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RESEARCH ARTICLE

Association of Genetic Polymorphisms in Base excision Repair Pathways and Cervical Cancer Risk Factors in a Tertiary Care Centre

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Abstract

Background and Objective: Cervical cancer is one of the most frequent neoplastic disorders affecting women, with about half a million new cases diagnosed globally each year. Reduced DNA repair capacity (DRC) is linked to an increased risk of cancer, particularly cervical cancer. DNA repair gene polymorphisms may play a role in genomic instability and carcinogenesis. Cervical cancer is linked to a number of risk factors that have been verified. The goal of this study was to compare genotypes of DNA repair genes XRCC1-194, XRCC1-280, XRCC1-399, and XRCC3-241 with distinct histological subtypes in patients and controls. **Material and Methods:** To test this theory, 168 cervical cancer patients with histological confirmed cases and 184 healthy control women was inducted in the study. For genotyping we used CTPP method (Arg194Trp, Arg280His, and Arg399Gln & XRCC3-T241M). **Results:** A positive association was observed between the polymorphisms of XRCC1 genes, that is, in codons 194 [P=0.03, odds ratio (OR) =2.39, 95% confidence interval (CI)=5.2–1.1], 280 (P=0.01, OR=4.1, 95% CI=11.5–1.3), and 399 (P=0.01, OR=3.4, 95% CI=8.6–1.3) in cervical cancer As well as risk factor like early age of pregnancy, high number of parity are also likely to be contributing in disease development. **Conclusion:** Our results suggested that, XRCC1399 gene is an important candidate gene for susceptibility to cervical cancer. Although the sample size was small, the present study indicate a statistical association between cervical cancer and XRCC1 SNPs. Future studies are needed that may provide a better understanding of the association between gene polymorphism and cervical carcinoma risk factors are assessed.

Keywords: XRCC1- Gene polymorphism- cervical cancer- DNA repair- XRCC3

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Introduction

Cervical cancer prevalence and mortality have steadily dropped in many of the devolved countries during the previous four decades [1]. The drop has been attributed to increased usage of cervical cancer screening tests such as Papanicolau (Pap) testing. In less developed or developing countries, [2] however, this is not the case. Due to a lack of access to screening and the expensive cost of HPV vaccinations, cervical cancer is more common in underdeveloped countries than in affluent countries [3]. Cervical cancer has a tremendous impact on the lives of women all over the world, with one out of every five women in India being diagnosed with the disease. India's screening coverage is poor, despite the existence of national norms, due to infrastructure, financial constraints, and a big population [4]. As a result, cervical cancer is frequently detected through opportunistic screening or after symptoms appear.

Cervical cancer is caused by a mix of genetic and environmental factors [5]. Actions are also influenced by sexual activity and lifestyle circumstances. The HPV virus causes cervical cancer in asexually active people [6]. Cervical cancer is not passed down through the generations, and food has little born on its prevention.

The risk of cervical cancer increases with the age of first sexual intercourse, with a lower age or proximity to menarche increasing the risk. Before the age of 18, sexual

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activity is a factor [7]. There is a two-fold increase in the risk of cervical cancer when comparing the age of first intercourse to 21 years of age. When compared to one partner, the danger nearly doubles with two and triples with six or more partners [8].

Early menarche may be a factor in the Indian context, as it can lead to early marriage and then early coital exposure, which can lead to early pregnancy and thus early childbirth. Furthermore, early marriage may be to blame for long marriages and multiparty relationships. Early marriage, early coitus, early pregnancy, early childbirth, long marriage spans, and multiparty in the aetiology of cervical cancer have all been proven. As a result, early menarche can be influenced by the interactions and interdependence of these risk factors [9]. This may explain why it has been linked to a positive cancer cervix outcome in several studies.

High parity has long been suspected of being linked to an increased risk of cervical cancer, but prior studies have failed to account for the powerful effect of the human papillomavirus (HPV) [10]. To figure out what impact reproductive variables play in the progression of HPV infection to cancer. For decades, high parity has been thought to be linked to a higher risk of cervical cancer.

