TP53 Codon 72 Polymorphism and the Risk of Colorectal Cancer in an Azerbaijani Population

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ABSTRACT

Background: *We aimed to evaluate the association between the TP53 Arg72Pro gene polymorphism and risk of colorectal cancer in an Azerbaijani population.*

Methods: *A total of 141 patients with colorectal cancer and 150 gender- and age-matched controls were involved in the study. The genotypes of the TP53 gene Arg72Pro polymorphism were detected by polymerase chain reaction-based restriction fragment length polymorphism analysis.*

Results: *We found that the heterozygous genotypes Arg/Pro (odds ratio, 1.128; 95% CI, 0.657-1.937) and mutant Pro/Pro (odds ratio, 1.274; 95% CI, 0.648-2.504) were more frequent in colorectal cancer patients compared to healthy controls. The frequency of the mutant Pro allele (odds ratio, 1.122; 95% CI, 0.809-1.554) was revealed in 47.5% of colorectal cancer patients and in 44.7% of healthy controls. There was no association observed between TP53 Arg72Pro polymorphism and risk of colorectal cancer in an Azerbaijani population ($P > .05$).*

Conclusion: *Our findings indicate a lack of relationship between TP53 Arg72Pro polymorphism and risk of colorectal cancer. Furthermore, we have found no statistical differences in the frequency of genotype and allele by sex, age, histological grade, tumor stage, smoking status, and alcohol consumption in this study.*

Keywords: *Arg72Pro polymorphism, Azerbaijani population, Colorectal cancer, TP53 gene*

INTRODUCTION

Although substantial improvements in the diagnosis and treatment of colorectal cancer (CRC) have been made in the last decade, effective treatments are still severely lacking primarily due to the genetic heterogeneity of this tumor.[1,2] The *TP53* tumor suppressor gene coding the p53 protein is one of the most frequently heterogeneously altered genes increasing the risk of cancer, as it is involved in many important cellular events, including cell cycle regulation, programmed cell death, and DNA repair.[3-5] Single-nucleotide polymorphism (SNP) at codon 72 of *TP53* (rs1042522) has recently become a target for intensive research as it can affect both the risk of cancer development and the results of anticancer therapy,[6,7] and encodes proline (CCC) or arginine (CGC), which are essential to trigger apoptosis.[8] The *TP53* Arg72Pro mutation, a transition of CGC to CCC (Arg to Pro), results in 3 different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro.[9] A protein produced as a result of these mutations demonstrates a reduced capacity to bind to a specific DNA sequence that regulates the p53 transcriptional pathway.[2] This leads to the altered performance of the p53 protein in the induction of growth arrest and apoptosis, which is associated with chemoresistance and poor patient survival.[10]

Multiple studies have confirmed that the *TP53* codon 72 polymorphism is associated with an increased risk for CRC.[11,12] The results published so far, however, are controversial with respect to CRC susceptibility. Both population- and hospital-based investigations involving different ethnic groups have reported a positive association of CRC with the Pro72 allele variant[6,9,13-17] and the Arg72 variant,[18,19] although others have not detected any association.[20-22] One of the important aspects in this connection is that the polymorphism at codon 72 varies in different ethnicities and this difference might contribute to the diverse cancer risk patterns in different ethnic populations.[9,23] There is no study that has been reported about the relationship between *TP53* Arg72Pro polymorphism and risk of CRC in an Azerbaijani population. Thus,

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the purpose of the current study was to determine the association between *TP53* Arg72Pro polymorphism and the risk of CRC in an Azerbaijani population.

MATERIALS AND METHODS

Subjects

In the present study, we involved 141 recently diagnosed CRC patients and 150 healthy controls. Patients were recruited between October 2016 and October 2020 and the protocol for the study was approved by the ethics committee of the hospital. All participants gave their written consent for the participation in the study. We excluded the patients with hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) from our study. The final diagnosis of patients was confirmed by pathology. The healthy control individuals were selected at random from those who underwent colonoscopy within the colon cancer screening program. We excluded the healthy individuals having positive family cancer histories from the study. Each individual was interviewed by a written questionnaire to gather study-oriented information such as age, gender, family history, smoking habits, and alcohol consumption. The location of tumor, its stage, and its histological type and grade were documented using surgery and pathology reports. From each participant, a blood sample was obtained and stored at 4°C to use for DNA purification and PCR-RFLP analysis.

