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ORIGINAL PAPER

Contribution of *XPD* (Lys751Gln) and *XRCC1* (Arg399Gln) Polymorphisms in Familial and Sporadic Breast Cancer Predisposition and Survival: An Indian Report

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Abstract The etiology of a significant proportion of familial breast cancers is still poorly understood, with known high penetrance gene mutations accounting for only a small proportion of the cases. The increased risk of breast cancer for the majority of women with a family history likely reflects shared minor low penetrant genetic factors. In the present case-control study undertaken to examine the influence of DNA damage repair gene polymorphisms in familial and sporadic breast cancer susceptibility, 219 Sporadic and 140 familial breast cancer patients and 367 controls were genotyped using PCRRFLP. Odds Ratios (ORs) and 95% Confidence Intervals (95%CIs) were calculated by unconditional logistic regression adjusted to age. Variant genotypes *XRCC1* Arg/Gln or Gln/Gln and *XPD* Lys/Gln or Gln/Gln increased both familial and sporadic breast cancer susceptibility. However, when the intra group risk was compared, the risk due to the *XPD* polymorphic genotypes Lys/Gln or Gln/Gln was significantly lower among familial breast cancer patients compared to sporadic breast cancer patients [OR=0.61; 95%CI= 0.39–0.94; p value=0.024) whereas the risk implied by *XRCC1* variant genotype was not significantly different between the familial and nonfamilial groups of breast cancer patients [OR=0.97; 95%CI=0.63–1.49; p value= 0.882]. Both these variant genotypes were not associated with the disease characteristics or survival of either familial or sporadic breast cancer patients. This study represents an addition to previous published work on GSTs from the same study population and substantiates the hypothesis that the impact of the low penetrance gene polymorphisms differ by family history of the disease.

Keywords Familial breast cancer · Low penetrance genes · Single nucleotide polymorphisms · Survival · XRCC1 · XPD

Abbreviations

BRCA1	breast cancer 1
BRCA2	breast cancer 2
XRCC1	X-ray repair cross-complementing group 1
XPD	xeroderma pigmentosum group D
SNPs	single nucleotide polymorphisms
PCR-RFLP	polymerase chain reaction-restriction fragment length polymorphism
OR	odds ratio
95%CI	95% confidence interval

Introduction

Breast cancer incidence is increasing rapidly in many developing countries including India and in this South Indian population where the work was carried out, it is the leading malignancy among women. Family history of the disease is particularly an important well-established risk factor described to breast cancer. However, inheritance of the known high penetrant *BRCA1* and *BRCA2* gene mutations accounts for only a minority of the overall family risk of breast cancer [1]. The increased risk of breast

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cancer for the majority of women with a family history likely reflects shared minor low penetrant genetic factors and, to a lesser extent, shared environmental factors. In this way, identification of genetic susceptibility factors that account for low to moderate breast cancer risk is an important step in the definition of individual risk to this malignancy.

Mammalian cells have evolved distinct pathways to repair different types of DNA damage (lesions as reactive oxygen species, oxidized bases, bulky DNA adducts and DNA strand breaks) caused by environmental factors such as ionizing radiation and chemical carcinogens and various endogenous and exogenous estrogens. Few earlier studies have demonstrated a strong association of higher levels of DNA damage and deficient DNA repair capacity in breast cancer patients and unaffected first/second degree relatives in breast cancer families [2, 3]. Genetic polymorphisms in DNA repair genes are very common events, and there are contradictory reports on the influence of these polymorphisms in DNA repair capacity and cancer susceptibility [4–6]. Interestingly, studies by Figueiredo et al. [7] (Ontario Breast Cancer Family Registry) and Costa et al. [8] (Portuguese population) reported that *XRCC1* polymorphism might contribute differentially to familial and sporadic breast cancer susceptibility. But reports by Dufloth et al. [9] and Brewster et al. [10] indicated a weak or no role for these polymorphisms as candidate familial breast cancer susceptibility genes. These reports suggest that SNPs of selected DNA repair genes may contribute differently to familial susceptibility to breast cancer in different ethnic population groups. Further population-based case—control studies are needed to evaluate the association between polymorphisms of *XPD* and *XRCC1* and familial breast cancer among other ethnic populations of women.

