RESEARCH ARTICLE

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Association between the Arg72Pro Genotypes in the *TP53* Gene and Ile655Val in the *HER2* Gene and the Risk of Developing Breast Cancer in the Population of Amapá, Northern Brazil

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Abstract

Background: The polymorphisms Arg72Pro in the *TP53* gene (rs1042522) and Ile655Val in the *HER2* gene (rs1136201) have been related to susceptibility to several types of cancer. Different studies show the association of these polymorphisms with breast cancer, so our aim in this study was to investigate whether the Arg72Pro and Ile655Val polymorphisms have any influence on the risk of developing breast cancer in women from the city of Macapá, Amapá, located in the brazilian amazon region. **Methods and Results:** We then analyzed 80 DNA samples from women with breast cancer and 83 DNA samples from women without the disease, by the Restriction Fragment Length Polymorphism - Polymerase Chain Reaction (PCR-RFLP) technique. The genotype frequencies for rs1042522 were Ar/Arg 23.7%, Arg/Pro 47.5% and Pro/Pro 28.5% in patients and in controls Ar/Arg 69.8%, Arg/Pro 19.2% and Pro/Pro 10.8%. For the *HER-2* gene the frequency of Ile/Ile, Ile/Val and Val/Val genotypes was 82.5%, 17.5% and 0% in the patients and 75.9%, 20.4% and 3.6% in the controls. The presence of at least one altered allele in rs1042522 and rs1136201 polymorphisms was found in 91.25% of patient samples. **Conclusion:** This study found a significant association between the Arg/Pro and Pro/Pro genotypes in the *TP53* gene and the Ile/Val genotype in the *HER-2* gene and breast cancer risk, however, we emphasize that more studies need to be carried out in the investigated population to consolidate our results.

Keywords: Gene *TP53*- Gene *HER-2*- Breast cancer- Macapá- Brazil

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Introduction

The exposure to environmental factors and adoption of certain lifestyle habits can be extremely important to the development of breast cancer that, like other types of cancer, has a multifactorial origin where 93 to 95% of the cases are influenced mainly by sporadic events, and in 5 to 7% of the cases genetic factors are more closely related to the risk of developing this type of cancer, which are known as Family Breast Cancer (FBC) in these cases (Renault, 2017).

The State of Amapá is located in the North region of Brazil, with a territorial area of 142,470,762 km^2 and an estimated population of 861,773 inhabitants, with a Human Development Index-HDI of 0.708. In the years 2016-2017, 82 new cases of breast cancer were officially diagnosed in the State population, according to data from the State Department of Health (Secretaria de Saúde do Estado do Amapá-SESA) based on treatments performed at UNACON (Unidade de Alta Complexidade em Oncologia).

According to INCA, for each year of the trienniumin 2020-2022 the state for breast cancer was 70 new cases for every 100 thousand women. Taking into account the IBGE population numbers for the year 2018 (last update) of 829,494 inhabitants, of which approximately 51.5% are female (approximately 427,189 women), in estimates approximately 299 women will be diagnosed by the end of 2022 following the estimated numbers made available by INCA (2019).

The *TP53* gene is located at chromosome 17 (p17.1.). (NCBI, 2020). This gene encodes a nuclear phosphoprotein, called p53. This phosphoprotein is a tumor suppressor that responds to various cellular stresses to regulate the expression of target genes, thereby inducing stop at cell cycle, apoptosis, senescence, DNA repair or changes in metabolism (Lane, Crawford, 1979; Gottlieb, Vousden, 2010).

The polymorphism rs1042522, also known as Arg72, Arg72Pro and G72C occurs at the exon 4 of the *TP53* gene, more specifically at codon 72. Codon 72 of the *TP53* gene can encode both amino acids, arginine (CGC) and

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proline (CCC), depending on the allelic state of the locus. Mutant alleles are originated from a base substitution (G/C) resulting in a change in the primary structure of the protein (Arg/Arg) (Thomas et al., 1999; Tada et al., 2001; Bojesen, Nordestgaard, 2008).

