



GENETIC POLYMORPHISMS OF DNA REPAIR GENES (XPC, XPG) AND BREAST CANCER SUSCEPTIBILITY IN MAHARASHTRIAN POPULATION: A HOSPITAL BASED CASE-CONTROL STUDY

***Datkhile KD^{1.}, Bhosale SJ^{2.}, Patil MN^{1.}, Durgawale PP¹ and Kakade SV³**

¹Molecular & Genetic Laboratory,

²Department of Surgery,

³Department of Preventive and Social Medicine Krishna Institute of Medical Sciences University, Taluka-Karad, Dist-Satara, Pin-415 110, Maharashtra, India

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ABSTRACT

Breast cancer is a major concern of women health in developing countries, including India. In this study, we aimed to find out polymorphisms in DNA repair genes, Xeroderma pigmentosum complementation group C (XPC) and XPG in patients of breast cancer from Maharashtra and to evaluate their association with breast cancer development. We conducted a case control study including 170 breast cancer cases and 200 hospital based age and sex matched healthy controls to estimate the role of genetic polymorphisms of XPC at codon 939 of the exon 15 and XPG at codon 1104 of exon 15 in the context of breast cancer risk for the Maharashtrian population. We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to analyze gene polymorphisms. We did not find significant difference in the genotype distribution between breast cancer patients and controls for each polymorphisms studied. Thus, the case-control study suggests that the functional XPC or XPG polymorphisms could not play an important role in the development of breast cancer in a rural Maharashtrian population.

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INTRODUCTION

Breast cancer (BC) is the second most common cancer in women worldwide. India has 1/6th of the world's population suffering from BC as the leading cause of cancer deaths among women in rural areas [1]. The development of breast cancer is a complex process and depends of multiple factors, including age, personal development, exposure to microbes, dietary exposures, medical interventions, family history of cancer, exposure to heterocyclic compounds and environmental pollutants and morphographic breast density [2-3]. Etiological factors for a country like India with very big population, diverse cultures and geographical variations probable risk factors are literacy, diet, menstrual and reproductive history, use of contraceptives and early age of first delivery[4-5]. Although many epidemiological risk factors have been identified, the cause of breast cancer is most often unknowable. It is assumed that along with the environmental factors, combination of individual lifestyle habits and genetic factors may add to breast carcinogenesis. The genetic factors are also considered of great importance to

cancer risk. There are more than 130 genes involving in the DNA repair pathways. Four common DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and double-strand break repair (DSBR) pathways take active part in DNA repair. Among them, NER is a critically important pathway which plays an important role in removing DNA lesions caused by UV radiation or chemical agents [6]. Xeroderma pigmentosum complementation group C (XPC) and Xeroderma pigmentosum complementation group G (XPG) are the components of the NER pathway. In humans, XPC is one of the seven XP complementation groups (XPA to XPG) functions as an early damage detector and plays an important role of molecular matchmaker in the early steps of global genomic NER [7]. Also, XPG have been identified to function as an endonuclease that can cleave the damaged DNA at the multiple sites of the lesion during the DNA repair process [8]. Hundreds of polymorphisms in DNA repair genes associated with cancer risk have been identified. Some of them have been frequently studied and there is a growing body of evidence that polymorphisms of these genes may have some significance in cancer development. Previous studies have revealed that XPC and XPG gene polymorphisms are associated with development of several malignancies

***Corresponding author: Datkhile KD**
Molecular & Genetic Laboratory,

including cancer of digestive system, head and neck, colorectal, prostate, larynx and bladder [9-14] but in some of the studies there is uncertainty in results [15-16]. In particular, there are a few studies reporting on the association between XPC and XPG gene polymorphisms and the development of breast cancer, but the results are unconvincing [15, 17-19]. Therefore, the influence of the polymorphisms of XPC and XPG genes on DNA repair capacity is still unclear. In earlier studies we have shown that polymorphisms in BER pathway genes especially XRCC1, XRCC5, XRCC7 genes could play role in susceptibility of BC in rural population of south-western Maharashtra [20-21]. In continuation with this, we also hypothesized that the inherited polymorphisms in XPC and XPG genes may contribute to genetic susceptibility to BC. To test this hypothesis we focused on identifying genetic polymorphisms of XPC and XPG genes to evaluate their role in BC if any. In this study, we conducted a case-control study to investigate the role of XPC and XPG gene polymorphisms in the development of breast cancer in a rural population of western Maharashtra from India. We determined the genotypic frequency of polymorphisms of the (A) XPC A2920C at codon939 of the exon 15 and (B) XPG at codon 1104 of exon 15 using the restriction enzymes PvuII and NlaIII respectively.

