RESEARCH ARTICLE

Impact of Polymorphism in Base Excision Repair and Nucleotide Excision Repair Genes and Risk of Cervical Cancer: A Case-Control Study

Kailas D Datkhile[1]*, Pratik P Durgawale[1], Madhavi N Patil[1], Rashmi A Gudur[2], Anand K Gudur[2], Satish R Patil[1]

Abstract

Background: Last few years, several studies all over the world revealed the association of DNA repair genes with risk of developing different type of cancers, but were ambiguous to support the evidences in case of cervical cancer risk. These differences in earlier studies directed us to study the association of polymorphisms of BER genes (XRCC1, hOGG1, XPC) and NER genes (XPC, XPD) with cervical cancer susceptibility in the women of rural population of Maharashtra. **Materials and Methods:** The genetic polymorphism in BER and NER pathway genes was studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using DNA isolated from intravenous blood samples of patients and normal controls. The study included 400 clinically confirmed cervical cancer patients and 400 healthy women from a tertiary care hospital (Krishna Hospital and Medical Research Centre) of south-western Maharashtra. The association of polymorphisms was confirmed by Odds ratio (OR) with 95% confidence interval. **Results:** The single nucleotide polymorphism (SNP) of BER genes including XRCC1, hOGG1 and APE1 were analyzed and the results were noted that 27466AA (OR=4.88; 95% CI: 3.61- 6.60; p<0.0001) and 28152AA (OR=2.89; 95% CI: 1.57- 5.31; p=0.0005) genotypes of XRCC1 (rs25489, rs25487) were significantly associated with cervical cancer risk. The 1245GG genotype of hOGG1 (rs1052133) (OR=45.30; 95% CI: 3.76- 7.46; p=0.001) also showed significant correlation, whereas 2197GG genotype of APE1 (rs1130409) gene showed negative association with cervical carcinogenesis (OR=0.59; 95% CI: 0.35- 0.97; p=0.005). Similarly when we studied SNPs of NER genes including XPC and XPD genes, 21151TT genotype of XPC (rs 2228000) was positively associated with cervical cancer development and 23591AA genotype of XPD (rs1799793) showed negative association (OR=0.34; 95% CI: 0.17- 0.64; p=0.001). **Conclusion:** The findings from this study supported that rs25489, rs25487SNPs of XRCC1, rs1052133 of hOGG1 and rs2228000 of XPC may increase cervical cancer risk, whereas rs1130409 SNP of APE1 and rs1799793 SNP of XPD gene lower the risk of cervical cancer in the studied population.

Keywords: Cervical cancer- SNP- PCR-RFLP- BER- NER

Introduction

Nowadays, cervical cancer (CC) has become the most challenging and threatening health issue in women throughout the world which brings about morbidity and huge economic burden. Globally, CC ranked third among women with 604, 127 new cases and 341, 831 deaths in year 2020. In India, CC lead to second largest cause of cancer causing deaths among women with 123, 907 new cases and 77, 348 women were died in 2020 accounting 9.1% of total cancer deaths in the country (GLOBOCAN, 2020). In rural India the frequency of CC is likely to be high because of illiteracy, unawareness and disease hiding tendency of the women. Etiology of CC is weakly defined where lifestyle, hormonal, environmental factors along with genital infections like Human Immunodeficiency virus (HIV) and Human papillomavirus (HPV) have been established as risk factors for carcinogenesis. But, all women exposed to earlier mentioned factors do not develop CC, which revealed that there are still other means playing role in cervical carcinogenesis. Besides these certain host genetic factors are also involved in susceptibility of carcinogenesis; however, exact mechanism of pathogenicity is not fully understood. Exposure to the physical and chemical agents can lead to the oxidative DNA damage in human body. Several DNA repair enzymes are present in cells which are essential to correct the damaged nucleotides produced by oxidative

[1]Department of Molecular Biology, Genetics Krishna Institute of Medical Sciences, Deemed to Be University Malkapur, Karad Satara, Maharashtra, Pin: 415 539, India. [2]Department of Oncology, Krishna Institute of Medical Sciences, Karad, India. *For Correspondence: hodgeneticslab@kimskarad.in

damage and retain the genomic stability and integrity. In human cells hundreds of elements are concerned in DNA repair system where base excision repair (BER) and nucleotide excision repair (NER) are the two mechanisms involved in single strand break repair system. The most important genes including X-ray cross complementing group 1 (*XRCC1*), 8-oxoguanine DNA glycosylase 1 (*hOGG1*), apurinic/ apyrimidinic endonuclease 1 (*APE1*) are involved in BER pathway. A xeroderma pigmentosum complementation group C (XPC) xeroderma pigmentosum complementation group D (*XPD*) gene has a significant role in NER mechanism. The polymorphisms in DNA repair genes modulate DNA repair efficiency of DNA repair enzymes which have been suggested to be associated with cancer risk. Therefore, there has been increasing interest in identifying associations between SNPs in DNA repair (*BER* and *NER*) genes and susceptibility of various cancers including cervical cancer. Number of studies extensively demonstrated that the *SNPs* of *BER* genes altered susceptibility of various types of cancers including breast (Wang et al., 2018), lung (Chen et al., 2015) gastric (Kaur et al., 2020), and head and neck cancer Xia et al., 2021). The polymorphism in *NER* pathway genes are also demonstrated by other researchers for their involvement in development of breast (Samson et al., 2010), lung (Jin et al., 2014) and gastric cancer (Zhou et al., 2021). However, the evidences are inconsistent where some SNPs showed increased risk of certain cancers whereas other revealed no association same SNPs with other type of cancer such as gastric association of same SNPs (Hua et al., 2016), prostate (Fu et al., 2017) and breast (Yumei et al., 2020). Similarly, Indian studies also signified the role of SNPs of *BER* genes in development of lung (Uppal et al., 2014), head and neck (Choudhury et al., 2014), gastric (Ghosh et al., 2016) and breast cancer (Nagpal et al., 2020). The polymorphisms in NER pathway genes including *XPC* showed association with risk of prostate (Mandal et al., 2012), head and neck cancer (Yadav et al., 2018). On the other hand, other stated no involvement of either of *BER* or *NER* genes with risk of lung (Singh et al., 2016), gastric cancer (Nisar et al., 2018) in North Indian population as well as breast cancer from Western (Datkhile et al., 2017) and Southern Indian population (Francis et al., 2018).

