RESEARCH ARTICLE

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Impact of Interaction between Single Nucleotide Polymorphism of *XRCC1, XRCC2, XRCC3* with Tumor Suppressor *Tp53* Gene Increases Risk of Breast Cancer: A Hospital Based Case-Control Study

Kailas D. Datkhilea[1]*, Rashmi A. Gudur[2], Suresh J. Bhosale[2], Pratik P. Durgawale[1], Nilam J. Jagdale[1], Ashwini L. More[1], Anand K. Gudur[2], Satish R. Patil[1]

Abstract

Background: At present very little information is available on combined effects of DNA repair genes with tumor suppressor gene polymorphisms and their association with cancer susceptibility. No such association studies have been carried out with breast cancer or any other cancer from India. Present study was conducted to study the combined effects of SNPs of *XRCC1*, *XRCC2, XRCC3* with Arg72Pro and Arg249Ser SNPs of *TP53* gene in risk of BC in rural parts of India. **Methods:** The polymorphisms of Arg194Trp, Arg280His, Arg399Gln of *XRCC1*, Arg188His of *XRCC2* and Thr241Met of *XRCC3* with Arg72Pro and Arg249Ser of *TP53* gene polymorphisms was studied by polymerase chain reaction-based restriction fragment length polymorphism (PCR–RFLP) method. The association among the polymorphisms with breast cancer risk was studied by Odds ratio within 95% confidence interval and SNP-SNP interaction were confirmed by logistic regression analysis. **Results:** The results of genotype frequency distribution of *XRCC1*, *XRCC2*, *XRCC3* genotypes showed positive association between *XRCC1* Arg280His polymorphism and BC risk (OR=4.54; 95% CI: 3.36- 6.15; p<0.0001). Also the heterozygous genotypes Arg188His of *XRCC2* (OR=1.58; 95% CI: 1.13- 2.21; p=0.007) and Thr241Met genotype of *XRCC3* (OR=2.13; 95% CI: 1.44- 3.13; p=0.0001) were associated with BC risk. The combination of heterozygous Arg280His genotype of *XRCC1* along with Arg72Pro genotype of *TP53* increased the risk of BC (OR=4.53; 95% CI: 2.85-7.20); p<0.0001). Similarly, the combined effect of heterozygous Arg/His genotype of *XRCC1* with heterozygous Arg/Ser genotype of *TP53* at codon 249 showed significant association with increased BC risk (OR=5.08; 95% CI: 2.86-9.04); p<0.0001). **Conclusion:** The findings derived from our study concluded that the heterozygous variant Arg280His genotype of *XRCC1* and Thr241Met polymorphism of *XRCC3* in combination with heterozygous arginine72proline genotype and heterozygous Arg249Ser polymorphism of *TP53* showed significant association with breast cancer risk in Maharashtrian women.

Keywords: Breast Cancer- SNP- PCR-RFLP- *XRCC1- XRCC2- XRCC3- p53*

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Introduction

Breast cancer (BC) is the most common malignancy increasing enormously in different regions of the world and is the second major cause of cancer causing deaths among women worldwide. According to the global cancer statistics evidence, BC ranked highest and accounted 2261, 419 (11.7%) new cases and 684, 996 (6.9%) deaths in year 2020 (Sung et al 2021). The latest report published on the global burden of BC predicted that there will be increase of more than three million new cases per year and one million deaths annually (Arnold et al 2022). In India, BC is the leading cause of cancer causing deaths accounts for roughly 178,361 (13.5%) of all cancer cases and 90,408 (10.6%) of all deaths in 2020 (GLOBOCAN, 2021). Especially in rural parts of India, the rate of incidence of BC is likely high as the unawareness, illiteracy, delayed diagnosis and hiding tendency of women. Age, use of alcohol or tobacco, other environmental, dietary and life style related factors, birth control methods, hormone therapy are the hypothetical risk factors for developing BC. Along with those defined risk factors, now days host genetic factors are given more attention for their involvement in breast carcinogenesis (Collins and Politopoulos 2011; Cobain et al., 2016). Exposure to various physical or chemical carcinogens

*[1]Department of Molecular Biology & Genetics, Krishna Vishwa Vidyapeeth (Deemed to be University), Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra) India. [2]Department of Oncology, Krishna Vishwa Vidyapeeth (Deemed to be University), Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra) India. *For Correspondence: hodgeneticslab@kvv.edu.in*

may cause effective DNA damage in various forms such as single strand breaks, double strand breaks which may alter the cellular functions and lead to the development of cancerous cell. Several DNA repair genes including base excision repair (BER) and nucleotide excision repair (NER) genes along with tumor suppressor p53 genes are involved in maintaining genomic stability and cellular integrity. The functional variations in those genes caused by various carcinogens have been proposed as potential manipulators which may influence the genetic susceptibility of individuals towards carcinogenesis including breast cancer.

The single nucleotide polymorphisms (SNPs) are one the hallmarks of genomic variations involved in susceptibility of carcinogenesis; however, opportunities remained open to further explore their involvement in regulating breast carcinogenesis. The most important SNPs of X-ray repair cross-complementing group 1 (*XRCC1*), *XRCC2* and *XRCC3* genes are assessed for their importance in risk of various cancer including lung (Huang et al 2013, Chen et al., 2016) gastric (Kaur et al., 2020), HNC (Xia et al., 2021) and breast cancer (Dashti et al., 2019, Yu and Wang 2023). Similarly the polymorphisms of tumor suppressor gene p53 at codon 72, codon 249 were also studied and confirmed for their role in various cancers including lung (Matikodu et al., 2003), gastric (Song et al., 2011), ovarian (Alqumber et al., 2014), bladder (Zang et al., 2018) and cervical cancer (Ratre et al., 2019; Yu et al., 2022). Though multiple genes are studied for their association with BC, the information on combined effects of SNP-SNP interaction between the genes accountable for the increase of BC risk remained inadequate with further of scope understand their cumulative effects in breast carcinogenesis. Looking towards the literature on cancer causing deaths, we noted BC as the major health concern among women of rural India due to its increased mortality and morbidity rates. We also noticed lack of information on the genetic polymorphism, gene to gene interactions of the cancer causing oncogenes and their association with BC risk. It is very important to study the combined effects of polymorphic variants in closely associated genes including DNA repair genes and tumor suppressor genes to assess their interactive role in the disease pathogenesis and individuals susceptibility towards breast cancer.

