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Original Research Article

Association of genetic polymorphisms in XRCC4, XRCC5, XRCC6 and XRCC7 in cervical cancer susceptibility from rural population: a hospital based case-control study

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ABSTRACT

Background: Cervical cancer is a major concern of health risk, moreover the leading cause of cancer causing deaths in women of rural India. This study was aimed to assess the risk of cervical cancer development in association with polymorphisms in XRCC4, XRCC5, XRCC6 and XRCC7 genes in rural population of south-western Maharashtra.
Methods: This study included 350 cervical cancer proven cases and 400 age and sex matched controls. We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to analyze the association XRCC4, XRCC6 and XRCC7 gene polymorphisms with cervical cancer development in women of Western Maharashtra.
Results: The result from our study showed that allele frequencies of selected genes were not statistically different between the groups for XRCC4, XRCC5 and XRCC6. 6721 >T allele of XRCC7 *(*6721G>T) (OR= 2.34; 95% CI= (2.34 (1.60-3.43); p= <0.0001) significantly increased the risk of cervical cancer.
Conclusions: This study indicates that XRCC7 gene polymorphisms play a role in modifying genetic susceptibility of individuals towards cervical cancer among women from rural Maharashtra. This case-control study also revealed negative association of XRCC6 gene in cervical carcinogenesis in the rural Indian population.

Keywords: Cervical cancer, Genetic polymorphisms, PCR-RFLP

INTRODUCTION

Cervical Cancer (CC) is fourth most common cancer and well-known reason of cancer causing death in women worldwide.[1] After breast cancer, it is the common cause of cancer death accounting 70% in low income countries whereas in developed countries widespread cervical screening programs dramatically reduced cervical cancer predominance. Over the last two decades, it is universally implicated that along with tobacco and alcohol, persistent infection with high risk human papilomavirus and other sexually transmitted agents are necessary etiologic factors for cervical carcinogenesis. Findings from rural parts of India have showed higher incidence of CC in different age groups where the prevalence rate could be probably due to inadequate preventive measures for management of CC.[2] Although tobacco, alcohol and HPV are the main etiologic factors for three fourth of the cancer cases, no definite etiologic factor can be identified in one fourth of the population with CC. In those cases development of CC could be influenced by genetic factors.[3] Identification of such genetic determinants associated with CC may contribute to understand mechanisms underlying behind development of cancer. Earlier it was hypothesized that

the functional variations in DNA repair genes may be associated with repair efficiency of DNA and influences an individual's risk of cancer development.[4] Variety of DNA repair mechanisms play a central role in maintenance of genomic integrity with different repair pathways, but it is not yet clear which DNA repair pathways are most important for protection against CC. The XRCC4, XRCC5, XRCC6 and XRCC7 are few of them involved in DNA double strand break repair by two important repair subpathways; homologous recombination repair (HRR) and Non-homologous end joining (NHEJ). Amongst the polymorphisms of the DNA repair genes, several functional genetic variants have been identified in the NHEJ pathway genes particularly XRCC4, XRCC5 and XRCC6 which have shown a relationship with the susceptibility to multiple cancers.[5-7]

However, the results of former studies remain controversial rather than convincing in terms of the association between polymorphisms of XRCC genes and risk of different cancer types, nevertheless the influence of those polymorphisms on DNA repair capacity are still ambiguous. Several studies showed the association of XRCC4 and XRCC5 polymorphisms with breast cancer, oral cancer and hepatocellular carcinoma risk, but some of them led to conflicting results.[8,10,6] Also, XRCC6 and XRCC7 variants are found not to be associated with breast cancer, lung cancer risk.[11,12]