Oral contraceptive use has been linked to the development of cervix tumours. The most recent oral contraceptive form has been linked to an increased risk of disease [11]. Like OC, Smokeless tobacco Consumption (SLT) have been identified with 28 compounds that are carcinogenic have been isolated from SLT. Nicotine is absorbed straight into the body through the mucous membranes of the mouth or nose in the case of SLT. Furthermore, nicotine levels in the blood are similar in SLT users and smokers, and it stays in the bloodstream for a longer time. Oral malignancies, cardiovascular disorders, low birth weight, and mental illnesses have all been linked to SLT usage [12].

In multiple studies, a decreased DNA repair capability has been associated to an increased risk of cancer. Many DNA repair genes have genetic polymorphisms, which can influence gene function and DNA repair capability. These findings, combined with evidence that inherited DNA repair deficiencies are associated to an increased risk of cancer, support the theory that genetic variances in DNA repair genes may play a role in cancer risk. As a result, the current study looked at the relationship between, Arg194Trp, Arg280His, and Arg399Gln, XRCC3-T241M and HPV type (16, 18) infection and the risk of cervical cancer in the north Indian population.

Materials and Methods

Sample Collection

Cases of histologically proven primary cervical cancer were recruited from the city of Lucknow (Era's Lucknow Medical College & Hospital), while controls were chosen at random from healthy postmenopausal women who requested gynaecological tests. The criteria for selection included no positive findings during examination, no history of cancer. Sexual and reproductive history was obtained using a standardized questionnaire. And each participant signed an informed consent. A total of 168 cervical cancer patients with histological confirmation and 184 healthy control women were interviewed, filled out questionnaires, and agreed to give blood samples for genotyping.

Protocol for DNA Isolation: For SNP of DNA repair genes

DNA extraction from blood sample was extracted using the standard Phenol: Chloroform Isoamyl Alcohol:

HPV 16/18 RT-PCR Reaction Protocol

The volumes of Reaction Mix and Enzyme Mix per reaction was multiplied with the number of samples, which includes the number of controls and sample prepared. Molecular Grade Water is used as the negative control. Mix completely then spin down briefly in a centrifuge. Pipette 36µl (22.5µl for Smart Cycler II) Master Mix with micropipette of sterile filter tips to each real time PCR reaction plate/tubes.

Genotyping of DNA Repair Genes

Genotyping was based upon a duplex polymerase chain reaction technique with confronting-two-pair primer (PCR-CTPP) method. The amplified DNAs are allele-specific in their sizes, so that the DNA products can be applied directly for electrophoresis without the digestion by a restriction enzyme. All of the primers were mixed together in the same tube. A total volume of 25 l was used for PCR amplification, which included about 100 ng of genomic DNA, 0.5 µl of each primer, and 12.5 µl of DreamTaq green PCR master mix (2X) (Thermo Scientific, USA) (0.5 µl H2O, 2X DreamTaq green buffer, dream Taq DNA polymerase, dATP, dCTP, dGTP, dTTP, 0.4 mM each, and 4 mM MgCl2 . Initial denaturation at 94oC for 5 minutes was followed by 30 cycles of 94oC for 1 minute, 66oC for 1 minute, 72oC for 45s, and a final extension at 72oC for 5 minutes. PCR products were separated on a 2 percent agarose gel using 50 bp probes. Ladder.

The sample size for both case and controls was calculated using QUANTO software, $\chi 2$ analysis were used to assess deviation from Hardy–Weinberg equilibrium and to compare the genotype/allele frequency between the patients and the controls. Odds ratios (ORs) were obtained by unconditional logistic regression analysis. All statistical analyses were carried out using the SPSS software, version 17.0 (SPSS Inc., Chicago, Illinois, USA). The OR was calculated using unconditional logistic regression for risk genotypes with the wild-type genotype as a reference.