Cervical cancer is a major death causing disease observed in women of rural India. When we looked into other published data, we noticed insufficiency of the studies on association of the genetic polymorphisms in *BER* and *NER* genes with CC risk in rural Indian women. Still there are few reports on other ethnic groups stated correlation between *XRCC1* gene polymorphism with CC risk in Brazilian population (Colacino-Silva et al., 2017). The *hOGG1 Ser326Cys* and *APE1 Asp148Glu* polymorphisms showed association with cervical carcinogenesis in Chinese population (Chen et al., 2019). Studies on other inflammatory genes reported the association of polymorphism in TNF- α with risk of cervical cancer (Hamadani et al., 2017). Very recently, Das et al., (2021) evidenced the risk of CC in association with *XPC* gene polymorphism in Bangladeshi women. Though, the polymorphisms in BER and NER have been extensively studied; their role in cervical carcinogenesis

has not been clearly defined and produced conflicting annotations (Konthala et al., 2017; Zeng et al., 2017; Abbas et al., 2019). Therefore, to establish overall understanding of possible relationships between *BER* and *NER* gene polymorphisms and development of CC in rural Indian women, we conducted an hospital based case-control study where the possible association with CC risk was assessed in terms of genotype distribution and gene environment interactions in the cases and controls. The aim of this study was to evaluate the association of *rs1799782* (exon-6), *rs25489* (exon-9), rs25487 (exon-10) SNPs of *XRCC1*; *rs1052133* (exon-7) SNP of hOGG1; *rs1130409* (exon5) *SNP* of *APE1* genes and the SNPs of *NER* genes, (*rs2228000* (exon-9), *rs2228001* (exon-15) of *XPC* gene; *rs238406* (exon-6), *rs1799793* (exon-10), *rs13181* (exon-23) of *XPD* gene with the risk of cervical cancer in rural women of south-western Maharashtra.

Materials and Methods

Selection of study subjects

This hospital based case-control study was conducted on 400 newly diagnosed CC 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 in a Krishna Hospital and Medical Research Centre (KH & MRC) Karad, during the year 2015-2019. The disease free controls were randomly chosen from a group of women visiting to KH&MRC for blood donation and other purposes. 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.

Genomic DNA isolation from whole blood

Five milliliter (mL) of intravenous blood from CC patients and normal controls was collected in sterile EDTA containing vacutainer after receiving their written informed consent. 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

The genotyping of BER (*XRCC1*, *hOGG1*, *APE1*) and NER (*XPC, XPD*) isoforms was studied by PCR-RFLP. A total of 20 microliter (μL) of PCR reaction mixture consisted of 0.2 μg of genmic DNA, 1X PCR buffer containing Tris HCl (pH.8), KCL, EDTA, DTT, 25mM MgCl$_2$, 0.2 mM each dNTPs, 1U of Taq DNA polymerase (Bangalore GeNei) and 10 picomole of each forward and reverse primers for represented in Table 1. The PCR amplification of *BER* and *NER* genes were performed in a Master Cycler Gradient PCR machine (Eppendorf India Limited).

After PCR amplification, the RFLP analysis for the studied genotypes of XRCC1 (Arg194Trp, Arg280His, Arg399Gln) hOGG1 (Ser326Cys) and APE1 (Asp148Glu) were carried out with the help of 1 unit of PvuII, RsaI

and NciI restriction enzymes respectively. Similarly, 1 unit of BfaI and MboII were used for digestion of PCR products of APE1 and hOGG1 codons 148 and 326 respectively. The RFLP analysis of *NER* genes including XPC (Val499Arg and Lys939Gln) genotypes were carried out using appropriate restriction enzymes XhaI and XbaI respectively. The PCR products for XPD (Arg156Arg, Asp312Asn and Lys751Gln) were digested with TfiI, StyI and PstI restriction endonucleases respectively at 37°C for 16hrs. Following the restriction digestion the digested products were separated on 1-3% low EEO agarose (GeNei, Merck Biosciences) gel, stained with ethidium bromide and photographed with gel documentation system. The variant and wild type genotypes were analyzed based on their restriction digestion pattern.

Statistical Analysis

The association between the XRCC1, hOGG1, APE1, XPC, XPD genotypes and risk of developing CC was studied using logistic regression model with adjustment of confounder variables. Logistic regression model was used to calculate the OR and 95% confidence intervals (CI) with adjustment of variables to determine the CC risk associated with genotypes. The p-value was evaluated to get the level of association where $p \leq 0.005$ was considered as statistically significant.