At present little is known about the genetic information on the combined interactive effects of DNA repair genes with *TP53* gene polymorphisms and their association with susceptibility towards gastric (Engin et al., 2011), cervical (Liu et al., 2019) and breast cancer (Rodrigues et al., 2011, Krivokuca et al., 2016, Isakova et al., 2020). But, no studies on the interactions of polymorphisms of DNA repair genes and tumor suppressor genes and their association with BC or any other cancer were reported from India. Therefore, present study was aimed to ascertain the gene to gene interactions and contribution of combined effects of the SNPs Arg194Trp exon 6 (rs1799782), Arg280His exon 9 (rs25489), Arg399Gln exon 10 (rs25487) of *XRCC1*, Arg188His exon 3 (rs3218536) of *XRCC2* and Thr241Met exon 7 (rs861539) of *XRCC3* with Arg72Pro exon 4 (rs1042522) and Arg249Ser exon 7(rs28934571) SNPs of tumor suppressor *TP53* gene polymorphisms in increasing the risk of BC in rural parts of India. We also assessed the relationship between *XRCC1*, *XRCC2 XRCC3* and *TP53* and the clinicopatholohical characterstics including tumor size, tumor grade, nodal status and hormone receptor status of breast cancer patients.

Materials and Methods

Study subjects

This hospital based case-control study was conducted on 400 newly diagnosed and histopathologically confirmed BC patients and equal number of healthy female controls. All cases ranged in age from 20-80 years (47.61 ± 13.86) (Mean ± SD) were sequentially enrolled immediately after diagnosis during the year 2018-2021. The cases already receiving treatment for malignancy were excluded. The clinicopathological characteristics were obtained from the hospital clinical records. The controls were 400 healthy women volun¬teers without any history of any disorders. The control group and the study group resided in the same geographical location (Western Maharashtra region). Controls were frequency matched to cases by the age group at enrolment. Trained interviewers used a structured questionnaire to collect demographic and clinical data from the participants. The study protocol was approved by Institutional Ethics Committee for the utilization of human subjects in the research.

SNP Selection and Genotyping

Genomic DNA was isolated from venous blood of BC cancer patients and normal controls by a modified method where red blood cells are processed with red cell lysis buffer (10mM Tris-HCl pH 7.6, 320 mM sucrose, 5mM MgCl2, 1% Triton X-100, pH 7.6), thereafter treated with nucleic lysis buffer (10mM Tris-HC1, 11.4 mM sodium citrate, 1 mM EDTA, 1 % SDS, pH 8.0). After treatment with 100 µg/mL concentration of proteinase K at 550C and subsequently RNase A (100 µg/mL) at 370C, precipitated and purified DNA was checked on 1% agarose gel for its quality as well as quantity.

The polymorphisms of *XRCC1* (rs1799782, rs25487, rs25489), *XRCC2* (rs3218536), *XRCC3* (rs861539) were detected by polymerase chain reaction-based restriction fragment length polymorphism (PCR–RFLP) method based on previously described studies (Datkhile et al 2018). The DNA samples were also genotyped for the SNPs of *TP53* codon 72 (rs1042522), *TP53* codon 249 loci (rs28934571) by PCR-RFLP. The polymorphisms of p53 were chosen for this study based on previously described studies (Vijayaraman et al 2012). The results of genotyping obtained from PCR-RFLP were further validated by direct DNA sequencing (Barcode Biosciences, Bangalore) of PCR products of randomly selected representative samples and the results exhibited cent percent concordance.

Statistical analysis

The association among *XRCC1*, *XRCC1*, *XRCC2*, *XRCC3* and *TP53* genotypes and risk of developing BC was studied by calculating the Odds ratio (OR) within 95% confidence interval (CI) based on Chi square analysis. The SNP-SNP interaction were confirmed by logistic

regression using SPSS IBM Version 11.0) software. The chi-square test was used to test the deviations from Hardy-Weinberg equilibrium in the genotype frequencies of the cases and controls. The p-value was evaluated to get the level of association where p ≤0.05 was considered to indicate significance.

Results

Demographic and clinicopathological features of study subjects

In this case-control study we assessed the SNPs rs1799782, rs25487, rs25489 of *XRCC1*, rs3218536 of *XRCC2* and s861539 of *XRCC3*and rs1042522, rs28934571 SNPs of *TP53* from 400 confirmed BC cases and same number of controls. The age of BC patients ranged from 23-85 years with mean ± SD: 52.43 ±12.40; Median age, 50yrs) whereas healthy control females ranged from 24-81 yrs (Mean ± SD: 42.37 ±13.90; Median age 40yrs) with no much difference in age distribution between cases and controls (p =0.01). When we checked for tobacco habit status we observed significant association with BC (OR 3.07; 95%CI, 2.29-4.12; p<0.0001) in women of rural population. The clinicopathological characteristics of BC patients including hormone status, histological subtypes, histological grade, tumor localization, tumor size were recorded which showed that out of 400 BC cases 299 (74.75%) were diagnosed with invasive ductal carcinoma, 27 (6.75%) had medulary carcinoma, 12 (3%) had mucinous and invasive apocrine carcinoma and 15 (3.75 %) had lobular carcinoma. Most of the BC patients 205 (51.25%) were in >III stage histological grade and 195 (48.75%) were in I and II stage. When hormone receptor status was considered, out of 400 cases, 218 (54.50) were positive for estrogen receptor (ER), 197 (49.25) were progesterone receptor (PR) positive and 57 (14.25) were human epidermal growth factor receptor 2 (Her2) positive and 343 (85.75) were Her2 negative. Out of these, 134 (33.50%) showed triple negative status for these prognostic markers.

