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WG1-WG3-WG5

GENE ENVIRONMENT INTERACTIONS: THE CASE OF ASBESTOSIS

DiMoPEx

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Introduction

It was suggested that both asbestos exposure and genetic factors influence the development of asbestosis (1, 2, 3, 4). Reactive oxygen and nitric species (ROS and RNS) are known to be involved in the pathogenesis of this disease (5). Superoxide dismutases (SOD), catalase (CAT), and glutathione S-transferases (GST) are part of the enzyme defense against ROS and RNS. Asbestos may also upregulate the activity of inducible nitric oxide synthase (iNOS) and increased production of nitric oxide (NO) may play a role in the development of asbestosis.

The aim of this study was to investigate gene-environment interactions as risk factors for developing asbestosis in workers occupationally exposed to asbestos.

Methods

A nested case-control study was performed. The subjects were selected from the cohort of 2,080 workers who were presented at the State Board for the Recognition of Occupational Asbestos Diseases between 1998 and 2004. All the subjects included in the study were employed in the asbestos cement manufacturing plant of Salonit Anhovo, Slovenia.

The study population included:
262 subjects with asbestosis (cases)
265 subjects with no asbestos disease (controls)

Data on smoking were obtained from all subjects using a standardized questionnaire and checked at interviews. For each worker the duration of exposure was calculated. The data on the cumulative asbestos exposure were available for all the subjects from the previous study (6).

The diagnosis of asbestosis or "no asbestos-related disease" was confirmed by experts of the State Board for the Recognition of Occupational Asbestos Diseases (Figure 1) and was based on the Helsinki Criteria for Diagnosis and Attribution of Asbestos Diseases (7) and on the American Thoracic Society recommendations (8).

DNA from all the cases and controls was isolated from capillary blood samples collected on FTA Mini Cards (Whatmann Bioscience) (Figure 2). *MnSOD* Ala–9Val, *ECSOD* Arg213Gly, *CAT* –262C>T, *GSTP1* Ile105Val and Ala114Val were genotyped using real-time PCR assays, *GSTT1*-null and *GSTM1*-null using multiplex PCR, while the number of CCTTT repeats in the *iNOS* promoter was determined using PCR followed by sequencing.

The regular statistical methods were used to analyze the data. To assess the causal relationship between asbestosis, genotypes, cumulative asbestos exposure, and standard confounders (age, sex, smoking), univariate logistic regression was first used, followed by multivariate logistic regression modeling.

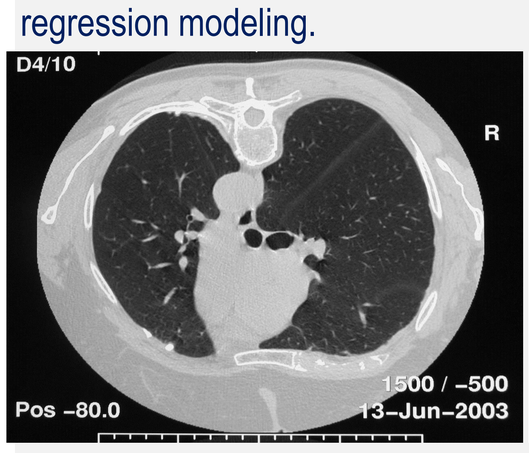

Figure1. Asbestosis: Chest High Resolution Computer Tomography.

Figure 2. FTA Mini cards for collection, archiving and purification of nucleic acids from blood samples.

Results (alternative heading: Deliveralbles).

The mean age of cases was 61 years and that of controls 57 years (t = 5.18, p = 0.00). No difference in smoking was observed between the cases and controls. In both groups, approximately 46.0 % (117 cases and 120 controls) were ever smokers (χ^2 = 0.01, p = 0.91). The duration of exposure and the cumulative asbestos exposure were significantly higher in cases than in controls. Asbestosis was associated with a logarithm of cumulative asbestos exposure (OR = 3.21, 95% CI 2.43–4.23), but not with smoking (Table 1).

