

ASBESTOSIS AND CATALASE GENETIC POLYMORPHISM

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Catalase (CAT) is part of the enzymatic defense system against reactive oxygen species (ROS), known to be involved in the pathogenesis of asbestosis. This study investigates whether CAT -262 C>T genetic polymorphism influences the risk of asbestosis in workers occupationally exposed to asbestos.

The nested case-control study included 262 cases with asbestosis and 265 controls with no asbestos-related disease. Data on cumulative asbestos exposure and smoking were available. A real-time PCR assay was introduced for genotyping CAT -262 C>T promoter polymorphism.

A slightly elevated risk of asbestosis was observed in subjects with the CAT -262 TT genotype compared to others (OR=1.36, CI 0.70-2.62). This risk did not change substantially after adjustment by sex, age, and smoking, but the involvement of cumulative asbestos exposure changed the OR to 1.91 (CI 0.93-3.91). These findings indicate that the CAT -262 TT genotype may be slightly associated with an increased risk of asbestosis. No synergistic effect was found between cumulative asbestos exposure and the CAT -262 TT genotype, but cumulative asbestos exposure acted as a confounder. These results are an important contribution to understanding the interactions between genetic and environmental factors that may modify the risk of asbestosis.

KEY WORDS: *asbestos exposure, causal relationship, nested case control study, real-time PCR*

Asbestosis is one of the most frequent diseases associated with asbestos exposure (1-3). The causal relationship between asbestos exposure and asbestosis has been proven in numerous epidemiological studies (4-7), but little is still known about the genetic factors that may influence individual susceptibility to this disease (8-10).

The pathogenesis of asbestosis is still poorly understood. Studies on animal models and cell cultures indicate that asbestos fibres generate reactive oxygen and nitric species (ROS and RNS) (3, 11-13). Asbestos may stimulate the production of ROS in two different ways. The first mechanism is due to the participation of redox-active iron in asbestos that catalyses the formation of hydroxyl radicals (OH[·]), whereas the second mechanism is characterised by

production of ROS by alveolar macrophages during the phagocytosis of asbestos fibres (14-16).

ROS generated by asbestos have been shown to be important signals for the induction of transcription and the production of inflammatory and fibrotic cytokines, oncogenes, and factors causing dysregulation of growth control (13, 17). The most important ROS involved in the pathogenesis of asbestos-related lung diseases are superoxide anion (O₂^{·-}), hydroxyl radical (OH[·]), and hydrogen peroxide (H₂O₂) (11, 18-20).

Oxidative stress can cause damage to cellular macromolecules; however, antioxidant defense enzymes that neutralize ROS are normally present in the cells and act as protectors. Catalase is an endogenous antioxidant enzyme that catalyses the reduction of H₂O₂ to water (H₂O) and oxygen (O₂),

and therefore plays a major role in controlling H₂O₂ concentrations in human cells (21-23). Together with other antioxidant enzymes, it plays an important role in the primary defense against oxidative stress (21-23).

The results of several studies suggest that reduction in catalase activity may play an important role in the host response to oxidative stress, and could be associated with increased risk of certain diseases (23-26).

The human gene coding for catalase is located on chromosome 11p13 and consists of 13 exons (27). Several rare polymorphisms have been reported in the catalase gene (22). The most common single nucleotide polymorphism (SNP) in the promoter region of the catalase gene (*CAT*) consists of a cytosine (C) to thymine (T) substitution at position -262 in the promoter region (*CAT*-262 C>T) (22). The association between *CAT*-262 C>T polymorphism and catalase activity or catalase levels has been investigated in several studies (22, 23, 28). Forsberg et al. found significantly higher catalase levels in individuals carrying the -262 T allele in comparison to individuals homozygous for the C allele (22). In contrast, in a study by Nadif et al., *CAT*-262 C>T polymorphism was significantly associated with erythrocyte catalase activity: the lowest was found in subjects with the TT genotype, an intermediate level in individuals with the CT genotype, and the highest in those with the CC genotype (28). Similar results were obtained in a cross-sectional study by Ahn et al., who found a dose-response reduction in catalase activity, with the highest geometric mean in individuals with the *CAT*-262 CC genotype, intermediate for those with the CT genotype, and the lowest for those with the TT genotype (23). Bastaki et al. also observed lower average catalase activity in subjects with the *CAT*-262 TT genotype compared to those with the CC genotype (29).