Comparative analysis of genotype frequency distribution of XRCC1, XRCC2, XRCC3 and p53 genes in breast cancer cases and controls

The results of frequency distribution of *XRCC1*, *XRCC2*, *XRCC3* genotypes and allele in both cases and control groups showed that significant positive association with 4.5 fold was noted between *XRCC1* (rs25489) polymorphism and BC risk (OR=4.54; 95% CI: 3.36- 6.15; p<0.0001) in the studied population. Similarly, our results also indicated that the heterozygous genotypes G31479A of rs3218536 SNP of *XRCC2* (OR=1.58; 95% CI: 1.13- 2.21; p=0.007) and (C18067T) genotype of rs861539 SNP of *XRCC3* (OR=2.13; 95% CI: 1.44- 3.13; p=0.0001) were associated with BC risk in current study, but the homozygous variant genotypes of both the genes showed no association with BC risk. The genotype and allele frequency distribution of *XRCC1*, *XRCC2*, *XRCC3* polymorphisms determined in BC cases and healthy age and sex matched controls is summarized in Table 1. The distribution of codon 72 and codon 249 genotypes of p53 in patients and control did not deviate from the Hardy-Weinberg equilibrium. When we studied frequency distribution of arginine and proline genotypes of codon 72 in the exon 4, the Arg/Arg genotype of the patients (26.50%) and controls (23.00) and Pro/Pro genotypes of Cases (20.00%) and controls (23.75%), we find no significant statistical association of the Pro/Pro (OR 0.73: 95% CI 0.48-1.09; p< 0.132) and Arg/Pro heterozygous variant (OR 0.28: 95% CI 0.62-1.22; p< 0.426) with BC risk. The genotype frequencies in cases and controls demonstrated no statistically significant association of the 249 Ser genotype (OR 1.34: 95% CI 0.94-1.92; p= 0.103) with BC risk. The frequency of each genotype was 79% for Arg and 21% for Ser in patients with cancer (n=400), and 83.50 for Arg and 16.50 for Ser in normal controls (n=400).

The recessive and dominant genetic models were applied to confirm the association of the studied SNPs of *XRCC1*, *XRCC2*, *XRCC3* and *p53* genes. When we attempted to study the genetic polymorphism of *XRCC1* with BC risk in recessive genotype model, we noted significant negative association of rs25489 SNP of *XRCC1* with breast cancer risk (OR=0.21; 95% CI: 0.16-0.29); p<0.0001), whereas other rs25487 and rs1799782 SNPs did not show any correlation with BC risk. Similarly the recessive model for *XRCC2* (rs3218536) (OR=0.63; 95% CI: 0.45-0.86); p=0.004), and *XRCC3* (rs861539) (OR=0.50; 95% CI: 0.36-0.70); p=0.0001), drawn negative association with BC risk in the studied population. When we used recessive model for variant genotype of *p53* (rs1042522) (OR=1.20; 95% CI: 0.87-1.66); p=0.251) and (rs28934571) (OR=0.74; 95% CI: 0.52-1.06); p=0.103) showed no relationship with BC risk (Table 2). When we applied dominant model to confirm the association of *XRCC1*, *XRCC2* and *XRCC3* genes, we noted that only rs25489 SNP of *XRCC1* showed negative association with BC risk and other two rs25487 and rs1799782 SNPs of *XRCC1* and *XRCC2* (rs3218536) and *XRCC3* (rs861539) did not show any significant relation with BC risk in the studied population. However, the lack of significance observed in dominant model of *p53* (1042522, rs2893457) (OR=1.24; 95% CI: 0.89-1.74); p=200) and (OR=0.74; 95% CI: 0.52-1.06); p=0.103). The results of association between SNP variants of *XRCC1*, *XRCC2*, *XRCC3* and *p53* genes with breast cancer risk in the dominant model are shown in Table 3.

Combined effects of XRCC1, XRCC2, XRCC3 genotypes with p53 gene polymorphisms for their association with breast cancer risk

The combination of variant genotypes of *XRCC1* Arg280His and homozygous wild type genotype of *p53* Arg72Pro increased the risk of BC with 2.44 folds where as combination of heterozygous Arg/His alongwith homozygous His/His variant genotype of *XRCC1* at codon 280 showed 2.85 fold increased risk of BC in the studied population. The combined effects of genotype frequency distribution of *XRCC1*, *XRCC2*, *XRCC3* with codon 72 of *p53* gene and their association with BC risk is indicated in Table 4. We found statistically significant associations of the combinations of the polymorphic *XRCC1* genotype at

Table 1. The Distribution of Genotype and Allele Frequencies of DNA Repair Genes (*XRCC1, XRCC2, XRCC3*) and Tumor Suppressor (*TP53*) Gene Polymorphisms in Untreated Breast Cancer Cases and Healthy Controls

