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Scientific Paper

ASSOCIATION BETWEEN *XRCC1* ARG399GLN AND *P53* ARG72PRO POLYMORPHISMS AND THE RISK OF GASTRIC AND COLORECTAL CANCER IN TURKISH POPULATION

Ayse Basak ENGIN[1], Bensu KARAHALIL[1], Ali Esat KARAKAYA[1], and Atilla ENGIN[2]

Gazi University, Faculty of Pharmacy Department of Toxicology[1], Gazi University, Faculty of Medicine, Department of General Surgery, Beşevler[2], Ankara, Turkey

Gastric cancer is one of the most common cancers of the gastrointestinal system, and its overall five-year survival rate is still 15 % to 20 %, as it can mostly be diagnosed at an advanced stage. On the other hand, although colorectal cancer has a rather good prognosis, mortality is one half that of the incidence.
As carcinogenesis is believed to involve reactive radicals that cause DNA adduct formation, impaired repair activity, and weakened tumour suppression, it would help to understand the role of the polymorphisms of nucleotide excision repair enzyme XRCC1 and of tumour suppressor gene *p53* in gastric and colorectal cancers. Our study included 94 gastric cancer patients, 96 colorectal cancer patients, and 108 cancer-free individuals as control with the aim to see if there was an association between *XRCC1* Arg399Gln and *p53* Arg72Pro polymorphisms and cancer susceptibility. DNA was extracted from peripheral blood cells and genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism. Polymorphism *p53* Arg72Pro was not associated with either gastric or colorectal carcinoma, while *XRCC1* Arg399Gln was not associated with the increased risk of colorectal cancer. However, *XRCC1* homozygous Gln allele at codon 399 was associated with 2.54 times higher risk of gastric cancer.

KEY WORDS: *DNA adduct, gene-gene interaction, PCR-RFLP*

Genetic factors that alter repair of the damaged gastric and colon cell DNA leading to carcinoma have still been poorly understood. Accumulation of constantly generated reactive species during cellular metabolism and extracellular processes may contribute to carcinogenesis caused by oxidative DNA damage. p53, a tumour suppressor protein encoded in humans by the *TP53* gene (1) regulates the cell cycle and preserves the stability of the human genome to prevent cancer initiation (2). It is estimated that almost 50 % of cancer cases carry a mutation of the *p53* gene (3,

4). On the other hand, polymorphisms of genes involved in multiple steps of carcinogenesis may also account for genetic difference in susceptibility to gastric and colorectal carcinomas (5). Polymorphism in exon 4, in the domain of transactivation of the p53 protein, results in an amino acid replacement from arginine (Arg) to proline (Pro). However, functional changes caused by this substitution are unknown. Inconsistent results have been found for the Pro variant allele of the *p53* gene as a risk factor of various cancers (5). The X-ray repair cross-complementing group 1

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(XRCC1) protein is involved in the repair of DNA base damage and single-strand DNA breaks. One of the common polymorphisms of the gene is at codon 399. This polymorphism leads to an amino acid replacement of Arg with glutamine (Gln) and can alter gene function. Previous studies have reported that the Gln allele at codon 399 is significantly associated with a higher level of DNA adducts (6, 7), increased sister chromatid exchange frequencies (8, 9), and increased sensitivity to ionising radiation (9). Therefore, the presence of homozygous Gln allele may alter cancer susceptibility and disease progression. In clinical studies, this polymorphism has been associated with the risk of several cancers and has also been used as a predictor of colorectal, bladder, and gastric cancers after chemotherapy (10-12). However, factors such as population stratification, ethnicity, and patient selection criteria may account for the discrepancies in findings. The aim of our study was to investigate the relation between *p53* Arg72Pro and *XRCC1* Arg399Gln polymorphisms and susceptibility to gastric and colorectal carcinomas.