So, it has been of interest to investigate the influence of single nucleotide polymorphisms (SNPs) of genes involved in DNA damage repair in familial and sporadic breast cancer susceptibility risk in a south Indian population. Of particular interest were polymorphisms $Lys^{751}Gln$ of the xeroderma pigmentosum group D (*XPD*) and $Arg^{399}Gln$ of the X-ray repair cross-complementing group 1 (*XRCC1*) genes, which are involved in the nucleotide excision (NER) and the base excision (BER) DNA repair pathways, respectively. The role of these DNA repair SNPs in disease progression and survival of both familial and sporadic breast cancer patients were also analyzed.

Subjects and Methodology

This case-control study of incident cases of breast cancer was conducted in a South Indian population. The recruited patients comprised of females with histological confirmation of breast cancer attending the out patient clinic of Regional Cancer Centre, Thiruvananthapuram, South India from May 2000 to April 2006. The familial and sporadic breast cancer patients were identified based on a face to face interview followed by detailed pedigree analysis and selection was made based on IARC selection criteria [11]. Around 95% of the patients interviewed were willing to participate in the study. Altogether there were 726 study subjects including 359 breast cancer patients (219 Sporadic and 140 familial) of 20 to 79 years age and 367 controls. Female controls without any history of any type of cancer and without family histories of cancer from the same geographic area were identified from out patient department of a near by hospital. The study protocol was approved by the Institution Review Board and Ethics committees of the institution. Two ml blood was collected from each study subject after obtaining a written informed consent.

The *XPD* codon 751 and *XRCC1* codon 399 genotyping was carried out using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique with appropriate primers (5′-CTGCGATTAAAGGC TGTGGA-3′ and 5′-TCAAACATCCTGTCCCTACT-3′ for *XPD*; and 5′-TTGTGCTTTCTCTGTGTCCA-3′ and 5′-TCCTCCAGCCTTTTCTGATA-3′ for *XRCC1*). The PCR mixture 20 μl, consisting of 20pmol of each primer, 0.2 mM each dNTP and 1X buffer, 1U Taq polymerase and genomic DNA 100 ng was amplified; at 94°C for 5 min for denaturation, followed by 30 cycles of 30 s at 94°C, 30s at 61°C and 45s at 72°C, followed by 7 min at 72°C for final extension. Restriction digestion was carried out using restriction enzymes Pst I (for *XPD* codon 751) and MspI (for *XRCC1* codon 399) according to the manufacturer's (New England Bio Lab, USA) protocol. Genotypes were determined by identifying the characteristic band patterns on agarose gel electrophoresis visualized by ethidium bromide staining. The Pst I restricted products of *XPD* codon 751 Lys allele was identified by the presence of 234 bp fragment, whereas Gln allele was represented by 171 bp and 63 bp fragments and there was an invariant band of 110 bp. For *XRCC1* codon 399, there were two fragments of 221 bp and 374 bp for the Arg allele, and a single 615 bp fragment for the Gln allele. Any sample with ambiguous result (due to low PCR yield) was reanalyzed, and a random selection of 10% of all samples was repeated. No discrepancies were discovered upon replicate testing.

The association of the *XPD* and *XRCC1* SNPs with familial or sporadic breast cancer susceptibility and disease stage was examined by using unconditional logistic regression analyses adjusted to age to calculate the ORs and 95%CIs. Since the number of study subjects was comparatively smaller the individuals with heterozygous and homozygous variant genotypes were put together for

statistical analyses. Survival was calculated for each participant from the date of diagnosis until the date of death or the date of last follow-up contact (for surviving patients). Survival estimates were based on the Kaplan–Meier survival function, and the Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Results

In this study, we used PCR-RFLP to examine the influence of single nucleotide polymorphisms of the DNA damage repair genes, *XRCC1* and *XPD* in familial and sporadic breast cancer susceptibility, disease stage and overall survival. The study subjects comprised of 726 women including 219 sporadic breast cancer patients, 140 familial breast cancer patients and 367 controls. Selected characteristics of patients included in the study are represented in Table 1.

