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Association of rs1042522 SNP with Clinicopathologic Factors of Breast Cancer Patients in the Markazi Province of Iran

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Abstract

BACKGROUND: The nucleotide changes in different genetic loci increased the incidence risk of breast cancer.

AIM: The aim of present study was to investigate genotype distribution at codon 72 of the TP53 gene (rs1042522) in breast cancer patients to achieve a potential diagnostic marker related to some demographic feathers.

METHODS: In our case-control study, blood samples were collected from a total of 34 patients harboured breast cancer. DNA was extracted, and nested-PCR was performed. Products were digested with AccII and subsequently were sequenced. Results were compared with samples characteristics.

RESULTS: The PCR results indicated the correct implementation of extraction and amplification protocol. The genotypic distribution at codon 72 of TP53 in control group was 20%, 62.4% and 16.6% for Arg (wildtype), Arg/Pro (heterozygous) and Pro (homozygous variant) respectively. Also, this distribution in the patient group was 23.52% homozygous, 50% heterozygous, and 26.47% another homozygous variant (Adjusted odds ratio: 1.12 and 95%CI = 0.57 to 2.2, P = 0.03). The absence of Arg at codon 72 of TP53 is relevant with age higher than 40 years and metastasis to other organs.

CONCLUSION: Polymorphism at codon 72 of TP53 was associated with high-grades of breast cancer risk and different responses to chemotherapy treatment. It is recommended genotype distribution of codon 72 of TP53 before chemotherapy.

Introduction

Breast cancer (BC) is one of the most common types of cancer that causes mortality rates each year. Despite advances in early diagnosis and proper treatment for this disease, it remains the main cause of death among women [1], [2], [3]. The most common sites of BC metastasis are bones, lunge and liver. Metastasis of BC to the brain less occur. The growth of cancer cells in BC is considered in three stages. BCs stage I or II are in the initial stage. If the tumour extends to the underlying muscles of the chest wall or skin, BC is type III. This Stage also includes BCs involving inflammatory system, in which case the breast is red or swollen [4], [5], [6]. BC stage IV refers to tumours that metastasise to the outside of the breast and the lymph nodes, as well as to the brain, bones, skin, and other organs. The basics of cancer genetics is the occurrence of changes in signalling pathways and genes regulatory networks [5]. Changes in different codons of the genes, including

BRCA1, *BRCA2*, and *TP53* etc. increase the risk of developing breast cancer. In some cases due to a mutation in *TP53*, the occurrence of BC can be accompanied by brain tumours and leukaemia. *TP53* (also known as *BCC7*, *LFS1*) is a TSG. This gene is encoded on the human chromosome 17 at position p13.1 (HGNC ID: 11998). Different transcripts are reported for this gene (Figure 1). Some of these transcripts are not protein coding (ENSG00000141510). This gene is very important in the coordination of the cell cycle as well as in preventing the development of cancer [2].

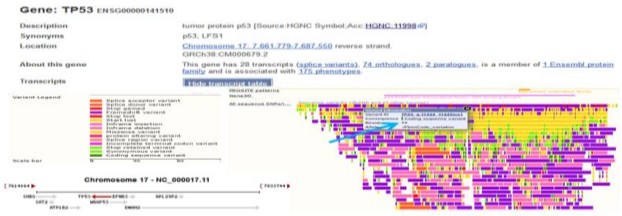

Figure 1: View of the TP53 chromosome position and the Ensemble databank of variants and SNPs of the TP53 gene. The codon 72 is shown by the blue arrow