Recent studies indicate that genetic polymorphisms play an important role in susceptibility to the development of asbestosis (7, 9-10, 30-31). To our knowledge, the association between asbestosis and *CAT*-262 C>T polymorphism has not been studied so far.

To thoroughly investigate the interactions between genetic and environmental factors that could influence the risk of asbestosis, we designed a series of studies focusing on the most common polymorphisms of metabolic enzymes involved in the antioxidant response and xenobiotic detoxification in a large cohort of workers occupationally exposed to asbestos

from a small geographic area with an ethnically homogenous population (32).

This study investigated the influence *CAT*-262 C>T polymorphism on the risk of asbestosis in workers occupationally exposed to asbestos.

SUBJECTS AND METHODS

The study subjects were recruited from a cohort of 2,080 workers occupationally exposed to asbestos who were presented at the Board for the Recognition of Occupational Asbestos Diseases from 1 January 1998 to 31 December 2003. From this cohort, 356 cases diagnosed with asbestosis as an occupational disease and 356 controls with no asbestos-related disease were selected for a nested case-control study. The controls were matched to the cases by age and sex. However, 52 cases and 53 controls refused to take part in the study, 40 cases and 29 controls died in the period between the recognition of the occupational disease and the start of the study, and two cases and nine controls developed a malignant disease during the same period. Consequently, the final number of cases included in the study was 262 and that of controls 265.

All study cases and controls were employed at the Slovenian asbestos cement manufacturing plant Salanit Anhovo, where there were three major production processes: cement production, production of asbestos-cement pipes, and production of corrugated sheets (33).

Smoking data were obtained for each case and control at the interview using a standardised questionnaire (33, 34).

For each subject, data on cumulative asbestos exposure were available from the previous study (33).

The diagnosis of asbestosis or "no asbestos-related disease" for each case and control was verified by experts from the Board for Recognition of Occupational Asbestos Diseases according to the Helsinki Criteria for Diagnosis and Attribution of Asbestos Diseases (35) and the American Thoracic Society proposal (36). Two experts teams from the Clinical Institute of Occupational Medicine in Ljubljana participated, each consisting of an occupational physician, a radiologist, and a pulmonologist.

For genotyping, capillary blood samples from the fingertips of all cases and controls were collected on

FTA Mini Cards (Whatmann Bioscience). Genomic DNA was extracted from the FTA cards using Blood Prep chemistry on the ABI PRISM™ 6100 Nucleic Acid PrepStation (Applied Biosystems, Foster City, CA) and stored at -20 °C until genotyping.

A custom TaqMan SNP genotyping assay (ABI, Foster City, CA) was used to determine CAT -262 C>T polymorphism. Primer and probe sets were designed as follows: -262 F: 5'GCCTGAAGGATGCTGATAACCG', -262 R: 5'CAATTGGAGAGCCTCGCC', -262 C probe FAM-CCGGGATAGCCGAA, and -262 T probe VIC-CCCGGAATAGCCGAA. Real-time PCR was performed under universal conditions on ABI 7900HT in a 5 µL reaction mix containing 0.125 µL of TaqMan SNP genotyping assay (ABI, Foster City, CA), 2.5 µL of TaqMan Universal PCR Master Mix (ABI, Foster City, CA), and 120 ng of DNA. Genotyping was randomly repeated in 20 % of samples to check for typing reliability. TaqMan SNP genotyping assays were validated on 100 samples genotyped using the PCR-RFLP method. To determine CAT -262 C>T polymorphism, the region encompassing the polymorphic site was amplified and PCR products were digested with *Sma*I (New England Biolabs) as previously described (22).

Standard descriptive statistics were used. The differences in the means of variables between cases and controls were analysed using the *t*-test. A χ^2 test was used to determine whether the observed differences in proportions between the study groups were statistically significant. The odds ratios (OR) and corresponding 95 % confidence intervals (CI) were

calculated first using univariate logistic regression, followed by multivariate logistic regression modelling to assess the causal relationship between asbestosis, cumulative asbestos exposure, genotypes, and confounders. A possible synergistic effect was calculated between asbestos exposure and genotypes using dummy variables.

The study was approved by the Slovenian Ethics Committee for Research in Medicine and was carried out in line with the Helsinki Declaration.

RESULTS

The mean ages of cases and controls were 61 and 57 years, respectively. No significant difference in sex distribution was found between cases and controls. No difference was observed with regard to smoking (Table 1) (7, 31).