Results

A total of 400 CC cases and equal number of age matched controls were recruited for this case-control study. The mean age of patients was 47.61 ± 13.86 years (range 20-80 years) and that of controls 42.37 ± 13.90 (range 20-75 years). The percentages of CC cases ≤ 50 were (65.50%) and more than 50 were (34.50%) whereas that of controls (71.50%) and (28.50%) consecutively. There was no significant difference between cases and control groups with respect to age (OR: 1.32; 95%CI, 0.97-1.78; p=0.06), diet (OR: 0.86; 95%CI, 0.63-1.17; p=0.06) and tobacco habit status (OR: 1.06; 95%CI, 0.827-1.37; p=0.64). The clinical and demographic characteristics stratification analysis showed that long term and heavy tobacco habits significantly found to be associated with risk of CC (OR: 2.63; 95%CI, 1.93-3.58; p=0.001) in rural women. Surprisingly, it was observed that CC occurred in patients (78.57 %) who got married at early age and conceive soon (15-20 yrs). There was a significant difference between controls and patient population with respect to age of marriage (OR: 3.74; 95%CI, 2.76-5.06; p<0.0001).

Comparative analysis of association between genotypic polymorphisms of BER genes XRCC1, hOGG1, APE1 and cervical cancer risk

The frequency distribution of *XRCC1, hOGG1* and *APE1* genotype and allele in both cases and control groups showed that no significant association of XRCC1 (rs1799782) with cervical carcinogenesis was observed while significant relationship was noted between XRCC1 (rs25489) (OR=4.88; 95% CI: 3.61- 6.60; p<0.0001) and XRCC1 (rs25487) (OR=2.89; 95% CI: 1.57- 3.31; p=0.0005). The allele frequency of 27466A of XRCC1 (rs25489) was detected significantly associated (OR=4.88; 95% CI: 3.61-6.60); p<0.0001) with CC development. Our result indicate that homozygous variant AA genotype of codon 284 and AA genotype of codon 399 of XRCC1 were significantly associated with 4.88 and 2.89 fold higher risk of CC. Similarly, the variant hOGG1 codon 326 was

Table 1. Primer Sequences and Details of the PCR Conditions

Gene/ Genotype	Primer Sequence (Forward/Reverse)	PCR Conditions	PCR product size
XRCC1 (C26304T)	Forward: 5'-gcc agg gcc cct cct tca a-3'	95°C- 10 min, 30 cycles of 95°C- 30 sec,	485 bp
	Reverse: 5'-tac cct cag acc cac gag t-3';	61°C- 30 sec, 72°C- 30 sec, 72°C- 10 min	
XRCC1 (G27466A)	Forward: : 5'-cca gct cca act cgt acc-3';	95°C- 10 min, 30 cycles of 95°C- 30 sec,	257 bp
	Reverse: 5' atg agg tgc gtg ctg tcc-3';	61°C- 30 sec, 72°C- 30 sec, 72°C- 10 min	
XRCC1 (G28152A)	Forward: : 5'-cag tgg tgc taa cct aat c-3';	95°C- 10 min, 30 cycles of 95°C- 20 sec,	871 bp
	Reverse: 5'-agt agt ctg ctg gct ctg g-3',	56°C- 30 sec, 72°C- 30 sec, 72°C- 10 min	
hOGG1 (C1245G)	Forward: 5'-ctg ttc agt gcc gac ctg cgc cga-3'	95°C- 5 min, 35 cycles of 95°C- 30 sec,	247 bp
	Reverse: 5'-atc ttg ttg tgc aa ac tgac-3',	64°C- 30 sec, 72°C- 30 sec, 72°C- 10 min	
APE1 (T2197G)	Forward: 5'-ctg ttt cat ttc tat agg cta-3'	95°C- 5 min, 35 cycles of 95°C- 20 sec,	164 bp
	Reverse: 5'-agg aac ttg cg aaa ggc ttc-3'.	55°C- 20 sec, 72°C- 20 sec, 72°C- 10 min	
XPC (C21151T)	Forward: 5'-cgg ctc tga ttt tga gct ctc c-3';	95°C- 5 min, 30 cycles of 95°C- 20 sec,	210 bp
	Reverse: 5'-gct tga aga gct tga gga tgg c-3';	55°C- 20 sec, 72°C- 20 sec, 72°C- 5 min	
XPC (A33512C)	Forward: 5'-gga ggt gga ctc tct tct gat g-3'	95°C- 5 min, 35 cycles of 95°C- 30 sec,	765 bp
	Reverse: 5'-tag atc cca gca gat gac c-3'	52°C- 45 sec, 72°C- 30 sec, 72°C- 5 min	
XPD (C22541A)	Forward: 5'- tgg agt gct atg gca cga tct ct -3'	95°C- 5 min, 30 cycles of 95°C- 30 sec,	644 bp
	Reverse: 5'- cca tgg gca tca aat tcc tgg ga -3'	60°C- 30 sec, 72°C- 30 sec, 72°C- 5 min	
XPD (G23591A)	Forward: 5'-ctg ttg gtg ggt gcc cgt atc tgt tgg tct-3'	95°C- 5 min, 35 cycles of 95°C- 30 sec,	751 bp
	Reverse: 5'-taa tat cgg ggc tca ccc tgc agc act tcc t- 3'	62°C- 45 sec, 72°C- 30 sec, 72°C- 5 min	
XPD (A35931C)	Forward: 5'- gcc cgc tct gga tta tac g -3'	95°C- 5 min, 30 cycles of 95°C- 30 sec,	436 bp
	Reverse: 5'- cta tca tct cct ggc ccc c -3'	55°C- 30 sec, 72°C- 30 sec, 72°C- 5 min	

Table 2. The Distribution of Genotype and Allele Frequencies of BER Pathway Gene Polymorphisms in Untreated Cervical Cancer Cases and Healthy Controls