Mutations in *TP53* can lead to the growth of functionally defective proteins, with conformational changes and that present a longer half-life than the wild-type p53 protein (Yan, Tzeng, 1996). More than 50% of human tumors acquire a mutation or exclusion of the *TP53* gene during tumor progression (St. Jude Children's Research hospital, 2020).

Human epidermal growth factor receptor 2 (*HER-2* or ERBB-2) is an important prognostic and predictive gene investigated in breast cancer development (Shah, Chen, 2011; Borges et al., 2012). *HER-2* is a proto-oncogene, a member of the family of epidermal growth factors, located at chromosome 17 (17q.12) and encodes a transmembrane receptor with tyrosine kinase activity (Yarden, Sliwkowski, 2001; Borges et al., 2012).

HER-2 specific genotypes are associated with increased aggressiveness of the disease, worse prognosis, shorter disease-free survival, rapid tumor growth, increased risk of recurrence after surgery, resistance to hormonal therapy and reduced response to conventional chemotherapy (Shah, Chen, 2011). In the codon 655, isoleucine (ATC) can be replaced by valine (GTC) (rs1136201) in the transmembrane domain, change that is described to influence in breast cancer development risk (AbdRaboh et al., 2013). The presence of Valine at codon 655 significantly increases cancer tumorigenesis.

HER-2 is a proto-oncogene and the amplification of its expression was first reported by Slamon et al. (1987) in a study of 189 primary human breast carcinomas. The results presented revealed that 30% of the samples presented amplification in the gene, where tumors with alterations in these receptors present a more aggressive evolution, with worse clinical evolution for their carriers.

Its overexpression is sufficient to induce the cell to a neoplastic transformation, and it is present in invasive and metastatic breast cancer, pre-neoplastic lesions, mammary carcinoma in situ, and several neoplasms (MENENDEZ; VELLON; LUPU, 2004). Of the total cases of CM, 15 to 20% have overexpression of the *HER-2* protein, they are then called *HER-2* positive, this condition is considered to have the worst prognosis, since it gives the cancer cell a more aggressive behavior, with increased growth and proliferation, greater invasiveness and metastasis (CONITEC, 2017).

In this study, we analyzed the DNA extracted from the peripheral blood collected from 80 women diagnosed with breast cancer and 83 healthy women with the aim to investigate the potential influence of the polymorphisms in codon 72 at *TP53* gene and codon 655 at *HER-2* gene on the risk of developing breast cancer in the population of the city of Macapá.

Materials and Methods

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Human Research Ethics Committee from the Federal University of Amapá, under the Certificate of Presentation for Ethical Appreciation (CPEA) number 07398519.3.0000.0003.

Samples

Eighty DNA samples from peripheral blood obtained from 80 patients diagnosed with breast cancer treated at the high complexity unit in Oncology of the State of Amapá (UNACON) and 83 control samples from healthy women were analyzed. Informed consent was obtained from all individual participants included in the study.

Genotyping

rs1042522 polymorphism genotyping

Genomic DNA was isolated following the protocol of the bioscience® extraction kit. The genotype was identified through the Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR-RFLP) analysis, according to Rivu et al. (2017) with modifications. The identification of the Arg72Pro (C72G) polymorphism was conducted with the forward 5'-TTC ACC CAT CTA CAG TCC -3 ' and reverse 5'-CTC AGG GCA ACT GAC CGT -3' primers. The amplification cycle was 95 ºC for 5 minutes, 35 cycles of 95 ºC for 30 seconds, 55 ºC for 30 seconds and 72 ºC for 30 seconds, final extension of 5 minutes at 72 ºC and 4 ºC. The identification of the 309 bp fragment was visualized on a 2.0 % agarose gel with ethidium bromide. The PCR product was digested with restriction enzyme BstUI (0.5 µl) (New England Biolabs) by incubation at 60 ºC for 16 hours, generating two fragments of 175 and 134 bp (proline allele) and 309 bp (arginine allele).