However, no reports are available in literature about the XRCC4, XRCC5, XRCC6 and XRCC7 genes and their association with development of cervical cancer risk in Indian or other population. Thus, the association between genetic polymorphism of NHEJ pathway genes (XRCC4, XRCC5, XRCC6 and XRCC7) and susceptibility to CC is still an open challenge. In this study we focused on the reported polymorphisms with the greater allele frequencies of XRCC genes to evaluate their role in CC. We performed a hospital-based case control study using a PCR-RFLP assay to genotype the polymorphisms of selected DNA repair genes in relation to CC susceptibility in a rural population of south-western Maharashtra from India. We determined the genotypic frequency of polymorphisms of the (i) XRCC4 gene at codon 247 (rs3734091), G-1394T (rs6869366) and Intron 7 (rs1805377). Also, the present study intended to investigate the associations between the XRCC5 (2R/1R/0R), XRCC6 promoter 61 (61C>G) and XRCC7 (6721 (G>T)) gene polymorphisms and the development of CC in Maharashtrian population.

METHODS

This study was a hospital based case-control study. Study participants included 350 newly diagnosed CC patients and 400 healthy, cancer free, sex matched individuals as controls. All cases ranged in age from 20-80 years (Mean±SD) (48.67±13.78) were recruited immediately after being diagnosed during the year 2014-2017. Five milliliter (mL) of intravenous blood from patients and normal controls was collected in sterile vacutainer after receiving written informed consent. Genomic DNA extraction was carried out from the peripheral blood sample using Purelink genomic DNA extraction and purification kit (Invitrogen, Life technologies) following the manufacturer's instructions. Genotyping of XRCC4, XRCC6 and XRCC7 genes was performed by PCR-RFLP methods with appropriate primer sets. The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: XRCC4 codon 247, XRCC4 G1394T, XRCC4 intron7, XRCC6 61 (C>G) and XRCC7 6721 (G>T).

The XRCC5 2R/1R/0R polymorphisms were identified by PCR. The PCR amplification were carried out separately under different conditions in 20 micro liter (µL) reaction mixtures containing 1X PCR buffer 0.2 mM each dNTP, 10 picomole (pmol) of each primers, 1U Taq DNA polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA. The primers selected to amplify the exons of XRCC4 containing the polymorphisms of interest were; XRCC4-1 (cd247) sense primer:5'-GCT AAT GAG TTG CTG CAT TTT A-3' antisence primer: 5'-TTT CTA GGG AAA CTG CAA TCT GT-3', XRCC4-2 (G1394T) sense primer: 5'- GAT GCG AAC TCA AAG ATA CTG A-3' antisence primer: 5'- TGT AAA GCC AGT ACT CAA ACT T -3'; XRCC4-3 (Intron7) sense primer: 5'- TTC ACT TAT GTG TCT CTT CA -3' antisence primer: 5'- AAC ATA GTC TAG TGA ACA TC -3'; XRCC5(2R/1R/0R) senseprimer:5'- AGG CGG CTC AAA CAC CAC AC -3'antisence primer: 5'- CAA GCG GCA GAT AGC GGA AAG -3' ; XRCC6 (61C>G) sense primer: 5'- TCT CCA CTC GGC TTT TCT TCC A -3' antisence primer: 5'- TCT CCC TCC GCT TCG CAC TC - 3'and XRCC7 (6721G>T) sense primer: 5'- CGG CTG CCA ACG TTC TTT CC -3' antisence primer: 5'- TGC CCT TAG TGG TTC CCT GG - 3'.

The PCR conditions for amplification of XRCC4-1 codon 247 of 308 bp: initial denaturation at 95^0C for 10 minutes (min) followed by 30 cycles of 95^0C-30 seconds (sec) , 55^0C- 30 sec, 72^0C-30 sec and final extension at 72^0C for 10 min; XRCC4-2 (G1394) of 300bp: initial denaturation at 95^0C for 10 minutes (min) followed by 30 cycles of 95^0C-30 seconds (sec) , 53^0C- 30 sec, 72^0C-30 sec and final extension at 72^0C for 10 min and XRCC4-3 intron 7 of 237bp: initial denaturation at 95^0C for 10 minutes (min) followed by 30 cycles of 95^0C-30 seconds (sec) , 48^0C-30 sec, 72^0C-30 sec and final extension at 72^0C for 10 min.