DNA Purification and Arg72Pro Genotyping

DNA was purified from the whole blood samples of all individuals using the QIAamp DNA Blood Mini Kit according to the protocol (Qiagen, Hilden, Germany). Arg72Pro polymorphism was determined by PCR-RFLP methods. The PCR reactions were performed in a total volume of 25 µl that contained 0.1 µg genomic DNA, 0.02 U Taq DNA polymerase (Solis BioDyne, Tartu, Estonia), 10x Taq DNA polymerase buffer, 10 pmol each of forward and reverse primers (sense: 5′-ATCTACAGTCCCCCTTGCCG-3′ and antisense: 5′-GCAACTGACCGTGCAAGTCA-3′), and 0.25 mM each of dNTPs, and 1.5 mM of $MgCl_2$. The amplification conditions were 5 minutes of denaturing at 95°C, followed by 35 cycles of 30 seconds at 95°C, 45 seconds at 56°C, and 1 minute at 72°C, and final elongation at 72°C for 5 minutes, respectively. The 296-bp PCR fragment was cleaved by the restriction enzyme BstUI (NEB, Mass, USA) for 3 hours, at a 37°C incubation temperature. All samples were separated by electrophoresis in 2% agarose gel. Genotypes were visualized on agarose gel as homozygous uncut wild-type Arg/Arg 296 bp, heterozygous Arg/Pro consisting of 296 bp, 169 bp, and 127 bp, and homozygous mutant Pro/Pro genotype 169 bp and 127 bp, respectively (Figure 1).

Statistical Analysis

Statistical analysis was performed using The Statistical Package for Social Sciences (SPSS) version 22.0 software (IBM Corp.; Armonk, NY, USA). The associations between the *TP53* codon 72 polymorphism and CRC risk were estimated by computing the ORs and their 95% CIs from multivariate logistic regression analyses with adjustment for sex, age, smoking, alcohol consumption, allele, and genotype frequencies for the *TP53* gene, and first-degree family history of CRC. A *P*-value of .05 was considered statistically significant.

RESULTS

A total of 141 patients with histologically confirmed diagnosis of CRC were included in the analysis. One hundred fifty cancer-free individuals were randomly selected from the patients who underwent colonoscopy within the colon cancer screening program. The demographic and clinical characteristics of the patients and healthy individuals are summarized in Table 1. Eighty-four patients were men and 57 were women, while the control group consisted of 66 men and 84 women. A statistically significant difference was found when comparing the patient and control group by the gender factor (P = .008). The

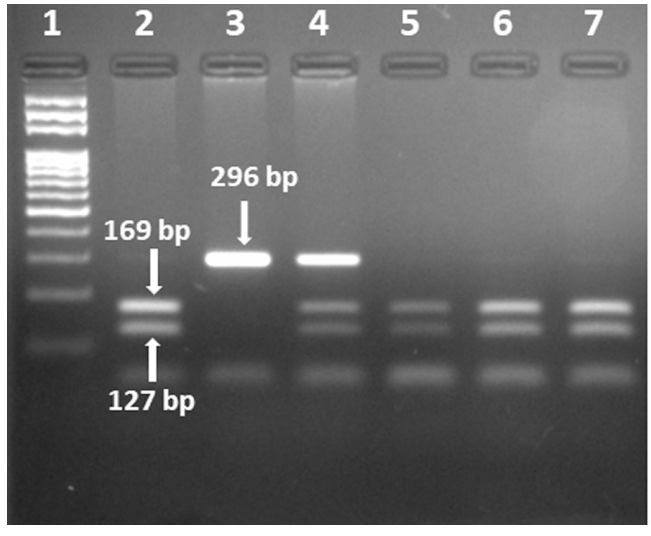

Figure 1. The image of agarose gel electrophoresis which demonstrates the analysis of PCR products of Arg72Pro polymorphism of the P53 gene: lane 1, ladder (100 bp); lanes 2, 5, 6, 7 homozygous mutant Pro/Pro; lane 3, wild-type Arg/Arg; lane 4, heterozygous Arg/Pro.

Table 1. Demographic Characteristics of the Patients and Healthy Individuals

Characteristics	Patients, N = 141 (%)	Controls, N = 150 (%)	*P*
Gender			
Male	84 (59.6%)	66 (44%)	.008
Female	57 (40.4%)	84 (56%)	
Age			
Age interval	35-84	32-82	.152
Mean	63 ± 10.1	60.9 ± 11.5	
Histological grade			
G1	12 (8.5%)		
G2	92 (65.2%)		
G3	37 (26.3%)		
Tumor stage			
T1	2 (1.4%)		
T2	17 (12.1%)		
T3	113 (92.9%)		
T4	9 (6.4%)		
Smoking status			
Smokers	52 (36.9%)	58 (38.7%)	.554
Non-smokers	82 (58.2%)	79 (52.7%)	
Unknown	7 (4.9%)	13 (8.6%)	
Alcohol consumption			
Yes	46 (32.6%)	54 (36%)	.612
No	88 (62.5%)	91 (60.7%)	
Unknown	7 (4.9%)	5 (3.3%)	

median age of patients was 63 years (35-84) and it was 60.9 years (32-82) for healthy individuals. No statistical significance was found when comparing both age groups ($P > .05$). In addition, there was no significant difference between the groups in terms of smoking and alcohol use. Table 1 also summarizes the tumor stage and gradation of patients.

