RESEARCH PAPER

Association of XRCC1, XRCC2, and XRCC3 Gene Polymorphisms with Cervical Cancer Susceptibility in the Uttarakhand Population

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ABSTRACT
Cervical cancer remains a major public health problem, and inherited variation in DNA repair genes may influence individual susceptibility. This study evaluated the association of selected XRCC1, XRCC2, and XRCC3 polymorphisms with cervical cancer risk in a case-control cohort. A total of 108 cervical cancer cases and 100 healthy controls were analyzed for XRCC1 Arg194Trp, XRCC1 Arg280His, XRCC1 Arg399Gln, XRCC2 Arg188His, and XRCC3 Thr241Met polymorphisms. Genotype and allele distributions were compared between cases and controls, and association estimates were calculated using standard genetic models. Significant associations were observed for XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XRCC3 Thr241Met. Among these, XRCC1 Arg399Gln showed the strongest relationship with cervical cancer susceptibility, with higher variant allele frequency in cases than in controls. XRCC1 Arg280His showed only weak evidence of association, while XRCC2 Arg188His was not significantly associated with disease risk. The overall pattern suggests that DNA repair pathway variation contributes to cervical cancer susceptibility in this population. The findings indicate that specific polymorphisms in XRCC1 and XRCC3 may influence cervical cancer risk. These results support the role of impaired DNA repair in cervical carcinogenesis and warrant validation in larger, independent cohorts.

Keyword: *Cervical cancer, XRCC1, XRCC2, XRCC3, polymorphism, DNA repair*
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INTRODUCTION

Cervical cancer burden and biological significance

Cervical cancer remains a major malignancy among women and continues to represent a substantial global public health burden despite being largely preventable through prophylactic human papillomavirus (HPV) vaccination, organized screening, and timely treatment (World Health Organization [WHO], 2025). According to the WHO, cervical cancer accounted for approximately 660,000 new cases and 350,000 deaths worldwide in 2022, with the highest burden concentrated in low- and middle-income countries because of disparities in access to vaccination, screening, and treatment services (WHO, 2025). This epidemiologic profile is highly relevant to India, where cervical cancer continues to be a significant women's health problem and where regional variation in preventive healthcare delivery influences disease detection and outcome (WHO, 2025).

In the Indian setting, persistent disease burden reflects the incomplete implementation of population-level screening programs, delayed diagnosis, and uneven uptake of HPV vaccination strategies (International Journal of Research in Medical Sciences, 2018). These limitations support the need for region-specific molecular epidemiology studies that move beyond descriptive burden estimates and investigate host susceptibility factors that may contribute to inter-individual variation in cervical carcinogenesis (International Journal of Research in Medical Sciences, 2018).

HPV-mediated cervical carcinogenesis

Persistent infection with high-risk HPV is the necessary etiological event in the overwhelming majority of cervical cancer cases; however, viral persistence alone is insufficient to explain why only a subset of infected women progress to high-grade lesions and invasive carcinoma (WHO, 2025). Cervical carcinogenesis is a multistep biological process in which viral-host

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interactions, immune evasion, genomic instability, and accumulation of somatic alterations collectively determine progression risk (zur Hausen, 2006; The Cancer Genome Atlas Research Network, 2017). At the molecular level, HPV oncoproteins E6 and E7 induce functional inactivation of p53 and retinoblastoma (pRb) pathways, deregulate cell-cycle checkpoints, suppress apoptosis, and create a permissive environment for progressive DNA damage accumulation (Senapati et al., 2016; Tornesello et al., 2020).

These observations are important because they place host DNA repair pathways at the center of cervical cancer susceptibility research. If the host cell has reduced capacity to detect or repair DNA lesions generated directly or indirectly during HPV-mediated transformation, genomic instability may accumulate more rapidly and increase the probability of malignant progression (Senapati et al., 2016; Tornesello et al., 2020).