Gene	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XRCC1	CC/CC	309 (77.25)	316 (79.00)	1 (Reference)
C26304T	CC/TT	85 (21.25)	78 (19.50)	1.11 (0.78-1.57)
Arg194Trp	TT/TT	6 (1.50	6 (1.50)	1.02 (0.32-3.20)
cd194 Exon-6	CC/TT+TT/TT	91 (22.75)	84 (21.00)	1.01 (0.79-1.54)
rs1799782	C allele	352 (88.00)	355 (88.75)	1 (Reference)
	T allele	48 (12.00)	45 (11.25)	1.07 (0.69-1.65)
XRCC1	GG/GG	146 (36.50)	295 (73.75)	1 (Reference)
G27466A	GG/AA	0 (0.00)	0 (0.00)	NA
Arg280His	AA/AA	254 (63.50)	105 (26.25)	4.88 (3.61-6.60)
cd280 Exon-9	GG/AA+AA/AA	254 (63.50)	105 (26.25)	4.88 (3.61-6.60)
rs25489	G allele	146 (36.50)	295 (73.75)	1 (Reference)
	A allele	254 (63.50)	105 (26.25)	4.88 (3.61-6.60)
XRCC1	GG/GG	156 (39.00)	246 (61.50)	1 (Reference)
G28152A	GG/AA	211 (52.75)	136 (34.00)	2.44 (1.82-3.28)
Arg399Gln	AA/AA	33 (8.25)	18 (4.50)	2.89 (1.57-5.31)
cd399 Exon-10	GG/AA+AA/AA	244 (61.00)	154 (38.50)	2.49 (1.87-3.32)
rs25487	G allele	261 (65.25)	314 (78.50)	1 (Reference)
	A allele	139 (34.75)	86 (21.50)	1.94 (1.41-2.66)
hOGG1	CC/CC	81 (20.25)	202 (50.50)	1 (Reference)
C1245G	CC/GG	83 (20.75)	87 (21.75)	2.37 (1.60-3.53)
Ser326Cys	GG/GG	236 (59.00)	111 (27.75)	5.30 (3.76-7.46)
cd326 Exon-7	CC/GG+GG/GG	319 (79.75)	198 (49.50)	4.01 (2.93-5.49)
rs1052133	C allele	123 (30.75)	245 (61.25)	1 (Reference)
	G allele	277 (69.25)	155 (38.75)	3.55 (2.65-4.76)
APE1	AA/AA	318 (79.50)	273 (68.25)	1 (Reference)
T2197G	AA/CC	53 (13.25)	85 (21.25)	0.53 (0.36-0.78)
Asp148Glu	CC/CC	29 (7.25)	42 (10.50)	0.59 (0.35-0.97)
Cd148 Exon-5	AA/CC+CC/CC	72 (19.50)	127 (31.75)	0.48 (0.34-0.67)
rs1130409	A allele	344 (86.00)	315 (78.75)	1 (Reference)
	C allele	56 (14.00)	85 (21.25)	0.60 (0.41-0.87)

Significance $p < 0.005$; OR, Odds ratio; CI, Confidence Interval

also associated with 5.30 fold higher risk of CC in studied population. We observed strong correlation of hOGG1 (rs1052133) (OR=5.30; 95% CI: 3.76-7.46); $p < 0.001$) with CC risk in the studied women population. The frequency of 1245G allele of rs1052133 showed significant increase in cases as compared to controls (OR=3.55; 95% CI: 2.65-4.76); $p < 0.0001$). The comparative results of genotype analysis of APE1 (rs130409) showed negative association with CC development (OR=0.59; 95% CI: 0.35-0.97); p=0.04); wherein, variant 2197G allele showed no association in CC risk in the studied population. The genotype and allele frequency distribution of polymorphisms in *XRCC1, hOGG1, APE1* genes were shown in Table 2. When we studied the polymorphism of variant genotypes of *BER* genes with CC risk in a recessive genotype model, we noted negative correlation of XRCC1 (SNP: rs25489), (OR=0.20; 95% CI: 0.15-0.27); $p < 0.0001$) (SNP: rs25487) (OR=0.40; 95% CI:

0.30-0.53); $p < 0.0001$) and hOGG1 (SNP: rs1052133) (OR=0.24; 95% CI: 0.18-0.34); $p < 0.0001$). The recessive model for variant genotype of APE1 (rs1130409) showed significant relationship with CC risk (OR=2.05; 95% CI: 1.47-2.86); $p < 0.0001$) (Table 4). However, the lack of significance observed in dominant model of XRCC1 (rs1799782, rs25487) and APE1 (rs1130409), but negative relationship occurred in (XRCC1 (rs25489) (OR=0.20; 95% CI: 0.15-0.27); $p < 0.0001$), and hOGG1 (rs1052133) (OR=0.26; 95% CI: 0.19-0.35); $p < 0.0001$) (Table 5).

Comparative analysis of association between genotypic polymorphisms of NER genes XPC, XPD and cervical cancer risk

When we studied genotype and allele frequency distribution of the *NER* genes including XPC and XPD, we observed significant difference of XPC (rs2228000) (OR=4.46; 95% CI: 3.20-6.28); $p < 0.0001$) between CC

Table 3. The Distribution of Genotype and Allele Frequencies of NER Pathway Gene Polymorphisms in Untreated Cervical Cancer Cases and Healthy Controls

