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Association between the *TP53* and *CYP2E1*5B* gene polymorphisms and non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. Genetic polymorphisms in tumour suppressor genes and genes encoding xenobiotic metabolising enzymes alter the activity of their corresponding enzymes and are important individual susceptibility factors for NSCLC. Because of the lack of information in literature, the aim of our study was to investigate the role of the tumour suppressor gene *TP53* (Arg72Pro) and the xenobiotic metabolising *CYP2E1*5B* gene polymorphisms on the risk of NSCLC development. The study population consisted of 172 patients and 172 controls (156 men and 16 women in each group). Genetic polymorphisms were determined with real-time polymerase chain reaction (PCR) and PCR restriction fragment length polymorphism (PCR-RFLP). Multivariate analysis showed a significant association with NSCLC for the combination between the *TP53* codon72 Arg/Pro and the Pro/Pro genotypes (OR 2.21, 95 % CI 1.39–3.51; p=0.001). We also analysed whether combinations of these gene variants with *GSTM1*, *GSTT1*, *GSTP1* exon 5 (Ile105Val), and *GSTP1* exon 6 (Ala114Val) gene polymorphisms were associated with the NSCLC risk. A significant increase in the risk was observed for the following combinations: *TP53* codon72 variant with *GSTM1* null (OR 2.22, 95 % CI 1.23-4.04; p=0.009), *GSTT1* null (OR 2.98, 95 % CI 1.49-5.94; p=0.002), and *GSTP1* (Ala114Val) variant genotypes (OR 3.38, 95 % CI 1.54-7.41; p=0.002). Further studies with larger samples are needed to verify these findings.

KEY WORDS: *carcinogen metabolism;* CYP2E1*; genetic polymorphism; GST; NSCLC*

Lung cancer is the most common cancer type in the world, which affects men in particular. It is also the leading cause of death among cancers (1). Histologically, about 80 % of lung cancers are non-small cell lung carcinomas (NSCLC). The inbuilt phase I and II biotransformation enzyme systems inactivate environmental carcinogens, especially those present in tobacco smoke, depending on the regulating polymorphisms. Epidemiological studies show that genetic differences and interactions among genetic variants might modify lung cancer susceptibility (2, 3). Therefore, it is important to identify individual genetic and acquired factors that modify lung cancer risk in order to develop preventive strategies based on this information. This is particularly true for identifying polymorphisms of tumour suppressor genes and xenobiotic metabolising enzyme genes. The *TP53* tumour suppressor gene is an essential regulator of the cell-cycle arrest, DNA repair, and apoptosis (4). An important single nucleotide polymorphism detected in *TP53* is Arg72Pro. This allele has been shown to decrease the activity of the corresponding protein, which is crucial for the apoptotic function of TP53 (5, 6). Recent studies have reported the association between this polymorphism and lung cancer (7-11).

CYP2E1 is an important phase I biotransformation enzyme that transforms *N*-nitrosamines, vinyl chloride, and benzene in tobacco smoke into mutagenic and carcinogenic metabolites (12). In NSCLC patients it has been found to be overexpressed (13). However, its *CYP2E1*5B* allele has been shown to reduce enzyme activity and microsomal oxidation capacity (14, 15).

The complex pathways of (pro)carcinogen metabolism and the possible interactions between the genes encoding enzymes and TP53 protein clearly indicate the need for their combined assessment as predisposing factors for NSCLC development. However, current findings on the overall impact of *TP53*, *CYP2E1*, and *GST* polymorphisms on NSCLC are limited and controversial (16-18). The aim of this study was to learn more about these impacts by investigating: a) the association between NSCLC risk and *TP53* (Arg72Pro) and *CYP2E1*5B* polymorphisms either alone or in combination and b) possible gene interactions as risk modifiers for NSCLC by combining *TP53* (Arg72Pro) and *CYP2E1*5B* polymorphisms with phase II enzyme coding gene polymorphisms *GSTM1*, *GST1*, *GSTP1* (Ile105Val) (rs1695), and *GSTP1* (Ala114Val)

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(rs1138272) that we have previously genotyped in NSCLC patients (19).