The frequencies of genotype and allele in the study groups, and the respective ORs and 95% CI are shown in Table 2. In the CRC patients, Arg/Arg, Arg/Pro, and Pro/Pro genotypes were seen in 26.2%, 52.5%, and 21.3% of the cases, respectively, whereas this ratio was 29.3%, 52% and 18.7% for healthy individuals. Heterozygous Arg/Pro was relatively high in the patient group, although it was found in equal proportions in both patients and controls.

Table 2. Distribution of *TP53* Codon 72 Polymorphism in Patients with CRC and in Healthy Individuals

	Colorectal Cancer, N (%)	Healthy Controls, N (%)	OR (95% CI)	*P*
Genotype				
Arg/Arg	37 (26.2%)	44 (29.3%)	1	-
Arg/Pro	74 (52.5%)	78 (52%)	1.128 (0.657-1.937)	.662
Pro/Pro	30 (21.3%)	28 (18.7%)	1.274 (0.648-2.504)	.482
Allele				
Arg	148 (52.5%)	166 (55.3%)	1	-
Pro	134 (47.5%)	134 (44.7%)	1.122 (0.809-1.554)	.490

The mutant Pro/Pro genotype was detected to be more common in patients than healthy individuals.

However, no statistically significant association was found between the heterozygous Arg/Pro (OR: 1.128; 95% CI: 0.657-1.937, $P = .662$) and mutant Pro/Pro (OR: 1.274; 95% CI: 0.648-2.504, $P = .482$) genotypes of the *TP53* gene and the risk of CRC disease. The allele frequency of mutant Pro was 47.5% in the patients and 44.7% in the control group, respectively. Similarly, this was not statistically significant (OR: 1.122; 95% CI: 0.809-1.554, $P = .490$). The frequency of genotypes according to the stage and grade of the tumor is shown in Table 3. The heterozygous Arg/Pro genotype was higher in patients with tumor grade G1, while the mutant Pro/Pro genotype was more common in patients with tumor grade G3. In tumor stages, the Arg/Pro genotype was more common in T1 and T2, while the Pro/Pro genotype was more common in T3. There was no statistical difference in terms of genotypes in tumor grade and stages ($P > .05$).

Table 3. Tumor Characteristics and *TP53* Genotypes

	Arg/Arg, N (%)	Arg/Pro, N (%)	Pro/Pro, N (%)	*P*
Tumor grade				
G1	3 (25)	9 (75)	0	.096
G2	24 (26.1)	49 (53.3)	19 (20.6)	
G3	10 (27.1)	16 (43.2)	11 (29.7)	
Tumor stage				
T1	0	2 (100)	0	.089
T2	4 (23.5)	13 (76.5)	0	
T3	31 (27.4)	54 (47.8)	28 (24.8)	
T4	2 (22.2)	5 (55.6)	2 (22.2)	

Table 4. Distribution of *TP53* Arg72Pro Polymorphism in Smoking and Alcohol-Consuming Patients

Genotypes	Smokers, N (%)	Non-smokers, N (%)	OR (95% CI)	*P*
Arg/Arg	17 (32.7)	20 (24.4)	1	-
Arg/Pro	27 (51.9)	44 (53.7)	0.722 (0.323-1.614)	.427
Pro/Pro	8 (15.4)	18 (21.9)	0.523 (0.182-1.501)	.225
	Alcohol drinkers, N (%)	Non-drinkers, N (%)		
Arg/Arg	12 (26.1)	25 (28.5)	1	-
Arg/Pro	27 (58.7)	44 (50)	1.278 (0.553-2.957)	.566
Pro/Pro	7 (15.2)	19 (21.5)	0.768 (0.254-2.321)	.639

We also analyzed the genotype frequency of the *TP53* gene in patients who smoke and consume alcohol (Table 4). The Arg/Pro (53.7%) and Pro/Pro (21.9%) genotype frequencies were more common in nonsmokers compared to smokers. Additionally, OR and 95% CI were calculated for both heterozygous (OR: 0.722; 95% CI: 0.323-1.614) and homozygous (OR: 0.523; 95% CI: 0.182-1.501) genotypes, respectively. There was no significant relationship between the Arg72Pro polymorphism and disease risk in smoking and non-smoking patients ($P > .05$). In the assessment of genotypes for use of alcohol, the Arg/Pro genotype was found to be higher in alcohol consumers (58.7%) and relatively lower (50%) in non-drinkers. The mutant Pro/Pro genotype was higher in non-drinkers (21.2%) than in alcohol consumers (15.2%). Similarly, these findings were also not statistically significant.