Gene	Genotype/ Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)	P value
XRCC1 C26304T Arg194Trp cd194 Ex-6 rs1799782	Arg / Arg	300 (75.00)	314 (78.50)	1 (Reference)	
	Arg / Trp	85 (21.25)	74 (18.50)	1.20 (0.84-1.70)	0.301
	Trp / Trp	15 (3.75)	12(3.00)	1.30 (0.60-2.84)	0.496
	Arg /Trp+Trp/Trp	100 (25.00)	86 (21.50)	1.21(0.87-1.69)	0.241
	Arg allele	342 (85.50)	351 (87.75)	1 (Reference)	
	Trp allele	58 (14.50)	49 (12.25)	1.21 (0.80-1.82)	0.35
XRCC1 G27466A Arg280His cd280 Ex-9 rs25489	Arg / Arg	159 (39.75)	300 (75.00)	1 (Reference)	
	Arg / His	0 (0.00)	0 (0.00)	NA	
	His / His	241(60.25)	100 (25.00)	4.54 (3.36-6.15)	<0.0001*
	Arg /His+His /His	241 (60.25)	100 (75.00)	4.54 (3.36-6.15)	<0.0001
	Arg allele	159 (39.75)	300 (75.00)	1 (Reference)	
	His allele	241(60.25)	100 (25.00)	4.54 (3.36-6.15)	<0.0001*
XRCC1 G28152A Arg399Gln cd399 Ex-10 rs25487	Arg / Arg	265 (66.25)	272 (68.00)	1 (Reference)	
	Arg / Gln	117 (29.25)	120 (30.00)	1.00 (0.73-1.35)	0.996
	Gln / Gln	18 (4.50)	8 (2.00)	2.30 (0.98-5.40)	0.053
	Arg /Gln+Gln / Gln	135 (33.75)	128 (32.00)	1.08 (0.80-1.45)	0.598
	Arg allele	323 (80.75)	332 (83.00)	1 (Reference)	
	Gln allele	77 (19.25)	68 (17.00)	1.16 (0.81-1.66)	0.409
XRCC2 (G31479A) Arg188His codon-188 exon-3 rs3218536	Arg/ Arg	279 (69.75)	314 (78.50)	1 (Reference)	
	Arg/His	107 (26.75)	76 (19.00)	1.58 (1.13-2.21)	0.007*
	His/ His	14 (3.50)	10 (2.50)	1.57 (0.68-3.60)	0.281
	Arg/His + His /His	121 (30.25)	86 (21.50)	1.58 (1.14-2.18)	0.004*
	Arg Allele	332 (83.00)	352 (88.00)	1 (Reference)	
	His Allele	68 (17.00)	48 (12.00)	1.50 (1.00-2.23)	0.045*
XRCC3 (C18067T) Thr241Met codon-241 exon-7 rs861539	Thr/Thr	279 (69.75)	328 (82.00)	1 (Reference)	
	Thr/Met	87 (21.75)	48 (12.00)	2.13 (1.44-3.13)	0.0001*
	Met/Met	34 (8.50)	24 (6.00)	1.66 (0.96-2.87)	0.064
	Thr/Met + Met/Met	121 (30.25)	72 (18.00)	1.97 (1.41-2.75)	0.0001*
	Thr Allele	322 (80.50)	352 (88.00)	1 (Reference)	
	Met Allele	78 (19.50)	48 (12.00)	1.77 (1.20-2.62)	0.003*
TP53 Arg72Pro Codon72 Ex-4 rs1042522	Arg / Arg	106 (26.50)	92 (23.00)	1 (Reference)	
	Arg / Pro	214 (53.50)	213 (53.25)	0.28 (0.62-1.22)	0.426
	Pro / Pro	80 (20.00)	95(23.75)	0.73 (0.48-1.09)	0.132
	Arg /Pro+Pro/Pro	294 (73.50)	308 (77.00)	0.82 (0.60-1.14)	0.251
	Arg allele	213 (53.25)	198 (49.50)	1 (Reference)	
	Pro allele	187 (46.75)	202 (50.50)	0.86 (0.65-1.13)	0.288
TP53 Arg249Ser Codon249 Ex-7 rs28934571	Arg / Arg	316 (79.00)	334 (83.50)	1 (Reference)	
	Arg / Ser	0 (0.00)	0 (0.00)	NA	
	Ser / Ser	84 (21.00)	66 (16.50)	1.34 (0.94-1.92)	0.103
	Arg/Ser+Ser/Ser	84 (21.00)	66 (16.50)	1.34 (0.94-1.92)	0.103
	Arg allele	316 (79.00)	334 (83.50)	1 (Reference)	
	Ser allele	84 (21.00)	66 (16.50)	1.34 (0.94-1.92)	0.103

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05

codon 280, *XRCC2* genotypes at codon 188 and *XRCC3* genotypes at codon 249 along with variant genotypes of *p53* at codon 249. The combinations of genotypes of *XRCC1*, *XRCC2*, and *XRCC3* with codon 249 of *p53* gene and their association with relative risk of breast cancer are presented in Table 5. The combination of heterozygous Arg/His and homozygous His/His variant genotype of *XRCC1* at codon 280 along with homozygous wild type

Table 2. Association between Breast Cancer Risk and the Single Nucleotide Polymorphism Variant of *XRCC1, XRCC2, XRCC3* and *TP53* Genes in the Recessive Model