PARTICIPANTS AND METHODS

This case-control study included 344 participants, 172 of whom were histologically confirmed NSCLC patients and 172 were matching controls by gender and mean age (±3 years). All NSCLC patients were enrolled at the Ataturk Pulmonary Diseases and Thoracic Surgery Hospital from February 2002 to November 2005. Their clinical data were collected from medical records. The staging and histological sub-typing of the lung carcinomas followed the international staging system for lung cancer and World Health Organisation histological classification of lung tumours (20). All other lung cancer types were excluded from the study.

Each patient had an interview to answer a detailed questionnaire about sociodemographic and history of smoking information. Pack years were calculated by multiplying packs smoked per day with years as a smoker.

The control group was recruited at a local healthcare centre and consisted of volunteers who were informed about the study during their routine health check-ups. The exclusion criteria were history of malignancy, pregnancy, chronic diseases, and diagnosed cancer of any type. Controls also completed a detailed questionnaire about smoking habits, work, and health history. The category of former smokers included NSCLC patients who had quit smoking at least one year before diagnosis and controls who had quit smoking at least one year before the interview. All participants were Caucasian and gave informed consent to participate in writing. The study was approved by the Medical Ethics Board of the Ataturk Pulmonary Diseases and Thoracic Surgery Hospital.

Genomic DNA samples for genetic polymorphism analysis were obtained from the blood drawn into coded 10 mL heparinised tubes and isolated with a DNA purification kit according to the manufacturer's instructions (Promega, Fitchburg, WI, USA). Isolated DNA was kept at -20 °C until use.

The *TP53* (Arg72Pro) polymorphism (rs1042522) was identified using the real-time polymerase chain reaction (PCR) as described by Talseth et al. (21). The *CYP2E1*5B* (RsaI/PstI, rs3813867/rs2031920) polymorphism was identified with the PCR-restriction fragment length polymorphism (PCR-RFLP) method described by Hayashi et al. (15) and confirmed by real-time PCR as described by Choi et al. (22).

Laboratory personnel were not informed about the source of DNA samples. For quality control we randomly selected 10 % of the samples, and the repeated genotyping procedures gave 100 % concordance. All genotyping data were independently reviewed by two authors.

Statistical analysis

For the comparison of mean age and pack-years between cases and controls we used Student's *t*-test. Multivariate logistic regression was used to calculate odds ratios (OR) between genotypes and NSCLC and 95 % confidence intervals adjusted for age, gender, and smoking status. Gene-smoking interaction adjusted for age was tested on the multiplicative scale by entering product terms in the multivariate logistic models. *P* values below 0.05 were considered significant. For statistical analysis we used the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the demographic information for all participants. NSCLC patients had significantly higher values of pack years smoked than controls (56 and 15 respectively) ($p<0.05$).

Table 2 shows the distribution of the *TP53* and *CYP2E1* genotypes and adjusted ORs for NSCLC. When calculating the ORs, we took wild-type or positive genotypes as reference. As we did not detect the homozygous mutant genotype (**5B/*5B*) (c2/c2) of *CYP2E1* in either group, we combined heterozygous and homozygous genotypes of other polymorphisms for the statistical analysis throughout the study and have presented the results accordingly. The

Table 1 *Participants' demographics*

	NSCLC patients (n=172)	Controls (n=172)
Age (years)		
Mean	56	53
Range	26-75	28-78
Gender, n (%)		
Male	156 (91)	156 (91)
Mean age	57	52
Age range	34-75	28-78
Female	16 (9)	16 (9)
Mean	55	65
Age range	26-70	32-76
Smoking, n (%)		
Current smoker	102 (59)	96 (56)
Former smoker	55 (32)	22 (13)
Non smoker	15 (9)	54 (31)
Pack years, mean*	56	15
Histological type of NSCLC, n (%)		
SCC	65 (38)	
AC	59 (34)	
UNSCLC	48 (28)	

**includes current and former smokers (ever smokers)*
SCC: squamous cell carcinoma, AC: adenocarcinoma, UNSCLC: unspecified non-small cell lung cancer

TP53 (Arg72Pro) polymorphism was in agreement with the Hardy-Weinberg equilibrium in the controls but not in the NSCLC patients.