MATERIALS AND METHODS

Patients and controls

This prospective randomised study included 94 consecutive gastric cancer patients [mean age ± standard error of mean (SEM): (60.3±1.4) years; mean body mass index (BMI): (23.7±0.4) kg m^{-2}; 30 women and 64 men], 96 consecutive colorectal cancer patients [mean age: (62.1±1.4) years; BMI: (25.7±0.4) kg m^{-2}; 40 women and 56 men], and 108 cancer-free patients [age: (56.3±1.3) years; BMI: (26.9±0.5) kg m^{-2}, 51 women and 57 men] who were admitted to Gazi University, Faculty of Medicine, Department of General Surgery for surgical intervention. None of the patients had malignant or metabolic disorders, cardio-pulmonary or metabolic risks that could be an obstacle for the surgery. The primary disease of the cancer patients was suitable for surgical intervention.

The study did not include patients with immune system disorders who could not receive surgical treatment or neoadjuvant chemotherapy due to the advanced stage of cancer, patients who had malnutrition, autoimmune diseases, systemic inflammatory response syndrome, intra-abdominal sepsis, chronic granulomatosis, collagen tissue or neurodegenerative diseases.

All participants' rights were protected and informed consents obtained according to the Helsinki Declaration. A local ethics committee approved the study protocol.

We isolated DNA from peripheral blood of each individual by extracting it with sodium perchlorate/chloroform (13). *p53* (GenBank ID: F261892S10) Arg72Pro and *XRCC1* (GenBank ID: L47234) Arg399Gln genotypes were determined using the polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) according to modified

Table 1 *Odds ratios for colorectal cancer according to the genotypes of* p53 *Arg72Pro and* XRCC1 *Arg399Gln polymorphism*

Genotype	Control Group n (%)	Colorectal Cancer Group n (%)	OR (95 % CI)	p
p53				
Arg / Arg	52 (48.1)	50 (52.1)	1	
Arg / Pro	42 (38.9)	41 (42.7)	1.015 (0.569 to 1.812)	0.959
Pro / Pro	14 (13.0)	5 (5.2)	0.371 (0.125 to 1.107)	0.068
	n (allele frequency)	**n (allele frequency)**		
Arg	146 (0.68)	141 (0.73)		
Pro	70 (0.32)	51 (0.27)		
	n (%)	**n (%)**		
XRCC1				
Arg / Arg	50 (46.3)	47 (49.0)	1	
Arg / Gln	49 (45.4)	37 (38.5)	0.803 (0.448 to 1.440)	0.462
Gln / Gln	9 (8.3)	12 (12.5)	1.418 (0.548 to 3.673)	0.470
	n (allele frequency)	**n (allele frequency)**		
Arg	149 (0.69)	131 (0.68)		
Gln	67 (0.31)	61 (0.32)		

OR - odds ratio, CI - confidence interval

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protocols of Toruner (14) and Kocabas (15), respectively. For each individual, 50 ng of DNA was used for the amplification reaction. PCR primers for *p53* Arg72Pro were F 5'-TCCCCCCTTGCCGTCCCAA-3' and R 5'-CGTGCAAGTCACAGACTT-3' and for *XRCC1* Arg399Gln F 5'-CAGTGGTGCTAACCTAATC-3 and R 5'-AGTAGTCTGCTGGCTCTGG-3'. Briefly, for *p53* Arg72Pro genotyping, 1.5 mmol L^{-1} MgCl$_2$, 0.2 mmol L^{-1} of each dNTP, 0.05 µmol L^{-1} of each primer, and 0.1 U µL^{-1} Taq polymerase were used to perform PCR. Thermal cycling conditions were 94 °C for 5 min, followed by 35 cycles of amplification (denaturation at 94 °C for 30 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s) and a final elongation at 72 °C for 7 min. PCR products were digested with Bsh 1236I (Fermentas Company, Lithuania) and separated by electrophoresis on 2 % agarose gel (14). PCR tube for the genotyping of *XRCC1* Arg399Gln contained 2 mmol L^{-1} MgCl$_2$, 0.3 mmol L^{-1} of each dNTP, 0.4 µmol L^{-1} of each primer and 0.5 U µL^{-1} Taq polymerase. Thermal cycling conditions were 94 °C for 2 min, followed by 35 cycles of amplification [denaturation at 94 °C (30 s), annealing at 58 °C (45 s), and extension at 72 °C (45 s)], and a final elongation at 72 °C for 7 min. PCR products were digested with MspI (Fermentas Company, Lithuania) and visualised on 2 % agarose gel (15). Genotyping results for both polymorphisms were confirmed by DNA control sequences.