Genes	Genotype	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)	P value
XRCC1 Arg194Trp rs1799782	Trp/Trp + Arg/Trp	100 (25.00)	86 (21.50)	1 (Reference)	
	Arg/Arg	300 (75.00)	314 (78.50)	0.82 (0.59-1.14)	0.241
XRCC1 Arg280His rs25489	His/His+Arg/His	241 (60.25)	100 (25.00)	1 (Reference)	
	Arg/Arg	159 (39.75)	300 (75.00)	0.21 (0.16-0.29)	<0.0001*
XRCC1 Arg399Gln rs25487	Gln/Gln/Arg/Gln	135 (33.75)	128 (32.00)	1 (Reference)	
	Arg/Arg	265 (66.25)	272 (68.00)	0.492 (0.68-1.24)	0.598
XRCC2 Arg188His rs3218536	His/His+Arg/His	121 (30.25)	86 (21.50)	1 (Reference)	
	Arg/Arg	279 (69.75)	314 (78.50)	0.63 (0.45-0.86)	0.004*
XRCC3 Thr241Met rs861539	Met/Met+Thr/Met	121 (30.25)	72 (18.00)	1 (Reference)	
	Thr/Thr	279 (69.75)	328 (82.00)	0.50 (0.36-0.70	0.0001*
TP53 Arg72Pro r s1042522	Pro/Pro+Arg/Pro	294 (73.50)	308 (77.00)	1 (Reference)	
	Arg/Arg	106 (26.50)	92 (23.00)	1.20 (0.87-1.66)	0.251
TP53 Arg249Ser rs28934571	Ser/Ser+Arg/Ser	84 (21.00)	66 (16.50)	1 (Reference)	
	Arg/Arg	316 (79.00)	334(83.50)	0.74 (0.52-1.06)	0.103

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05

Arg/Arg genotype of *p53* codon 249 increased the BC risk (OR=4.90; 95% CI: 3.49-6.86); p<0.0001) similarly the combined effect of heterozygous Arg/His genotype with homozygous variant His/His genotype of *XRCC1* at codon 280 and heterozygous Arg/Ser and homozygous variant Ser/Ser genotype of of *p53* at codon 249 showed significant association with increased BC risk (OR=5.08; 95% CI: 2.86-9.04); p<0.0001) in the studied population. On the other hand the combination of variant genotypes of *p53* Arg249Ser and *XRCC1* Arg194Trp (p=0.06), Arg399Gln (p=0.197) did not increase the risk of BC. The combined effects of Arg/His and His/His genotypes of

Table 3. Association between Breast Cancer Risk and the Single Nucleotide Polymorphism Variant of *XRCC1, XRCC2, XRCC3* and *TP53* Genes in the Dominant Model

Genes	Genotype	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)	P value
XRCC1 Arg194Trp rs1799782	Trp/Trp	15 (3.75)	12 (3.00)	1 (Reference	
	Arg/Trp + Arg/Arg	385 (96.25)	388 (97.00)	0.79 (0.36-1.71)	0.557
XRCC1 Arg280His rs25489	His/His	241 (60.25)	100 (25.00)	1 (Reference)	
	Arg/His/Arg/Arg	159 (39.75)	300 (75.00)	0.21 (0.16-0.29)	<0.0001*
XRCC1 Arg399Gln rs25487	Gln/Gln	18 (4.50)	8 (2.00)	1 (Reference)	
	Arg/Gln+Arg/Arg	382 (95.50)	392 (98.00)	0.43 (0.18-1.00)	0.052
XRCC2 Arg188His rs3218536	His/His	14 (3.50)	10 (2.50)	1 (Reference)	
	Arg/His + Arg/Arg	386 (96.50)	390 (97.50)	0.70 (0.31-1.61)	0.409
XRCC3 Thr241Met rs861539	Met/Met	34 (8.50)	24 (6.00)	1 (Reference)	
	Thr/Met +Thr/Thr	366 (91.50)	376 (94.00)	0.68(0.39-1.18)	0.174
TP53 Arg72Pro r s1042522	Pro/Pro	80 (20.00)	95(23.75)	1 (Reference)	
	Arg/Pro+ Arg/Arg	320 (80.00)	305 (76.25)	1.24 (0.89-1.74)	0.2
TP53 Arg249Ser rs28934571	Ser/Ser	84 (21.00)	66 (16.50)	1 (Reference)	
	Arg/Ser+Arg/Arg	316 (79.00)	334 (83.50)	0.74 (0.52-1.06)	0.103

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05

Table 4. Distribution and Combined Effects of Genotype Frequencies of *XRCC1, XRCC2, XRCC3* with Codon 72 of *TP53* Gene and Their Association with Relative Risk of Breast Cancer