Table 1. Duration of exposure and cumulative asbestos exposure in cases and controls.

	Cases (n = 262)			Controls (n = 265)			
Indicators of exposure	Mean	SD	Range	Mean	SD	Range	
Duration of exposure (months)	**267.62**	**110.93**	**6 – 456**	**229.80**	**126.04**	**3 – 506**	t = 3.65 p = .000
Cumulative exposure (fibers/cm^3-years)	37.67	86.43	0.01 – 869.72	11.23	23.47	0.01 – 149.21	t = 4.78 p = .000

OR of asbestosis was 1.50 (95% CI 1.01–2.24) for ***MnSOD*** –9Ala/Ala compared to combined Ala/Val+Val/Val genotypes and 0.61 (95% CI 0.40–0.94) for the ***GSTT1*-null** genotype. The other investigated polymorphisms were not associated with risk of asbestosis (**Tables 2 and 3**).

Table 2. The risk of asbestosis for *MnSOD*, *ECSOD*, *CAT* and *iNOS* genotypes.

	MnSOD Ala/Ala		*EcSOD* Arg/Gly		*CAT* -262TT		*iNOS* LL	
Genotype	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Unadjusted	**1.50**	**1.01 – 2.24**	1.63	0.62 – 4.27	1.36	0.70 – 2.62	1.20	0.85 – 1.69
Adjusted by								
Gender	**1.49**	**1.00 – 2.23**	1.61	0.61 – 4.22	1.34	0.70 – 2.60	1.20	0.85 – 1.70
Age	1.46	0.97 – 2.19	1.49	0.56 – 3.96	1.31	0.67 – 2.57	1.19	0.84 – 1.69
Smoking (ever/never)	**1.49**	**1.00 – 2.23**	1.65	0.63 – 4.32	1.37	0.71 – 2.66	1.17	0.83 – 1.66
Cumulative exposure	1.48	0.96 – 2.28	2.07	0.72 – 5.94	1.91	0.93 – 3.91	1.19	0.82 – 1.73

Table 3. The risk of asbestosis for *GST* genotypes.

	GSTM1-null		*GSTT1*-null		*GSTP1* Ile105Val		*GSTP1* Ala114Val	
Genotype	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Unadjusted	1.01	0.71 – 1.43	**0.61**	**0.40 – 0.94**	1.52	0.70 – 2.62	1.20	0.85 – 1.69
Adjusted by								
Gender	1.00	0.70 – 1.42	**0.62**	**0.40 – 0.94**	1.53	0.70 – 2.60	1.20	0.85 – 1.70
Age	0.94	0.66 – 1.35	**0.63**	**0.40 – 0.97**	1.49	0.67 – 2.57	1.19	0.84 – 1.69
Smoking (ever/never)	0.99	0.70 – 1.41	**0.63**	**0.41 – 0.97**	1.54	0.71 – 2.66	1.17	0.83 – 1.66
Cumulative exposure	0.99	0.70 – 1.41	**0.63**	**0.41 – 0.97**	1.41	0.93 – 3.91	1.19	0.82 – 1.73

The associations between *MnSOD* Ala–9Val polymorphism and the risk of asbestosis and between *iNOS* genotypes and asbestosis were modified by *CAT* –262 C > T polymorphism (p = 0.038; p = 0.031). A strong interaction was found between *GSTM1*-null polymorphism and smoking (p = 0.007), *iNOS* $(CCTTT)_n$ polymorphism and smoking (p = 0.054), and between *iNOS* $(CCTTT)_n$ polymorphism and cumulative asbestos exposure (p = 0.037).

Discussion/Conclussions

The findings of our study into asbestosis in agreement with other studies suggest that in addition to environmental and/or occupational exposure to different hazards and lifestyle factors, the genetic factors as well as the interactions between different genotypes, genotypes and lifestyle factors, and between genotypes and environmental/occupational exposure to hazards have an important influence on the development of diseases and should be further investigated.

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