rs1136201 polymorphism genotyping

The identification of the A655G polymorphism was through the PCR-RFLP technique. The 148 bp fragment was amplified with the forward 5'-AGA GCG CCA GCC CTC TGA CGT CCAT-3 ' and reverse 5'-TCC GTT TCC TGC AGC AGT CTC CGCA-3' primers. The amplification cycle was 95 ºC for 5 minutes, 35 cycles of 95 ºC for 30 seconds, 62 ºC for 30 seconds and 72 ºC for 30 seconds, final extension of 7 minutes at 72 ºC and 4 ºC. The 148bp fragment identification was visualized on a 2.5% agarose gel with ethidium bromide. The PCR product was digested with restriction enzyme BsmAI (New England Biolabs), the reaction was incubated at 37 ºC for 16 hours, generating two fragments of 116 and 32 bp (Valina allele) and 148 bp (Ileucine allele).

Statistical analysis

All statistical analyzes were carried out using the R software, a comparison was made between the allele and genotypic frequencies of the patients and the control group through analysis using the chi-square test (X^2). Logistic regression was performed using odds ratios (ORs) and 95% confidence intervals (95% CI) to assess possible associations between genetic variants of the disease and susceptibility to cancer. Where the P value less than 0.05 will be defined as statistically significant.

Results

TP53 gene Arg72Pro genotype

The results of the genotypic and allelic frequency from case and control samples for rs1042522 polymorphism are shown in Table 1. The percentage of distribution observed for the Arg/Arg genotype was lower among patients (23.7%) than among controls (69.9%), and while 47.5% of the patients presented heterozygous genotype (Arg/Pro), 19.2% of the control sample presented the genotype. A significant result was also observed for the Pro/Pro homozygous genotype, which was observed in 28.7% of the patients.

The genotypes and alleles of the rs1042522 polymorphism were statistically associated with the risk of breast cancer. The significant increase in risk was found when comparing the associations between heterozygotes and contrasting alleles (CG vs GG: OR = 7.2500, 95% CI 3.3208-15.8280, X^2 = 26.964, P = <0.0001), (G vs C: OR = 4.2910, 95% CI = 2.6334-6.9919, X^2 = 36.165, P = <0.0001), respectively as presented at Table 2.

HER-2 gene I655V genotype

The genotypic and allele frequency for the codon 655 of the *HER-2* gene is shown in Table 1, the results showed that the heterozygous genotype Ile/Val was the most frequent in patients (82.5%), while in controls the homozygous genotype Ile/Ile was the most frequent (75.9%). The Val/Val genotype was found only in the control samples (3.6%). After analyzing the allele frequency, the allele A was observed with significant frequency in the controls (86.1%) as well as it was the most frequent allele among the patients (58.7%).

The association between cancer risk and *HER-2* gene

Table 1. Genotype and Allele Frequencies of the Polymorphism rs1042522 gene TP53 and the rs1136201 Gene HER2 in Breast Cancer Patients and a Control Sample from the Municipality of Macapá

rs1042522	Genotype frequency (%)			Allele frequency (%)	
	Arg/Arg(G/G)	Arg/Pro(G/C)	Pro/Pro(C/C)	G	C
Patients (n=80)	19 (23.7)	38 (47.5)	23 (28.8)	76(47.5)	84(52.5)
Controls (n=83)	58 (69.9)	16 (19.3)	9(10.8)	132(79.5)	34 (20.4)
Total (n=163)	77 (47.2)	54(33.2)	32(19,6)	208(65.0)	118(36.8)
		X^2 = 34.798 P= < 0.0001		X^2 = 32.165 P= < 0.0001	
rs1136201	Genotype frequency (%)			Allele frequency (%)	
	Ile/Ile (A/A)	Ile/Val (A/G)	Val/Val(G/G)	A	G
Patients (n=80)	14 (17.5)	66 (82.5)	0	94 (58.7)	66 (41.2)
Controls (n=83)	63 (75.9)	17 (20.4)	3 (3.6)	143 (86.1)	20 (12.0)
Total (n=163)	77 (48.1)	83 (51.8)	3 (1.8)	237 (74.0)	86 (26.8)
		X^2 = 63.076 P= < 0.0001		X^2 = 63.076 P= < 0.0001	

