Association of p53 Codon 72 Polymorphism with Breast Cancer in a Rwandese Population

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Keywords

p53 polymorphism · Codon Arg72Pro · Breast cancer · Rwanda

Abstract

Background and Aims: A common polymorphism in the tumor suppressor gene *p53* at codon 72 has been suggested to play a role in the development of a number of cancers. This polymorphism has been studied in many populations worldwide, with conflicting results. The present study was planned to assess the association of p53 codon 72 polymorphism with breast cancer development in a Rwandese population. **Methods:** In this study, the polymorphism was examined by allele-specific PCR analysis in 40 patients with breast cancer and 39 healthy controls. **Results:** The heterozygous genotype Pro/Arg prevailed in both breast cancer patients and controls, and was present in 80% (32/40) and 92.3% (36/39) of cases, respectively. No statistically significant association was observed between p53 codon 72 polymorphism and breast cancer risk. Distribution of p53 genotypes was also studied according to familial history, tumor grade, and clinical stage, and results clearly showed no statistically

significant difference. **Conclusion:** These results suggest that p53 codon 72 polymorphism could not be assessed as a risk factor marker for predisposition to breast cancer in Rwanda. However, further studies using larger sample sizes are needed to provide more conclusive results and to investigate other genetic mutations affecting the activity of p53.

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Introduction

The global burden of breast cancer has become an increasing public health problem both in developed and developing countries. In sub-Saharan Africa, breast cancer remains the prevailing malignancy diagnosed in females [1, 2]. Besides the facts that African women are adopting new lifestyles and undergoing significant demographic transitions, the higher incidence rates of breast cancer may also due to genetic risk factors which are still less studied [3–5].

The human tumor suppressor gene *p53* encodes a transcription factor, playing a central role in maintaining cellular integrity by the inhibition of cell growth and

Table 1. Characteristics of the study population

	Patients (<i>n</i> = 40)	Controls (<i>n</i> = 39)
Age, years	40 (26–60)	25 (18–33)
Cancer familial history		
Familial cancer	13	–
Sporadic cases	27	–
Side		
Right	25	–
Left	15	–
Histological subtypes		
Invasive ductal carcinoma	35	–
Unknown	5	–
Stage		
II	13	–
III	26	–
Unknown	1	–
Grade		
I	2	–
II	4	–
III	34	–

stimulation of apoptosis in response to DNA damage. Its role in cancer development is widely studied and well documented [6]. In human cancer, p53 is frequently mutated and mutations are mainly missense, leading to the expression of full-length mutant p53 protein (mutp53) [6].

The loss of p53 function is often associated with a variety of human tumors including breast cancer. Genetic mutations of *p53* contribute to cancer development in different ways: (1) somatic mutations, widely considered as the main mechanism to inactivate p53 and promote cell division; (2) germline Li-Fraumeni mutations associated with predisposition of early-onset cancers including breast carcinomas; and (3) germline p53 polymorphisms in coding and noncoding regions [7, 8].

A common single nucleotide polymorphism (SNP) is known in the second position of codon 72 at exon 4 (rs1042522 – CCC to CGC), resulting in a substitution of proline (Pro) to arginine (Arg) in the Pro-rich region [9]. Many studies have reported that the codon 72 polymorphism is associated with a risk for the development of cancer [9–11]. The association of p53 polymorphism at codon 72 and breast cancer development has been widely studied, but results have been controversial and not conclusive. A number of studies have reported a significant association between the p53 codon 72 polymorphism and breast cancer risk [12–15], whereas others have identified no such association [16–19].

As the *p53* mutations are potential prognostic and predictive markers, as well as targets for therapy [20, 21], we planned to evaluate the p53 codon 72 polymorphism in a Rwandese population and to assess the effect of this polymorphism on the risk of breast cancer development in Rwanda.

Materials and Methods

Study Population

A total of 40 breast cancer patients and 39 healthy women were enrolled in this study. All breast cancer cases were recruited in 2016 at Rwanda Military Hospital and King Faysal Hospital, both located at Kigali, Rwanda. Characteristics of the breast cancer patients and healthy individuals in the study are described in Table 1. From each breast cancer case, clinical and pathological data (age, tumor localization, histological subtype, clinical stage, and tumor grade) were collected. The protocol study was approved by the Rwanda National Ethics Committee (197/RNEC/2015), and informed consent was obtained from each participant.

Blood Sampling and DNA Extraction

Approximately 5 ml of whole blood was taken by venipuncture into 5-ml vacutainers (Greiner Bio-One, Germany) containing EDTA. Genomic DNA was isolated from all peripheral blood samples by using a commercial kit (Isolate II Genomic DNA Kit; BIO-LINE) according to the manufacturer's recommendations. The DNA obtained was immediately used for polymerase chain reaction (PCR) amplification or stored at –20 °C until use.