Gene & Genotype		Breast cancer Group N=400 n (%)	Control Group N=400 n (%)	Crude OR	95% CI	p value
XRCC1	*TP53*					
codon-194	codon-72					
Arg/Arg	Arg/Arg	79 (19.75)	80 (20.00)	1 (Ref)		
Arg/Trp+Trp/Trp	Arg/Arg	27 (6.75)	27 (6.75)	1.01	0.54-1.87	0.968
Arg/Arg	Arg/Pro+Pro/Pro	221 (55.25)	234(58.50)	0.95	0.66-1.37	0.808
Arg/Trp+Trp/Trp	Arg/Pro+Pro/Pro	73 (18.25)	59 (14.75)	1.25	0.78-1.99	0.339
XRCC1	*TP53*					
codon-280	codon-72					
Arg/Arg	Arg/Arg	42 (10.50)	79 (19.75)	1 (Ref)		
Arg/His+His/His	Arg/Arg	65 (16.25)	28 (7.00)	4.35	2.44-7.79	<0.0001
Arg/Arg	Arg/IPro+Pro/Pro	117 (29.25)	220 (55.00)	1	0.64-1.54	0.998
Arg/His+His/His	Arg/Pro+Pro/Pro	17644.00)	73 (18.20)	4.53	2.85-7.20	<0.0001
XRCC1	*TP53*					
codon-399	codon-72					
Arg/Arg	Arg/Arg	71 (17.75)	73 (18.25)	1 (Ref)		
Arg/Gln+Gln/Gln	Arg/Arg	35 (8.75)	34 (8.50)	1.05	0.59-1.87	0.846
Arg/Arg	Arg/IPro+Pro/Pro	194 (48.50)	197 (49.25)	1.01	0.69-1.48	0.949
Arg/Gln+Gln/Gln	Arg/Pro+Pro/Pro	100 (25.00)	96 (24.00)	1.07	0.69-1.64	0.754
XRCC2	*TP53*					
codon-188	codon-72					
Arg/Arg	Arg/Arg	69 (17.25)	75 (18.75)	1 (Ref)		
Arg/His+His/His	Arg/Arg	37 (9.25)	28 (7.00)	1.43	0.79-2.59	0.228
Arg/Arg	Arg/Pro+Pro/Pro	210 (52.50)	237 (59.25)	0.96	0.66-1.40	0.844
Arg/His+His/His	Arg/Pro+Pro/Pro	84 (21.00)	60 (15.00)	1.52	0.95-2.42	0.077
XRCC3	*TP53*					
codon-241	codon-72					
Thr/Thr	Arg/Arg	74 (18.50)	87 (21.75)	1 (Ref)		
Thr/Met+Met/Met	Arg/Arg	32 (8.00)	19 (4.75)	1.98	1.03-3.78	0.038
Thr/Thr	Arg/Pro+Pro/Pro	205 (51.25)	239 (59.75)	1	0.70-1.44	0.963
Thr/Met+Met/Met	Arg/Pro+Pro/Pro	89 (22.25)	55 (13.75)	1.9	1.20-3.00	0.005

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05

XRCC2 Arg241His with Arg/Ser and Ser/Ser genotypes of *p53* Arg249Ser were associated with increase in the risk of BC (OR=2.26; 95% CI: 1.15-4.42); p<0.01) in the studied population. Similarly combinations of variant genotypes of *p53* Arg249Ser and *XRCC3* Thr242Met increased the BC risk by 4.22 fold in the BC patients (OR=4.22; 95% CI: 1.88-9.44); p<0.0005).

Correlation between XRCC1, XRCC2, XRCC3 and Tp53 polymorphisms and clinicopathologic characteristics among breast cancer cases

In continuation with the progressive association of DNA repair genes and tumor suppressor genes with BC risk, we also checked the tumor pathological characteristics and their relation with distribution of SNPs of *XRCC1*, *XRCC2*, *XRCC3* genes and *TP53* gene in BC development (Table 6). We observed a negative association with the heterozygous 280Arg/His genotype and tumor size >2 (OR = 0.61; 95% CI = 0.41-0.93; p = 0.02). Also, when we compared hormone receptor status and their correlation with single nucleotide polymorphisms of DNA repair genes, all other SNPs of *XRCC1*, *XRCC2* showed no association, except *XRCC3* (Thr241Met) showed negative association with

Table 5. Distribution and Combined Effects of Genotype Frequencies of *XRCC1, XRCC2, XRCC3* with Codon 249 of *TP53* Gene and Their Association with Relative Risk of Breast Cancer

Gene & Genotype		Breast cancer Group N=400 n (%)	Control Group N=400 n (%)	Crude OR	95% CI	p value
XRCC1	*TP53*					
codon-194	codon-249					
Arg/Arg	Arg/Arg	238 (59.50)	262 (65.50)	1 (Reference)		
Arg/Trp+Trp/Trp	Arg/Arg	79 (19.75)	75 (18.75)	1.15	0.80-1.66	0.422
Arg/Arg	Arg/Ser+Ser/Ser	62 (15.50)	52 (13.00)	1.31	0.87-1.97	0.191
Arg/Trp+Trp/Trp	Arg/Ser+Ser/Ser	21 (5.25)	11 (2.75)	2.1	0.99-4.45	0.06
XRCC1	*TP53*					
codon-280	codon-249					
Arg/Arg	Arg/Arg	123 (30.75)	253 (63.25)	1 (Reference)		
Arg/His+His/His	Arg/Arg	193 (48.25)	81 (20.25)	4.9	3.49-6.86	<0.0001
Arg/Arg	Arg/Ser+Ser/Ser	37 (9.25)	47 (11.75)	1.61	1.00-2.62	0.05
Arg/His+His/His	Arg/Ser+Ser/Ser	47 (11.75)	19 (4.75)	5.08	2.86-9.04	<0.0001
XRCC1	*TP53*					
codon-399	codon-249					
Arg/Arg	Arg/Arg	214 (53.50)	233 (58.25)	1 (Reference)		
Arg/Gln+Gln/Gln	Arg/Arg	100 (25.00)	101 (25.25)	1.07	0.77-1.50	0.658
Arg/Arg	Arg/Ser+Ser/Ser	53 (13.25)	41 (10.25)	1.4	0.89-2.20	0.134
Arg/Gln+Gln/Gln	Arg/Ser+Ser/Ser	33 (8.25)	25 (6.25)	1.43	0.82-2.49	0.197
XRCC2	*TP53*					
codon-188	codon-249					
Arg/Arg	Arg/Arg	223 (55.75)	262 (65.50)	1 (Reference)		
Arg/His+His/His	Arg/Arg	95 (23.75)	72 (18.00)	1.55	1.08-2.20	0.015
Arg/Arg	Arg/Ser+Ser/Ser	55 (13.75)	52 (13.00)	1.24	0.81-1.88	0.309
Arg/His+His/His	Arg/Ser+Ser/Ser	27 (6.75)	14 (3.50)	2.26	1.15-4.42	0.016
XRCC3	*TP53*					
codon-241	codon-249					
Thr/Thr	Arg/Arg	223 (55.75)	269 (67.25)	1 (Reference)		
Thr/Met+Met/Met	Arg/Arg	93 (23.25)	64 (16.00)	1.75	1.21-2.52	0.002
Thr/Thr	Arg/Ser+Ser/Ser	56 (14.00)	59 (14.75)	1.14	0.76-1.71	0.514
Thr/Met+Met/Met	Arg/Ser+Ser/Ser	28 (7.00)	8 (2.00)	4.22	1.88-9.44	0.0005