The unconditional logistic regression analysis adjusted for age showed that compared to *XPD* Lys/Lys genotype, *XPD* Lys/Gln or Gln/Gln genotypes were at increased risk for both sporadic (OR=3.58; 95%CI=2.52–5.08) and familial (OR=2.18; 95%CI=1.47–3.24) breast cancer (Table 2). The *XRCC1* polymorphic genotypes also showed a statistically significant association with both familial and sporadic breast cancer susceptibility risk. Here, the Odds Ratios for *Arg/Gln* or *Gln/Gln* genotypes among familial and sporadic breast cancer patients were 1.57 (95%CI= 1.06–2.33) and 1.62 (95%CI=1.16–2.27) respectively (Table 2). The susceptibility risk among both groups of breast cancer patients was compared and it was interesting to note that the risk due to the *XPD* genotypes *Lys/Gln* or *Gln/Gln* was significantly lower for familial patients compared to sporadic breast cancer patients (OR=0.61; 95%CI=0.39–0.94) (Table 3). But unlike *XPD* genotypes, the risk implied by *XRCC1* variant genotypes was not significantly different between familial breast cancer patients and breast cancer patients without a family history (OR=0.97; 95%CI=0.63–1.49).

The details regarding the clinical characteristics like stage, tumour size, nodal status and distant metastasis of the disease were collected from the medical records and the association between the genotypes and clinical characteristics of breast cancer patients was analyzed using unconditional logistic regression analysis. Both *XRCC1* $Arg^{399}Gln$ and *XPD* $Lys^{751}Gln$ polymorphisms didn't show any association with the clinical characteristics of disease among either familial or sporadic breast cancer patients (Table 4).

The breast cancer patients included in the study were followed up for survival analysis for a maximum of 84 months. Both Kaplan–Meier survival analysis and multivariate Cox proportional hazards model analysis showed a worse survival for patients identified in an advanced disease stage (3&4) irrespective of family history (Fig. 1, Table 5). But none of the SNP genotypes included in this study had any significant role in the survival of either familial or sporadic breast cancer cases (Figs. 2, 3) (Table 5).

Discussion

Genes involved in DNA repair and in the maintenance of genomic integrity play a crucial role in providing protection against the mutations that lead to cancer [12, 13]. X-ray repair cross complementing group 1 (XRCC1) protein is thought to act as scaffold protein for both single-strand

Table 1 Distribution of patient characteristics

Characteristics		Familial breast cancer patients number (%)	Sporadic breast cancer patients number (%)
Mean age ± SD		42.51±11.38	49.07±8.51
Tumor size	<5 cm	96 (68.6%)	123 (56.2%)
	>5 cm	44 (31.4%)	96 (43.8%)
Node	Absent	66 (47.1%)	84 (38.4%)
	Present	74 (52.9%)	135 (61.6%)
Metastasis	Absent	129 (92.1%)	193 (88.1%)
	Present	11 (7.9%)	26 (11.9%)
Disease stage	1&2	95 (67.9%)	116 (53.2%)
	3&4	45 (32.1%)	102 (46.8%)
Estrogen receptor	Positive	20 (25.0%)	57 (34.1%)
	Negative	60 (75.0%)	110 (65.9%)
	Missing	60	52
Progesterone receptor	Positive	20 (29.4%)	35 (30.7%)
	Negative	48 (70.6%)	79 (69.3%)
	Missing	72	105

Table 2 Association of *XRCC1* and *XPD* variant genotypes with familial and sporadic breast cancer risk