MATERIALS AND METHODS

Study subjects

Hospital based, case-control study conducted in rural areas of western Maharashtra from India. Study participants included newly breast cancer diagnosed 170 patients and 200 healthy, cancer free, age matched women were selected as controls living in the same residential areas as the cases. All cases ranged in age from 24 -77 years (Mean \pm SD) 50.50 ± 12.00 were recruited immediately after being diagnosed. Trained interviewers used a structured questionnaire to collect personal data from the participants regarding demographic factors.

Genomic DNA isolation from whole blood

Genomic DNA was extracted from the peripheral blood sample using Purelink genomic DNA extraction and purification Kit (Invitrogen, Life technologies) following the manufacturer's instructions.

Genotyping assays

Genotyping experiments were performed by PCR-RFLP methods with appropriate primer sets (Table 1). The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: (A) XPC A2920C at codon 939 of the exon 15 and (B) XPG at codon 1104 of exon 15. The PCR amplification were carried out separately under different conditions in 20 micro liter (μ L) reaction mixtures containing

1X PCR buffer (10 mili molar (mM) Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl₂, 0.01% gelatin), 0.2 mM each dNTP, 10 picomole (pmol) of each primer listed in Table-1, 1U *Taq DNA* polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA template. The reaction mixtures were subjected to PCR amplification with a Master Cycler Gradient PCR (Eppendorf). After performing PCR programme for each of the reactions, the PCR products were analyzed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer. The agarose gels were stained with ethidium bromide (10 mg/mL) and visualized under UV Transilluminator and photographed in gel documentation system (BioRad Laboratories). After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme as shown in table-1 for genotyping. Ten micro liters (μ L) of the PCR products were digested at 37°C overnight with specific restriction enzymes in 20 μ L reaction mixtures containing buffer supplied with each restriction enzyme. After the overnight incubation, digestion products were then separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with gel documentation system.

Statistical analysis

The associations between the *XPC* and *XPG* genotypes and risk of BC were studied using odds ratio (OR). Both the univariate and multivariate logistic regression analyses were employed to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to determine the cancer risk associated with genotypes. All statistical analyses were performed using SPSS 11.5 for windows software.

RESULTS

Characteristics of the study subjects

During the study period, 170 patients with BC met the eligibility criteria for this study and 200 controls were selected to match these cases. The characteristics of age and sex matched cases and controls are presented in Table 2. The (Mean \pm SD) age in years was 50.50 ± 12.00 for the cases and 40.60 ± 13.7 ($P < 0.01$) for the controls, however there was no significant difference in mean age between cases and controls.

Association of polymorphisms in XPC and XPG gene and Breast cancer

We performed a study showing distribution of XPC & XPG genotypes and concordance of the polymorphisms in patients with BC and controls is presented in Table-3.

Table 1 Details of PCR and RFLP procedures and expected products of XPC and XPG genes.

Gene	Primers Forward/Reverse	PCR conditions	PCR Product	Restriction enzyme	Restriction products
<i>XPC</i> <i>A2920C</i>	5'-gga ggt gga ctc tct tct gat g-3'	95°C- 5 min, 35 cycles of 95°C- 30 sec, 52°C-	765 bp	1Uof PvuII	A/A: 765 bp A/C: 765bp, 585bp, 180 bp C/C: 585bp, 180 bp
<i>Lys939Gln</i> <i>codon 939 Ex-15</i>	5'tag atc cca gca gat gac c- 3'	45 sec, 72°C- 30 sec, 72°C- 5 min			
<i>XPG C3507G</i> <i>His1104 Asp</i>	5'-gac ctg cct ctc aga atc atc -3'	95°C- 5 min, 35 cycles of 95°C- 30 sec, 55°C-	271 bp	1Uof NlaIII	G/G: 271bp G/C: 271bp, 227bp, 44bp C/C:227bp,44bp
<i>codon1104 Ex-15</i>	5'- cct cgc acg tct tag ttt cc-3'	45 sec, 72°C- 30 sec, 72°C- 5 min			