The amplification conditions for XRCC5 are initial denaturation at 95^0C-10 min, followed by 30 cycles of 95^0C-30 sec, 62^0C-30 sec, 72^0C-30 sec, 72^0C-10 min which generates 266bp of 2R/2R allele, 245bp 1R/1R and

224 bp of 0R/0R allele. The PCR amplification program for XRCC6 and XRCC7 were; initial denaturation at 95^0C for 10 min followed by 30 cycles of 95^0C-30 sec, 56^0C-30 sec, 72^0C-30 sec and final extension at 72^0C for 10 min producing 320 bp and 368 bp amplicons respectively.

After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzymes including 1U of BbsI for XRCC4-1, HincII for XRCC4-2 and 1U of Tsp509I for XRCC4-3 respectively for genotyping. Also, amplicons of XRCC6 and XRCC7 were digested with 1U of BanI and PvuII respectively. Ten micro liters (µL) of the PCR products were digested at 37°C overnight with specific restriction enzymes in 20µL reaction mixtures containing buffer supplied with each restriction enzyme. After overnight incubation at 37^0C, restriction digestion products were separated on a 2-3% low EEO agarose (GeNei, Merck Biosciences) gel at 100 V for 30 min, stained with ethidium bromide and photographed with gel documentation system.

Statistical analysis

The association between the XRCC4, XRCC5, XRCC6 and XRCC7 genotypes and risk of CC development were studied using odds ratio (OR). Both the univariate and multivariate logistic regression analyses were employed to calculate the adjusted ORs and 95% confidence intervals (CIs) to determine the CC risk associated with genotypes.

RESULTS

Characteristics of the study subjects

To study the association of nucleotide polymorphisms in XRCC4, XRCC5, XRCC6 and XRCC7 genes with risk of cervical cancer development, we stratified the patients and controls according to median age at diagnosis. The mean age in years was 48.67 (median: 47, range 20-80) for the cases and 42.37 (median: 40, range 20-80) for the controls. Analysis of the polymorphism in XRCC4, XRCC5, XRCC6 and XRCC7 genes.

Table 1: The genotype frequencies of XRCC gene polymorphisms in untreated CC patients and controls.

GENE	Genotype	Cases n= 350 (%)	Control n = 400 (%)	Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	*p* value
XRCC4-1 cd247	C/C	321 (91.71)	379 (94.75)	1		1	
	A/A	29 (08.29)	21 (05.25)	1.50 (0.83-2.71)	0.17	1.94(1.05-3.58)	0.03
XRCC4-2 G1394T	G/G	226 (64.57)	255 (63.75)	1		1	
	T/T	124 (35.43)	145 (36.25)	0.97(0.72-1.31)	0.87	0.92 (0.66-1.27)	0.62
XRCC4-3 Intron-7	G/G	253 (72.29)	297 (74.25)	1		1	
	A/A	97 (27.71)	103 (25.75)	1.10 (0.79-1.52)	0.54	1.08 (0.77-1.52)	0.63
XRCC5 2R/1R/0R	2R/2R	157 (44.86)	209 (52.25)	1		1	
	1R/1R	145 (41.43)	145 (36.25)	1.33 (0.97-1.81)	0.07	1.32 (0.96-1.82)	0.86
	0R/0R	48 (13.71)	46 (11.50)	1.38 (0.88-2.18)	0.15	1.46 (0.91-2.35)	0.11
	1R/1R+0R/0R	193 (55.14)	191 (47.75)	1.34 (1.00-1.79)	0.04	1.36 (1.01-1.84)	0.03
XRCC6-61C>G	C/C	190 (54.29)	189 (47.25)	1		1	
	C/G	147 (42.00)	165 (41.25)	0.88 (0.65-1.19)	0.42	0.91 (0.67-1.24)	0.56
	G/G	13 (03.71)	46 (11.50)	0.28 (0.14-0.53)	0.0001*	0.29 (0.15-0.57)	<0.0001
	C/G+G/G	160 (45.71)	211 (52.75)	0.75 (0.56-1.00)	0.05	0.78 (0.58-1.05)	0.10
XRCC7 6721 G > T	G/G	68 (19.43)	153 (38.25)	1		1	
	G/T	160 (45.71)	130 (32.50)	2.76 (1.91-3.99)	<0.0001*	2.8 (1.92-4.07)	<0.0001*
	T/T	122 (34.86)	117 (29.25)	2.34 (1.60-3.43)	<0.0001*	2.28 (1.54-3.37)	<0.0001*
	G/T+T/T	282 (80.57)	247 (61.75)	2.56 (1.84-3.58)	<0.0001*	2.58 (1.84-3.61	<0.0001*