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05

progesterone receptor in BC patients (OR= 0.59; 95% CI = 0.38-0.91; p = 0.018). When we analyzed correlation of *p53* genotypes with clinicopathologic characterstics among 400 breast cancer cases, we observed that there were no significant correlations between the *Tp53* codon 72 alleles (Pro or Arg) or codon 249 alleles (Ser or Arg) and patients' clinicopathological parameters (Table 6).

Discussion

Recent advancements in cancer genetics plays a crucial role in cancer management where single nucleotide polymorphisms are considered as potential markers associated with genetic susceptibility towards cancer. Several experimental data on the contribution of SNPs of different genes revealed their importance in process of carcinogenesis. Amongst them, Arg194Trp, Arg280His, Arg399Gln of *XRCC1*; Arg188His of *XRCC2*; Thr241Met of *XRCC3* are more frequently studied SNPs of DNA repair genes and their association with different cancers. Similarly Arg72 Pro and Arg249Ser are the commonly studied SNPs of *TP53* for their protective role or increased association with cancer risk. In this case-control study, we have tried to explore the association of SNPs DNA

Table 6. Associations between *XRCC1, XRCC2, XRCC3* and *TP53* Polymorphisms and Tumor Characteristics in Breast Cancer Patients from Population of Maharashtra

Gene	Genotype	Tumor Size(n= 400)		Lymph node(n= 400)		ER(n=400)		PR (n= 400)		Her2 (n=400)	
		≤2	>2	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
XRCC1	Arg/Arg	116	184	39	261	136	164	148	152	259	41
	Arg/Trp+Trp/Trp	39	61	12	88	46	54	54	46	86	14
	OR (95% CI)	1(Ref)	0.98 (0.61-1.56)	1(Ref)	1.09 (0.54-2.18)	1(Ref)	0.97 (0.61-1.53)	1(Ref)	0.82 (0.52-1.30)	1(Ref)	1.02 (0.53-1.97)
	p value		0.952		0.795		0.907		0.419		0.933
XRCC1	Arg/Arg	55	104	23	136	71	88	79	80	139	20
	Arg/His+His/His	111	130	28	213	111	130	123	118	206	35
	OR (95% CI)	1(Ref)	0.61 (0.41-0.93)	1(Ref)	1.28 (0.71-2.32)	1(Ref)	0.94 (0.63-1.41)	1(Ref)	0.94 (0.63-1.41)	1(Ref)	1.18 (0.65-2.13)
	p value		0.024*		0.404		0.782		0.791		0.58
XRCC1	Arg/Arg	111	154	38	227	118	147	135	130	230	35
	Arg/Gln+Gln/Gln	54	81	13	122	64	71	67	68	115	20
	OR (95% CI)	1(Ref)	1.08 (0.71-1.64)	1(Ref)	1.57(0.80-3.06)	1(Ref)	0.89 (0.58-1.34)	1(Ref)	1.05 (0.69-1.59)	1(Ref)	1.14 (0.63-2.06)
	p value		0.717		0.184		0.584		0.803		0.659
XRCC2	Arg/Arg	122	157	37	242	128	151	144	135	241	38
	Arg/His+His/His	44	77	14	107	54	67	58	63	104	17
	OR (95% CI)	1(Ref)	1.35 (0.87-2.11)	1(Ref)	1.16 (0.60-2.25)	1(Ref)	1.05 (0.68-1.61)	1(Ref)	1.15 (0.75-1.77)	1(Ref)	1.03 (0.55-1.92)
	p value		0.17		0.641		0.817		0.499		0.908
XRCC3	Thr/Thr	108	171	38	241	119	160	130	149	242	37
	Thr/Met+Met/Met	58	63	13	108	63	58	72	49	103	18
	OR (95% CI)	1(Ref)	0.68 (0.44-1.05)	1(Ref)	1.30 (0.67-2.55)	1(Ref)	0.68 (0.44-1.05)	1(Ref)	0.59 (0.38-0.91)	1(Ref)	1.14 (0.62-2.10)
	p value		0.086		0.429		0.083		0.018*		0.666
TP53	Arg/Arg	37	69	14	92	42	64	46	60	87	19
	Arg/IPro+Pro/Pro	127	167	37	257	140	154	156	138	258	36
	OR (95% CI)		0.70 (0.44-1.11)	1(Ref)	1.05 (0.54-2.04)	1(Ref)	0.72 (0.45-1.13)	1(Ref)	0.67 (0.43-1.06)	1(Ref)	0.63 (0.34-1.17)
	p value		0.137		0.869		0.157		0.088		0.147
TP53	Arg/Arg	135	181	43	273	137	179	155	161	277	39
	Arg/Ser+Ser/Ser	30	54	8	76	45	39	47	37	68	16
	OR (95% CI)	1(Ref)	1.34 (0.81-2.21)	1(Ref)	1.49 (0.67-3.31)	1(Ref)	1.39 (0.86-2.23)	1(Ref)	0.75 (0.46-1.22)	1(Ref)	1.67 (0.88-3.16)
	p value		0.247		0.321		0.173		0.261		0.115