Table 2 Distribution comparisons of selected demographic characteristics of breast cancer cases and healthy controls from rural areas of Maharashtra in India

Variable	Cases N=170		Controls N=200		P-Value based on χ^2
Age (Mean \pm SD) years	50.04 \pm 12.06		46.60 \pm 13.73		<0.05
	No.	(%)	No.	(%)	
≤ 50	95	55.88	149	74.50	
51-60	38	22.35	32	16.00	
61-70	28	16.47	15	7.50	
>70	9	5.30	4	2.00	
Tobacco smoking Status					<0.05
Tobacco users	94	55.30	82	41.00	
Tobacco no users	76	44.70	118	59.00	
Mastectomy status					<0.001
Left MRM	97	57.06	0	0.00	
Right MRM	73	42.94	0	0.00	
Age @ 1 st delivery (yrs)					<0.0001
15-20	126	74.12	75	37.50	
21-25	37	21.76	111	55.50	
26-30	6	3.53	11	5.50	
31-35	1	0.59	3	1.50	
Hormone Status					0.00
ER/PR+ve	102	60.00	0	0.00	
ER/PR-ve	68	40.00	0	0.00	
Her2 +ve	24	14.12	0	0.00	
Her2 -ve	146	85.88	0	0.00	
ER/PR/Her2+ve	7	0.07	0	0.00	
ER/PR/Her2-ve	46	27.06	0	0.00	
Diet					0.01
Vegetarian	40	23.53	64	32.00	
Mixed	130	76.47	136	68.00	
Education					<0.001
High School	71	41.76	75	37.50	
HighSchoolgraduate (12 y)	8	4.71	26	13.00	
College /Graduate	12	7.06	25	12.50	
No School	79	46.47	74	37.00	
Economic status					<0.05
Middle	42	24.71	52	26.00	
Poor	104	61.18	103	51.50	
Rich	24	14.11	45	22.50	
Family history of Cancer					0.1
Yes	42	24.71	0	0.00	
No	128	75.29	0	0.00	

products upon treatment with PvuII yielded wild-type (A2920) allele of 765bp fragments and the polymorphic (C2920) allele produces 2 fragments of 585 and 180 bp. The frequency of XPC 2920AA homozygotes was 53.13% in cases and 55.00 % in controls whereas the frequency of 2920CC allele was lower but not significant in the cases (8.75 %) than in the controls (8.50%). The frequency of XPC2920AC heterozygotes was 38.12 % in cases and 36.50 % in controls (Table-3). Thus, the A→C polymorphisms in exon 15 at nucleotide does not result in an amino acid change at codon 939 in cases as compared to controls. The average frequency of allele does not show variation which is in agreement with previous reports.

Analysis of the XPG Asp1104His rs17655of exon 15

The C→G distribution in codon 1104 of the exon15 results in His →Asp substitution. The frequency of XPG 3507 CC wild type homozygotes was 63.75 % in cases and 51.50 % in controls whereas XPG3507 GG variant homozygotes was 2.50 % in cases and 5.50 % in controls. The frequency of XPG3507CG heterozygotes was 33.75% in cases and 43.00% in controls (Table-3). The frequency of the XPG 3507G allele was not significantly higher in the cases (2.50%) than in the controls (5.50%) which is at the lower end of the previously reported allele frequencies. We did not find any significant difference in genotype or allele frequencies in patients with cancer and controls.

Association of age at 1st delivery and hormone receptor status with breast cancer risk

In Maharashtrian patients, the median age of onset of breast cancer is 50 years, substantially lower than observed in other reports. To evaluate the association of the polymorphisms with the young age at diagnosis of BC, we stratified the patients as ≤50 (n=95) or >50 (n=75) years of age and compared with age matched sample of controls which did not show risk of BC at the age bellow median. Also, the association of BC with age at first delivery was considered in this study which showed that early age of first delivery i.e.15-

Table 3 The genotype frequencies of XPC & XPG gene variants in untreated breast cancer patients and controls