In addition, the *TP53* gene has a variety of anti-cancer activities, such as apoptosis, genome stability (preventing the appearance of mutation in the genome) and preventing angiogenesis [3]. P53 Protein plays a major role in the initiation of apoptosis. The amount of P53 protein increases when the cell is exposed to stress [3], [6]. The defects in DNA repair are often the result of mutations, which may lead to the loss of DNA repairing proteins activity. DNA polymorphisms may also alter the structure of repairing enzymes and reduce their repair ability. Key polymorphisms in some genes, including *TP53*, may increase the risk of BC and may lead to a difference in treatment. Several SNPs have been recorded for this gene. One of these polymorphisms is the nucleotide change in codon 72 of this gene which can lead to a missense amino acid residue conversion Arg (CGC) to Pro (CCC). Rs1042522 is one of 25 important SNPs reported to increased risk for BC [7]. The G and C of this polymorphism allele encode an Arg and Pro respectively at position 72 of the P53. It has been reported that alteration of this codon is likely to be associated with an increased risk of some of the diseases [8], [9], [10], [11]. This association is related to population type. African population with two copies of G (G;G) in rs1042522 in TP53 were 2.15 times more susceptible to die due to rectal cancer than those with (C;G) or (C;C) at mentioned polymorphism. Also in Caucasians, there was no association between survival and rs1042522. In Asadi et al., study were detected no association between rs1042522 C > G polymorphism and Risk of Colorectal Cancer in the Iranian Azari Population [12]. In his another study, also was detected No association between rs1042522 C > G SNP and neuroblastoma risk using TaqMan genotyping [13]. There has been no report on the relationship between the rs1042522 polymorphism in *TP53* and tumour grade, age, Body mass index (BMI) and the response rate to chemotherapy in BC patients of Markazi province of Iranian population. The aim of present study was to evaluate the polymorphism at codon 72 of *TP53* in patients with BC and investigate the relationship between genotype distributions with above factors in patients with BC in aforementioned Iranian population.

Materials and Methods

In present case-control study, samples were collected from Ayatollah-Khansari hospital in Arak city. This study was performed between November 2016 and June 2017. A total of 34 pathological and clinical data were classified for the collected breast cancer samples (median age: 48 years). Also, normal samples from non-tumour individuals were equal numbers of patients group. Three ml of blood was collected from each sample in CBC test vial. The study was approved by the Research Ethics Committee of Arak University of Medical Sciences (Ethics number *618B/3090*). Participants of present study agreed with and signed a consent form.

DNA extraction was performed from 500 µl whole blood using the Diatom DNA Kit (IsoGene, Moscow, Russia) based on its instruction. Samples were loaded on 1% agarose gel, (YTA, Iran).

In Polymerase chain reaction, 50 mM MgCl2 (Cinagene, Iran), 10X Buffer (Cinagene, Iran), 10 mM dNTP (Cinagene, Iran), 1unit Taq polymerase (Cinagene, Iran), and specific primers at a suitable concentration of 10 pmol were used. Annealing temperature for the primers [9] was optimised at 52.7°C.

In this study, PCR products of the first stage were used in a thermocycler machine (Eppendorf, Germany) as a template in the second stage PCR using a pair of internal primers in order to more specificity and enhancing the amplified bands. A non-template sample was used as a negative control. The sequence of these primers is shown in Table 1.

Table 1: The used primer sequence in this study

Primer ID	Sequence (5'-3')
p53 F	GCTCTTTTCACCCATCTACAG
p53 R	TGAAGTCTCATGGAAGCCAGC
P53 Inner-F	TCCCCCTTGCCGTCCCAA
P53 Inner-R	CGTGCAAGTCACAGACTT

Restriction enzyme digestion was performed by *Acc*II (Vivantis, Malasia) at 37°C for 3-16 hours. Production of one fragment of 300bp indicated the presence of the wildtype allele (Arg). The presence of the variant allele (Pro) was determined by the observation of two fragments of 160 bp and 140bp. The produced amplicons were sent for sequencing.

The sequencing was carried out with the ABI Applied Biosystem machine-Model 3730XL (Macrogene, South Korea). Sequencing results were analysed using Chromas, Mega 4.0, Blast and Blat software.

Validation of genotypes was evaluated by comparison of sequences results with data banks such as UCSC. Chi-sq Hardy-Weinberg equilibrium (HWE) test calculator were used for biallelic markers including SNPs. The difference between the groups was determined by one-way ANOVA GraphPad prism 7.0. P values less than 0.05 were considered statistically significant.