Genotype		Control N=367 (%)	Familial N=140 (%)	OR (95%CI)	P value	Sporadic N=219 (%)	OR (95%CI)	P value
XPD Lys/Gln	Lys/Lys	247 (67.3%)	68 (48.6%)	1		80 (36.5%)	1	
	Lys/Gln	98 (26.7%)	59 (42.1%)	2.19 (1.44–3.33)	0.001*	102 (46.6%)	3.21 (2.21–4.67)	0.001*
	Gln/Gln	22 (6.0%)	13 (9.3%)	2.15 (1.03–4.48)	0.042*	37 (16.9%)	5.19 (2.89–9.32)	0.001*
	Lys/Gln or Gln/Gln	120 (32.7%)	72 (51.4%)	2.18 (1.47–3.24)	0.001*	139 (63.5%)	3.58 (2.52–5.08)	0.001*
XRCC1 Arg/Gln	Arg/Arg	193 (52.6%)	58 (41.4%)	1		89 (40.6%)	1	
	Arg/Gln	126 (34.3%)	60 (42.9%)	1.59 (1.04–2.42)	0.034*	94 (42.9%)	1.62 (1.12–2.33)	0.010*
	Gln/Gln	48 (13.1%)	22 (15.7%)	1.53 (0.85–2.73)	0.156	36 (16.4%)	1.63 (0.99–2.68)	0.056
	Arg/Gln or Gln/Gln	174 (47.4%)	82 (58.6%)	1.57 (1.06–2.33)	0.025*	130 (59.4%)	1.62 (1.16–2.27)	0.005*

*p value<0.05

break repair and base excision repair (BER) activities [14]. It has been shown that XRCC1 interacts with DNA Polb, DNA LigIII and APE1, through a BRCA C-terminal domain (BRCT-1) [14]. One common *XRCC1* polymorphism, $Arg^{399}Gln$, located in exon 10, and which lies within the BRCT-1 domain [15], have been linked with a variety of cancers [16]. Another important DNA repair gene is xeroderma pigmentosum group D (XPD) protein representing a subunit of the TFIIH complex which has important roles in transcription and nucleotide excision repair (NER) pathways. XPD participates in the local unwinding of DNA helix to allow RNA transcription machinery to access the promoter and to permit the NER machinery to access the lesion [17]. One common *XPD* polymorphism, $Lys^{751}Gln$, located in exon 23, in the important domain of interaction between XPD protein and its helicase activator, inside the TFIIH complex [18] has been associated with a differential DNA repair capacity [19–21].

Despite evidence of functional significance of selected SNPs of the *XPD* [22, 23] and *XRCC1* DNA repair genes [4, 24–27,], data from hospital and population-based case—control studies have shown inconsistent findings on association between the *XPD* Lys751Gln and *XRCC1* Arg399Gln polymorphisms and risk of sporadic breast cancer [7, 28–32]. While most of the previous studies found no significant role for *XRCC1* $Arg^{399}Gln$ polymorphic variants in breast carcinogenesis [7, 30, 31, 33–40], there are reports showing positive associations also. One previous report from south Indian population [41], showed an increased risk for sporadic breast cancer risk for individuals with ^{399}Gln allele of the *XRCC1* gene (OR=2.14; 95% CI= 1.29–3.58). The present study included both sporadic and familial breast cancer patients and the *XRCC1* variant genotype was found to be significantly associated with both groups of breast cancer patients in this south Indian population. Our result on the role of *XRCC1* codon 399 polymorphism in sporadic breast cancer risk (OR=1.62; 95%CI=1.16–2.27) substantiates the previous study [41] result. But a North Indian report by Patel et al. [42] is contradictory to these South Indian reports and did not show any association between the at risk genotype *XRCC1* codon 399 *Arg/Gln* or *Gln/Gln* with breast cancer (OR= 0.98; 95%CI=0.75–1.28). A study by Duell et al. [28] found a correlation between XRCC1 codon 399 polymorphism and breast cancer susceptibility in African-American women (OR 1.7), but not in Caucasian women. So also, Kim et al. [29] observed a significant association between *XRCC1 399Arg* homozygosity and breast cancer suscepti-

Table 3 ORs for *XRCC1* and *XPD* variant genotypes in familial breast cancer compared to sporadic breast cancer

