research article

The influence of genetic variability of DNA repair mechanisms on the risk of malignant mesothelioma

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Background. Malignant mesothelioma (MM) is a rare aggressive tumour of mesothelium caused by asbestos exposure. It has been suggested that the genetic variability of proteins involved in DNA repair mechanisms affects the risk of MM. This study 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 MM risk.

Patients and methods. In total, 237 cases with MM and 193 controls with no asbestos-related disease were genotyped for *ERCC1* and *XRCC1* polymorphisms.

Results. *ERCC1* rs3212986 polymorphism was significantly associated with a decreased risk of MM (odds ratio [OR] = 0.61; 95% confidence interval [CI] = 0.41–0.91; p = 0.014). No associations were observed between other genetic polymorphisms and MM risk. Interactions between polymorphisms did not significantly influence MM risk. Interaction between *ERCC1* rs11615 and asbestos exposure significantly influenced MM risk (OR = 3.61; 95% CI = 1.12–11.66; p = 0.032). Carriers of polymorphic *ERCC1* rs11615 allele who were exposed to low level of asbestos had a decreased risk of MM (OR = 0.40; 95% CI = 0.19–0.84; p = 0.016). Interactions between other polymorphisms and asbestos exposure did not significantly influence MM risk.

Conclusions. Our findings suggest that the genetic variability of DNA repair mechanisms could contribute to the risk of developing MM.

Key words: malignant mesothelioma; DNA repair mechanisms; ERCC1; XRCC1; genetic polymorphism

Introduction

Malignant mesothelioma (MM) is a rare and aggressive tumour of the serosal membranes with poor prognosis. It is mainly localized to the pleura, but could also arise in the peritoneum, pericardium and tunica vaginalis.[1-3] MM is more commonly found in men than in women. It occurs mainly in adults, 75% of patients are older than 65 years.[4] The majority of MM cases could be attributed to occupational or environmental exposure to asbestos.[3,5-7] The global incidence is expected to continue to increase due to a long latency period, which could range from 15 to 60 years.[8] Although the association between asbestos exposure and occurrence of MM is well established, the mechanism of carcinogenesis is not fully explained.[9,10] Nevertheless, some studies reported genotoxic effects of asbestos.[11-13] It has been suggested that the DNA damage may be caused by the direct influence of asbestos fibres that interfere with mitosis or by the indirect effect caused by the release of reactive oxygen

species (ROS) and reactive nitrogen species (RNS) from macrophages. It is well established, that oxidative stress triggers DNA repair mechanisms, however, their role in the development of MM has not been fully studied yet.[12,13] It has been suggested that the genetic variability of proteins involved in DNA repair mechanisms affects the risk of MM. In particular, excision repair cross-complementing group 1 (ERCC1) and X-ray repair cross-complementing protein 1 (XRCC1) may be involved and genes coding for these proteins are known to be polymorphic.[14,15]

ERCC1 is a protein involved in the repair of DNA by nucleotide excision repair (NER). Together with the Xeroderma pigmentosum F it forms an endonuclease, which also participates in homologous recombination and base excision repair (BER).[16] The ERCC1 protein plays crucial role in NER, so some studies suggested that *ERCC1* polymorphisms could attribute to increased risk of several malignant diseases.[17,18] The gene for the ERCC1 protein is located on the chromosome 19q13.32 and consists of 10 exons.[19] Numerous polymorphisms of *ERCC1* gene have been described, rs11615 and rs3212986 being the most commonly studied ones. Single nucleotide polymorphism (SNP) *ERCC1* rs11615 results in the replacement of cytosine (C) with thymine (T) without amino acid substitution. Studies have shown that carriers of this SNP have an increased risk of head and neck squamous cell carcinomas, breast cancer and a reduced risk of ovarian cancer.[18,20,21] The SNP *ERCC1* rs3212986 causes the replacement of T with guanine (G) in the 3′ untranslated region. It has been associated with an increased risk of colorectal cancer and a reduced risk of hepatocellular carcinoma.[22,23]

XRCC1 is an important protein involved in BER and the repair of DNA single-strand breaks (SSBR). It does not have enzymatic activity, but acts as a scaffolding protein that interacts with repair enzymes.[24] The *XRCC1* gene is located on chromosome 19q13.2 and consists of 17 exons. Recent studies have been investigating association between *XRCC1* polymorphisms and the development of various types of cancer. More than 60 polymorphisms of this gene are known. The most common are rs25487, rs25489 and rs1799782.[25] SNP *XRCC1* rs25487 causes the replacement of G with adenine (A), causing the substitution of glycine (Gln) with arginine (Arg) in codon 399 (p.399Gln>Arg).[26] This polymorphism has been associated with an increased risk of developing thyroid and lung cancer.[27,28] Other common *XRCC1* polymorphism is rs1799782, which causes the replacement of C with T and consequently the replacement of Arg with tryptophan (Trp) at position 194 (p.194Arg> Trp). A Chinese study described that the SNP *XRCC1* rs1799782 is associated with an increased risk of lung cancer.[28]