Statistical analysis

The results were expressed as mean±SEM, where appropriate. The deviation from the Hardy-Weinberg equilibrium was checked among cases and controls using the chi-square test with one degree of freedom. Odds ratios (ORs) with 95 % confidence intervals (CIs) were determined with logistic regression models in order to evaluate the association between gastric or colorectal cancer and *p53* Arg72Pro and *XRCC1* Arg399Gln polymorphisms. Data were analysed using the statistical package SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Gastric cancer patients, colorectal cancer patients, and cancer-free patients were genotyped in order to determine *p53* Arg72Pro and *XRCC1* Arg399Gln polymorphisms. None of the genotype distributions deviated from the Hardy-Weinberg equilibrium. Neither of the polymorphisms was associated with colorectal cancer (Table 1). However, the risk of gastric cancer was found to be 2.54 times higher in the homozygous carriers of variant *XRCC1* Arg399Gln allele (Table 2; p<0.05). Evaluation by dominant model and model of heterozygote advantage for both *p53* Arg72Pro and *XRCC1* Arg399Gln polymorphisms did not reach

Table 2 *Odds ratios for gastric cancer according to the genotypes of* p53 *Arg72Pro and* XRCC1*Arg399Gln polymorphism*

Genotype	Control Group n (%)	Gastric Cancer Group n (%)	OR (95 % CI)	p
p53				
Arg / Arg	52 (48.1)	40 (42.6)	1	
Arg / Pro	42 (38.9)	41 (43.6)	1.269 (0.699 to 2.303)	0.433
Pro / Pro	14 (13.0)	13 (13.8)	1.207 (0.511 to 2.853)	0.668
	n (allele frequency)	**n (allele frequency)**		
Arg	146 (0.68)	121 (0.64)		
Pro	70 (0.32)	67 (0.36)		
	n (%)	**n (%)**		
XRCC1				
Arg / Arg	50 (46.3)	35 (37.2)	1	
Arg / Gln	49 (45.4)	43 (45.7)	1.254 (0.691 to 2.273)	0.456
Gln / Gln	9 (8.3)	16 (17.0)	2.540 (1.008 to 6.397)	0.044*
	n (allele frequency)	**n (allele frequency)**		
Arg	149 (0.69)	113 (0.60)		
Gln	67 (0.31)	75 (0.40)		

*OR - odds ratio, CI - confidence interval, *p< 0.05, considered as statistically significant.*

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statistical significance in either colorectal or gastric cancer (all; p>0.05). On the other hand, the combination of the mutant genotypes of *p53* Arg72Pro and *XRCC1* Arg399Gln did not increase the risk of colorectal or gastric cancer (Tables 3 and 4; p>0.05). Gastric cancer risk was 1.91 times higher in men than in women [OR at 95 % CI: 1.909 (1.074 to 3.393), p<0.027]. However, there was no association between either of the polymorphisms and gastric or colorectal cancer when evaluated separately for women and men (p>0.05).

DISCUSSION

Eariler studies on the association between p53 Arg72Pro and *XRCC1* Arg399Gln polymorphisms and gastric and colorectal carcinomas revealed inconsistent results that might be attributed to a number of genetic and ethnic factors (16-27). The p53 tumour suppressor protein is essential in cell cycle control and maintenance of genomic stability (28). Yi et al. (5) propose that independent of transcription, p53 favours apoptosis in cells with DNA damage (5). The loss of p53 function

is one of the key factors in cancer development (29). The Arg/Pro polymorphism at codon 72 is one of the ten polymorphisms that have been detected in human p53 so far (30). Sreeja et al. (31) have shown that the Pro allele at codon 72 may alter the enzyme activity of p53. The Pro allele seems to favour p53 binding to p73, a p53 homologue and transcription factor of some *p53* target genes, which may lead to alterations in the activation of some *p53*-interacting genes (32). Regarding to these assumptions, Van Oijen et al. (29) have found both the mutation and retention of the Arg allele. Bae et al. (33) have shown that a difference at a single codon of the *p53* gene can alter the protein. Moreover, the distribution of p53 codon 72 polymorphism changes with ethnicity. Studies from Switzerland and the USA showed that almost 50 % of the population had the Arg/Arg genotype of *p53* at codon 72 (16, 17). However, two separate studies from China established different genotype distributions for the *p53* Arg72Pro polymorphism (18, 19). According to Almeida et al. (34), genotype distribution in a Brazilian population was 60 % for homozygous *p53* Arg/Arg, 28.2 % for heterozygous *p53* Arg/Pro, and 11.8 % for homozygous *p53* Pro/Pro. Compared to