Gene	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XPC	CC/CC	80 (20.00)	181 (45.25)	1 (Reference)
C21151T	CC/TT	60 (15.00)	88 (22.00)	1.54 (1.01-2.34)
Val499Arg	TT/TT	260 (65.00)	131 (32.75)	4.46 (3.20-6.28)
cd499 Exon-8	CC/TT+TT/TT	320 (80.00)	219 (54.75)	3.30 (2.41-4.52)
rs2228000	C allele	110 (27.50)	225 (56.25)	1 (Reference)
	T allele	290 (72.50)	175 (43.75)	3.38 (2.52-4.55)
XPC	AA/AA	195 (48.75)	198 (49.50)	1 (Reference)
A33512C	AA/CC	166 (41.50)	175 (43.75)	0.96 (0.72-1.28)
Lys939Gln	CC/CC	39 (9.75)	27 (6.75)	1.46 (0.86-2.48)
cd939 Exon-15	AA/CC+CC/CC	205 (51.25)	202 (50.50)	1.03 (0.78-1.35)
rs2228001	A allele	278 (69.50)	285 (71.25)	1 (Reference)
	C allele	122 (30.50)	115 (28.75)	1.08 (0.80-1.47)
XPD	CC/CC	126 (31.50)	145 (36.25)	1 (Reference)
C22541A	CC /AA	212 (53.00)	185 (46.25)	1.31 (0.96-1.79)
Arg156Arg	AA/AA	62 (15.50)	70 (17.50)	1.01 (0.67-1.54)
cd156 Exon-6	CC/AA+ AA/AA	274 (68.50)	255 (63.75)	1.23 (0.92-1.65)
rs238406	C allele	232 (58.00)	237 (59.25)	1 (Reference)
	A allele	168 (42.00)	163 (40.75)	1.08 (0.80-1.47)
XPD	GG/GG	345 (86.25)	198 (49.5)	1 (Reference)
G23591A	GG/AA	39 (9.75)	175 (43.75)	0.12 (0.08-0.18)
Asp312Asn	AA/AA	16 (4.00)	27 (6.75)	0.34 (0.17-0.64)
cd312 Exon-10	GG/AA+AA/AA	55 (13.75)	202 (50.50)	0.12 (0.08-0.17)
rs1799793	G allele	364 (91.00)	285 (71.25)	1 (Reference)
	A allele	36 (9.00)	115 (28.75)	0.24 (0.16-0.36)
XPD	AA/AA	178 (44.50)	187 (46.75)	1 (Reference)
A35931C	AA/CC	197 (49.25)	181 (45.25)	1.14 (0.85-1.52)
Lys751Gln	CC/CC	25 (6.25)	32 (8.00)	0.82 (0.46-1.43)
cd751Exon-23	AA/CC+CC/CC	222 (55.50)	213 (53.25)	1.09 (0.82-1.44)
rs13181	A allele	276 (69.00)	277 (69.25)	1 (Reference)
	C allele	124 (31.00)	123 (30.75)	1.01 (0.74-1.36)

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

cases and controls, whereas (XPC (*rs2228001*) did not show significance in the studied rural women. In our results we noted negative role of XPD (*rs1799793*) with cervical carcinogenesis (OR=0.34; 95% CI: 0.17-0.64); p=0.001) which was not significant and the (*rs238406, rs13181*) SNPs were not observed to be associated with CC risk in studied population. The genotype and allele frequency distribution of polymorphisms in *XPC, XPD* genes were shown in Table 3. The recessive and dominant genetic models to show the association of *SNPs* of *XPC, XPD* genes explored the significant relationship of *XPD* (*rs1799793*) with CC risk (OR=6.39; 95% CI: 4.52-9.04); p<0.0001). The XPC (*rs2228000*) SNP showed negative association (OR=0.30; 95% CI: 0.22-0.41); p<0.0001) with risk of CC in the recessive model where as no relationship was observed between (*rs2228001*) SNP of XPC, (*rs238406, rs13181*) SNPs of XPD. The dominant model showed negative association of XPC (*rs22228000*)

(OR=0.26; 95% CI: 0.19-0.35); p<0.0001) with CC risk and lack of involvement of XPC (*rs2228001*) was reported in CC development. The results are shown in Table 6 and Table 7. In the same model, *rs238406, rs1799793* and *rs13181 SNPs* of XPD were not associated with CC risk in the rural women of south-western Maharashtra.

Correlation of interaction between genotypic polymorphisms of BER and NER genes with demographic characteristics of the cases and controls

The interactions between various demographic parameters like age, age of first pregnancy and tobacco exposure were compared with the data of variant genotype frequencies of both *BER* and *NER* genes among the cases and control women of the rural population. Table 8 illustrates the data of the correlation of *XRCC1* (*rs1799782, rs25489, rs25487*), hOGG1 (*rs1052133*) and APE1 (*rs1130409*) genotypes and their interaction

Table 4. Association between Cervical Cancer Risk and the Single Nucleotide Polymorphism Variant of base Excision Repair Genes in the Recessive Model

Gene	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XRCC1	Trp/Trp + Arg/Trp	91 (22.75)	84 (21.00)	1 (Reference)
Arg194Trp	Arg/Arg	309 (77.25)	316 (79.00)	0.90 (0.64-1.26)
rs1799782				
XRCC1	His/His+Arg/His	254 (63.50)	105 (26.25)	1 (Reference)
Arg280His	Arg/Arg	146 (36.50)	295 (73.75)	0.20 (0.15-0.27)
rs25489				
XRCC1	Gln/Gln/Arg/Gln	244 (61.00)	154 (38.50)	1 (Reference)
Arg399Gln	Arg/Arg	156 (39.00)	246 (61.50)	0.40 (0.30-0.53)
rs25487				
hOGG1	Cys/Cys/Ser/Cys	319 (79.75)	198 (49.50)	1 (Reference)
Ser326Cys	Ser/Ser	81 (20.25)	202 (50.50)	0.24 (0.18-0.34)
rs1052133				
APE1	Glu/Glu+Asp/Glu	72 (19.50)	127 (31.75)	1 (Reference)
Asp148Glu	Asp/Asp	318 (79.50)	273 (68.25)	2.05 (1.47-2.86)
rs1130409				