DISCUSSION

In the current study, we investigated the genotype frequencies and associated causal role of the Arg72Pro polymorphism of the *TP53* gene in CRC in the Azerbaijani population, since no previous reports are available. We have demonstrated that the Arg/Pro and Pro/Pro variants of the *TP53* gene codon 72 are not associated with risk of CRC in the Azerbaijani population. There was no association of *TP53* Arg/Pro and Pro/Pro genotypes and with tumor stages, histological grades, alcohol-consumption, and smoking status in our study. The frequency of the wild type Arg allele compared to mutant Pro was similar in our population, whereas it can differ in different populations. For example, up to 40% of Caucasian Americans are homozygous for (Arg/Arg) R72, compared to only ~8% of African Americans.[6]

The recent meta-analysis using 18 studies demonstrated an association between the *TP53* Pro allele and Pro/Pro genotype with the risk of CRC in an Asian population, but not the Arg/Arg genotype, which is compatible with our result.[9] On the contrary, Perez et al[19] (2006) have shown high frequency (2-fold higher) of the Arg/Arg variant of the p53 codon 72 in patients with CRC from Argentina and possible preventative effect of the Pro/Pro variant with an increased frequency in healthy controls.[19] The meta-analysis of Lee et al[24] (2011) revealed significant association of the Pro allele in p53 Arg72Pro with the increased risks of gastrointestinal cancers, especially in an Asian population.[24] Aizat et al (2011) reported that the Pro/Pro homozygous variant genotype demonstrated significantly higher risk of CRC in a Malaysian population. This group reported that the individuals with Pro/Pro genotype and older than 50 years had significantly higher CRC risk. Katkoori et al[10] (2017) reported an association between P72 and aggressiveness of CRC, due to its overexpression in CRC patients of African American origin.[10] A Bangladeshi study revealed an increased risk of association between CRC susceptibility and Arg/Pro heterozygosity and Pro/Pro mutant homozygosity along with the combined genotype (Arg/Pro + Pro/Pro).[25] The results of a study from Iran did not support the relationship between *TP53* codon 72 polymorphism and CRC, but in stage IV patients, the Pro/Pro genotype was found to be increased.[26] Such inconsistent results may be associated with the uneven distribution of *p53* codon 72 polymorphism in different geographic regions and ethnicities.[9]

The recent studies have shown that the Pro/Pro variant of p53 codon 72 is essential for the activation of the p53-related DNA repair pathway, resulting higher DNA-repair efficacy.[27,28] However, the Arg72 variant (the Arg/Arg variant of p53 codon 72) protein induces faster apoptosis and represses alteration more competently than the Pro72 protein.[29] In spite of the fact that the both variants of the p53 Arg72Pro protein show normal DNA-binding activities, there are convincing findings indicating biochemical and functional differences between them, which might explain the differential susceptibility to

various cancers.[8,29] In the knock-in mice model with the P72 and R72 variants, a study[30] has shown that the P72 variant induces increased apoptosis under ionizing radiation. This group also reported that the P72 mice had a markedly enhanced response to inflammatory challenge compared to the R72 mice. Since the *TP53* Pro72 variant is reported to induce the cell cycle more efficiently than the *TP53* Arg72 variant, but with lower potential to trigger apoptosis,[29] the observed association between the Pro72 allele variant and CRA risk could suggest that *TP53*-induced apoptosis could be critical during early CRC development.

CONCLUSION

The Arg/Pro and Pro/Pro variant of the *TP53* gene is not suggested for the risk of CRC in an Azerbaijani population, whereas the Arg/Pro and mutant Pro/Pro genotypes are more common in CRC patients. Among non-smokers, both heterozygous Arg/Pro and mutant Pro/Pro genotypes were more frequent than in smokers, but without statistical significance. Heterozygote Arg/Pro was higher in patients who consumed alcohol, while in contrast, the mutant genotype Pro/Pro was more frequent among non-drinkers, either statistically not different. The lack of consistent association of the TP53 Arg72Pro polymorphism with CRC risk in different studies necessitates the need for further studies considering ethnic differences, genetic heterogeneity in the pathogenesis of CRC, different environmental factors, and sample size limitation.

Ethics Committee Approval: This study was approved by the medical ethics committee of Scientific Center of Surgery.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – V.Y., B.B.; Design – B.B.; Supervision – H.A.; Resources – H.A.; Materials – B.B.; Data Collection and/or Processing – M.Y.; Analysis and/or Interpretation – V.Y., B.B.; Literature Search – V.Y., B.B.; Writing Manuscript – V.Y., B.B.; Critical Review – H.A.

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Declaration of Interest: The authors have no conflict of interest to declare.

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