RAPID COMMUNICATION

TP53 and *XRCC1* polymorphisms and breast cancer prognosis: a case-case study

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INTRODUCTION

Breast cancer is the most common cause of cancer death and the most common type of cancer in women.[1] The State of Rio de Janeiro has the highest frequency of this disease in Brazil.[2] Breast cancer is a significant public health burden. A combination of genetic factors and individual lifestyle habits influences breast cancer risk and tumor behavior. Breast cancer etiology is complex and heterogeneous in its clinical presentation.[3]

TP53 (tumor protein 53) and *XRCC1* (x-ray cross complementing group 1), a tumor suppressor and a DNA repair gene, respectively, contribute to cancer progression. The *TP53* gene may cause variation in susceptibility to cancer and give clues about disease progression.[4] Furthermore, several genes involved in DNA repair, such as *XRCC1*, carry genetic polymorphisms that may lead to alterations in DNA repair capacity and affect susceptibility to various cancers, including breast cancer.[5-7]

Two of the most studied polymorphisms in the *TP53* gene are a 16 bp duplication in intron 3 and an arginine to proline substitution in codon 72 in exon 4. This last variation alters the structure of the protein p53,[8] resulting in different biochemical and biological properties.[9] The Arg72 variant induces apoptosis with about five times more efficiency than the Pro72 variant.[10,11] However, the Pro72 variant is more efficient at inducing cell cycle arrest in the G1 phase, allowing better repair of damaged DNA.[12]

XRCC1 is important in the base excision repair process (BER). The gene has two common polymorphisms in codons 194 (Arg194Trp) and 399 (Arg399Gln) that affect the amino acid sequence. Codon 194 is located in the linker region that connects the domains that interact with poly(ADP-ribose) polymerase (PARP) and DNA polymerase β.[6] It is related to the binding domains of various proteins including proliferating cell nuclear antigen (PCNA), apurinic/apyrimidinic endonuclease 1 (APE1), and 8-hydroxyguanine DNA-glycosylase (hOGG1). This area is rich in proline, serine, arginine, and lysine residues. Hence, the change from a positively charged Arg to a hydrophobic Trp could affect the binding and efficient repair of DNA.[13,14] Codon 399 is located in the C-terminal domain of a breast cancer susceptibility protein 1 (BRCT1) area. Chinese hamster ovary cell lines that carry non-conservative amino acid substitutions in this domain, which binds to PARP, exhibit decreased DNA repair.[15]

Here we investigate the possible relationship between the genetic background of breast cancer patients, including *TP53* and *XRCC1* polymorphisms, and tumor clinical pathological features such as tumor grade, estrogen and progesterone receptor status, tumor size, and nodal status.

MATERIALS AND METHODS

We recruited 128 unrelated patients between May 2005 and November 2008 at the Department of Mastology, Fernandes Figueira Institute in Rio de Janeiro (IFF-Fiocruz/Brazil). All patients were diagnosed with infiltrating ductal carcinoma (IDC) and answered questions from a structured questionnaire. Clinicopathological parameters were obtained from hospital clinical records. We used the classification of Scarff-Bloom-Richardson modified by Elston and Ellis as a prognostic parameter and separated the cases in two groups of increasing tumor aggressiveness: low/intermediate with an Elston Grade (EG) of I/II and high with an EG of III. This study was approved by the Ethics Committee of the Fernandes Figueira Institute and all participants signed an informed consent.

Genomic DNA was isolated from peripheral blood (n = 99) and non-tumor breast tissue (n = 29) according to standard procedures.[16] *TP53* polymorphisms were detected by amplifying genomic DNA with primers previously described.[17] *XRCC1* polymorphisms were assessed by PCR-RFLP as previously described.[18] We were unable to genotype eight samples for *TP53* polymorphisms and three for *XRCC1* polymorphisms. To ensure the quality of our genotyping results, all genotypes were confirmed by sequencing after PCR during the standardization of the method.

Data analysis was performed using the computer software GraphPad Instat 3.06 for Windows (San Diego California, USA). Fisher's exact test was used to compare the variables when the number of samples was equal to or less than 5. A p value < 0.05 was defined as significant. The observed numbers for each genotype were compared with those expected for a population in Hardy-Weinberg

Equilibrium by using a goodness of fit Chi-square (χ^2) test applied by the Hardy-Weinberg Equilibrium calculator program.[19]

RESULTS

To evaluate the association between breast cancer prognosis and the genetic background of breast cancer patients, we decided to carry out a case-case analysis on patients with infiltrating ductal carcinoma (IDC) and with the most studied variant alleles of the *TP53* and *XRCC1* genes.