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

with demographic factors for the risk of CC. The data on genotypic distribution of XRCC1 (*rs1799782, rs25487*) showed no correlation with homozygous wild genotype or heterozygous and variant genotypes with any of the stratified demographic characteristics. The logistic regression analysis showed statistically significant association of XRCC1 (*rs25489*) with age of cancer occurrence (>50) (OR=5.42; 95% CI: 3.11-9.46); p<0.0001), lower age of 1st pregnancy (OR=3.71; 95% CI: 2.51-5.48); p<0.0001) and tobacco habits (OR=4.90; 95% CI: 2.91-8.24); p<0.0001). Similar results also observed in case of hOGG1 (*rs1052133*) associated with >50 yrs

age, < 20 yrs first pregnancy age and tobacco exposure (OR=4.13; 95% CI: 2.39-7.15); p<0.0001), (OR=5.08; 95% CI: 3.36-7.67); p<0.0001) and (OR=3.45; 95% CI: 2.07-5.75); p<0.0001) respectively. Table 9 demonstrates the association *XPC, XPD* gene polymorphism using logistic regression analysis with demographic variables in CC cases and controls. Among the *XPC* and *XPD* genes, rs2228000 SNP of XPC showed significantly increased susceptibility to CC when correlated with stratified demographic factors age of cancer occurrence (OR=3.84; 95% CI: 2.16-6.83); p=0.0001), age of first pregnancy (OR=3.22; 95% CI: 2.15-4.82); p=0.0001) and tobacco

Table 5. Association between Cervical Cancer Risk and the Single Nucleotide Polymorphism Variant of base Excision Repair Genes in the Dominant Model

Gene	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XRCC1	Trp/Trp	6 (1.50	6 (1.50)	1 (Reference
Arg194Trp	Arg/Trp + Arg/Arg	394 (98.50)	394 (98.50)	1.00 (0.32-3.12)
rs1799782				
XRCC1	His/His	254 (63.50)	105 (26.25)	1 (Reference)
Arg280His	Arg/His/Arg/Arg	146 (36.50)	295 (73.75)	0.20 (0.15-0.27)
rs25489				
XRCC1	Gln/Gln	33 (8.25)	18 (4.50)	1 (Reference)
Arg399Gln	Arg/Gln+Arg/Arg	367 (91.75)	382 (95.50)	0.52 (0.28-0.94)
rs25487				
hOGG1	Cys/Cys	236 (59.00)	111(27.75)	1 (Reference)
Ser326Cys	Ser/Cys+ Ser/Ser	164 (40.00)	289 (72.25)	0.26 (0.19-0.35)
rs1052133				
APE1	Glu/Glu	29 (7.25)	42 (10.50)	1 (Reference)
Asp148Glu	Asp/Glu+Asp/Asp	371(92.75)	358 (89.50)	1.50 (0.91-2.46)
rs1130409				

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

Table 6: Association between Cervical Cancer Risk and the Single Nucleotide Polymorphism Variant of Nucleotide Excision Repair Genes in the Recessive Model

.FPVFF	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XPC	Arg/Arg+Val/Arg	320 (80.00)	219 (54.75)	1 (Reference)
Val499Arg	Val/Val	80 (20.00)	181 (45.25)	0.30 (0.22-0.41)
rs2228000				
XPC	Gln/Gln+Lys/Gln	205 (51.25)	202 (50.50)	1 (Reference)
Lys939Gln	Lys/Lys	195 (48.75)	198 (49.50)	0.97 (0.73-1.28)
rs2228001				
XPD	Arg/Arg+Arg/Arg	274 (68.50)	255 (63.75)	1 (Reference)
Arg156Arg	Arg/Arg	126 (31.50)	145 (36.25)	0.80 (0.60-1.08)
rs238406				
XPD	Asn/Asn+Asp/Asn	55 (13.75)	202 (50.50)	1 (Reference)
Asp312Asn	Asp/Asp	345 (86.25)	198 (49.5)	6.39 (4.52-9.04)
rs1799793				
XPD	Gln/Gln+Lys/Gln	222 (55.50)	213 (53.25)	1 (Reference)
Lys751Gln	Lys/Lys	178 (44.50)	187 (46.75)	0.91 (0.69-1.21)
rs13181				

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

habits (OR=4.24; 95% CI: 2.53-7.11); p=0.0001).However XPD (rs1799793) may act as protective factor for CC when correlated with age of cancer occurrence, age at first pregnancy and tobacco exposure (OR=0.25; 95% CI: 0.13-0. 74); p=0.0001), (OR=0.05; 95% CI: 0.03-0.08); p=0.0001) and (OR=0.26; 95% CI: 0.14-0.45); p=0.0001) respectively.