Genotype		Sporadic *N*=219 (%)	Familial *N*=140 (%)	OR (95%CI)	P value
XPD Lys/Gln	Lys/Lys	80 (36.5%)	68 (48.6%)	1	
	Lys/Gln	102 (46.6%)	59 (42.1%)	0.68 (0.43–1.07)	0.098
	Gln/Gln	37 (16.9%)	13 (9.3%)	0.41 (0.20–0.84)	0.015*
	Lys/Gln or Gln/Gln	139 (63.5%)	72 (51.4%)	0.61 (0.40–0.94)	0.024*
XRCC1 Arg/Gln	Arg/Arg	89 (40.6%)	58 (41.4%)	1	
	Arg/Gln	94 (42.9%)	60 (42.9%)	0.98 (0.62–1.56)	0.930
	Gln/Gln	36 (16.4%)	22 (15.7%)	0.94 (0.50–1.75)	0.840
	Arg/Gln or Gln/Gln	130 (59.4%)	82 (58.6%)	0.97 (0.63–1.49)	0.882

*p value<0.05

Table 4 Association of *XRCC1* and *XPD* variant genotypes with clinical characteristics of familial and sporadic breast cancer patients

		XRCC1				*XPD*			
		Arg/Arg	Arg/Gln or Gln/Gln	OR (95%CI)	P value	Lys/Lys	Lys/Gln or Gln/Gln	OR (95%CI)	P value
Familial breast cancer cases	Stage								
	1&2	39 (67.2%)	56 (68.3%)	1		48 (70.6%)	47 (65.3%)	1	
	3&4	19 (32.8%)	26 (31.7%)	0.95 (0.46–1.96)	0.896	20 (29.4%)	25 (34.7%)	1.28 (0.63–2.60)	0.502
	Tumor								
	<5 cm	38 (65.5%)	58 (70.7%)	1		47 (69.1%)	49 (68.1%)	1	
	>5 cm	20 (34.5%)	24 (29.3%)	0.79 (0.38–1.62)	0.513	21 (30.9%)	23 (31.9%)	1.05 (0.51–2.15)	0.892
	Node								
	Negative	25 (43.1%)	41 (50.0%)	1		34 (50.0%)	32 (44.4%)	1	
	Positive	33 (56.9%)	41 (50.0%)	0.76 (0.38–1.49)	0.421	34 (50.0%)	40 (55.6%)	1.25 (0.64–2.43)	0.511
	Metastasis								
	Absent	53 (91.4%)	76 (92.7%)	1		62 (91.2%)	67 (93.1%)	1	
	Present	5 (8.6%)	6 (7.3%)	0.84 (0.24–2.88)	0.778	6 (8.8%)	5 (6.9%)	0.77 (0.22–2.65)	0.680
Sporadic breast cancer cases	Stage								
	1&2	46 (51.7%)	70 (54.3%)	1		36 (45.0%)	80 (58.0%)	1	
	3&4	43 (48.3%)	59 (45.7%)	0.90 (0.53–1.55)	0.708	44 (55.0%)	58 (42.0%)	0.59 (0.34–1.03)	0.065
	Tumor								
	<5 cm	47 (52.8%)	76 (58.5%)	1		42 (52.5%)	81 (58.3%)	1	
	>5 cm	42 (47.2%)	54 (41.5%)	0.79 (0.46–1.37)	0.408	38 (47.5%)	58 (41.7%)	0.79 (0.45–1.37)	0.407
	Node								
	Negative	36 (40. 4%)	48 (36.9%)	1		30 (37.5%)	54 (38.8%)	1	
	Positive	53 (59.6%)	82 (63.1%)	1.16 (0.67–2.02)	0.598	50 (62.5%)	85 (61.2%)	0.94 (0.54–1.66)	0.843
	Metastasis								
	Absent	76 (85.4%)	117 (90.0%)	1		70 (87.5%)	123 (88.5%)	1	
	Present	13 (14.6%)	13 (10.0%)	0.65 (0.29–1.48)	0.303	10 (12.5%)	16 (11.5%)	0.91 (0.39–2.11)	0.828