Table 3 *Odds ratios for colorectal cancer according to the combination of genotypes of* p53 *Arg72Pro and* XRCC1*Arg399Gln polymorphisms*

p53 Genotype	*XRCC1* Genotype	Control Group n (%)	Colorectal Cancer Group n (%)	OR (95 % CI)	p
Arg / Arg	Arg / Arg	25 (23.1)	27 (28.1)	1	
Arg / Arg	Arg / Gln Gln / Gln	27 (25.0)	23 (24.0)	0.789 (0.362 to 1.717)	0.550
Arg / Pro Pro / Pro	Arg / Arg	25 (23.1)	20 (20.8)	0.741 (0.332 to 1.650)	0.462
Arg / Pro Pro / Pro	Arg / Gln Gln / Gln	31 (28.7)	26 (27.1)	0.777 (0.366 to 1.650)	0.510

OR; odds ratio, CI; confidence interval

Table 4 *Odds ratios for gastric cancer according to the combination of genotypes of* p53 *Arg72Pro and* XRCC1*Arg399Gln polymorphisms*

p53 Genotype	*XRCC1* Genotype	Control Group n (%)	Gastric Cancer Group n (%)	OR (95 % CI)	p
Arg / Arg	Arg / Arg	25 (23.1)	14 (14.9)	1	
Arg / Arg	Arg / Gln Gln / Gln	27 (25.0)	26 (27.7)	1.720 (0.737 to 4.013)	0.208
Arg / Pro Pro / Pro	Arg / Arg	25 (23.1)	21 (22.3)	1.500 (0.626 to 3.596)	0.363
Arg / Pro Pro / Pro	Arg / Gln Gln / Gln	31 (28.7)	33 (35.1)	1.901 (0.839 to 4.305)	0.122

OR - odds ratio, CI - confidence interval

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literature data, Turkish population has a similar genotypic distribution as Caucasians.

In our study, we have not found any association between *p53* Arg72Pro polymorphism and increased risk of either gastric or colorectal cancer. In contrast, Xi et al. (35) found a relation between the increased risk of gastric carcinoma and *p53* Arg72Pro polymorphism and said that bad prognosis was associated with *p53* mutation. In a Japanese study, Hiyama et al. (36) found similar allele frequencies in both control and gastric cancer patients. Similarly, an Argentine study (20) found that individuals with the Pro/Pro genotype had an increased risk of colorectal cancer. Evaluating 1000 incident gastric cancer patients and 1300 controls, Liu et al. (37) found no independent effects of *p53* Arg72Pro on gastric cancer risk. A study from the USA (38) found no association between colorectal cancer and *p53* Arg72Pro polymorphism, but Jones et al. (39) identified *p53* Pro allele at codon 72 as a risk factor for colorectal cancer in combination with environmental factors. Case-control studies in Japan and Turkey failed to find a relation between the *p53* polymorphism and colorectal cancer (40, 41).

XRCC1 acts as a central scaffolding protein and plays a crucial role in the removal of endogenous and exogenous DNA damage (6, 7). Our study has shown that the distribution of the *XRCC1* homozygous mutant genotype in Turkish population is between Asian and Caucasian populations, while heterozygous Arg/Gln allele distribution in *XRCC1* codon 399 was similar in both Asian and Caucasian populations (21, 23, 24). Surprisingly, we have found a different frequency of homozygous mutant genotype of *XRCC1* than the previous study by Kocabas et al. (15). This contradiction might be attributed to different ethnic groups and divergent genetic pool in Turkey.