GENE	Genotype	CASES (n= 170) (%)	CONTROL (n = 200) (%)	Odds' Ratio (OR) (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
XPC	Lys/Lys	74 (43.50)	85 (42.50)	1		1	
A2920C	Lys/Gln	81 (47.60)	100 (50.00)	0.93 (0.60-1.42)	0.74	1.11 (0.67-1.83)	0.66
Lys939Gln	Gln/Gln	15 (8.80)	15 (7.50)	1.14 (0.52-2.50)	0.72	1.21 (0.49-2.97)	0.67
codon 939	Lys/Gln+	96 (64.00)	115 (57.50)	0.95 (0.63-1.44)	0.84	1.13 (0.71-1.80)	0.60
Ex-15	Gln/Gln						
XPG	His/His	111 (65.30)	117 (58.50)	1		1	
His1104 Asp	His/Asp	51 (30.00)	73 (36.50)	0.73 (0.47-1.14)	0.17	1.29 (0.77-2.16)	0.32
C3507G	Asp/Asp	8 (4.70)	10 (5.00)	0.84 (0.32-2.21)	0.72	1.46 (0.48-4.40)	0.49
codon1104							
Ex-15	His/Asp+ Asp/Asp	59 (39.30)	83 (41.50)	0.74 (0.49-1.14)	0.18	1.32 (0.82-2.13)	0.24

We have analyzed the distribution and association between the previously described polymorphisms of cd939 of exon 15 in XPC and cd1104 of exon 15 in XPG gene of rural Maharashtrian population

Analysis of the XPC A2920C Lys 939 Gln of exon 15

The amplification of XPC codon 939 resulted in the product of 765 bp. The PvuII enzyme was used to detect the XPCA2920C at codon 939 of exon 15. The PCR amplified

significantly associated with increased BC risk. The genotype distributions for the individual polymorphisms along with the statistical analysis are shown in table-4. When we conducted the association of BC risk with the hormone receptor (ER/PR) status of the tumors we found that (ER/PR +ve (n= 102) and ER/PR-ve (n= 68) (table-5), showed higher risk of BC.

Table 4 Genotype Frequencies of XPC and XPG gene Polymorphism in Breast Cancer Cases with ER/PR status

Gene	Genotype	ER/PR +ve N=102	ER/PR -ve N=68	OR	95% CI	χ^2	P-value
<i>XPC</i>	Lys/Lys	46 (0.45)	22 (0.32)	1			
<i>A2920C</i>	Lys/Gln	42 (0.41)	26 (0.38)	0.77	0.38-1.56	0.71	0.47
<i>Lys939Gln</i>	Gln/Gln	14 (0.14)	20 (0.30)	0.33	0.14-0.78	2.52	0.01
<i>codon 939</i>	Lys/Gln+						
<i>Ex-15</i>	Gln/Gln	56 (0.55)	46 (0.68)	0.58	0.30-1.10	1.65	0.09
<i>XPG</i>	His/His	65 (0.64)	44 (0.65)	1			
<i>C3507G</i>	His/Asp	33 (0.32)	16 (0.23)	1.39	0.68-2.83	0.92	0.35
<i>His1104 Asp</i>	Asp/Asp	4 (0.04)	8 (0.12)	0.33	0.09-1.19	1.68	0.09
<i>codon1104</i>	His/Asp+						
<i>Ex-15</i>	Asp/Asp	37 (0.36)	24 (0.35)	1.04	0.55-1.98	0.13	0.89

Table 5 Stratification analysis of the demographic factors including age, tobacco smoking and age at first delivery and distribution of genotypes with odds ratio of the XPC and XPG genes in the patients with breast cancer and the control group from rural population of western Maharashtra.