Results

The result for demographic analysis is shown on table 1, the age range of 41 to 50 years have the most number of cases. While the age range for first pregnancy was found to be in 26 to 30 years. Other parameter like age at menarche parity and smokeless tobacco consumption are all been shown in (Table 1).The genotype frequency of the C to T

Table 1. Showing Demographic and Clinicopathological Characteristics of Case and Control

Age range of Sample				
Age range	Control N (184) (%)	Case N (168) (%)	Odds Ratio	P value
20-30	14 (7.6)	21 (12.5)	Reference	
31-40	57 (29.34)	26 (15.47)	0.3	0.003
41-50	89 (48.36)	63 (37.3)	0.47	0.04
51-60	10 (5.43)	17 (10.11)	1.13	0.81
61-70	13 (7.06)	38 (22.61)	1.95	0.15
71-80	1 (.54)	2 (1.19)	1.33	0.82
81-90	0 (0)	1 (0.59)	0	0.41
Age at menarche				
<13 years	47 (25.54)	48 (28.57)		
13-14 years	73 (39.67)	100 (59.52)	1.34	0.25
>14 years	64 (34.78)	20 (11.90)	0.31	0.002
Use of Oral contraceptives				
Non user	77 (41.84)	59 (35.11)		
User	107 (58.15)	109 (64.88)		0.19
Parity				
Nullipara	0	0		
≤2	49 (26.63)	16 (9.52)	Reference	
3 to 5	108 (58.69)	128 (76.19)	3.63	0.00002
≥ 6	27 (14.67)	24 (14.28)	2.72	0.01

polymorphism XRCC194, homozygous wild type gene CC is 31 percent in controls and 25.59 percent in cases. Heterozygous CT gene is 19.64 percent in cases and 20.65 percent in controls. A significant association of TT alleles was found with Odds Ratio of 2.39 indicating an increased risk for TT in cervical cancer (2.39, CI: 3.05-0.99, p=0.05) .While the Alleles was found to be significantly associated with OR=2.03, p0.004, CI=3.33-1.24) compared to the control indicated in (Table 2).

The genotype frequency of XRCC 280 of G to A polymorphism, the frequency of Homozygous Wild type gene GG shows a frequency of 29.3 % in control compared to 20.83% in, Heterozygous GA gene shows a frequency of 19.64 % in cases compared to 20.65% in control. A significant association of TT alleles was found with Odds Ratio of 2.39 indicating an increased risk for TT in cervical cancer (2.39, CI: 3.05-0.99, p=0.05) .While the Alleles was found to be significantly associated with OR=2.03, p0.004, CI=3.33-1.24).

The genotype frequency of XRCC 399 of G to A polymorphism, the frequency of Homozygous Wild type gene GG shows a frequency of 28.26 % in control compared to 21.42% in cases, Heterozygous GA gene shows a frequency of 17.26 % in cases compared to 18.47% in control. A significant association of AA alleles was found with Odds Ratio of 3.44 indicating an increased risk for AA in cervical cancer (3.44, CI: 8.64-1.34, p=0.01) .While the Alleles A was found to be significantly associated with OR=2.22, p=0.002, CI=3.71-1.33) compared to the control.

XRCC3 Thr241Meth genotype frequencies among cases and controls. The frequencies for TT in controls and cases were 30.4% and 47.23%. While the heterozygote CT genotype has a frequency of 34.9% and 27.41% for control and cases respectively (OR=1.15,CI=1.93-0.69,p=0.59). The homozygous recessive gene CC shows a frequency of 34.7% and 25.41%. The alleles C has a frequency of 52.44% in the control group and a frequency of 41.96% in case group (OR=0.44, CI=0.56-0.30, p=0.0001).

Discussion

A growing body of research based on parental aggregation studies and study of inherited genetic variations has revealed the host genetic variants may also play a role in cervical cancer aetiology over the last few decades. Using the PCR- CTPP approach, we assessed the relative expression levels of four DNA repair genes in 352 patients. We have tried to look for a link between their genotype distributions and cervical precancer and invasive cancer. These polymorphisms have been found to have functional importance and may play a role in the interindividual variation in DNA repair ability in the general population as well as cancer patients' low DNA repair effectiveness [13, 14].