X^2, qui-square

Table 2 Association between the Risk of Breast Cancer and the rs1042522 polymorphisms of the *TP53* Gene and the rs1136201 of the *HER-2* Gene

Polymorphism	Comparison	Association test*
	patients group x control group	OR (95% CI)
G72C	Homozygous (CC vs GG)	7.8012(3.0823-19.7444)
	Heterozygous (CG vs GG)	7.2500(3.3208-15.8280
	Contrasting Alleles (G vs C)	4.2910(2.6334-6.9919)
A655G		
	Homozygous (GG vs AA)	0.961
	Heterozygous (AG vs AA)	17.4706(7.9518-38.3840)
	Contrasting Alleles (A vs G)	5.0202 (2.8563-8.8234)

OR, odds ratios; CI, confidence interval; *The frequencies used are described in Table 1

Table 3 Association between the Polymorphism Arg72Pro e I655V in Breast Cancer Patients and Control Group

	With SNP's Arg72Pro + I655V n (%)	Without SNP's Arg72Pro and I655V n (%)
Patients (n=80)	73 (91.25)	7 (8.75)
Controls (n=83)	41 (49.40)	42 (50.60)
Total (n=163)	114 (69.94)	49 (30.06)

OR, odds ratio; CI, confidence interval; X^2, qui square

A655G polymorphism genotypes and alleles is also shown in Table 1. Significantly increased cancer risk with the *HER-2* gene was found by comparing associations between heterozygotes and alleles contrasts (AG vs AA: OR = 17.4706, 95% CI = 7.9518-38.3840, X^2 = 60.110, P = <0.0001), (A vs G: OR = 5.0202, 95% CI = 2.8563-8.8234, X^2 = 34.711, P = < 0.0001).

The genotype frequency of both polymorphisms associated is presented in table 3, the results showed that the presence of associated genotypes in the patient group is (91.25%). While in the control group, this difference is minimal (49.40%) when compared to controls without polymorphisms (Table 3).

Discussion

In this study we analyzed the involvement of the polymorphisms rs1042522 in codon 72, gene *TP53* and rs1136201 in codon 655, gene *HER-2* in patients diagnosed with breast cancer in the city of Macapá, Amazon region of Brazil. Our results showed that both polymorphisms can be associated with breast cancer in our population. Based on the origins of colonization and formation of the "amapaense" population and the large dimensions of Brazil with different miscegenation patterns among the regions of the country (Giolo et al. 2012). Therefore, it is impossible to infer that the results for these variants found in our study are the same as those found in other regions of the country; regionalized studies are needed to confirm whether the genetic composition of the population is an important factor for the distribution of these alleles in the population. This type of study is scarce in Brazilian populations and paves the way for investigations of the relationship between breast cancer and genetic polymorphisms in specific populations around the country.

Mutations in the *TP53* gene are the most frequent genetic changes in human malignant tumors, occurring in about 60% of neoplasms. These *TP53* mutations are associated with instability in cell development and cycle progression (Kara et al. 2010; McGraw, Zhang, Rollison, 2015). In this study, the most frequent P53 genotype among the patients was the heterozygous Arg/Pro with 47.5%, followed by Pro/Pro 28.7% and Arg / Arg 23.7%. In the control samples, the genotypic frequency found for the Arg / Arg, Arg / Pro and Pro/Pro genotypes had the percentage of 69.8%, 19.2% and 10.8% respectively. Studies revealed that the homozygous Arg72 allele has 15 times increased capacity to induce apoptosis activity than the 72Pro allele. This high capacity to induce apoptosis is due to its mitochondrial location that allows p53 to have a direct interaction with the BAK protein. Consequently, the less apoptotic 72Pro allele represents a greater ability to lead to the proliferation of cancer cells (Dumont et al., 2003; Leu et al., 2004). In our study 52.5% of the patients presented the C allele (72Pro) and in the controls the most frequent was the G allele (Arg72).