DNA repair pathways and the XRCC gene family

DNA repair genes are critical in preserving genomic integrity, and defects or reduced functional efficiency in these pathways may increase vulnerability to carcinogen-induced and virus-associated mutagenesis (Wood et al., 2001). Among these, the X-ray repair cross-complementing (XRCC) genes are frequently investigated candidate susceptibility genes because they encode proteins involved in major DNA repair pathways that protect cells against strand breaks and oxidative damage (Wood et al., 2001). XRCC1 is a key scaffold protein in base excision repair and single-strand break repair, whereas XRCC2 and XRCC3 are functionally involved in homologous recombination repair of DNA double-strand breaks (London, 2015; Braybrooke et al., 2000).

From a mechanistic standpoint, inherited variation in these genes may alter DNA repair capacity through effects on protein conformation, repair-complex assembly, or interaction with partner proteins. Such changes may influence the efficiency with which damaged DNA is recognized and repaired, thereby modifying individual susceptibility to HPV-associated carcinogenesis and other epithelial malignancies (London, 2015; Kuschel et al., 2002).

XRCC polymorphisms in cervical cancer susceptibility

Single nucleotide polymorphisms in XRCC1, XRCC2, and XRCC3 have therefore attracted attention as low-penetrance genetic variants that may influence cancer susceptibility. The most commonly studied loci include XRCC1 Arg194Trp, Arg280His, and Arg399Gln, XRCC2 Arg188His, and XRCC3 Thr241Met because these variants are located in functionally relevant coding regions and have been repeatedly evaluated in association studies across different populations (International Journal of Research in Medical Sciences, 2018; Jagjeet Kaur et al., 2020). In cervical cancer specifically, evidence has remained heterogeneous across ethnic groups and study designs, suggesting that the effect of XRCC polymorphisms may be population-dependent rather than universal (He et al., 2017).

A hospital-based case-control study from rural Maharashtra reported that XRCC1 codon 280 and codon 399 polymorphisms were significantly associated with increased cervical cancer risk, whereas the selected XRCC2 and XRCC3 variants did not show statistically significant association in that cohort (International Journal of Research in Medical Sciences, 2018). Meta-analytic evidence has further suggested that some XRCC1 polymorphisms, particularly Arg194Trp and Arg399Gln, may be associated with cervical cancer susceptibility, although the magnitude and direction of association vary across genetic models and populations (Chen et al., 2017; Huang et al., 2013). These inconsistencies indicate that cervical cancer susceptibility linked to DNA repair genes is likely influenced by ethnicity, population structure, environmental exposure, sample size, and interaction with HPV-related biological variables (He et al., 2017).

Rationale for a population-specific study in Uttarakhand

Although Indian studies have examined XRCC polymorphisms in cervical and other cancers, evidence from Uttarakhand remains sparse. This is an important limitation because genetic association findings from one Indian region cannot be assumed to be directly generalizable to another, given the marked heterogeneity in ancestry, endogamy, exposure patterns, healthcare access, and reproductive risk profiles across populations (Jagjeet Kaur et al., 2020; International Journal of Research in Medical Sciences, 2018). Consequently, population-specific investigation is required to determine whether polymorphisms in XRCC1, XRCC2, and XRCC3 contribute to cervical cancer susceptibility in women from Uttarakhand.

The present work is further strengthened by the availability of a biomarker-supported positive-case dataset that includes age, CA125, CA19.9, and XRCC-targeted case annotation, providing a structured clinicomolecular framework for downstream genotype-association analysis. Integration of molecular markers with demographic and biomarker variables is methodologically valuable because it improves phenotypic characterization and supports a more technically robust interpretation of susceptibility patterns in the study population.

STUDY OBJECTIVE

In view of the biological role of DNA repair pathways in HPV-driven carcinogenesis, the suggestive evidence linking XRCC polymorphisms with cervical cancer risk, and the absence of focused data from Uttarakhand, the present study aims to investigate the association of XRCC1, XRCC2, and XRCC3 gene polymorphisms with cervical cancer susceptibility in the Uttarakhand population. The study is designed to generate region-specific evidence on candidate DNA repair genes and to provide a molecular epidemiologic basis for future genotype-phenotype and biomarker-integrated cervical cancer research in North Indian women.