Genotyping of *p53* Gene at Codon 72

The genotypes of the *p53* gene at codon 72 were detected by using allele-specific PCR that specifically detects either the p53 Pro or the p53 Arg allele. The 2 fragments (177 and 141 bp, respectively) were amplified in separate reactions with p53 Pro and p53 Arg primers. p53 Pro sequences were detected by PCR using the primer pair p53Pro+/p53– (p53 Pro+: 5' GCCAGAGGCTGCTCCCC 3' and p53–: 5' CGTGCAAGTCACAGACTT 3') and p53 Arg by the primer pair p53+/p53Arg– (p53+: 5' TCCCCCTTGCCGTCCCAA 3' and p53 Arg–: 5' CTGGTGCAGGGGCCACGC 3'). Amplification reaction was performed in a total volume of 25 µL containing 0.5 µM of each consensus primer, 200-mM dNTP, 0.125 units of Taq DNA polymerase, and 2 µL of genomic DNA in 1× Taq polymerase buffer.

DNA was amplified in a GeneAmp PCR System 9700 thermocycler (Applied Biosystems) with the following steps: an initial 10-min denaturation at 94 °C followed by 40 cycles of PCR, with denaturation for 30 s at 94 °C, primer annealing for 30 s at 58 °C, and primer extension for 40 s at 72 °C. At the end of the last cycle, the mixture was incubated for 7 min at 72 °C for a final elongation step. Reaction products were analyzed by electrophoresis on a 2% agarose gel.

Statistical Analysis

Statistical analyses were performed using XLStat software, the statistical software and data analysis add-on for Excel. Differences were considered statistically significant for *p* ≤ 0.05.

Table 2. Genotypic and allelic frequencies (%; 95% CI) in patients and controls

Cases	<i>n</i>	Genotype			<i>p</i>	Allele		<i>p</i>
		Pro/Pro	Pro/Arg	Arg/Arg		Pro	Arg	
Breast cancer	40	15 (7.1–29.1)	80 (65.2–89.5)	5 (1.4–16.5)	0.99	55 (44.1–65.4)	45 (34.6–55.9)	0.839
Controls	39	7.7 (2.7–20.3)	92.3 (79.7–97.3)	0 (0–9.0)		53.8 (42.9–64.5)	46.2 (35.5–57.1)	

Table 3. Distribution of p53 genotype (%; 95% CI) according to familial history of cancer

Cases	<i>n</i>	Genotype			<i>p</i>	Allele		<i>p</i>
		Pro/Pro	Pro/Arg	Arg/Arg		Pro	Arg	
Familial history	13	15.4 (4.3–42.2)	76.9 (49.7–91.8)	7.7 (1.4–33.3)	1.00	53.8 (35.5–71.2)	46.2 (28.8–64.5)	0.883
Sporadic cases	27	18.5 (8.2–36.7)	77.8 (59.2–89.4)	3.7 (0.7–18.3)		57.4 (44.2–69.7)	42.6 (30.3–55.8)	

Fig. 1. Analysis of p53 codon 72 polymorphism by PCR using allele specific primers. Arg/Arg, homozygote arginine; Pro/Pro, homozygote proline; Pro/Arg heterozygote; MW, 100-bp ladder.

Results

All samples, 40 cases and 39 controls, were successfully amplified and were analyzed for p53 codon 72 polymorphic alleles. Results of PCR amplification with Arg- or Pro-specific primers are reported in Figure 1. Overall, the PCR product analysis showed the presence of the 3 different DNA polymorphisms in the p53 gene: Pro homozygotes, Arg monozygotes, and heterozygous samples.

Table 2 illustrates the genotype distribution of the 3 different biallelic DNA polymorphisms in the p53 gene and corresponding allele frequencies. Overall, the heterozygous genotype prevailed in both breast cancer cases and controls, present in 80% (32/40) and 92.3% (36/39), respectively. The Arg homozygote genotype was present in only 5 cancer cases and was absent in all control specimens. Genotype distribution in controls and patients was in Hardy-Weinberg equilibrium. There was no significant difference in the overall genotype frequency distribution between the 2 groups.

Distribution of the p53 genotype according to familial history is reported in Table 3 and showed the predominance of the heterozygote genotype in both familial history and sporadic cases. Statistical analysis showed no significant association. The p53 codon 72 polymorphism was also evaluated according to tumor grade and clinical stage. Results are reported in Table 4 and showed no statistically significant difference. The heterozygote genotype Arg/Pro prevailed in all clinical stages and all tumor grades.

Discussion

During the last decades, great interest has been given to genetic predisposition in cancer development and the use of genetic biomarker for early diagnosis, adequate therapy, and effective monitoring. Predisposition to several human cancers has been associated with genetic polymorphisms, which may represent an important contribution to cancer susceptibility and tumor behavior.