So far only two studies investigated the influence of the genetic variability of proteins involved in DNA repair mechanisms on the development of MM. The first study investigated the influence of *XRCC1* rs25487 and rs1799782, and *XRCC3* rs861539 and rs861535 polymorphisms on the development of MM and found that carriers of polymorphic allele *XRCC1* rs25487 have an increased risk on the development of this cancer.[14] The second study investigated the influence of *ERCC1* rs11615, rs2298881, rs3212948 and rs3212965, and *XRCC1* rs25487, rs3213245, rs1799782, rs3213247, rs12973352, rs2854496, rs2307174, rs2023614, rs1799778, rs3213356, rs3213371 and rs3213403 polymorphisms on the risk of MM. It has been reported that carriers of polymorphic alleles *ERCC1* rs11615 and *XRCC1* rs25487 have an increased risk of MM. The interaction between these polymorphisms also contributed to an increased risk of developing MM.[15]

According to our knowledge and available literature the influence of the *ERCC1* rs3212986 polymorphism as well as the impact of interactions between polymorphisms of proteins involved in DNA repair mechanisms and asbestos exposure on the risk of developing MM has not been studied yet.

The aim of this study was to investigate whether functional polymorphisms in *ERCC1* and *XRCC1* genes influence the risk of MM, to study the influence of the interactions between *ERCC1* and *XRCC1* polymorphisms on MM risk as well as to investigate the effect of the interactions between these polymorphisms and asbestos exposure on MM risk.

Patients and methods

Patients

A retrospective case-control study included 237 patients with pleural or peritoneal MM treated at the Institute of Oncology Ljubljana between November 2001 and October 2016, along with 193 controls who worked and were occupationally exposed to asbestos in the asbestos cement factory of Salonit Anhovo, Slovenia. The controls were evaluated at the State Board for the Recognition of Occupational Asbestos Diseases between January

1999 and December 2003 and did not have any asbestos-related disease.

The study was approved by the Slovenian Ethics Committee for Research in Medicine and was carried out according to the Declaration of Helsinki.

Methods

Patients with pleural MM were diagnosed by ultrasound-guided biopsy or thoracoscopy and patients with peritoneal MM were diagnosed by laparoscopy. The diagnosis was confirmed by a histopathological examination by an experienced pathologist.[5]

The asbestos exposure was determined by semiquantative method. For all controls and some patients with MM, the data on cumulative asbestos exposure in fibres/cm^3-years were available. On the basis of this data, the subjects were divided into three groups: low (< 11 fibers/cm^3-years), medium (11–20 fibres/cm^3-years) and high (> 20 fibres/cm^3-years) asbestos exposure. For those patients with MM where cumulative asbestos exposure data were not available, a precise work history was obtained and their asbestos exposure was deduced from comparison to a group of subjects with known cumulative asbestos exposure at a given working place. Also in this case the exposure was divided into three groups: low, medium and high asbestos exposure. A personal interview with each of the subjects was performed to obtain the data on smoking using a standardized questionnaire.[5,29]

DNA of the MM patients and some controls without asbestos-related diseases was available from our previous studies.[5] DNA from the rest of the controls was isolated from capillary blood collected on Whatman FTA cards during this study using MagMax™ DNA Multi-Sample Kit (Applied Biosystems, Foster City, California, USA). Competitive allele-specific and real-time polymerase chain reaction (PCR) based KASP and TaqMan assays were used for the analysis of *ERCC1* rs11615, rs3212986 and *XRCC1* rs1799782, rs25487 polymorphisms as recommended by the manufacturer (KBioscience, Hoddesdon, Herts, UK and Thermo Fisher Scientific, USA). Amplification was not successful in 19 subjects for *ERCC1* rs11615, in 17 for *ERCC1* rs3212986, in 12 for *XRCC1* rs1799782 and in 20 subjects for *XRCC1* rs25487 polymorphism due to limited DNA samples.

Statistical methods

Standard descriptive statistics were first performed. To determine the differences in age between the cases and controls the non-parametric Mann-Whitney (U) test was performed.