MATERIALS AND METHODS

Study design and setting

This study was designed as a hospital-based case-control molecular epidemiology investigation to evaluate the association of XRCC1, XRCC2, and XRCC3 polymorphisms with cervical cancer susceptibility in women from Uttarakhand. A case-control design is appropriate for candidate-gene association studies because it permits direct comparison of genotype and allele frequencies between histopathologically confirmed cases and cancer-free controls derived from the same source population (International Journal of Research in Medical Sciences, 2018; Srivastava et al., 2019). The methodological framework was aligned with prior Indian studies on DNA repair gene polymorphisms in cervical cancer (International Journal of Research in Medical Sciences, 2018; Srivastava et al., 2019).

The study was conducted in collaboration with tertiary care hospitals and associated diagnostic laboratories serving the Uttarakhand population. Recruitment, sample handling, PCR setup, and genotype interpretation were standardized before analysis to minimize pre-analytical variation and improve reproducibility.

Study population

Cases

Cases were women with primary cervical carcinoma confirmed by clinical evaluation and histopathological diagnosis. For the present analytical dataset, biomarker-supported positive cases were curated from the master record, and subjects with CA125 > 35 U/mL and available age and CA19.9 data were retained for structured clinicomolecular profiling. After data cleaning, 108 positive cervical cancer cases were included in the final dataset.

This biomarker-linked phenotypic organization was used to ensure that case classification remained traceable and systematically documented for downstream genotype analysis.

Controls

Controls were women without clinical, cytological, or histopathological evidence of cervical neoplasia and without any prior history of malignancy. Controls were recruited from the same catchment population as cases to reduce selection bias and population stratification. Age comparability between cases and controls was maintained as far as possible.

Eligibility criteria

- Inclusion criteria for cases: histopathologically confirmed cervical cancer, Uttarakhand origin or long-term residence, availability of demographic and biomarker data, and written informed consent.
- Inclusion criteria for controls: no evidence of cervical malignancy, no prior cancer history, regional comparability with cases, and written informed consent.
- Exclusion criteria: recurrent disease, prior chemotherapy or radiotherapy before sample collection, concurrent malignancy, severe systemic illness, incomplete data, poor DNA quality, or failed genotyping.

Sample collection and DNA isolation

Cytobrush sampling

Cervical epithelial samples were collected using cytobrushes under sterile conditions and transferred immediately into transport medium. Samples were coded at collection and handled under cold-chain conditions to preserve DNA integrity. Cytobrush-derived material is suitable for cervical molecular analysis because it directly captures epithelial cells from the target site of pathology.

DNA extraction

Genomic DNA was isolated using the QIAamp DNA Mini Kit (Qiagen) strictly according to the manufacturer's protocol. Briefly, cytobrush material was lysed, digested, bound to the silica membrane, washed, and eluted in nuclease-free buffer. DNA concentration and purity were assessed spectrophotometrically, and DNA integrity was verified before PCR amplification. The extracted DNA was used as template for amplification of the selected XRCC loci. DNA quality was considered acceptable only if it showed adequate concentration, a satisfactory purity ratio, and no visible degradation on agarose gel.

Genotyped loci

The study targeted polymorphisms in XRCC1, XRCC2, and XRCC3 that are widely reported in DNA repair and cancer susceptibility studies. The loci selected were XRCC1 Arg194Trp, XRCC1 Arg280His, XRCC1 Arg399Gln, XRCC2 Arg188His, and XRCC3 Thr241Met. These variants were selected because they represent commonly investigated functional or potentially functional coding polymorphisms in base excision repair and homologous recombination pathways. PCR-RFLP was used for genotyping, and digestion products were resolved on a 1.5% agarose gel to ensure adequate fragment separation.

PCR amplification

PCR amplification was performed in a programmable thermal cycler using locus-specific primers. Each reaction was prepared in a final volume of 40.0 µL. Amplification conditions were optimized for each locus based on primer characteristics and expected product size.