Discussion

Cervical cancer burden is reported to be huge in low income countries.Different SNPs of *BER* and *NER* genes have been frequently studied for their role in determining cancer risk, but still there remained uncertainty in their precise association with other cancerswhere inconsistent the data pointed both increased or decreased risks (Hua et al., 2016; Fu et al., 2017; Yumei et al., 2020). In view of these conflicting results we examined the genotypic frequencies of *BER* and *NER* genes in a case-control study from rural women of south-western Maharashtra. The SNPs selected in this study were XRCC1 (*Arg194Trp, Arg280His, Arg399Gln*), hOGG1 (*Ser326Cys*), APE1 (*Asp148Glu*), XPC (*Val499Arg, Lys939Gln*) and XPD (*Arg156Arg, Asp312Asn, Lys751Gln*). The results

Table 7. Association between Cervical Cancer Risk and the Single Nucleotide Polymorphism Variant of Nucleotide Excision Repair Genes in the Dominant Model

Gene	Genotype/Allele	Cases (n= 400) (%)	Control (n =400)(%)	OR (95% CI)
XPC	Arg/Arg	260 (65.00)	131 (32.75)	1 (Reference)
Val499Arg	Val/Arg+Val/Val	140 (35.00)	269 (67.25)	0.26 (0.19-0.35)
rs2228000				
XPC	Gln/Gln	39 (9.75)	27 (6.75)	1 (Reference)
Lys939Gln	Lys/Gln+Lys/Lys	361 (90.25)	373 (93.25)	0.67 (0.40-1.11)
rs2228001				
XPD	Arg/Arg	62 (15.50)	70 (17.50)	1 (Reference)
Arg156Arg	Arg/Arg+Arg/Arg	338 (84.50)	330 (82.50)	1.15 (0.79-1.68)
rs238406				
XPD	Asn/Asn	16 (4.00)	27 (6.75)	1 (Reference)
Asp312Asn	Asp/Asn+Asp/Asp	384 (96.00)	373 (82.50)	1.73 (0.92-3.27)
rs1799793				
XPD	Gln/Gln	25 (6.25)	32 (8.00)	1 (Reference)
Lys751Gln	Lys/Gln+ Lys/Lys	375 (93.75)	368 (92.00)	1.30 (0.75-2.24)
rs13181				

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

Table 8. Association of *XRCC1, hOGG1* and *APE1* Gene Variants with Demographic Variables Including Age of Cancer Occurrence, Age at First Pregnancy, and Tobacco Smoking in Cervical Cancer Cases and Control Group from Population of Maharashtra

Gene	Genotype	Age (yrs) (Cases/Control)		Age (yrs) @ 1st pregnancy (Cases/Control)		Tobacco status (Cases/Control)	
		≤ 50 N=262/286	> 50 N=138/114	15-20 N=303/183	21-35 N=97/217	Users N=206/112	Non-Users N=194/288
XRCC1	C/C	204/225	105/91	239/138	70/178	166/89	143/227
C26304T	C/T+T/T	58/61	33/23	64/45	27/39	40/23	51/61
rs1799782	OR (95% CI)	1.04 (0.69-1.57)	1.24 (0.68-2.27)	0.82 (0.53-1.26)	1.76 (1.00-3.09)	0.93 (0.52-1.65)	1.32 (0.86-2.03)
XRCC1	G/G	93/207	53/88	113/126	33/169	83/86	63/209
G27466A	G/A+A/A	169/79	85/26	190/57	64/48	123/26	131/79
rs25489	OR (95% CI)	4.76 (3.31-6.84)	5.42 (3.11-9.46)	3.71 (2.51-5.48)	6.82(4.02-11.58)	4.90 (2.91-8.24)	5.50 (3.70-8.17)
XRCC1	G/G	95/190	61/56	125/96	31/150	85/68	71/178
G28152A	G/A+A/A	167/96	77/58	178/87	66/67	121/44	123/110
rs25487	OR(95% CI)	3.47 (2.44-4.94)	1.21 (0.74-2.00)	1.57 (1.08-2.27)	4.76 (2.84-7.97)	2.20 (1.37-3.51)	2.80 (1.92-4.08)
hOGG1	C/C	52/145	29/57	55/97	26/105	39/50	42/152
C1245G	C/G+G/G	210/141	120/57	248/86	71/112	167/62	152/136
rs1052133	OR (95% CI)	4.15 (2.83-6.08)	4.13 (2.39-7.15)	5.08 (3.36-7.67)	2.56 (1.51-4.31)	3.45 (2.07-5.75)	4.04 (2.67-6.11)
APE1	T/T	208/201	120/72	254/130	64/143	166/69	152/205
T2197G	T/G+G/G	54/85	18/42	49/53	33/74	40/43	42/83
rs1130409	OR (95% CI)	0.61 (0.41-0.90)	0.25 (0.13-0.48)	0.47 (0.30-0.73)	0.99 (0.60-1.65)	0.38 (0.23-0.64)	0.68 (0.44-1.04)

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

obtained in this study indicated that relative increase in 280His, 399Gln variant genotypes of XRCC1 and 326 Cys genotype of hOGG1indicate significant association with risk of CC. Similar association was also observed in *NER* gene including 499Arg genotype of XPC. A number of studies validated the polymorphism in *XRCC1, hOGG1, APE1, XPC* and *XPD* genes and their role in breast, lung, gastric and many other types of cancers

(Dai et al., 2015; Wang et al., 2018; Balkan et al., 2020; Kaur et al., 2020; Zhou et al., 2021). However, very little knowledge exists on the association of *BER* and *NER* gene polymorphism and cervical cancer susceptibility (Bajpai et al., 2016; Chen et al., 2019; Das et al., 2021). Also, few other Indian studies discovered the positive significance of polymorphism of DNA repair genes with cancer development (Ghosh et al., 2016; Yadav et al.,

Table 9. Association of *XPC* and *XPD* Gene Variants with Demographic Variables Including Age of Cancer Occurrence, Age at First Pregnancy, and Tobacco Smoking in Cervical Cancer Cases and Control Group from Population of Maharashtra