We found a significant association between the *TP53* codon72 heterozygous (Arg/Pro) genotype and the risk of NSCLC (OR 2.87; 95 % CI 1.70-4.85; *p*=0.001). The association was not significant between *TP53* codon72 mutant (Pro/Pro) genotype and NSCLC (OR 1.34, 95 % CI 0.52-3.49; *p*=0.546), possibly due to the low number of Pro/Pro genotype carriers in both the NSCLC (n=13) and control group (n=15). When we combined the *TP53* codon72 Arg/Pro and Pro/Pro genotypes, we found a significant association between NSCLC risk and the genotypes containing variant allele, as shown in Table 2. The analysis of NSCLC subtypes showed a significant risk of squamous cell carcinoma and unspecified NSCLC in patients carrying the variant (Pro) allele of the *TP53* codon72 (OR 3.50; 95 % CI 1.76–6.99; *p*=0.001 and OR 3.22, 95 % CI 1.49–6.95; *p*=0.003, respectively) but not of adenocarcinoma (1.34, 95 % CI 0.72-2.51; *p*=0.360).

Table 3 shows no significant difference between *TP53* and *CYP2E1* gene interactions and the risk of NSCLC (top results). We then looked further to find if these variant genotypes would be associated with increased NSCLC risk if combined with the *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms from our earlier study (19) and found a significant association for *TP53* codon72 Arg/Pro and Pro/Pro in combination with the *GSTM1* null genotypes. A similar significant association with NSCLC risk was found for the combinations of *TP53* codon72 Arg/Pro and Pro/Pro with the *GSTT1* null and the *GSTP1* (Ala114Val) genotypes (Table 3).

In contrast, the combination of *TP53* codon72 with the *GSTP1* (Ile105Val) variant was not significantly associated with the NSCLC risk, nor were the *CYP2E1* genotype combinations with *GSTM1*, *GSTT1*, *GSTP1* (Ile105Val) and *GSTP1* (Ala114Val) genotypes (Table 3).

We did not analyse the risk of histological subtypes with combined genotypes because of the small number of subjects in each subgroup.

As for the multivariate analysis of gene interactions with cigarette smoking, we found no significant association with the NSCLC risk (data not shown).

DISCUSSION

This is the first study demonstrating the association between *TP53* (Arg72Pro) polymorphism and the NSCLC risk in a Turkish population. Individuals carrying this variant had a 2.2 times higher risk than controls. *TP53* polymorphisms have widely been studied in NSCLC, but the results are contradictory. Three studies reported a significantly increased risk (23-25), one (26) reported an insignificant risk increase, and three (9, 17, 27) reported no significant association between *TP53* codon72 polymorphism and NSCLC. Along with Liu et al. (23), Yang et al. (24), and Loginov et al. (25), we, however, believe to be on the right track, since this *TP53* variant has lower activity in apoptosis and its association with an increased NSCLC risk is plausible.

Studies investigating the effect of the *CYP2E1*5B* polymorphism on NSCLC risk also reported inconsistent results (17, 28-32).

After the analysis of NSCLC subtypes, we found that the variant (Pro) allele carriers of *TP53* codon72 were significantly associated with the risk of SCC but not AC. Tan et al. (18) also reported an association with SCC, but Liu et al. (23) reported a significantly increased risk of AC