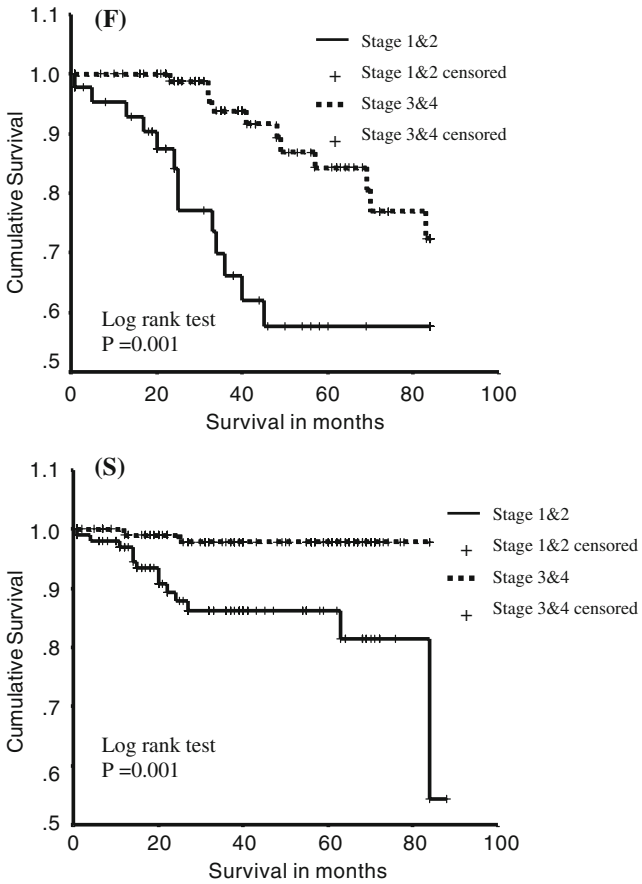

Fig. 1 Association between disease stage and survival of familial (*F*) and sporadic (*S*) breast cancer patients

bility (OR=2.4; 95%CI=1.44–10.30) among Korean women.

In general, *XPD* $Lys^{751}Gln$ (A35931C) has not been associated with breast cancer risk [8, 32, 37, 43–45]. But, Terry et al. [46] found a significant association between the polymorphism and breast cancer (OR=1.21; 95%CI=1.01–1.44). To the best of our knowledge, there are no previous reports available regarding the association between *XPD* codon 751 polymorphism and breast cancer from India, ours being the first. In our study, a significant role for this polymorphism was observed in both sporadic (OR=3.58; 95%CI=2.52–5.08) and familial (OR=2.18; 95%CI=1.47–3.24) breast cancer predisposition. Our reports on strong association of *XPD* variant genotype with both familial and sporadic breast cancer patients are contradictory to the few available reports by Dufloth et al. [9], Brewster et al. [10] and Costa et al. [8], among Brazilian, USA, and Portuguese groups of patients respectively, indicating a weak or no role for these polymorphisms as breast cancer susceptibility genes in breast cancer cases with and without a family history. However sample sizes of women with breast cancer, whether familial or sporadic, considered in those studies might have been insufficient to show any small true differences between the groups.

When the susceptibility risk in both groups of breast cancer patients was compared, it was interesting to note that the risk due to the *XPD* genotypes *Lys/Gln* or *Gln/Gln* was significantly lower for familial patients compared to sporadic breast cancer patients in the present study. [OR=

Table 5 Association of *XRCC1* and *XPD* variant genotypes with survival of familial and sporadic breast cancer patients