The housekeeping protein X-ray cross-complementing gene 1 (XRCC1) is involved in base excision repair (BER) and single-strand break repair. The constitutive response to endogenous mutagens and external exposures, such as tobacco smoke, is mediated by these overlapping mechanisms [15, 16]. XRCC1-mediated mechanisms, in particular, repair damage to DNA bases, the deoxyribose phosphate backbone, and oxidation or covalent attachment of no bulky electrophiles [17]. Repair intermediates, such as a basic sites and SSB, are often more genotoxic and cytotoxic than the initial lesion, hence resolving this

Table 2. Stratification of DNA Repair Gene Genotypes in the Patients with CC and Control Group

		Control 184 no (%)	Case (168) no (%)	OR	p- value	95% CI
XRCC1-194						
Genotype	CC	94 (51.08)	58 (34.52)	Reference		
	CT	49 (26.66)	33 (19.64)	1.09	0.75	(1.89-0.63)
	TT	41 (22.28)	77 (45.83)	3.04	0.00001	(5.02-1.84)
	CT+TT	90 (48.91)	110 (65.47)	1.98	0.001	(3.04-1.29)
Alleles	C	237 (64.44)	149 (45.42)	Reference		
	T	131 (35.51)	187 (57.01)	2.27	0.00001	(3.07-1.68)
XRCC1-280						
Genotype	GG	82 (44.56)	62 (36.90)	Reference		
	GA	61 (33.15)	37 (22.02)	0.8	0.41	(1.36-0.47)
	AA	41 (22.28)	69 (41.07)	2.23	0.001	(3.70-1.34)
	GA+AA	102 (55.43)	106 (63.09)	1.37	0.14	(2.11-0.90)
Alleles	G	225 (61.14)	161 (49.08)	Reference		
	A	143 (38.85)	175 (53.35)	1.72	0.0003	(2.32-1.28)
XRCC1-399						
Genotype	GG	94 (51.08)	52 (30.95)	Reference		
	GA	51 (27.71)	46 (27.38)	1.63	0.05	(2.75-0.97)
	AA	39 (21.19)	70 (41.66)	3.24	0.00001	(5.45-1.93)
	GA+AA	90 (58.91)	116 (69.04)	2.33	0.001	(3.61-1.51)
Alleles	G	239 (64.95)	150 (45.73)	Reference		
	A	129 (35.05)	186 (56.70)	2.3	0.00001	(3.11-1.70)
XRCC3-241						
Genotype	TT	56 (30.4)	79 (47.23)	Reference		
	CT	65 (34.9)	59 (27.41)	0.64	0.07	1.05-0.39
	CC	63 (34.7)	41 (25.41)	0.45	0.22	0.74-0.27
	CT+CC	129 (70.10)	100 (59.53)	0.55	0.006	0.85-0.36
Alleles	T	121 (32.8)	217 (64.58)	Reference		
	C	193 (52.44)	141 (41.96)	0.41	0.0001	0.56-0.30

Significant value shown in bold; OR, Odds ratio; CI, Confidence interval; p value, <0.05

genetic damage quickly is critical. At codons 194, 280, and 399 of the XRCC1 gene, three frequent polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) have been discovered. XRCC1 function may be affected by these neoconservative amino acid substitutions. Variant alleles may reduce repair kinetics, influencing susceptibility to negative health impacts such as cancer, as a result of this alteration in protein biochemistry.

The observed mean age at menarche for cases in this study was estimated to be 13 years. Although the impact of early menarche on the outcome of CC is controversial [18] this finding is consistent with previous research. Menarche was once thought to signify the start of ovulation as well as the beginning of hormonal changes in childhood and adolescence. In a prior study [19], have shown statistically significant link between later menarche age and the risk of ovarian cancer. Furthermore, other research found an inverse relationship between growing rates of overweight/obesity in childhood and adolescence and menarche age [20-22]. In our study age at menarche less than 13 showed strong association with XRCC1 -194 CT, TT and XRCC1399 AA genotype all showed strong association (Table 3).