In our sample, the Arg72Pro genotype and the C allele (72Pro) were statistically associated with breast cancer (Table 2). The significant increase in the risk of cancer in relation to the *TP53* variants was found when we observed the comparisons between the associations of heterozygous and contrasting alleles (GC vs GG: OR = 7.2500, 95% CI 7.9518-38.3840, X^2 = 60,110, P = <0.0001), (G vs C: OR = 4.2910, 95% CI = 2.6334-6.9919, X^2 = 36.165, P = <0.0001), respectively. Similar results associating this genotype and allele were found in studies (Buyru, Tigli, Dalay, 2003; Rivu et al., 2017;Akhter et al. 2018; Ayoubi et al. 2018).

HER-2 belongs to the family of the human epidermal growth factor, commonly expressed at the surface of epithelial cells. In addition to the contribution to cell proliferation and differentiation, the activation of *HER-2* in normal cells promotes cell adhesion and motility (Riaz et al. 2016). The role of genetic changes in the *HER-2* kinase-binding domain contributes to tumorigenesis and has also been reported in many types of cancer (Olayioye et al., 2000; Fan et al. 2008).

The Ile655Val genotype is the most associated with the development of several types of cancer, mainly breast cancer which is extensively associated worldwide with this genotype18. In this study, the Ile655Val polymorphism was found to be associated with the risk of breast cancer in the investigated population (Tables 2 and 3). In the sample, 82.5% of the patients had the Ile655Val genotype (table 1), corroborating studies described in the literature (Kara et al., 2010; Lu, Wang, Liu,2010; Chen et al. 2014; Rivu et al. 2017). Among the controls, the most frequent genotype was Ile655Ile (75.9%), followed by Ile655Val (20.4%) and Val655Val (3.6%).

Lu et al (2010) found an association of the *HER-2* Ile655Val polymorphism with the Asian and African subgroups in breast cancer and no correlation was observed for Caucasians. On the other hand 26 suggested an inverse relationship, in a meta-analysis, found no association with the Asian ethnic group, but with African-American and Caucasian groups. The population from the northern region of Brazil, especially the city of Macapá, presents a great miscegenation rate. Its genetic constitution is composed principally of indigenous, Africans and Europeans.

Table 2 presents the statistical significance of the comparisons between the heterozygous genotype Ile655val with the homozygous Ile655Ile and the contrasting alleles (AG vs AA: OR = 17.4706, 95% CI 3.3208-15.8280, X^2 = 26.964, P = <0.0001) (AG vs AA: OR = 17.4706, 95% CI 7.9518-38.3840, X^2 = 60,110, P = <0.0001), (A vs G: OR = 5.0202, 95% CI = 2.8563-8.8234, X^2 = 34.711, P = <0.0001). In our samples, we did not find the homozygous genotype Val655Val among patients, only among controls.

When comparing the presence of association of the Arg72Pro and I655V polymorphisms, it was demonstrated that the concomitant presence of the polymorphisms leads to an increased risk among patients, whereas in the control group the difference found was minimal. The most frequent phenotypic profile among patients was heterozygosis for both Arg72Pro and I655V (n = 35, 43.75%), followed by homozygosity for Arg72Pro and heterozygosity for I655V (n = 19, 23.75%).

In conclusion, the Arg72Pro and Ile655Val genotypes were associated with the risk of breast cancer in our population. Statistical significance was observed in relation to the two variants of the *TP53* and *HER-2* genes, we believe that in the future these two genotypes may be used as genetic markers for breast cancer, but we emphasize that more studies need to be carried out in the investigated population to consolidate our results.

Author Contribution Statement

All authors contributed equally to this work, from material preparation, data collection and analysis, writing of the first version of the manuscript and comments. All read and approved the final manuscript.

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Approval

Approved as a master's thesis in the Graduate Program in Pharmaceutical Sciences at the Federal University of Amapá.

Ethical Declaration

Approval was granted by the Human Research Ethics Committee from the Federal University of Amapá, under the Certificate of Presentation for Ethical Appreciation (CPEA) number 07398519.3.0000.0003.

Conflict of interest

The authors this manuscript titled "Association between the Arg72Pro genotypes in the *TP53* gene and Ile655Val in the *HER2* gene and the risk of developing breast cancer in the population of Amapá, northern Brazil", declare there is no conflict of interest regarding the publication of this article;

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