The mean cumulative asbestos exposure was 37.67 fibres/cm³-years (SD=86.43) in cases and 11.23 fibres/cm³-years (SD=23.47) in controls. The difference in cumulative asbestos exposure between the cases and controls was statistically significant ($t=4.78, p=0.000$) (7, 31).

All cases and controls were genotyped for CAT -262 C>T gene polymorphism. However, amplification was not successful in six cases and three controls. The CAT -262 TT genotype was found in 22 cases and 17 controls, the CT genotype in 107 cases and 105 controls, and the CC genotype in 127 cases and 140 controls. When combining genotypes, there was no

Table 1 Study subjects by age, sex, and smoking status

Variables	Cases (N=262)	Controls (N=265)	Test	p value
Age / year				
Mean ± SD	61 ± 9.40	57 ± SD 9.34	t=5.18	p=0.000
Sex				
Male	186	183		
Female	76	82	$\chi^2=0.24$	p=0.628
Smoking				
Ever/never smokers	117/145	120/145	$\chi^2=0.01$	p=0.919
Average years Mean ± SD	25.92 ± 13.37	22.90 ± 12.90	t=1.77	p=0.078
Average pack-years Mean ± SD	21.92 ± 15.95	20.99 ± 16.37	t=0.44	p=0.659

statistically significant difference in the frequency of the TT genotype versus the frequency of the CT and CC genotypes between cases and controls ($\chi^2=0.82$, $p=0.364$) (Table 2).

Using logistic regression analysis, a positive association was found between asbestosis and cumulative asbestos exposure (OR=3.21, CI 2.43-4.23). On the other hand, a lack of association was observed between asbestosis and smoking (ever/never) (OR=0.98, CI 0.69-1.39). The OR of asbestosis was 1.27 (CI 0.64-2.53) for the CAT -262 TT versus CT genotype, 1.43 (CI 0.73-2.81) for the TT versus CC genotype, and 1.12 (CI 0.78-1.61) for the CT versus CC genotype. A slightly elevated OR of asbestosis was found for the CAT -262 TT genotype compared to the CT and CC genotypes (OR=1.36, CI 0.70-2.62) (Table 3). The risk of asbestosis for the TT genotype did not change substantially after adjustment for sex, age, and smoking (Table 3). However, the involvement of cumulative asbestos exposure changed the OR from 1.36 (CI 0.70-2.62) to 1.91 (CI 0.93-3.91) (Table 3), suggesting a confounding effect. In a subsequent analysis, a dummy variable was created by multiplying the TT genotype and cumulative asbestos exposure and included into logistic regression analysis together with the TT genotype and cumulative asbestos exposure, yielding an OR of 1.76 and p value of 0.369, showing no synergistic effect.

DISCUSSION

Interest in investigating the influence of both genetic and environmental factors on the development of diseases has recently been increasing (37-39). Among occupational diseases, asbestosis is one of the most frequently studied. Several studies have investigated the influence of genetic polymorphisms

of metabolic enzymes on the risk of asbestosis, mostly focusing on the polymorphisms of glutathione S-transferases (GSTs) M1, T1, P1 (GSTM1, GSTT1 and GSTP1), and manganese superoxide dismutase (MnSOD) (7-10, 30-31, 40). This study investigates the association between asbestosis and CAT -262 C>T polymorphism. To our knowledge, this is the first attempt to assess the relationship between asbestosis and genetic polymorphism of catalase, which is known to be one of the major enzymes involved in the primary defence against oxidative stress.

This study observes a slightly elevated risk of asbestosis for the CAT -262 TT genotype versus the CT and CC genotypes. The results could be explained as biologically plausible, especially considering the findings of more recent studies, which showed lower catalase activity in subjects with the TT genotype compared to those with the CT and CC genotypes (23, 28-29). Because catalase plays an integral role in the primary defence against ROS, which are known to be included in the pathogenesis of asbestosis (11-13), lower catalase activity in individuals with the CAT -262 TT genotype could explain our findings of a likely increased risk of asbestosis in individuals carrying this genotype. One of the possible explanations why the risk was only slightly elevated may be that not only catalase but also other enzymes such as glutathione peroxidase (GPX) are involved in detoxification of H_2O_2 , which is one of the ROS generated by asbestos fibres.

A dummy variable was used to test the possible synergistic effect between CAT genotypes and cumulative asbestos exposure. No such effect was observed. However, cumulative asbestos exposure was a confounder.