The dominant genetic models were used for all the comparisons. To analyse the association between genotypes, cumulative asbestos exposure, and standard confounders (age, gender) and MM,

TABLE 1. Characteristics of malignant mesothelioma (MM) patients, controls and the influence of these characteristics on MM risk

	MM patients (n = 237)	Controls (n = 193)	Test	OR (95% CI)	p
Gender					
Male n (%)	175 (73.8%)	128 (66.3%)	$\chi^2 = 2.889$	0.70	0.089
Female n (%)	62 (26.2%)	65 (33.7%)		(0.46–1.06)	
Age					
Years; median (25–75%)	66 (58–72)	56.2 (49.3–65.0)	U = 32583	1.08 (0.46–1.06)	< 0.001
Cumulative asbestos exposure[1]					
Low	36 (44.4%)	149 (77.2%)	$\chi^2 = 31.933$		**< 0.001**
Medium	24 (29.6%)	15 (7.8%)			
High	21 (25.9%)	29 (15.0%)			
Low	36 (44.4%)	149 (77.2%)	$\chi^2 = 27.916$	4.23[3]	**< 0.001**
Medium and high	45 (55.6)	44 (22.8%)		(2.44–7.36)	
Smoking[2]					
No	122 (53.0%)	106 (54.9%)	$\chi^2 = 0.149$	1.08	0.699
Yes	108 (47.0%)	87 (45.1%)		(0.74–1.58)	

[1] data available for 81 MM patients, [2] data missing for 7 MM patients, [3] medium and high exposure in comparison to low exposure

univariate logistic regression was first used, followed by multivariate logistic regression modelling. The interactions were calculated by logistic regression models using dummy variables.

Results

The patients' and controls' characteristics are shown in Table 1. There was no statistical difference in gender (p = 0.089) and smoking (p = 0.699) between the two groups. Groups differed significantly by age (p < 0.001) and cumulative asbestos exposure (p < 0.001). The median age was 66.0 years for patients and 56.2 years for controls. In univariate logistic regression analysis age, gender and smoking did not affect the risk of MM. The results showed that medium and high level of asbestos exposure increased the risk of MM 4-fold (odds ratio [OR] = 4.23; 95% confidence interval [CI] = 2.44–7.36; p < 0.001) in comparison to a low level of asbestos exposure (Table 1).

TABLE 2. The influence of polymorphisms on MM risk

Polymorphism	Genotype	MM patients	Controls	Unadjusted risk		Adjusted risk by gender and age	
		N (%)	N (%)	OR (95% CI)	p	OR (95% CI)	p
***ERCC1* rs11615**	TT	97 (41.8)[1]	64 (35.8)[2]				
	TC	94 (40.5)	87 (48.6)				
	CC	41 (17.7)	28 (15.6)	0.78 (0.52–1.16)	0.213	0.69 (0.45–1.06)	0.091
***ERCC1* rs3212986**	GG	142 (59.9)	84 (47.7)[3]				
	GT	77 (32.5)	75 (42.6)				
	TT	18 (7.6)	17 (9.7)	0.61 (0.41–0.91)	**0.014**	0.52 (0.34–0.80)	**0.003**
***XRCC1* rs1799782**	CC	196 (86.0)[4]	171 (90.0)[5]				
	CT	32 (14.0)	19 (10.0)	1.47 (0.80–2.69)	0.211	1.12 (0.58–2.16)	0.728
***XRCC1* rs25487**	CC	90 (38.0)	74 (42.8)[6]				
	CT	125 (52.7)	79 (45.7)				
	TT	22 (9.3)	20 (11.6)	1.22 (0.82–1.82)	0.327	1.03 (0.67–1.59)	0.890

For determining MM risk, carriers of at least one polymorphic allele were compared to non-carriers

[1]missing data for 5 patients; [2]missing data for 14 patients; [3]missing data for 17 patients, [4]missing data for 9 patients, [5]missing data for 3 patients, [6]missing data for 20 patients

TABLE 3. The influence of interactions between investigated genetic polymorphisms on MM risk