Results

The results of the amplification reaction indicated the accurate of the extracted DNA, the correct implementation of the temperature protocol and used primers. Figure 2 shows the 300bp amplicon of the *TP53* gene.

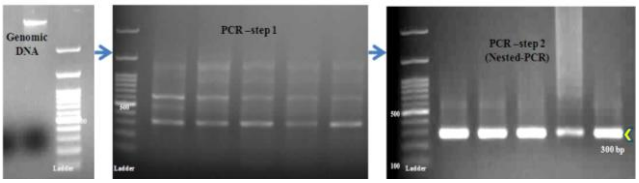

Figure 2: Steps of Nested-PCR steps in this study. The yellow arrow shows the 300 bp amplicon of TP53 gene

In below figure columns 1-4 indicated bands of heterozygous samples that have three bands (300, 160 and 140 bp). Also, Figure 3b shows the sequence analysis of the 8 homozygous amplicons.

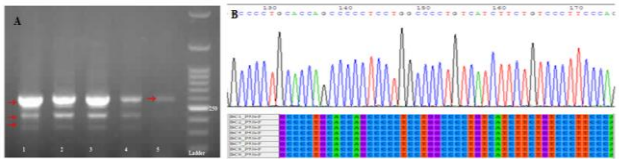

Figure 3: A) Agarose gel of digestion reaction. Column 1-4 showed heterozygote samples (Arg/Pro) and column 5 showed a homozygote wildtype (Arg); B) Nucleotide sequences from the sequencing of clinical samples (Chromas and Mega4 software)

The genotypic distribution in the patient group was 23.52% homozygous wildtype (Arg), 50% heterozygous (Arg/Pro), and 26.47% another homozygous variant (Pro). These genotypes in the control group were 20%, 62.4% and 16.6% for homozygous wildtype, heterozygous and homozygous variant respectively.

The C allele freq = 0.48; G allele freq = 0.52 was the frequency of changes in codon 72 of the *TP53* gene in patient group (HWE calculator, p < 0.05). The Chi-square in control group was not significant (X2 = 6.8, p > 0.05).

Table 2: different patterns from digestion reaction using *MboII* enzyme

Pattern of RFLP	Band (bp)	Genotype	Patients (%)	Odds Ratio	%90 CI	%95 CI	%99 CI	P value
Pattern A	300	GG homozygote	23.52	1.12	0.64-1.98	0.57-2.2	0.46-2.72	< 0.05
Pattern B	300, 160, 140	CG heterozygote	50	1.07	0.66-1.71	0.61-1.87	0.51-2.23	< 0.05
Pattern C	160, 140	CC homozygote	26.47	1.41	0.79 -2.51	0.71-2.8	0.57-3.48	< 0.05

The Figure 4 showed that there are a significant association between the changing at codon 72 (Arg72 Pro) of *TP53* gene sequences and the Age > 40, BMI > 22, WHR > 0.8, metastasis to other organs, positive ER and PR status and less response to chemotherapy in BC samples than the control group. These associations are statistically significant.