* Indicates significant Odds Ratio (p<0.005)

The distribution of polymorphisms in XRCC4, XRCC5, XRCC6 and XRCC7 genotypes in concurrence with development of CC is presented in Table 1. Among the XRCC4 polymorphisms investigated, codon 27, codon 1394 and intron 7 seems not to contribute to increased cervical cancer risk. Our findings suggest that the frequencies of genotype distribution of the A allele at XRCC4 codon 247 was 8.29% in the CC group to that in the control group (5.25%). Also, T allele at codon 1394 (35.43%) and A allele at intron 7 (27.71%) in CC cases were not much higher than in controls (36.25% and 25.75% respectively) (Table 1).

When we selected XRCC5 2R/1R/ 0R to investigate its associations with risk of CC, the genotypes of 2R/2R, 1R/1R, 0R/0R were 44.86%, 41.43% and 13.71% in CC cases where as that of matched controls showed 52.25%, 36.25%, and 11.50% genotypes respectively, which showed no association of XRCC5 with CC development. For the XRCC6 (61C>G) polymorphism, the frequencies of the CC, CG, and GG genotypes were 54.29%, 42.00%, and 3.71%, respectively, among cases with cervical cancer, and 47.25%, 41.25%, and 11.50%, respectively, among controls (Table 1). The homozygote variant G allele conferred a decreased risk of CC development

compared to the wild-type CC genotype (OR 0.28 (95% CI=0.14-0.53, p<0.0001). For the XRCC7 (6721G>T) polymorphism, the frequencies of the GG and TT genotypes were 19.43% and 34.86 % among CC cases and 38.25% and 29.25% among the controls. However, the difference was statistically significant (P<0.0001) in cases than in controls for the homozygote variant TT (OR=2.34; 95% CI=1.60-3.43), p<0.0001 and heterozygotes GT alleles OR=2.56; 95% CI=1.84-3.58 p<0.0001 in cases than controls (Table 1, 2 and 3).

Table 2: Stratification of age of cancer occurrence, tobacco smoking and distribution of XRCC genotypes in the patients with CC and control group from rural population of Maharashtra.