High parity has long been suspected of being linked to an increased risk of cervical cancer, but prior studies have failed to account for the powerful effect of the human papillomavirus (HPV). In our study we found no association with parity less than 2, while with number of parity greater than 2 we found association with XRCC-1399 and XRCC1- 280 genotype AA with CC (Table 3). In case of XRCC1-194 we found association with both the heterozygous CT and homozygous TT genotype In case with XRCC1-241 and APE-148we found a protective role with CT& CC genotype as shown in (Table 5). Finally our study concludes, childbirth raised the incidence of immediate precursor lesions to cervical cancer, especially in women who had a persistent high-risk HPV infection.

Oral contraceptive tablets are extensively used as a method of contraception since they are thought to be safe and effective by many women [23]. In our study sample 59 were non-OC consumer while 109 have taken OC (Table 4), we did not find any association with non OC group with respected to DNA repair polymorphism. While with OC user we found XRCC-194 TT and

Table 3. Associations between Repair Gene Polymorphism and Age at Menarche among Cervical Cancer Cases

SNP	Genotype	<13 years (48)%	OR	CI	p value	>13 years (120)%	OR	95% CI	p value
XRCC1-194	CC	9 (18.75)	References			35 (29.16)	Reference		
	CT	12 (25)	2.56	(6.49-1.01)	0.04	28 (23.33)	1.53	(2.81-0.84)	0.16
	TT	27 (56.25)	6.88	(15.91-2.97)	0.00001	57 (47.5)	3.73	(6.53-2.14)	0.00001
	CT+TT	39 (81.25)	4.53	(9.88-2.07)	0.00005	85 (70.83)	2.54	(4.13-1.56)	0.0001
	C	30 (31.25)	References			98 (48.83)	Reference		
	T	66 (68.75)	3.98	(6.44-2.46)	0.00001	142 (59.16)	2.62	(3.66-1.88)	0.00001
XRCC1-280	GG	17 (35.41)	References			46 (38.33)	Reference		
	GA	9 (18.75)	0.71	(1.70-0.30)	0.44	31 (25.83)	0.91	(1.59-0.52)	0.73
	AA	22 (45.83)	2.59	(5.40-1.24)	0.01	43 (35.83)	1.87	(3.27-1.07)	0.02
	GA+AA	31 (64.58)	1.47	(2.83-0.76)	0.25	74 (61.66)	1.29	(2.07-0.81)	0.28
	G	43 (44.79)	References			123 (51.24)	Reference		
	A	53 (55.20)	1.28	(2.01-0.81)	0.29	117 (48.75)	1.5	(2.08-1.08)	0.01
XRCC1-399	GG	14 (29.16)	References			36 (17.47)	Reference		
	GA	3 (6.25)	0.39	(1.44-0.11)	0.14	35 (34.95)	1.79	(3.19-1.01)	0.0002
	AA	31 (64.58)	5.34	(11.11-2.56)	0.00003	49 (47.57)	3.28	(5.80-1.86)	0.00003
	GA+AA	34 (70.83)	2.54	(5.04-1.28)	0.01	85 (82.52)	2.47	(4.01-1.52)	0.0002
	G	31 (32.29)	References			72 (34.95)	Reference		
	A	65 (67.70)	3.88	(6.27-2.41)	0.00001	134 (65.04)	3.45	(4.93-.41)	0.00001
XRCC3-241	TT	17 (35.41)	References			52 (43.33)	Reference		
	CT	9 (18.75)	0.45	(1.08-0.19)	0.07	30 (25)	0.49	(0.87-0.27)	0.01
	CC	22 (45.83)	1.11	(2.30-0.54)	0.77	35 (29.16)	0.58	(1.01-0.33)	0.05
	CT+CC	31 (64.58)	0.78	(1.52-0.40)	0.46	65 (54.16)	0.53	(0.86-0.33)	0.01
	T	43 (44.79)	References			134 (55.83)	Reference		
	C	53 (55.20)	0.77	(1.23-0.49)	0.27	100 (41.66)	0.47	(0.66-0.33)	0.000001

Significant value shown in bold; OR, Odds ratio; CI, Confidence interval; p value, <0.05

Table 4. Associations between Repair Gene Polymorphism and Use of Oral Contraceptive