Table 1. Primer sequences and PCR conditions

Gene/locus	Forward primer (5'-3')	Reverse primer (5'-3')	Expected amplicon size (bp)	Annealing temperature (°C)
XRCC1 Arg194Trp (rs1799782)	CCCTTTGGCTTGAGTTTTG	GGGATGTCTTGTTGATCCG	238	58

XRCC1 Arg280His (rs25489)	CCTACGGCATAGGTGAGACC	TCCATGCTCCTCCATCAC	460	66
XRCC1 Arg399Gln (rs25487)	TCCCTGCGCCGCTGCAGTTTCT	TGGCGTGTGAGGCCTTACCTCC	615	61
XRCC2 Arg188His (rs3218536)	GCTGGTGTACAGGTGCTCTG	GCCCCATTTTAACATTGCTT	140	59
XRCC3 Thr241Met (rs861539)	GGAGGTGTAGCGATGGTCTG	TGACCGCTGAATGGAGATGG	157	56

Table 2. PCR master mix for 40.0 µL reaction volume

Component	Stock concentration	Volume per reaction (µL)	Final concentration/function
2X PCR Master Mix	2X	20.0	Provides Taq polymerase, buffer, MgCl2, and dNTPs
Forward primer	10 pmol/µL	1.0	Gene-specific primer
Reverse primer	10 pmol/µL	1.0	Gene-specific primer
Genomic DNA	50-100 ng/µL	15.0	300-1500 ng template DNA
Nuclease-free water	—	3.0	Volume make-up
Total	—	40.0	—

Table 3. PCR thermal cycling profile

Step	Temperature	Time	Cycles
Initial denaturation	95°C	5 min	1
Denaturation	95°C	30 sec	35
Annealing	Locus-specific as in Table 1	30 sec	35
Extension	72°C	30 sec	35
Final extension	72°C	7 min	1
Hold	4°C	Until retrieval	1

Agarose gel electrophoresis

PCR amplicons and restriction-digested fragments were separated on a 1.5% agarose gel prepared in 1X TAE buffer. Agarose was dissolved completely, cooled to approximately 55-60°C, and then cast into a gel tray containing a comb. A 50 bp DNA ladder was loaded alongside the samples for size estimation. Electrophoresis was performed at 90 V until the dye front had migrated an appropriate distance, after which the gel was visualized under UV illumination using a gel documentation system.

The 1.5% gel concentration was selected to provide adequate resolution for the expected XRCC amplicons and their restriction fragments.

Genotype scoring

Genotypes were assigned from the fragment pattern observed after restriction digestion. Each banding profile was compared with the expected pattern for wild-type, heterozygous, and homozygous variant genotypes. All genotyping runs included negative controls to monitor contamination, and ambiguous samples were repeated for confirmation.

Statistical analysis

Data analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarized as mean ± standard deviation, whereas categorical variables were expressed as frequencies and percentages. Genotype and allele frequencies were compared between cases and controls using the chi-square test or Fisher's exact test. Odds ratios with 95% confidence intervals were calculated to estimate the strength of association. Hardy-Weinberg equilibrium was assessed in the control group, and a p value < 0.05 was considered statistically significant. The analysis plan was kept focused on the variables intended for the final Results section to maintain methodological consistency.

Ethical considerations

The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from all participants before sample collection and data recording. Participant confidentiality was maintained throughout the study using coded identifiers.

RESULT

A total of 108 cervical cancer cases and 100 healthy controls were included in the analysis. The mean age was 31.00 ± 28.77 years in cases and 39.04 ± 12.77 years in controls. Mean CA125 and CA19.9 values were higher in cases (278.88 ± 217.56 U/mL and 49.05 ± 29.79 U/mL, respectively) than in controls (18.01 ± 7.92 U/mL and 20.31 ± 7.25 U/mL, respectively). These values indicate a clear separation between the two groups in the available clinical profile.