	Genotype	No. of cases	Events (%)	Mean survival (Months)	Cox proportional hazards model	
					H.R. (95%CI)	P value
Familial breast cancer cases	Stage					
	1&2	95	11 (11.58%)	76	1	
	3&4	45	13 (28.89%)	60	3.73 (1.63–8.52)	0.002*
	XRCC1					
	Arg/Arg	58	11 (18.97%)	70	1	
	Arg/Gln or Gln/Gln	82	13 (15.85%)	72	0.91 (0.40–2.06)	0.820
	XPD					
	Lys/Lys	68	13 (19.12%)	67	1	
	Lys/Gln or Gln/Gln	72	11 (15.28%)	75	0.48 (0.21–1.09)	0.081
Sporadic breast cancer cases	Stage					
	1&2	116	2 (1.72%)	83	1	
	3&4	102	13 (12.75%)	76	9.15 (2.04–41.02)	0.004*
	XRCC1					
	Arg/Arg	89	9 (10.11%)	78	1	
	Arg/Gln or Gln/Gln	130	6 (4.62%)	81	0.39 (0.14–1.13)	0.083
	XPD					
	Lys/Lys	80	4 (5.48%)	73	1	
	Lys/Gln or Gln/Gln	139	11 (7.91%)	81	2.15 (0.67–6.94)	0.199

*p value<0.05

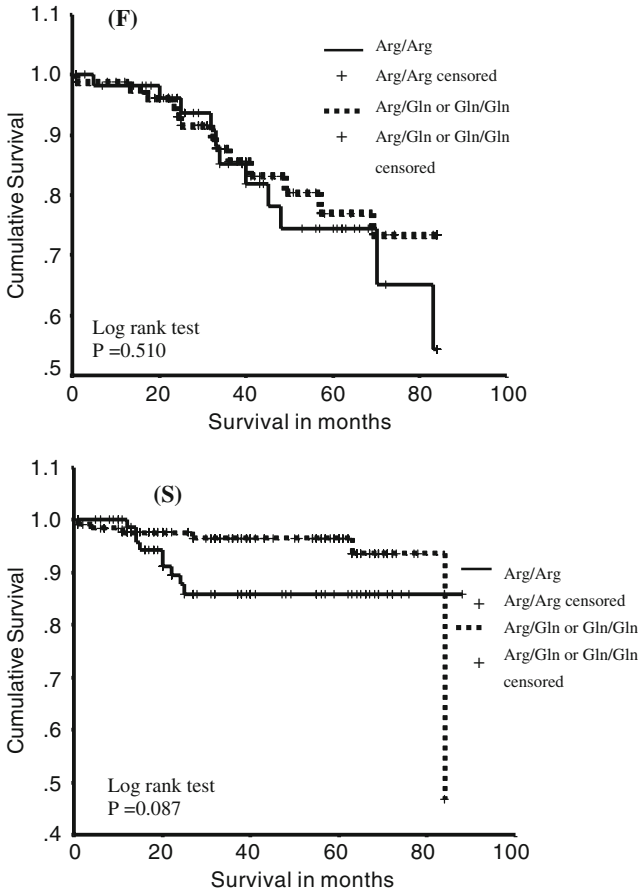

Fig. 2 Association of *XRCC1 Arg*^{399}*Gln* polymorphism with survival of familial (*F*) and sporadic (*S*) breast cancer patients

0.61; 95%CI=0.39–0.94; *p* value=0.024). But unlike *XPD* genotypes, the risk implied by *XRCC1* variant genotypes was not significantly different between familial breast cancer patients and breast cancer patients without a family history (OR=0.97; 95%CI=0.63–1.49; *p* value=0.882) in our study. This is comparable to the studies by Dufloth et al. [9] and Brewster et al. [10]. But, Figueiredo et al. [7] in a study among patients of Ontario Site of the Breast Cancer Family Registry reported that, compared to individuals without a family history of disease having Arg399Arg genotype, individuals with a family history having *Arg*^{399}*Arg* and *Arg*^{399}*Gln* genotypes have 2.92 (95% CI=1.47–5.79) and 3.85 (95%CI=1.94–762) fold risks respectively. Costa et al. [8] also suggested that *XRCC1* polymorphism might contribute differently to familial (OR=1.02; 95%CI=0.61–1.71) and sporadic (OR=0.54; 95%CI=0.35–0.84) breast cancer susceptibility in Portuguese population. Studies by Duell et al. [28] Kuschel et al. [47] and Figueiredo et al. [7] suggested that the impact of low penetrant polymorphic alleles like *XRCC1-Arg*^{399}*Gln* polymorphism differs by family history of the disease. A previous report by our own group on the role of GSTs in familial and sporadic breast cancer predisposition [48] and the present report on the role of *XPD* and *XRCC1* variant genotypes in familial and non familial breast cancer patients also suggest that low penetrant gene polymorphisms contribute differently to familial and sporadic breast cancer susceptibility in our population.