Gene 1			Gene 2			Interaction	
Genotypes	**OR (95% CI)**	**p**	**Genotypes**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
***ERCC1* rs 11615** TC + CC vs. TT	0.78 (0.52–1.16)	0.213	***ERCC1* rs3212986** GT + TT vs. GG	0.61 (0.41–0.91)	0.014	1.97[1] (0.42–9.17)	0.75
***ERCC1* rs 11615** TC + CC vs. TT	0.78 (0.52–1.16)	0.213	***XRCC1* rs1799782** CT vs. CC	1.47 (0.80–2.69)	0.211	1.30[2] (0.37–4.52)	0.680
***ERCC1* rs 11615** TC + CC vs. TT	0.78 (0.52–1.16)	0.213	***XRCC1* rs25487** CT + TT vs. CC	1.22 (0.82–1.82)	0.327	0.79[3] (0.34–1.86)	0.592
***ERCC1* rs3212986** GT + TT vs. GG	0.61 (0.41–0.91)	0.014	***XRCC1* rs1799782** CT vs. CC	1.47 (0.80–2.69)	0.211	1.49[4] (0.42–5.21)	0.537
***ERCC1* rs3212986** GT + TT vs. GG	0.61 (0.41–0.91)	0.014	***XRCC1* rs25487** CT + TT vs. CC	1.22 (0.82–1.82)	0.327	0.65[5] (0.29–1.47)	0.302
***XRCC1* rs1799782** CT vs. CC	1.47 (0.80–2.69)	0.211	***XRCC1* rs25487** CT + TT vs. CC	1.22 (0.82–1.82)	0.327	2.41[6] (0.66–8.80)	0.182

[1] rs 11615 ERCC1 TC + CC vs. TT * rs3212986 ERCC1 GT + TT vs. GG; [2] rs 11615 ERCC1 TC + CC vs. TT * rs1799782 XRCC1 CT vs. CC; [3] rs 11615 ERCC1 TC + CC vs. TT * rs25487 XRCC1 CT + TT vs. CC; [4] rs3212986 ERCC1 GT + TT vs. GG * rs1799782 XRCC1 CT vs. CC; [5] rs3212986 ERCC1 GT + TT vs. GG * rs25487 XRCC1 CT + TT vs. CC; [6] rs1799782 XRCC1 CT vs. CC * rs25487 XRCC1 CT + TT vs. CC

The frequency distribution of the studied genetic polymorphisms is shown in Table 2. Minor allele frequencies were 39.9% for *ERCC1* rs11615, 31.0% for *ERCC1* rs3212986, 5.0% for *XRCC1* rs1799782 and 34.5% for *XRCC1* rs25487 in the control group. All SNPs were in Hardy-Weinberg equilibrium in controls (all $p > 0.05$). Analysing the association between MM and the investigated genetic polymorphisms, the risk of MM was statistically significantly influenced only by *ERCC1* rs3212986 polymorphism (OR = 0.61; 95% CI = 0.41–0.91; p = 0.014). Carriers of at least one polymorphic *ERCC1* rs3212986 genotype GT or TT had a decreased risk of MM even when adjusting for age and gender. No association was observed between MM and other genetic polymorphisms (Table 2).

In further logistic regression modelling the interactions between *ERCC1* rs11615 and rs3212986 and *XRCC1* rs1799782 and rs25487 polymorphisms did not significantly influence the risk of MM (Table 3).

Analysing the influence of interactions between the *ERCC1* and *XRCC1* polymorphisms and the asbestos exposure on the risk of MM, the interaction between *ERCC1* rs11615 polymorphism and asbestos exposure statistically significantly increased the risk of MM (OR = 3.61, 95% CI = 1.12–11.66, p = 0.032). Other interactions between polymorphisms and asbestos exposure did not statistically significantly affect the risk of MM (Table 4).

Finally, we analysed the interaction between *ERCC1* rs11615 polymorphism and asbestos exposure in more detail. Table 5 shows that carriers of at least one polymorphic *ERCC1* rs11615 allele that have been exposed to low level of asbestos had a statistically significant decreased risk of MM (OR = 0.40; 95% CI = 0.19–0.84; p = 0.016). If their exposure was medium or high, the risk of MM was statistically significantly increased (OR = 3.00; 95% CI = 1.42–6.34; p = 0.004).

TABLE 4. The influence of interactions between the investigated polymorphisms and asbestos exposure on MM risk

Polymorphism	OR	95% CI	p
***ERCC1* rs11615**	**3.61**	**1.12–11.66**	**0.032**
***ERCC1* rs3212986**	1.93	0.61–6.10	0.262
***XRCC1* rs1799782**	1.85	0.33–10.48	0.489
***XRCC1* rs25487**	2.80	0.89–8.79	0.078

Discussion

The relationship between MM and asbestos exposure was first described in 1960, but relatively little has been known about the mechanisms of carcinogenesis and the influence of genetic factors on the development of this malignant disease.[30] In the current study we investigated the influence of *ERCC1* and *XRCC1* polymorphisms, interactions between studied polymorphisms, and interactions between these polymorphisms and asbestos exposure on the risk of MM.