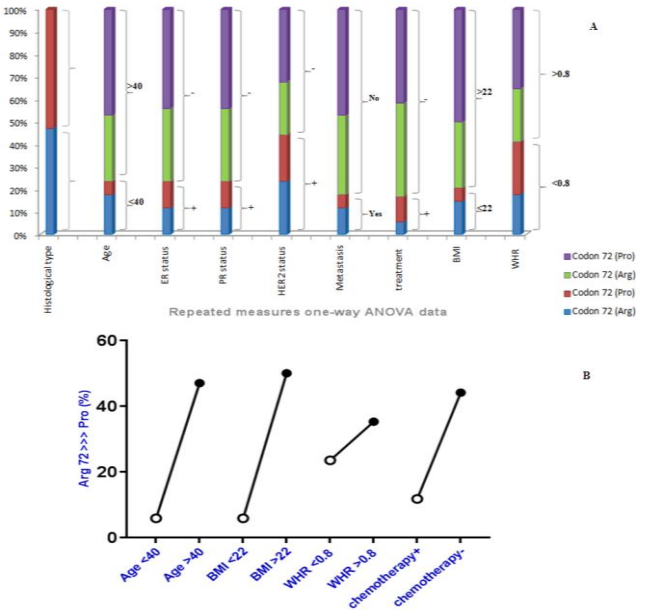

Figure 4: A) This chart shows the relationship between amplicons sequences and the characteristics of the used clinical samples; B) GraphPad Prism 7.0 software showed association between the Pro at codon 72 of TP53 gene and the Age > 40, BMI > 22, WHR > 0.8 and negative response to chemotherapy (One-way ANOVA test, P = 0.03)

Discussion

The incidence rates of BC increase with an ascending trend so that its frequency has doubled over the past 20 years. In Iran, BC is the most common type of cancer after stomach and oesophagus cancers. Therefore, diagnosis at first stages and study of the molecular mechanisms of BC are necessary [1], [2], [3]. Molecular events that regulate cell survival, apoptosis, growth and differentiation of the cell, played an important role in the overall kinetics of tumour growth as benign or

malignant [14]. Mutation of *TP53* is the most common genetic change in human cancers and is associated with poor response to treatment including chemotherapy and radiotherapy. Recent studies have shown the probably beneficial and valuable effects of gene therapy with the goal of *TP53* as a complementary therapy in cancers. Studies in 1997 and 1998 found that p53 plays a critical role in controlling of the cell cycle since its normal function not forces the cell to stop the cell cycle so that it can enter a period of interruption to repair the DNA damage. If the cell could not repair damage to the cell, it would commit suicide to prevent mutations in the cells [6], [7]. Injury to the *TP53* gene occurs during the life-span of the individual, but in rare cases, involved about 1% the cases of sporadic BCs [15], [16], [17], [18]. In a study in 2009, numbers of 1836 articles from 1986 to 2008 were reviewed for involved genes in BC [3]. In the *TP53* gene, the importance of codon 72 has been shown to identify changes in the various populations. This codon site is within the active site of the p53 protein. In studies conducted in 2006 and 2007, it was found that using some of the pathological characteristics of BC, such as the tumor size, negative status of PR, positive status of the lymph nodes and high differentiation can be predicted that a patient will be more likely to develop metastasis [19], [20], [21], [22]. Other studies showed significant differences in the prevalence of codon 72 in *TP53* polymorphism in endometriosis in a Brazilian population [23].

The present study showed that the frequency of changes in codon 72 of the *TP53* gene in the studied population was common and totally 76.7 % of the studied patients had this change. Also, there are associations between a polymorphism at microRNA binding site in BRCA2 with BC susceptibility [24], [25]. Also, there are an association of polymorphisms in FCGR2A and FCGR3A with a degree of Trastuzumab in the Adjuvant treatment of ERBB2/HER2- positive BC [26]. A study results at 2017 showed a significantly association between six SNPs including FGFR2 (rs2981582), HCN1 (rs981782), MAP3K1 (rs889312), TOX3 (rs3803662), ZNF365 (rs10822013), and RAD51B (rs3784099), with breast cancer risk [25]. A study in South Korea on persons with gastric cancer that treated with cisplatin and paclitaxel chemotherapy indicated that rs1042522 (G/G and C/G) genotypes compared to rs1042522 (C;C) were significantly associated with lower response rate to the chemotherapy treatment (35.7 vs. 66.7%, p-value 0.019) [28]. Another study at 2014 on patients with NSCLC showed that G/G genotype of rs1042522 was more resistant to the first-line chemotherapy drugs, such as cisplatin [29]. In the present study, we evaluated all changes in studied amplicon compared to the control samples by sequencing method. The results of our study indicated the relationship between the rs1042522 polymorphism with age, BMI, metastasis, positive status of PR and ER and treatment response rate in these patients (Table 3).