Table 2 *NSCLC risk association with TP53 and CYP2E1 polymorphisms*

Genotype	Controls, n (%)	NSCLC patients, n (%)	OR* (95%CI)	p value
TP53				
Arg/Arg	88 (51.16)	57 (33.14)	1	
Arg/Pro+Pro/Pro	84 (48.84)	115 (66.86)	2.21 (1.39-3.51)	**0.001**
CYP2E1				
*1A/*1A (c1/c1)	162 (94.19)	165 (95.93)	1	
*1A/*5B (c1/c2)	10 (5.81)	7 (4.07)	0.81 (0.28-2.31)	0.695
TP53	**Controls, n (%)**	**SCC patients, n (%)**	**OR* (95%CI)**	***p* value**
Arg/Arg	88 (51.16)	18 (27.69)	1	
Arg/Pro+Pro/Pro	84 (48.84)	47 (72.31)	3.50 (1.76-6.99)	**0.001**
TP53	**Controls, n (%)**	**AC patients, n (%)**	**OR* (95%CI)**	***p* value**
Arg/Arg	88 (51.16)	26 (44.07)	1	
Arg/Pro+Pro/Pro	84 (48.84)	33 (55.93)	1.34 (0.72-2.51)	0.360
TP53	**Controls, n (%)**	**UNSCLC patients, n (%)**	**OR* (95%CI)**	***p* value**
Arg/Arg	88 (51.16)	13 (27.08)	1	
Arg/Pro+Pro/Pro	84 (48.84)	35 (72.92)	3.22 (1.49-6.95)	**0.003**

**OR-odds ratio (95 % confidence interval) and* p *values obtained by multivariate logistic regression adjusted for age, gender, and smoking. Wild-type and positive genotypes were taken as reference*

Table 3 *NSCLC risk association with TP53, CYP2E1, and GST genotype combinations*

Genotype combinations	Controls (n)	NSCLC patients (n)	OR* (95 %CI)	*p* value
TP53, CYP2E1*5B				
Arg/Arg, *1A/*1A	82	53	1	
Arg/Pro, Pro/Pro, *1A/*5B	4	3	1.16 (0.25-5.39)	0.849
TP53, GSTM1				
Arg/Arg, positive	43	29	1	
Arg/Pro, Pro/Pro, null	48	72	2.22 (1.23-4.04)	**0.009**
Arg/Pro, null	40	63	2.35 (1.18-4.71)	**0.015**
Pro/Pro, null	8	9	1.55 (0.49-4.94)	0.455
TP53, GSTT1				
Arg/Arg, positive	72	43	1	
Arg/Pro, Pro/Pro, null	18	32	2.98 (1.49-5.94)	**0.002**
Arg/Pro, null	15	24	2.31 (1.04-5.13)	**0.040**
Pro/Pro, null	4	8	3.55 (0.92-3.69)	0.065
TP53, GSTP1 (Ile105Val)				
Arg/Arg, Ile/Ile	51	36	1	
Arg/Pro, Pro/Pro, Ile/Val, Val/Val	36	41	1.61 (0.87-2.99)	0.129
TP53, GSTP1 (Ala114Val)				
Arg/Arg, Ala/Ala	76	45	1	
Arg/Pro, Pro/Pro, Ala/Val, Val/Val	12	24	3.38 (1.54-7.41)	**0.002**
CYP2E1*5B, GSTM1				
*1A/*1A, positive	76	66	1	
*1A/*5B, null	7	1	0.16 (0.20-1.37)	0.095
CYP2E1*5B, GSTT1				
*1A/*1A, positive	130	121	1	
*1A/*5B, null	2	2	1.07 (0.15-7.75)	0.943
CYP2E1*5B, GSTP1 (Ile105Val)				
*1A/*1A, Ile/Ile	93	105	1	
*1A/*5B, Ile/Val, Val/Val	4	2	0.44 (0.79-2.47)	0.353
CYP2E1*5B, GSTP1 (Ala114Val)				
*1A/*1A, Ala/Ala	139	130	1	
*1A/*5B, Ala/Val, Val/Val	1	1	1.07 (0.07-17.27)	0.962

**OR-odds ratio (95 % confidence interval) and* p *values obtained by multivariate logistic regression adjusted for age, gender, and smoking. Wild-type and positive genotypes were taken as reference*

but not of SCC. These inconsistent findings need to be clarified in larger future studies.

Our analysis of the potential effect of gene interactions on NSCLC risk was motivated by the fact that cancer is a complex, multigene process and that individual susceptibility to cancer varies. The association between NSCLC risk and the *TP53* (Arg72Pro) polymorphism in combination with genes encoding enzymes involved in tobacco-specific carcinogen metabolism has not been well studied so far. In our study, the combination of the *TP53* codon72 and the *CYP2E1*5B* variants was not significantly associated with NSCLC. In Asian populations, the *CYP2E1*5B* polymorphism was found to be associated with lower NSCLC risk (32). Although this variant allele was relatively rare in our Caucasian participants compared to Asian populations, it may have countered the risk increased by the *TP53* codon72 variant, because their combination was not associated with NSCLC. However, we cannot exclude the possibility that the observed findings are pure chance.