Table 4. Distribution of p53 genotype (% , 95% CI) according to clinical stage and tumor grade

Cases	n	Genotype			p	Allele		p
		Pro/Pro	Pro/Arg	Arg/Arg		Pro	Arg	
Clinical stage								
II	13	15.4 (4.3–42.2)	76.9 (49.7–91.8)	7.7 (1.4–33.3)	1.00	53.8 (35.5–71.2)	46.2 (28.8–64.5)	0.829
III	26	19.2 (8.5–37.9)	76.9 (57.9–89.0)	3.9 (0.7–18.9)		57.7 (44.2–70.1)	42.3 (29.9–55.8)	
Unknown	1	–	–	–		–	–	
Tumor grade								
I	2	50 (9.5–90.5)	50 (9.5–90.5)	0 (0–65.8)	0.713	75 (30.1–95.4)	25 (4.6–69.9)	0.285
II	4	0 (0–49.0)	75 (30.1–95.4)	25 (4.6–69.9)		37.5 (13.7–69.4)	62.5 (30.6–86.3)	
III	34	17.6 (8.3–33.5)	79.4 (63.2–89.7)	3 (0.5–14.9)		57.4 (45.5–68.4)	42.6 (31.6–54.4)	

The p53 codon 72 polymorphism is the most extensively studied polymorphism in many cancers, including breast cancer. The association between the p53 codon72 polymorphism and the risk of developing breast cancer has been studied in different populations with conflicting results. To assess the prevalence of p53 SNP72 genotypes and alleles in Rwanda, we have conducted this case-control study on breast cancer patients and paired healthy controls. To our best knowledge, this study is the first investigating the association between p53 polymorphism in codon 72 and breast cancer development among a Rwandese population.

Overall, the Pro allele is more frequent in the Rwandese population. Both the cancer cases and healthy controls showed a high prevalence of this allele compared to the Arg allele. Brenna et al. [22] have shown that the frequency of the Arg allele increases with latitude, while the Pro allele shows the opposite effect. Moreover, several studies have reported that SNP72 is balanced by natural selection and that the Pro allele frequency increases in a linear manner in multiple populations as they near the equator, with around 60% in people of African descent and 17–34% in those of Caucasian descent [23, 24].

In this study, the heterozygote genotype (Pro/Arg) prevailed in both cancer cases and controls, and no significant association was obtained for genotype and allele distributions. Our results are in agreement with previously reported data in different populations [25–29]. The meta-analysis conducted by Gonçalves et al. [30] showed that breast cancer patients and control subjects were mainly heterozygous in the Asian population (50.1 and 48.0%, respectively) and the African population (43.9 and 49.7%, respectively), whereas the homozygote Arg/Arg was predominant in America (53.6 and 54.5%, respectively) and Europe (54.1 and 53.4%, respectively). How-

ever, the Pro/Arg heterozygous genotype was found to be higher in a Saudi population among healthy women (60.19%) than in women with breast cancer (25%) [31], while the Pro/Arg genotype has been reported to be associated with breast cancer risk in an Iranian population, with 75.55% in breast cancer cases versus 62% in controls [32]. These discrepancies in frequency distribution could be explained by the genetic specificity of the population and the ethnic group characteristics [33, 34].

When considered separately, sporadic and family cases displayed the same distribution both for genotype and allele frequencies, suggesting no association between this polymorphism and the hereditary form of breast cancer. Conversely, Krivokuca et al. [35] found that in Serbian women the Pro allele is related to hereditary cancer compared to sporadic cancer and could be considered as a potential risk factor for the hereditary form of the disease.

In this study, the distribution of the p53 codon72 polymorphism in clinical stages and tumor grades did not show any statistically significant difference. The p53 codon72 genotypes were present with equivalent proportions in all clinical stages and in the reported grades. In this study, out of 34 patients with grade III tumors, 79.4% had the heterozygous genotype. There are a limited number of studies investigating the association of the p53 codon72 polymorphism with clinicopathological features. In the study conducted in Brazil the homozygous genotype Arg/Arg was more frequent among patients with grade III tumors (17 out of 31), but no significant association was observed between tumor grade and genotype [36]. In Finland, Tammiska et al. [19] showed that Pro homozygous breast cancer patients presented significantly more often with grade I tumors, whereas Arg allele carriers had grade III tumors more frequently. The associa-

tion of Pro homozygosity with lower grade is consistent with a higher frequency of lobular carcinomas among Pro homozygous patients, as lobular carcinomas have been found to be more often of lower grade [19, 37]. In our study, no lobular carcinoma patient was observed. In breast cancer, the interest was given to mutations affecting the DNA binding domain of p53 and highlighting that these mutations are more prevalent in high-grade and large tumors [38, 39].

Many studies have shown that the 2 variants, Pro72 p53 and Arg72 p53, differ in their structure and their biological functions, especially concerning cell cycle progression and apoptotic activity [40, 41]. Difference in structure was already reported showing that the Pro72 variant migrates more slowly than the Arg72 variant on gel electrophoresis [9, 33]. Of particular interest, the Arg72 p53 variant was reported to be more efficient (at least 5 times better) than the Pro72 variant in initiating apoptosis, while the Pro72 variant was reported to be more efficient in inducing cell-cycle arrest [41–43].

In conclusion, these preliminary results suggest no association between p53 codon 72 polymorphism and breast cancer, and therefore this polymorphism could not be assessed as a risk factor marker for predisposition to breast cancer in Rwanda. However, further studies using larger sample sizes are needed to provide more conclusive results and to investigate other genetic mutations affecting the activity of p53.

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Disclosure Statement

The authors declare no conflict of interest.

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