Table 1 presents the demographical and clinicopathological data for the 128 patients in our study. The principal demographic characteristics of our patients are shown in Table 2 as a function of breast cancer prognosis assessed by Elston Grade classification (EG). None of the analyzed characteristics, including age, menopausal status, family history, or ethnicity, were differentially distributed between the patients with EG I/II (low/intermediate aggressiveness) and EG III (high aggressiveness). The allelic frequencies of the *TP53* polymorphisms PIN3 Ins16bp and Arg72Pro of 0.2 and 0.4, respectively, and of the *XRCC1* polymorphisms Arg194Trp and Arg399Gln of 0.07 and 0.25, respectively, were in accordance with Hardy-Weinberg equilibrium.[20-26] Then we proceeded with the association analysis between tumor pathological characteristics and the allelic distribution of the variants (Table 3). We found a statistically positive association with the 194Trp *XRCC1* allele and EG III (OR = 4.04; 95% CI = 1.30-12.35; p = 0.018).

Table 1 - Sociodemographic of and tumor characteristics in patients (n = 128).

Variables	n (%)
Age (yr)	
≤ 30	2 (1.56)
31 – 40	22 (17.19)
41 – 50	47 (36.72)
51 – 60	29 (22.66)
61 – 70	17 (13.28)
> 70	11 (8.59)
Ethnicity	
White	65 (50.78)
Non-White	61 (47.66)
ND[a]	2 (1.56)
Menopausal status	
Pre-menopausal	58 (45.31)
Post-menopausal	64 (50.00)
ND[a]	6 (4.69)
FH breast cancer	
Negative	75 (58.59)
1° degree*	11 (8.59)
2° and/or 3° degrees	27 (21.10)
ND[a]	15 (11.72)
Tumor size	
≤ 2 cm	57 (44.53)
> 2 cm a ≤ 5 cm	40 (31.25)
> 5 cm	3 (2.34)
ND[a]	28 (21,88)
Elston Grade	
I	28 (21.87)
II	61 (47.66)
III	23 (17.97)
ND[a]	16 (12.50)
Lymph node commitment	
Negative	45 (35.16)
Positive	49 (38.28)
ND[a]	34 (26.56)
ER	
Positive	52 (40.63)
Negative	26 (20.31)
ND[a]	50 (39.06)
PR	
Positive	51 (39.84)
Negative	28 (21.88)
ND[a]	49 (38.28)
HER2	
Negative	36 (28.12)
Positive	32 (25.00)
ND[a]	60 (46.88)

ND[a] = no data; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor type 2; FH = family history; *mother and/or sister.

Table 2 - Demographics of the subjects by Elston Grade status (n = 112).

Variables	Elston Grade status		p-value
	EG III n (%)	EG I/II n (%)	
Age (yr)			
≤ 30	1 (4.35)	2 (2.25)	
31 – 40	1 (4.35)	17 (19.10)	
41 – 50	6 (26.09)	35 (39.32)	0.260
51 – 60	9 (39.13)	20 (22.47)	
61 – 70	3 (13.04)	8 (8.99)	
> 70	3 (13.04)	7 (7.87)	
Menopausal status			
Pre-menopausal	6 (26.09)	41 (46.07)	
Post-menopausal	14 (60.87)	42 (47.19)	0.200
ND[a]	3 (13.04)	6 (6.74)	
FH breast cancer			
Negative	18 (78.26)	50 (56.18)	
1° degree	0	6 (6.74)	0.230
2° and/or 3° degrees*	3 (13.04)	20 (22.47)	
ND[a]	2 (8.70)	13 (14.61)	
Ethnicity			
White	12 (52.17)	44 (49.44)	
Non-White	10 (43.48)	44 (49.44)	0.540
ND[a]	1 (4.35)	1 (1.12)	

EG = Elston Grade; ND[a] = no data; ER = estrogen receptor; PR = progesterone receptor; FH = family history; * mother and/or sister.

DISCUSSION

Despite the advances in tumor classification and the development of new therapies, breast cancer evolution remains a mystery. *TP53* is a very important tumor suppressor gene and its product, the p53 protein, maintains DNA stability and normal cellular growth. It is at the center of several pathways that lead to cell cycle check points, DNA repair, and apoptosis.[27] The *TP53* polymorphisms PIN3 Ins16bp and Arg72Pro[28-30] and the *XRCC1* polymorphism Arg194Trp and Arg399Gln are the most studied variants of each gene.[31,32] However, since these studies are based on case-control analysis using different populations and methodologies, the results do not clarify the real load of the polymorphic variants. Here we report the results of a case-case study and determine the contribution of *TP53* and *XRCC1* polymorphisms to breast cancer prognosis. The histological grading system proposed by Scarff-Bloom-Richardson and modified by Elston and Ellis in 1991[33] is an important independent prognostic factor for invasive breast tumors. The two groups of patients in our study were rather homogenous in terms of age and ethnicity and our genotyping results for *XRCC1* variants Arg194Trp and

Table 3 - Associations between *TP53* and *XRCC1* polymorphisms and tumor characteristics