The results of this study must be considered in the context of observations by previous studies investigating the influence of genetic polymorphisms

Table 2 Frequencies of CAT genotypes in cases and controls

CAT genotype	Cases (N=256)		Controls (N=262)		χ^2	p value
	n	%	n	%		
TT	22	8.6	17	6.5		
CT	107	41.8	105	40.1	0.47*	0.495
CC	127	49.6	140	53.4	1.07**	0.302
CT + CC	234	91.4	245	93.5	0.82***	0.364

* χ^2 calculated for TT vs. CT

** χ^2 calculated for TT vs. CC

*** χ^2 calculated for TT vs. CT + CC

Table 3 Risk of asbestosis for the CAT -262 TT genotype versus the CT and CC genotypes

	OR	95 % CI
Unadjusted	1.36	0.70-2.62
Adjusted by		
Sex	1.34	0.70-2.60
Age	1.31	0.67-2.57
Smoking (ever/never)	1.37	0.71-2.66
Cumulative exposure	1.91	0.93-3.91

of certain other major enzymes involved in the detoxification of xenobiotics and inactivation of ROS and RNS on the risk of asbestosis (7-10, 30-31, 40-41). Important findings of our previous studies show that the *GSTT1*-null genotype, which results in the absence of an active enzyme, as well as the *GSTP1* genotype coding for an enzyme with high conjugation capacity, were associated with an increased risk of asbestosis (7, 31). In line with these reports, the results of this study, although statistically insignificant, could support the hypothesis that genetic polymorphisms of metabolic enzymes play an important role in the development of asbestosis. For this reason, we understand the findings of this study to be an important contribution to studying the influence of genetic factors on the risk of asbestosis and to new knowledge in investigating the role of *CAT* polymorphism in asbestosis, which has not been studied so far. The authors are aware that there may be a combined effect of all of the above mentioned polymorphisms. The relationship between them, which has yet to be proven, could be synergistic, additive, or independent.

All of the subjects included in this study were recruited in a small geographic area with an ethnically homogenous population, and no bias was introduced by genetic heterogeneity (32). Although approximately 26 % of the cases and controls were excluded from the study because they died, developed cancer, or did not wish to participate, there were no differences in the cumulative asbestos exposure or diagnosis of cancer between the participants and the excluded group.

In conclusion, our results suggest that the *CAT* -262 TT genotype may be associated with an increased risk of asbestosis. To clarify this finding, further studies are needed that include a larger number of subjects and that also investigate the *CAT* genotype-phenotype relationship.

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Izvleček**AZBESTOZA IN POLIMORFIZEM GENA ZA KATALAZO**

Katalaza (CAT) je del encimskega obrambnega sistema proti reaktivnim kisikovim spojinam (ROS), za katere je znano, da so vpletene v patogenezo azbestoze. V raziskavi preučujemo, ali genetski polimorfizem CAT -262 C>T vpliva na tveganje za nastanek azbestoze pri delavcih, ki so bili poklicno izpostavljeni azbestu. Ugnježena študija primerov s kontrolami je vključevala 262 primerov z azbestozo in 265 kontrol, ki niso imeli nobene bolezni, povezane z izpostavljenostjo azbestu. Na razpolago so bili podatki o celokupni izpostavljenosti azbestu in kajenju. Za genotipizacijo promotorskega polimorfizma CAT -262 C>T smo uporabili PCR v realnem času.

Rahlo povišano tveganje za azbestozo smo opazili pri osebah z genotipom CAT -262 TT (RO=1,36, IZ 0,70-2,62). Opisano tveganje se ni bistveno spremenilo po prilagoditvi po spolu, starosti in kajenju, pač pa se je razmerje obetov zvišalo po uvedbi celokupne izpostavljenosti azbestu na 1,91 (IZ 0,93-3,91).

Rezultati kažejo, da genotip CAT -262 TT lahko povežemo z rahlo povečanim tveganjem za razvoj azbestoze. Sinergističnega učinka med celokupno izpostavljenostjo azbestu in genotipom CAT -262 TT nismo opazili, celokupna izpostavljenost azbestu pa je delovala kot moteča spremenljivka. Rezultati predstavljajo pomemben prispevek k razumevanju sovplova genetskih in okoljskih dejavnikov, ki bi lahko spremenili tveganje za nastanek azbestoze.

KLJUČNE BESEDE: *izpostavljenost azbestu, PCR v realnem času, vzročna povezava, ugnježena študija primerov s kontrolami*

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