In our study, there was no association between the increased risk of colorectal carcinoma and *XRCC1* Gln allele at codon 399. This is in agreement with an Italian (25) and an English study (26). In a study with 207 cancer patients and 621 controls, Jin et al. (42) identified the *XRCC1* Gln allele at codon 399 as an independent factor for colorectal cancer.

Findings on the association between *XRCC1* Arg399Gln polymorphism and gastric cancer are also controversial. Studies by Lee et al. (24) and Geng et al. (43) in Asian populations, and studies by Huang et al. (22) in Polish and by Duarte et al. (21) in Brazillian population found no association while, Capella et al. (27) and Ratnasinghe et al. (23) established a

relationship between the *XRCC1* Arg allele at codon 399 and gastric cancer originating from different segments of the stomach. We too have found that individuals carrying homozygous Gln allele have a 2.54 times higher risk of gastric cancer.

In contrast, the combination of the mutant genotypes of *p53* Arg72Pro and *XRCC1* Arg399Gln did not alter the risk of either colorectal or gastric cancer. This suggests that the homozygous mutant alleles in these two unrelated genes do not affect each other in such way as to increase the risk of colorectal or gastric cancers.

Our study has also established a two times higher gastric cancer risk in men than in women, which is in accordance with global data (44).

However, there are several limitations to our study. Being hospital-based and case-control, it may be subject to selection bias. However, this bias is of no great concern, as our study focuses on a genotype-driven interaction rather than an environment-driven one. Our results are based on a limited number of single-nucleotide polymorphisms and additional, larger-scaled studies are needed to determine the interaction between genetic and environmental factors and the risk of gastric and colorectal carcinomas.

Controversial as they may be, however, our findings call for further evaluation of *XRCC1* polymorphism as a risk factor for gastric cancer.

Conflict of interest statement

All authors declare that they have no direct financial interest in the subject matter or materials discussed that could inappropriately influence the manuscript.

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Sažetak

POVEZANOST IZMEĐU POLIMORFIZAMA *XRCC1* ARG399GLN I *P53* ARG72PRO S RIZIKOM OD RAKA ŽELUCA I DEBELOGA CRIJEVA U TURSKOJ POPULACIJI

Rak želuca najčešći je oblik karcinoma probavnoga sustava, a ukupno mu je preživljenje i dalje 15 % do 20 %, budući da se većinom dijagnosticira u poodmakloj fazi razvoja. S druge pak strane, premda rak debeloga crijeva ima prilično dobru prognozu, smrtnost je i dalje 50 %.

Vjeruje se da je nastanak karcinoma povezan s reaktivnim radikalima koji uzrokuju stvaranje DNA-adukata, onemogućavaju popravak DNA te slabe supresiju tumora. Stoga bi bilo korisno razumjeti ulogu polimorfizama gena za enzim XRCC1 koji sudjeluje u popravku isjecanjem nukleotida i tumor-supresorskoga gena *p53* u nastanku raka želuca i debeloga crijeva. Naše je ispitivanje obuhvatilo 94 bolesnika s rakom želuca, 96 bolesnika s rakom debeloga crijeva te 108 kontrolnih ispitanika (koji nisu oboljeli od bilo kojeg oblika raka) s ciljem da se utvrdi povezanost između polimorfizama *XRCC1* Arg399Gln i *p53* Arg72Pro i sklonosti nastanku raka. DNA je dobiven iz stanica periferne krvi, a genotip utvrđen s pomoću metode lančane reakcije polimerazom - polimorfizma restrikcijskih fragmenata na osnovi dužine (PCR-RLFP). Polimorfizam *p53* Arg72Pro nije se pokazao povezanim s povećanim rizikom od raka želuca ili debeloga crijeva niti je *XRCC1* Arg399Gln bio povezan s povećanim rizikom od raka debeloga crijeva, ali je zato rizik od raka želuca u homozigotnih nositelja ovoga polimorfizma bio 2,54 puta veći.

KLJUČNE RIJEČI: *DNA-adukt, interakcija između gena, PCR-RFLP*

CORRESPONDING AUTHOR:

Ayse Basak Engin M.Sc., Ph.D.
Gazi University, Faculty of Pharmacy
Department of Toxicology
TR 06330 Hipodrom, Ankara, Turkey
E-mail: *abengin@gmail.com*