Table 3: Some demographic features of the studied samples and differences in genotypes distribution of *TP53* at codon 72 in this study (P value < 0.05)

Characteristic	Detail	Total no.	No. Of patients (%)	Gg arg(%)	Dif.	Gc arg /pro(%)	Dif.	Cc pro(%)	Dif.
Age	<40	8	23.52	8.82	-16.8	11.76	-38.24	2.94	-22.06
	>40	26	76.47	14.070	-10.3	38.23	-11.17	23.52	-1.48
Menopausal	No	16	47.05	11.76	-10.3	23.52	-26.48	11.76	-13.24
age	<52	3	8.82	2.94	-13.24	2.94	-47.06	2.94	-22.06
	>52	15	44.11	8.82	-22.06	17.64	-32.36	17.64	-7.36
Er status	Positive	8	23.52	5.88	-19.12	11.76	-38.24	5.88	-19.12
	Negative	26	76.47	17.64	-7.36	35.29	-14.71	23.52	-1.48
Pr status	Positive	8	23.52	5.88	-19.12	11.76	-38.24	5.88	-19.12
	Negative	26	76.47	17.64	-7.36	35.29	-14.71	23.52	-1.48
Her2 status	Positive	15	44.11	11.76	-13.24	20.58	-29.42	11.76	-13.24
	Negative	19	55.88	11.76	-13.24	26.47	23.43	17.64	-7.36
Metastasis	Yes	6	17.64	5.88	-19.12	8.82	-41.18	2.94	-22.06
	No	28	82.35	17.64	-7.36	41.17	-8.83	23.52	-1.48
Treatment	Chemo-therapy+	6	17.64	2.94	-22.06	8.82	-41.18	5.88	-19.12
	Chemo-therapy-	30	88.23	8.82	-16.8	41.17	-8.83	29.41	4.41
Bmi	>22	7	20.58	8.82	-16.8	8.82	-41.18	2.94	-22.06
	<22	27	79.41	14.70	-10.3	38.23	-11.77	26.47	1.47
Whr (waist to hip ratio)	<0.8	14	41.17	8.82	-16.8	20.58	-29.42	11.76	-13.24
	>0.8	20	58.82	11.76	-13.24	2.94	-47.06	17.64	-7.36
Histological type	Invasive ductal carcinoma	34	100	23.52	-1.48	50	0	26.47	1.48

dif: the difference between expected and observed genotypes in HWE equation; p2: GG, 2pq: G/C, q2: CC)

In the present study, we investigated that rs1042522 SNP may be associated with susceptibility to BC among Iranian women with higher age and BMI. The distribution of C Allele in individuals with age of higher than 40 years was 1.2 times more than lower ages. Also, the frequency of G allele is associated to lower BMI and WHR. Our data showed there was a direct association between C/G and C/C genotype of rs1042522 with a negative response to chemotherapy (1.13 times).

Based on the new issue of “personalised medicine” in modern medicine, patients can be treated according to their molecular feathers. Therefore, it can be inferred that determination of *TP53* variants for BC patients is suitable before the starting the treatment protocol. Cancer is a multi-factorial disease and, in addition to genetic, environmental factors such as smoking, family income etc. also contributes to its development. The results of this study revealed the lack of significant correlation between these factors including family income, Educational level, the age of marriage and cigarette smoking with the studied polymorphism (data not shown). However, any of these factors may be effective in the overall survival rate and severity of the disease.

However any of these factors may be effective in overall survival rate and severity of the disease. Performance of molecular diagnostic tests for the evaluation of cancer genes in medical centers is critical. Hence, the determination of polymorphism in the mentioned codon can be used as a potential candidate diagnostic marker for high risk BC.

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Author contributions

The first two authors contributed to this study and have equal role: clinical sample preparation; AA: designed study, performed the experiments, analysed data, interpreted data and manuscript preparation; TA: clinical sample preparation, SA, MA and MS: performed the experiments

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