Gene	Genotype	Age (yrs) (Cases/Control)		Age (yrs) @ 1st pregnancy (Cases/Control)		Tobacco status (Cases/Control)	
		≤ 50 N=262/286	> 50 N=138/114	15-20 N=303/183	21-35 N=97/217	Users N=206/112	Non-Users N=194/288
XPC	C/C	56/130	24/51	62/83	18/98	36/53	44/128
C21151T	C/T+T/T	206/156	114/63	241/100	79/119	170/59	150/160
rs2228000	OR (95% CI)	3.06 (2.10-4.46)	3.84 (2.16-6.83)	3.22 (2.15-4.82)	3.61(2.02-6.46)	4.24 (2.53-7.11)	2.72 (1.81-4.10)
XPC	A/A	126/145	69/53	149/92	46/106	108/64	87/134
A33512C	A/C+C/C	136/141	69/61	154/91	51/111	98/48	107/154
rs2228001	OR (95% CI)	1.11 (0.79-1.55)	0.86 (0.52-1.42)	1.04 (0.72-1.50)	1.05 (0.65-1.70)	1.20 (0.76-1.92)	1.07 (0.74-1.54)
XPD	C/C	87/98	39/47	99/66	27/63	67/44	59/101
C22541A	C/A+A/A	175/188	99/67	204/117	70/138	139/68	135/187
rs238406	OR(95% CI)	2.24 (1.52-3.29)	1.78 (1.05-3.01)	1.16 (0.79-1.70)	1.18 (0.69-2.02)	1.34 (0.83-2.16)	1.23 (0.83-1.82)
XPD	G/G	224/125	121/73	271/57	74/141	180/72	165/126
G23591A	G/A+A/A	38/161	17/41	32/126	23/76	26/40	29/162
rs1799793	OR (95% CI)	0.13 (0.08-0.19)	0.25 (0.13-0.47)	0.05 (0.03-0.08)	0.57 (0.33-1.00)	0.26 (0.14-0.45)	0.13 (0.08-0.21)
XPD	A/A	109/143	69/44	146/74	32/113	92/51	86/136
A35931C	A/C+C/C	153/143	69/70	157/109	65/114	114/61	108/152
rs13181	OR (95% CI)	1.40 (1.00-1.96)	0.62 (0.37-1.04)	0.73 (0.50-1.05)	2.01 (1.22-3.30)	1.03 (0.65-1.64)	1.12 (0.77-1.61)

Significance p< 0.005; OR, Odds ratio; CI, Confidence Interval

2018; Nagpal et al., 2020), while other failed to prove significant association (Singh et al., 2016; Datkhile et al., 2017; Nisar et al., 2018; Francis et al., 2018). We observed that 280His and 399Gln of XRCC1 and 326Cys of hOGG1 were collectively involved in CC development, but no evidence for the association of 194Trp of XRCC1 in cervical cancer risk. Based on the earlier studies indicated that, the Arg194Trp polymorphism was not associated with cervical cancer risk (Zeng et al., 2017). Our observations were in accordance with other association studies reported by (Bajpai et al., 2016; Charles et al., 2020) where XRCC1 (280His, 399Gln) SNPs were susceptible for CC risk. Our study also revealed that the heterozygote genotype of only 399 codon of XRCC1 corresponded the significant risk of CC. We observed statistically significant association with protective effect of APE-1 148Glu and XPD 312Asn genotypes for the CC with OR=0.59; 95% CI: 0.35-0.97; p=0.04 and (OR=0.34; 95% CI: 0.17-0.64); p=0.001 respectively. When we studied the contribution of demographic variables for their association with cancer risk, we observed an association of XRCC1 280His with tobacco habit (59.61%) with cervical carcinogenesis in rural women, while no association was observed between XRCC1 194 (C>T) and 399 (G>A) polymorphism, which was also reported by Charles et al., 2020). The association between CC and tobacco smoking has already been established (Sugawara et al., 2019; Ono et al., 2019). Polymorphism in XPC Val499Arg also plays a significant role as a risk modifier for CC, whereas other genotypes of XPC (Lys939Gln) and XPD (156Arg, 312Asn and 751Gln) were not involved in cervical carcinogenesis associated with tobacco habit. Overall, the findings of present case-control study implied that>50 year age, tobacco habit and 15 to 20 year age of marriage are associated with elevated risk of cervical cancer along with the significant relationship between the studied BER (*XRCC1:rs25489, hOGG1:rs1052133*) and NER (*XPC:rs2228000*) gene SNPs. The results of this analysis will require further confirmation with a larger cohort in order to better understanding of the genetic basis of cervical carcinogenesis.

In summary, this is the first study to report a risk modulation of cervical cancer with *BER* and *NER* gene polymorphisms in the women of south-western Maharashtra. This case-control study supported that the SNPs; XRCC1 (rs25489 and rs25487), hOGG1 (rs1052133) and XPC (rs2228000) may increase the risk of cervical cancer development, whereas APE1 (rs1130409) and XPD (rs1799793) lower the risk in the studied population.

Abbreviations
    CC: Cervical Cancer
    PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
    XRCC1: X-ray cross complementing group 1
    hOGG1: 8-oxoguanine DNA glycosylase 1
    APE1: apurinic/ apyrimidinic endonuclease 1
    XPC: Xeroderma pigmentosum complementation group C
    XPD: Xeroderma pigmentosum complementation group D
    SNP: Single Nucleotide Polymorphism
    OR: Odds Ratio
    CI: Confidence Interval
    μL: Microliter
    DNA: Deoxyribose Nucleic Acid
    EDTA: Ethylene Diamine Tetra Acetate
    SDS: Sodium dodecyl sulphate
    Pmole: Picomole

Author Contribution Statement

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

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Ethics Committee Approval
    The study protocol (KIMSDU/IEC/3/2013) was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences 'Deemed to be University', Karad.

Availability of data
    Not Applicable.

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