Gene	Genotype	Demographic Factors			
		Age, cases/controls		Tobacco status, cases/controls	
		≤ 50 N=216/286	> 50 N=134/114	Users N=189/112	Non-Users N=161/288
XRCC4-1	C/C	204/271	119/108	174/105	147/274
	A/A	12/15	15/6	15/7	14/14
	OR (95% CI) p value	1.06 (0.48-2.31) 0.87	2.26 (0.84-6.05) 0.10	1.29 (0.51-3.27) 0.58	1.86(0.686-4.01) 0.11
XRCC4-2	G/G	141/192	85/63	124/56	102/199
	T/T	75/94	49/51	65/56	59/89
	OR (95% CI) p value	1.08 (0.74-1.57) 0.66	0.71(0.42-1.18) 0.19	0.52(0.32-0.84) 0.007	1.29(0.86-1.94) 0.21
XRCC4-3	G/G	162/215	91/82	133/74	120/223
	A/A	54/71	43/26	56/38	41/65
	OR (95% CI) p value	1.00 (0.67-1.51) 0.96	1.49 (0.84-2.63) 0.17	0.81 (0.49-1.35) 0.43	1.17(0.74-1.83) 0.48
XRCC5	2R/2R	94/147	63/62	87/66	70/143
	1R/1R+0R/0R	122/139	71/52	102/46	91/145
	OR (95% CI) p value	1.37 (0.96-1.95) 0.08	1.34 (0.81-2.21) 0.24	1.68 (1.04-2.69) 0.03	1.28(0.86-1.88) 0.20
XRCC6	C/C	114/140	76/49	105/46	85/143
	C/G+G/G	102/146	58/65	84/66	76/145
	OR (95% CI) p value	0.85 (0.60-1.22) 0.39	0.57 (0.34-0.95) 0.03	0.55 (0.34-0.89) 0.01	0.88(0.59-1.29) 0.52
XRCC7	G/G	39/113	29/40	32/49	36/104
	G/T+T/T	177/173	105/74	157/63	125/184
	OR (95% CI) p value	2.96 (1.94-4.51) <0.0001*	1.95 (1.11-3.43) 0.01	3.81 (2.23-6.50 <0.0001*	1.96(1.26-3.05) 0.002

Association of age of cancer occurrence, diet, tobacco status and age at first pregnancy with cervical cancer risk

To examine the association of the polymorphisms with the age at diagnosis of CC, we stratified the patients as ≤50 (n=216) or >50 (n=134) years of age and compared with age matched sample of controls which interestingly showed that the XRCC7 (6721G>T) (OR=2.96; CI=1.94-4.51; p<0.0001) showed significant risk of CC at the age bellow median. When we studied plausible association of demographic factors and polymorphism in XRCC4, XRCC5, XRCC6 and XRCC7 genes, our results indicated nonvegeterian diet and tobacco chewing habits also showed connection with CC development (OR=2.51; CI=1.69-3.73; p<0.0001) for mixed diet and (OR=3.81; CI=2.23-6.51; p<0.0001) for tobacco chewing status (Table 2). Also, the association of CC with age at first pregnancy was considered in this study which showed that delayed age of first pregnancy i.e. 21-25 yrs, significantly associated with increased CC risk (OR=4.22; CI=2.08-8.57; p=0.0001) (Table 3).

DISCUSSION

To the best of our knowledge, there are no reports concerning any of XRCC4, XRCC5, XRCC6 and XRCC7 polymorphism in CC risk, therefore present study was planned to determine the genotypic frequency of polymorphisms of the DNA repair genes (i) XRCC4 at codon 247 (rs3734091), G-1394T (rs6869366) and Intron 7 (rs1805377). Polymorphisms *XRCC5 (*2R/1R/0R), *XRCC6* (-61C>G) and *XRCC7* (6721G>T) were selected to investigate the associations between polymorphisms

and risk of CC in Maharashtrian population. Findings from our results inferred that XRCC7 (6721T) variant allele was significantly higher in CC group than in control group whereas XRCC6 61G variant allele showed negative association in CC. Apart from CC, when the association of polymorphisms in NHEJ pathway genes with other cancer types were considered, few of the studies reported association between *XRCC4* gene polymorphisms with oral cancer, lung cancer and bladder cancer.[10,13,14]

Table 3: Stratification of age at first pregnancy and distribution of XRCC genotypes in the patients with CC and control group from rural population of Maharashtra.