Variables	*TP53*				*XRCC1*			
	PIN 3		Arg72Pro		Arg194Trp		Arg399Gln	
	1.1	1.2 + 2.2	Arg/Arg	Arg/Pro + Pro/Pro	Arg/Arg	Arg/Trp + Trp/Trp	Arg/Arg	Arg/Gln + Gln/Gln
Tumor size (n = 92)								
≤ 2 cm	34	20	18	36	51	7	29	29
> 2 cm	25	13	15	23	34	6	23	17
OR (95% CI)	1.00 (ref.)	0.88 (0.37 – 2.11)	1.00 (ref.)	0.77 (0.32 – 1.82)	1.00 (ref.)	1.29 (0.40 – 4.16)	1.00 (ref.)	0.79 (0.33 – 1.66)
[a]p		0.828		0.660		0.765		0.539
EG (n = 104)								
I / II	55	27	28	54	78	9	48	39
III	12	10	8	14	15	7	13	9
OR (95% CI)	1.00 (ref.)	1.70 (0.65 – 4.42)	1.00 (ref.)	0.91 (0.34 – 2.42)	1.00 (ref.)	**4.04 (1.30 – 12.35)**	1.00 (ref.)	0.85 (0.33 – 2.20)
[a]p		0.320		1.000		**0.018**		0.813
Lymph node (n = 88)								
Negative	28	15	15	28	37	8	28	17
Positive	28	17	15	30	42	6	23	25
OR (95% CI)	1.00 (ref.)	1.13 (0.47 – 2.70)	1.00 (ref.)	1.07 (0.44 – 2.59)	1.00 (ref.)	0.66 (0.21 – 2.08)	1.00 (ref.)	1.79 (0.78 – 4.09)
[a]p		0.827		1.000		0.568		0.212
ER (n = 72)								
Positive	33	15	20	28	43	8	26	25
Negative	16	8	9	15	21	4	16	9
OR (95% CI)	1.00 (ref.)	1.10 (0.39 – 3.13)	1.00 (ref.)	1.19 (0.43 – 3.25)	1.00 (ref.)	1.02 (0.28 – 3.79)	1.00 (ref.)	0.58 (0.22 – 1.56)
[a]p		1.000		0.802		1.000		0.332
PR (n = 73)								
Positive	32	15	18	29	43	7	25	25
Negative	18	8	11	15	22	5	17	10
OR (95% CI)	1.00 (ref.)	0.95 (0.34 – 2.67)	1.00 (ref.)	0.85 (0.32 – 2.24)	1.00 (ref.)	1.40 (0.40 – 4.91)	1.00 (ref.)	0.59 (0.23 – 1.53)
[a]p		1.000		0,805		0.744		0.341
HER2 (n = 63)								
Negative	27	7	17	17	32	4	19	17
Positive	17	12	9	20	25	7	20	12
OR (95% CI)	1.00 (ref.)	2.72 (0.89 – 8.28)	1.00 (ref.)	2.22 (0.79 – 6.26)	1.00 (ref.)	2.24 (0.59 – 8.52)	1.00 (ref.)	0.67 (0.25 – 1.77)
[a]p		0.100		0.199		0.325		0.468

ER = estrogen receptor; PR = progesterone receptor; [a]p = Fisher's exact test (common homozygote x heterozygote + rare homozygote); OR = odds ratio; CI = confidence interval.

Arg399Gln showed the distribution expected in a Brazilian population.[23-26] Together these observations indicate that our group of patients is adequate for a case-case study. Our study revealed a statistically significant relationship between the Arg194Trp genotype of *XRCC1* and Elston grade III, which indicates a poorly differentiated tumor and, consequently, is related to increased aggressiveness of the disease. The role of *XRCC1* in efficient BER has already been well determined[6,15,16] and it is acceptable that some gene alterations may change its biological activity and play roles in cancer evolution. A recently published meta-analysis of 37 studies suggests that Arg399Gln is associated with a trend of increased breast cancer risk.[31] Another meta-analysis of 10 studies on *XRCC1* haplotypes Arg194Trp and Arg399Gln showed that any conclusions are very difficult and complex.[32] Overall, no clear indication has been obtained from such studies. Dufflot et al.[34] investigated the associations of polymorphisms in the genes *XRCC1*, *XPD*, *XRCC3*, and *RAD5* with tumor characteristics in 94 breast cancer patients. While no polymorphisms were found to be associated with high tumor grade or estrogen receptor negativity, the XRCC1 Arg194Trp variant was not studied. Bewick et al.[35] found that *XRCC1* Arg399Gln may be predictive of the outcome of patients with metastatic breast cancer treated with DNA damaging chemotherapy. The same was observed in a study of Portuguese patients.[36] The authors investigated the possible influence of DNA repair polymorphisms on breast cancer clinicopathological features and described a possible correlation between the Gln/Gln genotype of *XRCC1* Arg399Gln and less aggressive tumors, which differs from our observations. Again, the authors did not analyze the Arg194Trp variant.

In summary, our study reveals that the *XRCC1* Arg194Trp variant is positively associated with breast tumors of Elston grade III, which is a measure of high tumor aggressiveness. However, this initial analysis involves a small sample size, which may contribute to low statistical power. Our findings indicate that further investigations are needed on a larger group to clarify the influence of the Arg194Trp *XRCC1* polymorphism in breast cancer development and prognosis.

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