In this study, the majority of patients with MM were older than 58 years. This is consistent with the findings of previous studies showing that this tumour occurs primarily in the elderly, which could be contributed by the long latency period.[3,4,8]

Our study did not detect any association between smoking and the risk of MM, which is in agreement with the findings of some previous studies.[31,32] On the contrary, a previous Slovenian study showed that smoking increased the risk of MM.[3] The relation between smoking and the risk of MM development has to be further investigated.

An important finding of our study is that the medium and higher levels of asbestos exposure is associated with a 4-fold higher risk of developing

TABLE 5. The influence of interaction between *ERCC1* rs11615 polymorphism and asbestos exposure on MM risk

	Asbestos exposure								OR for asbestos exposure inside category *ERCC1*	
	Low				Medium and high					
***ERCC1* rs11615**	**MM (N)**	**Controls (N)**	**OR (95% CI)**	**p**	**MM (N)**	**Controls (N)**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
TT	20	48	1	Ref.	14	16	2.10 (0.87–5.10)	0.101	2.10 (0.87–5.10)	0.101
TC+CC	15	91	0.40 (0.19–0.84)	0.016	30	24	3.00 (1.42–6.34)	0.004	7.58 (3.53–16.31)	< 0.001
OR for *ERCC1* inside category asbestos exposure			0.40 (0.19–0.84)	0.016			1.43 (0.58–4.50)	0.435		

MM compared to low level of exposure. Although it is assumed that there is no threshold dose for developing MM,[10] some studies have proven that the occurrence of MM is associated with the level of asbestos exposure at the beginning of employment and the length of exposure.[33,34]

A key finding of our study is that the carriers of at least one polymorphic *ERCC1* allele rs3212986 had a decreased risk of MM. According to our knowledge, the association between the *ERCC1* rs3212986 polymorphism and the MM has not been studied yet. The protective effect of the above mentioned polymorphism could be explained by the fact that the ERCC1 protein is involved in the NER, which removes the oxidatively induced DNA damage caused by ROS and RNS that are released from the inflammatory cells as a consequence of contact with asbestos. In accordance with the described cell defence mechanism against genomic instability and hence against carcinogenesis, the result obtained could be understood as biologically plausible.

Other investigated polymorphisms did not have a statistically significant effect on the risk of MM. Our results differ from the previous two Italian studies, which found an increased risk for MM in the carriers of polymorphic allele *ERCC1* rs11615 and *XRCC1* rs25487, [14,15] therefore additional research is needed to clarify these associations.

In this study, the interactions between studied polymorphisms did not have a statistically significant effect on the risk of MM. In contrast, the former Italian study indicated the effect of interactions between *ERCC1* rs11615 and *XRCC1* rs25487 polymorphisms on the increased risk of MM.[15]

According to our knowledge the influence of interactions between the studied polymorphisms and the asbestos exposure on the risk of MM have not been investigated so far. An important finding of our study is that the interaction between *ERCC1* rs11615 polymorphism and asbestos exposure affects the risk of MM, although we have not found an independent association between this polymorphism and MM. The analysis showed that the *ERCC1* rs11615 polymorphism modifies the influence of asbestos exposure on the development of MM. Carriers of the polymorphic alleles that had been exposed to low level of asbestos had a decreased risk of MM in comparison with carriers of a normal allele. If the carriers of the polymorphic *ERCC1* rs11615 alleles were exposed to medium or high level of asbestos, they had an increased risk of MM. The observed protective effect of the *ERCC1* rs11615 polymorphism could be explained by the fact that there may be fewer asbestos fibers in the lungs at low levels of asbestos exposure than in medium or high levels of exposure. Consequently less ROS and RNS may be released and the NER would be able to repair the damage despite reduced function, thereby preventing the development of MM. Thus, the protective effect of *ERCC1* rs11615 could be considered as biologically plausible. In medium or high level of asbestos exposure, the level of DNA damage could be higher and consequently NER may not be able to repair it optimally, which could lead to genomic instability and carcinogenesis of MM. The interactions between other genetic polymorphisms and the exposure did not influence the risk of MM.

A limitation of our study is that the information on smoking and asbestos exposure was not available for all subjects. Therefore some of the analyses were performed only on the subgroup of MM patients. The next drawback is that we failed to determine the genotype in some subjects due to the insufficient amount and the degraded DNA in samples isolated from Whatman FTA cards and contamination.

In conclusion, our study showed the protective effect of the *ERCC1* rs3212986 polymorphism on the risk of MM and the impact of the interaction between the *ERCC1* rs11615 polymorphism and asbestos exposure on the risk of developing this aggressive tumour. The results of this research could facilitate our understanding of carcinogenesis of MM.

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