Gene	Genotype	Demographic Factors			
		Age@1st Pregnancy Cases/Controls			
		15-20 N=277/183	21-25 N=72/178	26-30 N=0/34	31-35 N=1/5
XRCC4-1	C/C	257/173	63/173	0/29	1/4
	A/A	20/10	9/5	0/5	0/1
	OR (95% CI) p value	1.34(0.61-2.94) 0.45	4.94(1.59-15.31) 0.005	5.36(0.09-300) 0.41	1.00 (0.02-40.27) 1.0
XRCC4-2	G/G	159/121	47/110	0/22	0/2
	T/T	98/62	25/68	0/12	1/3
	OR (95% CI) p value	1.20(0.80-1.78) 0.36	0.86(0.48-1.52) 0.60	0.55(0.01-29.0) 0.77	0.46(0.01-16.80) 0.67
XRCC4-3	G/G	198/139	55/127	0/28	0/3
	A/A	79/44	17/51	0/6	1/2
	OR (95% CI) p value	1.26(0.82-1.93) 0.28	0.76(0.40-1.45) 0.41	4.38(0.07-242) 0.47	4.20(0.11-151.97) 0.43
XRCC5	2R/2R	127/93	29/89	0/23	1/4
	1R/1R+0R/0R	150/90	43/89	0/11	0/1
	OR (95% CI) p value	1.22(0.83-1.77) 0.29	1.48(0.85-2.58) 0.16	2.04(0.03-109) 0.72	3.66(0.04-274.53) 0.55
XRCC6	C/C	153/95	36/78	0/14	1/2
	C/G+G/G	124/88	36/100	0/20	0/3
	OR (95% CI) p value	0.87(0.60-1.27) 0.48	0.78(0.45-1.35) 0.37	0.70(0.01-37) 0.86	1.00(0.02-40.27) 1.0
XRCC7	G/G	57/62	11/77	0/10	0/4
	G/T+T/T	220/121	61/101	0/24	1/1
	OR (95% CI) p value	1.97(1.29-3.01) 0.001	4.22(2.08-8.57) 0.0001*	0.42(0.8-23.07) 0.67	9.00(0.22-362) 0.24

Also, studies have investigated the plausible association of XRCC4 polymorphisms with breast cancer risk in different ethnicities. Fu et al, reported the polymorphism of XRCC4 gene associated with breast cancer from Taiwanese population.[11] A population-based meta-analysis in Caucasian population from Poland and America investigated the polymorphisms in XRCC4 gene found a non-significant association with breast cancer susceptibility.[8] Likewise, earlier reports on *XRCC5* showed the positive association with increased risk of gastric cancer, colorectal cancer, esophageal cancer and head and neck cancer.[15-18] Fu et al, also reported that SNPs in *XRCC5* were not associated with breast cancer but *XRCC6* -61C> G polymorphism was associated with an increased risk of breast cancer. Also, *XRCC7* appears to be involved in the etiology of gliomas and bladder cancer.[19,20] A study from Iranian population showed a significant association of XRCC7 gene with thyroid cancer.[21] In contrast, other studies failed to identify significant associations of XRCC6 with risk of oral and lung cancer, and hepatocellular carcinoma risk[6] whereas some studies reported negative association between the *XRCC7* polymorphism and risk of thyroid cancer.[6,22-25] But, there are inadequate number of studies in Indian setup regarding the polymorphisms in NHEJ pathway genes and susceptibility of cancers with sparse results.

Mandal et al, showed association of XRCC4 (rs28360071) and (rs28360317) genotypes with prostate cancer risk.[26] But, at the same time studies from northern India showed negative association of XRCC4 (rs6869366) and (rs28360317) SNPs with urinary bladder cancer risk.[27] Also, a significant relationship between XRCC7, 6721GG genotype with hepatocellular cell

carcinoma, prostate cancer and urinary bladder cancer has been reported in northern Indian population.[7,28] Very recently it has been shown that XRCC6 and XRCC7 were not susceptible for lung cancer.[29] However, there are no reports on CC susceptibility in association with any of XRCC4, XRCC5, XRCC6 or XRCC7 in India or other countries. Therefore, in this study we have reported the association of XRCC7 (6721G>T) allele with CC development which is novel finding not reported before in Indian population with cervical carcinogenesis. Also, XRCC6-61C>G showed negative association with CC development in rural Indian Population which is identical to other studies reported in oral, lung, hepatocellular carcinoma of other populations.

CONCLUSION

In conclusion -61C>G allele of XRCC6 negatively associated whereas 6721G>T allele of XRCC7 strongly associated with CC development in rural population of South-western Maharashtra.

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