Gene	Genotype	Demographic Factors							
		Age (Cases/Control)		Tobacco status (Cases/Control)		Age @ 1 st Delivery (Cases/Control)			
		≤ 50 N=95/149	> 50 N=75/51	Tobacco Users N=94/82	Tobacco nonusers N=76/118	15-20 N= 126/74	21-25 N= 37/114	26-30 N= 6/9	31-35 N= 1/3
<i>XPC</i>	Lys/Lys	43/65	28/20	43/28	30/57	55/27	15/50	4/5	1/2
<i>A2920C</i>	Lys/Gln+	52/84	47/31	51/54	46/61	71/47	22/64	2/4	0/1
<i>Lys939Gln</i>	Gln/Gln								
<i>codon 939</i>	OR(95% CI)	0.93 (0.55-1.57)	1.08 (0.52-2.25)	0.61 (0.33-1.13)	1.43 (0.79-2.57)	0.74 (0.41-1.33)	1.14 (0.53-2.43)	0.62 (0.07-5.34)	0.55 (0.012-24.51)
<i>Ex-15</i>	P value	0.80	0.83	0.11	0.22	0.32	0.72	0.66	0.76
<i>XPG</i>	His/His	61/87	47/30	63/46	47/70	82/42	23/67	5/4	0/2
<i>C3507G</i>	His/Asp+	34/62	28/31	31/36	29/48	44/32	14/47	1/5	1/1
<i>Asp/Asp</i>									
<i>His1104 Asp</i>	OR(95% CI)	0.78 (0.45-1.33)	0.85 (0.41-1.76)	0.62 (0.34-1.16)	0.89 (0.49-1.62)	0.70 (0.39-1.26)	0.86 (0.40-1.85)	0.16 (0.01-1.98)	2.00 (0.05-78-25)
<i>codon1104</i>	P value	0.36	0.66	0.13	0.72	0.24	0.71	0.15	0.71
<i>Ex-15</i>									

*: Indicates significant Odds Ratio (p<0.05)
p value determined based on χ^2

DISCUSSION

In the present study, we conducted a case-control study to investigate the association between polymorphisms in the XPC, XPG genes and the development of BC in a Maharashtrian population, and we found no contribution of either XPC or XPG in relation to the development of breast cancer. Most of the reports indicate that *XPC* polymorphisms modulate the risk for lung, head and neck, breast and bladder cancer. We didn't observe the association of *XPC* Lys939Gln as well as *XPG* Asp1104His with increased BC risk. Although some studies showed the *XPC* Lys939Gln polymorphism significantly elevated the human bladder cancer risk, a recent pooled data meta-analysis indicated that the *XPC* Lys939Gln polymorphism was not related to cancer risk [22]. A meta-analysis of studies by Zhang *et al* [23] showed *XPC* Lys939Gln allele C associated with lung, breast, bladder, colorectal, esophageal, and other cancer risks. Previous studies also have reported that *XPG* gene polymorphisms are associated with several kinds of cancer in different ethnicities, such as HNC, gastric, bladder, colon and prostate cancer. Ma *et al.* [24] reported that *XPG* gene polymorphisms affect the risk of HNC in an American population. He *et al.* [25] reported that genetic variants of *XPG* contribute to the risk of gastric cancer. Zhang *et al.* [26] reported that the *XPG* polymorphism was significantly cor

related with prostate cancer susceptibility in a Chinese population. Zhu *et al.* [27] suggested that *XPG* variant genotypes were associated significantly with esophageal cancer risk in a Chinese population.

However, Meta analysis by Liu *et al.* (2014) reported that the *XPG* polymorphism was not associated with bladder cancer risk. Also, Steck *et al.* [28] did not find significant association between *XPG* gene polymorphisms and colon cancer risk. Meta-analysis conducted by Xu *et al.* [16] suggested that the *XPG* polymorphism is not associated with breast cancer risk. Thus, several previous studies have reported the association between *XPC* and *XPG* gene polymorphisms and the development of different cancer, but the results are inconclusive. However, no information was available on the association of polymorphisms of *XPC* and *XPG* and their susceptibility to BC from rural population of Maharashtra. Therefore in this study, we determined the relationship between the BC and genetic polymorphisms in *XPC* & *XPG* genes from a pool of unexplored rural Maharashtrian population. We conducted a case-control study to investigate the association between A2920C allele of exon 15 in *XPC* and C3507G allele of exon 15 in the *XPG* and the development of BC in a Maharashtrian population, and we found no contribution of either *XPC* or *XPG* to the development of breast cancer. Similar results were reported by Ding *et al.* [15] and Xu *et al* [16] where *XPG* polymorphism was not associated with breast cancer risk in other population. Such genotyping analysis of NER pathway genes will enhance our

ability to identify those individuals most susceptible to breast carcinogenesis in the rural Indian population.

CONCLUSION

The study suggests that functional XPC or XPG polymorphisms could not play role in the development of BC in a Maharashtrian population. Thus this analysis of negative correlation of DNA repair genes and BC may provide a deeper insight into the genetic and environment factors to cancer risk in the rural unexplored population but larger scale studies, including more detailed environmental exposure status and more detailed patient clinical information are needed to verify these findings.

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