotypes was also modified by CAT −262 C>T genotypes, where a higher asbestosis risk for the *iNOS* LL genotype versus the combined SL and SS genotypes was observed only among those who had *CAT* −262 TT genotype (OR = 4.78, 95% CI = 1.15–19.81) [6]. Taking into account that reactions between ROS and NO have been proposed to potentiate the cytotoxic and mutagenic effect of asbestos fibres [48, 51, 64, 71] and based on the assumption that NO produced by the catalytic activity of iNOS can function as a protective agent against toxic effects of H_2O_2 [123], which is detoxified by CAT [48, 74, 80, 82], and vice versa that H_2O_2 decreases the cytotoxicity of NO [124], this interaction could also be considered as biologically plausible [6].

Next, interactions between different genotypes and an important lifestyle factor—in our case smoking—have been tested. We observed that the *GSTM1*-null polymorphism did modify the association between smoking and asbestosis, although there was no independent association between either *GSTM1*-null polymorphism or smoking and asbestosis risk (OR = 2.67, 95% CI = 1.31–5.46) [6]. We can explain this modifying effect with the observation that both asbestos and smoking increase the production of ROS [46, 125, 126], which are known to be involved in the pathogenesis of asbestosis [23, 30, 46, 48–50]. It has been suggested that cigarette smoke and asbestos increase DNA damage and ROS production in pulmonary cells synergistically [125–127]. In line with these reports and considering the role of *GSTM1* in the defence against ROS [84–87], this observation could also be considered as biologically plausible [6]. Similarly, the association between smoking and asbestosis was modified by *iNOS* $(CCTTT)_n$ polymorphism (OR = 2.00, 95% CI = 0.99–4.03) [6]. Knowing that cigarette smoke is the largest source of NO that humans are exposed to and can also increase the expression and activity of iNOS [128, 129] and based on the suggestion that asbestos fibres may upregulate the activity

of iNOS and thus the production of NO, which is thought to play an important role in the initiation and progression of asbestosis [51, 70], this interaction could also be physiologically explained [6].

Finally, we present an example of the interaction between genotypes and environmental exposure, in our case occupational exposure to asbestos. In order to assess the interactions between the genotypes and occupational cumulative asbestos exposure, we have first constructed simple categorical models that included cumulative asbestos exposure categorised as follows: ≤11.23 fibres/cm^3-years and >11.23 fibres/cm^3-years (11.23 fibres/cm^3-years was the average cumulative asbestos exposure for the controls). In our analysis, we have observed that the association between asbestosis and cumulative asbestos exposure was modified by the iNOS $(CCTTT)_n$ genotypes (OR = 5.74; 95% CI = 3.30–9.99) [6].

9. Conclusions

The findings of our studies suggest that in addition to environmental and/or occupational exposure to different hazards and lifestyle factors, the genetic factors and the interactions between different genotypes, between genotypes and lifestyle factors and between genotypes and environmental/occupational exposure to hazards may have an important influence on the development of diseases and should be further investigated [6, 130–133]. In agreement with our observations, an increasing number of molecular epidemiological studies support the importance of investigating not only genetic predisposition but also gene-gene and gene-environment interactions when assessing the risk of developing diseases [134–136]. Novel high-throughput technologies may also allow the investigation of interactions between exposure to hazards and epigenetic changes in disease risk assessment [137].

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