SNP	Genotype	Non User (59)%	OR	CI	P value	User (109)%	OR	95% CI	p value
XRCC1-194	CC	27 (45.76)	References			47 (43.11)	References		
	CT	14 (23.72)	0.99	(2.07-0.48)	0.98	24 (22.01)	0.98	(1.79-0.54)	0.94
	TT	18 (30.50)	1.53	(3.08-0.76)	0.23	38 (34.86)	1.85	(1.85-4.65)	0.03
	CT+TT	32 (54.23)	1.24	(2.23-0.69)	0.47	62 (56.88)	1.38	(2.22-0.86)	0.18
	C	68 (57.62)	References			118 (54.12)	References		
	T	50 (42.37)	1.33	(2.03-0.87)	0.18	100 (93.22)	1.53	(2.16-1.09)	0.01
XRCC1-280	GG	26 (44.06)	References			39 (33.05)	References		
	GA	13 (22.03)	0.67	(1.47-0.32)	0.29	18 (15.52)	0.62	(1.19-0.32)	0.14
	AA	20 (33.89)	1.54	(3.08-0.77)	0.22	52 (47.70)	2.67	(4.67-1.52)	0.0005
	GA+AA	33 (55.93)	1.02	(1.84-0.57)	0.94	70 (64.22)	1.42	(2.33-0.88)	0.15
	G	65 (55.08)	References			96 (44.03)	References		
	A	53 (44.91)	1.28	(1.95-0.84)	0.24	122 (55.96)	2	(2.81-1.42	0.00005
XRCC1-399	GG	31 (52.54)	References			41 (37.61)	References		
	GA	8 (13.55)	0.48	(1.11-0.20)	0.08	19 (17.43)	0.85	(1.62-0.45)	0.63
	AA	20 (33.89)	1.56	(3.05-0.79)	0.19	49 (44.95)	2.88	(5.03-1.65)	0.0001
	GA+AA	28 (47.45)	0.94	(1.70-0.52)	0.84	68 (62.38)	1.73	(2.81-1.07)	0.02
	G	70 (59.32)	References			101 (46.33)	References		
	A	48 (81.32)	1.27	(1.94-0.83)	0.26	117 (53.66)	2.15	(3.02-1.53)	0.00001
XRCC3-241	TT	21 (35.59)	References			48 (44.03)	References		
	CT	7 (11.86)	0.28	(0.71-0.11)	0.005	32 (29.35)	0.56	(1.00-0.32)	0.04
	CC	31 (52.54)	1.27	(2.46-0.66)	0.48	29 (26.60)	0.52	(0.93-0.29)	0.02
	CT+CC	38 (8.40)	0.77	(1.43-0.42)	0.41	61 (55.96)	0.52	(0.89-0.33)	0.01
	T	49 (41.52)	References			128 (58.71)	References		
	C	69 (58.47)	0.88	(1.36-0.57)	0.57	90 (41.28)	0.44	(0.63-0.31)	0.00004

Significant value shown in bold; OR, Odds ratio; CI, Confidence interval; p value, <0.05

Table 5. Associations between Repair Gene Polymorphism and Parity among Cervical Cancer Cases