We have also analysed the interactions between *TP53* and *CYP2E1* gene polymorphisms and the GST gene (*GSTM1*, *GSTT1* and *GSTP1)* polymorphisms that we had previously determined in the same patients in our 2012 study (19) to see whether they may affect the NSCLC risk. Our results confirm the findings of Klinchid et al. (33), who found a significant association between the *TP53* codon72 variant and *GSTM1* null combination and NSCLC. The highest risk of NSCLC was associated with the *TP53* codon72 variant plus *GSTP1* (Ala114Val) variant combination (OR=3.38). This combination increases the

risk of NSCLC 1.5 times over either variant alone. These findings are consistent with the effect of the mutant *TP53*, which impairs the apoptosis of transforming tumour cells, while lower GST variant activity insufficiently detoxifies carcinogenic chemicals.

What may limit the interpretation of our findings is a relatively small sample size, yet they clearly point that the *TP53* (Arg72Pro) polymorphism alone and in combination with *GSTM1*, *GSTT1*, or *GSTP1* (Ala114Val) may increase the risk of NSCLC, the last combination in particular. Further studies with larger samples are needed to verify these findings.

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Conflict of interest

The authors declare none.

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Povezanost polimorfizama gena *TP53* i *CYP2E1*5B* s nemikrocelularnim karcinomom pluća

Nemikrocelularni karcinom pluća (engl. *non-small cell lung cancer – NSCLC*) najčešći je oblik karcinoma pluća. Polimorfizimi gena za supresiju tumora i gena koji kodiraju enzime za razgradnju ksenobiotika mijenjaju aktivnost tih gena te značajno utječu na individualnu sklonost nastanku *NSCLC*-a. Budući da u literaturi nema dovoljno saznanja o njihovu utjecaju na nastanak bolesti, cilj je ovoga ispitivanja bio utvrditi povezanost polimorfizama tumorskoga supresorskoga gena *TP53* (Arg72Pro), odnosno gena *CYP2E1*5B* za metabolizam ksenobiotika, s rizikom od *NSCLC*-a. Ispitivanje je obuhvatilo 172 bolesnika s *NSCLC*-om i 172 kontrolna ispitanika (po 156 muškaraca i 16 žena u svakoj skupini). Genski su polimorfizmi utvrđeni polimeraznom lančanom reakcijom u stvarnom vremenu (engl. *real-time polymerase chain reaction – RT-PCR*) te kombinacijom *PCR*-a s metodom cijepanja DNA restrikcijskim enzimima (engl. *restriction fragment length polymorphism – PCR-RFLP*). Multivarijantna analiza upozorava na značajnu povezanost kombinacije *TP53* kodon72 Arg/Pro i Pro/Pro genotipova s *NSCLC*-om (OR 2,21; 95 % CI 1,39-3,51; p=0,001). Također je analizirana povezanost kombinacija ovih genskih varijanta s polimorfizmima gena glutation S-tranferaze *GSTM1*, *GSTT1*, *GSTP1* ekson 5 (Ile105Val) i *GSTP1* ekson 6 (Ala114Val) s rizikom od *NSCLC*-a te utvrđeno značajno povećanje rizika kod sljedećih kombinacija: *TP53* kodon72 s *GSTM1* nula (OR 2,22; 95 % CI 1,23-4,04; p=0,009), *GSTT1* nula (OR 2,98; 95 % CI 1,49-5,94; p=0,002) i *GSTP1* (Ala114Val) (OR 3,38; 95 % CI 1,54-7,41; p=0,002). Da bi se potvrdili ovi preliminarni rezultati, potrebna su istraživanja na većim uzorcima.

KLJUČNE RIJEČI: CYP2E1*; genski polimorfizam;* GST*; metabolizam kancerogena; NSCLC*