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05, ER, estrogen receptor; PR, progesterone receptor, Her2, human epidermal growth factor receptor

repair genes (Arg194Trp, Arg280His, Arg399Gln of *XRCC1*; Arg188His of *XRCC2*; Thr241Met of *XRCC3*) and tumor suppressor *TP53* gene (Arg72Pro, Arg249Ser) and their combined effects towards the risk of BC in females of rural population of Maharashtra from India. We noted significant association of homozygous His/His variant genotype of Arg280His polymorphic locus of *XRCC1* gene and Thr/Met heterozygous genotype of Thr241Met SNP of *XRCC3* in modifying the risk of BC in Maharashtrian women. Also, the combination of Arg280His of *XRCC1* and Thr241Me of *XRCC3* with *p53* codon 72 (Arg72Pro) and codon 249 (Arg249Ser) polymorphism play a signifying role in susceptibility towards BC in the studied population. Earlier, several researchers attended the association studies where the SNPs of *XRCC1*, *XRCC2* and *XRCC3* were reported for their role in BC susceptibility (Wu et al., 2011, Kamali et al., 2017, Dashti et al 2019, Smolarz et al., 2019, Yu and Wang 2023), while some other studies reported contradictory opinion with no association of those SNPs with BC risk (Qureshi et al., 2014, Bin et al., 2015) in other population. *TP53* gene is also highly polymorphic in nature and the Arg72Pro (rs1042522) and Arg249Ser (rs28934571) are commonly studied SNPs for their association with several cancers, however, limited studies demonstrated the polymorphic variants of *TP53* i.e. proline at codon 72 and Serine at codon 249 associated with BC in some populations (Jafrin et al., 2020, Diakite et al., 2020) but others reported conflicting outcomes (Cheng et al., 2012, Hou et al., 2013, Zhao et al., 2022). However, very little information is available in literature on the combined gene to gene interactions of the polymorphisms of *XRCC1*, *XRCC2*, *XRCC3* and tumor suppressor gene *TP53* gene and their interaction with BC susceptibility(Rodrigues et al., 2011, Krivokuca et al., 2016, Isakova et al., 2020). In the present case-control study, the codon72 and codon 249 polymorphic sites in *TP53* were not associated with BC alone, but when *p53* codon 72 was considered in combination with DNA repair genes, the polymorphic *XRCC1* at codon 280 revealed statistically significant association with BC (OR = 4.53; 95% CI = 2.85-7.20; p<0.0001) as a result of gene to gene interaction of the polymorphic loci. Similarly the combination of rs28934571 SNP of *TP53* at codon 249 with rs25489 SNP of *XRCC1* at codon 280 also revealed significant association with risk of BC (OR = 5.08; 95% CI = 2.86-9.04; p<0.0001) in the studied population. The SNP-SNP interaction between *XRCC1* and *TP53* is considered to be influencing when heterozygous genotypes of both genes were present in majority of individuals. Also combination of *XRCC3* Thr241Met with *TP53* Arg249Ser and Arg249Ser SNPs were strongly associated with BC risk. To the best of our knowledge, the combined effects of SNPs of DNA repair genes (*XRCC1*, *XRCC2*, *XRCC3*) and tumor suppressor *TP53* genes have not been reported in BC or any other cancer in Indian scenario. Thus, this analysis of combined effects of SNP-SNP interaction between DNA repair genes and tumor suppressor genes confirmed the importance of genotype combinations in developing the risk of BC in studied population. Strong association of *XRCC1* at codon 280 in combination with *TP53* codon 72 and codon 249 has been signified from our results, but studies with larger sample size are needed to validate this confirmation because of insufficiency of literature related to the SNP-SNP combinations between different pathway genes and their association with cancer in specific populations.

In conclusion, the findings derived from our study noted that the heterozygous variant genotype of *XRCC1* at Arg280His polymorphism in combination with heterozygous arginine/proline genotype of *TP53* at codon 72 has significant association with breast cancer risk in Maharashtrian population. In similar direction, heterozygous Arg249Ser polymorphism of *TP53* and Arg280His of *XRCC1*showed strong association with breast cancer susceptibility in the studied population. Also a combination of heterozygous Thr241Met polymorphism of *XRCC3* along with heterozygous Arg72Pro and Arg249Ser polymorphism of *TP53* exhibited association with breast cancer risk. However, the results obtained from current study are based on limited number of SNPs and samples, which need to be confirmed by large scale studies to determine the interaction between multiple genes and the risk of breast cancer.

Abbreviations

BC: Breast Cancer
BER: base excision repair
NER: nucleotide excision repair
XRCC1: X-ray repair cross-complementing group 1
XRCC2: X-ray repair cross-complementing group 2
XRCC3: X-ray repair cross-complementing group 3
p53: Tumor Supressor *TP53* gene
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
SNP: Single Nucleotide Polymorphism
OR: Odds Ratio
CI: Confidence Interval
µL: Microliter
µg: Microgram
DNA: Deoxyribose Nucleic Acid
EDTA: Ethylene Diamine Tetra Acetate
SDS: Sodium dodecyl sulphate
SD: Standard deviation

Author Contribution Statement

Concept: KDD, RAG, SJB, AKG Design: KDD, SJB, AKG, Experimental Studies: KDD Clinical studies: AKG, RAG Data analysis: KDD, Statistical analysis: KDD, Manuscript preparation: KDD, RAG, SJB, AKG. All authors read and approved the final manuscript..

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The study protocol was approved by protocol committee of Krishna Institute of Medical Sciences (Deemed to be University).

Ethics Committee Approval

The study protocol was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences 'Deemed to be University', Karad.

Declaration of Conflict of interest

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

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