SNP	Genotype	<2 (16)%	OR	CI	p value	>2 (152)%	OR	95% CI	p=value
XRCC1-194	CC	7 (2.28)	References			44 (28.94)	References		
	CT	3 (18.75)	0.82	(3.32-0.20)	0.78	47 (30.92)	2.05	(3.51-1.20)	0.01
	TT	6 (3.75)	1.97	(6.21-0.62)	0.24	61 (40.13)	3.18	(5.42-1.86)	0.00001
	CT+TT	9 (56.25)	1.34	(3.76-0.48)	0.57	108 (71.05)	2.56	(4.04-1.63)	0.00004
	C	17 (53.12)	References			135 (44.40)	References		
	T	15 (46.87)	1.6	(3.30-0.77)	0.2	169 (55.59)	2.26	(3.09-1.66)	0.00001
XRCC1-280	GG	7 (43.75)	References			47 (30.92)	References		
	GA	1 (6.25)	0.19	(1.60-0.02)	0.1	32 (21.05)	1.74	(3.20-0.95)	0.07
	AA	8 (50)	2.29	(6.74-0.78)	0.12	73 (48.02)	3.11	(5.25-1.84)	0.00001
	GA+AA	9 (56.25)	1.03	(2.89-0.37)	0.94	105 (69.07)	1.8	(2.82-1.14)	0.01
	G	15 (46.87)	References			126 (41.44)	References		
	A	17 (53.21)	1.78	(3.68-0.86)	0.11	178 (58.55)	2.22	(3.03-1.63)	0.00001
XRCC1-399	GG	11 (68.75)	References			52 (34.20)	References		
	GA	3 (18.75)	0.5	(1.88-0.13)	0.29	31 (20.39)	1.1	(1.92-0.63)	0.74
	AA	2 (12.5)	0.44	(2.07-0.09)	0.28	68 (44.73)	3.15	(5.30-1.88)	0.00001
	GA+AA	5 (31.25)	0.47	(1.42-0.16)	0.17	99 (65.13)	1.99	(3.10-1.28)	0.002
	G	25 (78.12)	References			135 (44.40)	References		
	A	7 (21.87)	0.52	(1.23-0.22)	0.13	167 (54.09)	2.29	(3.13-1.68)	0.00001
XRCC3-241	TT	7 (43.75)	Reference			71 (46.71)	Reference		
	CT	2 (12.5)	0.24	(1.21-0.05)	0.06	43 (28.26)	0.51	(0.86-0.30)	0.01
	CC	7 (43.75)	0.86	(2.60-0.28)	0.78	37 (24.34)	0.45	(0.77-0.26)	0.003
	CT+CC	9 (56.25)	0.55	(1.55-0.19)	0.25	80 (52.63)	0.48	(0.75-0.31)	0.001
	T	16 (50)	Reference			185 (60.85)	Reference		
	C	16 (50)	0.63	(1.30-0.30)	0.2	117 (38.48)	0.4	(0.55-0.29)	0.00001

Significant value shown in bold; OR, Odds ratio; CI, Confidence interval; p value, <0.05

AA genotype of XRCC1-280 and 399 showing strong association with increased risk of CC. While reduced risk was found in XRCC3-241 CT and CC genotype. Though our results show significant association in the groups of OC use, (Table 4). In conclusion, use of OC pills for longer duration had definite higher risk for developing cervical cancer [24]. Further, cohort studies are needed for use of specific type of OC pills and risk of cervical cancer.

In our study we found no association with parity less than 2, while with number of parity greater than 2 we found association with XRCC-1399 and XRCC1- 280 genotype AA with CC (Table 5). In case of XRCC1-194 we found association with both the heterozygous CT and homozygous TT genotype In case with XRCC1-241 and APE-148we found a protective role with CT& CC genotype as shown in (Table 5). Finally our study concludes, childbirth raised the incidence of immediate precursor lesions to cervical cancer, especially in women who had a persistent high-risk HPV infection.

In Conclusion, in cervical dysplasia, cervical smear abnormalities, and cervical cancer, DNA damage has been linked to HPV, smoking, and other aetiologies. Emergent DNA damage causes genomic instability, which sets in motion an oncogenic cascade. Despite the presence of DNA repair genes, the prevalence of DNA damage exceeding has been associated to insufficient DNA damage repair. The ability of repair genes to repair DNA or the loss of DNA repair gene capability Polymorphisms in DNA repair genes, when combined with differences in their sequence, diminish or abolish the efficacy of these genes, hastening tumour growth. According to various research findings, polymorphism in the XRCC1 Arg194Trp and Arg399Gln gene area is most important in gynaecologic and non-gynaecologic carcinogenesis. This gene polymorphism was shown to be statistically significantly larger in patients diagnosed with cervical dysplasia in our study when compared to the control group.

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Author's contributions

Mark Rector Charles designed the project and wrote the manuscript. All figures were made by Pushpendra and Ale Eba. All authors read, discussed, improved and approved the final version of the manuscript.

Disclosure statement

The authors declare that no competing financial interests or otherwise exist.

Availability of data

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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