On looking at the association of *XRCC1* and *XPD* variant genotypes with the various clinical characteristics (like stage, tumour size, node status, distant metastasis etc.) of the sporadic and familial breast cancer patients, neither any significant association with any of the groups nor any difference between the two groups of patients emerged (Table 4). When survival of these groups of patients was considered, our study patients identified at stages 3&4 had a worse survival compared to patients identified in stages 1&2 which is a well documented factor. However, when the associations of the variant genotypes with the overall survival of both groups of breast cancer patients were

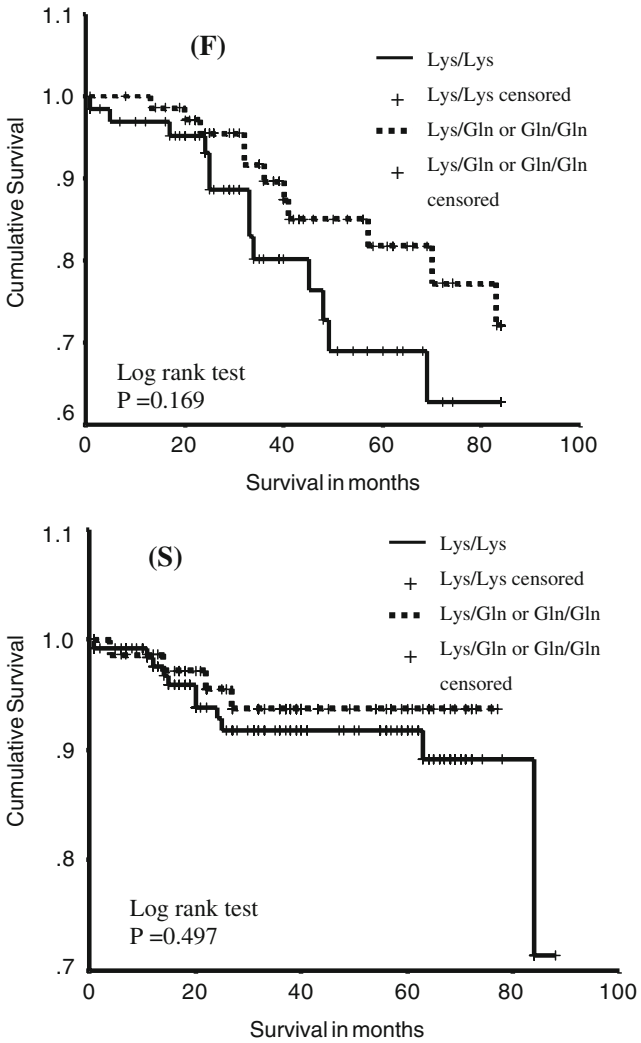

Fig. 3 Association of *XPD Lys*^{751}*Gln* polymorphism with survival of familial (*F*) and sporadic (*S*) breast cancer patients

considered, both the polymorphisms studied were associated with the overall survival of neither familial nor sporadic breast cancer patients.

A possible interpretation for the difference in the degree of association in the subgroup with family history may be that family history, particularly among first-degree relatives, broadly represents shared genes and environmental factors, and the presence of a single polymorphism with likely weak effects on the individual's phenotype may not be measurable except in the context of these supporting factors. Among individuals without a familial predisposition, the effect may be hidden by sum effects of other unidentified genetic and environmental factors and studying families with a history of cancer increases the efficacy of identifying candidate-susceptibility genes. It is intuitive that relationship between these polymorphisms and breast cancer might be complicated by the potential biologically plausible interactions with other genetic and environmental factors as these low penetrance genes are unlikely to be independent of such factors. So, design of other studies among different ethnic populations with a larger sample size for relevant subgroups that could better evaluate such gene-gene and gene-environment interactions is necessary.

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