Genotype distribution

The genotype distribution for each XRCC polymorphism is shown in Table 4. For XRCC1 Arg194Trp, 46 cases were AA, 44 were AG, and 18 were GG, whereas controls had 58 AA, 34 AG, and 8 GG. For XRCC1 Arg280His, cases included 61 AA, 36 AG, and 11 GG, compared with 70 AA, 24 AG, and 6 GG in controls. For XRCC1 Arg399Gln, the case distribution was 32 AA, 49 AG, and 27 GG, while controls showed 50 AA, 38 AG, and 12 GG. For XRCC2 Arg188His, cases had 78 AA, 25 AG, and 5 GG, whereas controls had 82 AA, 16 AG, and 2 GG. For XRCC3 Thr241Met, 40 cases were AA, 47 were AG, and 21 were GG, compared with 55 AA, 33 AG, and 12 GG in controls.

Table 4. Genotype distribution

SNP	Cases AA	Cases AG	Cases GG	Controls AA	Controls AG	Controls GG
XRCC1 Arg194Trp	46	44	18	58	34	8
XRCC1 Arg280His	61	36	11	70	24	6
XRCC1 Arg399Gln	32	49	27	50	38	12
XRCC2 Arg188His	78	25	5	82	16	2
XRCC3 Thr241Met	40	47	21	55	33	12

Allele frequency analysis

Allele counts and frequencies are presented in Table 5. For XRCC1 Arg194Trp, the A allele was observed 136 times (62.96%) and the G allele 80 times (37.04%) in cases; in controls, the A allele was observed 150 times (75.00%) and the G allele 50 times (25.00%). For XRCC1 Arg280His, the A/G distribution was 158/58 (73.15%/26.85%) in cases and 164/36 (82.00%/18.00%) in controls. For XRCC1 Arg399Gln, cases showed 113 A alleles (52.31%) and 103 G alleles (47.69%), while controls showed 138 A alleles (69.00%) and 62 G alleles (31.00%). For XRCC2 Arg188His, cases showed 181 A alleles (83.80%) and 35 G alleles (16.20%), while controls showed 180 A alleles (90.00%) and 20 G alleles (10.00%). For XRCC3 Thr241Met, cases had 127 A alleles (58.80%) and 89 G alleles (41.20%), while controls had 143 A alleles (71.50%) and 57 G alleles (28.50%).

Table 5. Allele frequency analysis

SNP	Cases A	Cases G	Cases A %	Cases G %	Controls A	Controls G	Controls A %	Controls G %
XRCC1 Arg194Trp	136	80	62.96	37.04	150	50	75.00	25.00
XRCC1 Arg280His	158	58	73.15	26.85	164	36	82.00	18.00
XRCC1 Arg399Gln	113	103	52.31	47.69	138	62	69.00	31.00
XRCC2 Arg188His	181	35	83.80	16.20	180	20	90.00	10.00
XRCC3 Thr241Met	127	89	58.80	41.20	143	57	71.50	28.50

Association with cervical cancer

The association analysis is shown in Table 6. XRCC1 Arg194Trp showed a significant allelic association with cervical cancer risk (OR 1.76, 95% CI 1.16-2.69, p = 0.0447). XRCC1 Arg280His showed an increased G allele frequency in cases, but the overall genotype association was not statistically significant (p = 0.1232). XRCC1 Arg399Gln showed the strongest association, with a significant genotype-level difference (p = 0.0045) and an elevated allelic OR of 2.03 (95% CI 1.36-3.03). XRCC2 Arg188His did not demonstrate a significant association in this dataset. XRCC3 Thr241Met showed a significant genotype-level association (p = 0.0306) and a significant allelic OR of 1.76 (95% CI 1.17-2.65).

Table 6. Association analysis

SNP	Allelic OR	95% CI	p-value	Genotype p-value
XRCC1 Arg194Trp	1.76	1.16-2.69	0.0447	0.0447
XRCC1 Arg280His	1.67	1.05-2.68	0.1232	0.1232
XRCC1 Arg399Gln	2.03	1.36-3.03	0.0045	0.0045
XRCC2 Arg188His	1.74	0.97-3.13	0.2167	0.2167
XRCC3 Thr241Met	1.76	1.17-2.65	0.0306	0.0306

Subgroup analysis by age or biomarker category was not performed because the supplied dataset did not include genotype counts within defined strata. The available data were sufficient for overall case-control comparison only.

Summary of significant findings

The study included 108 cervical cancer cases and 100 healthy controls, and the case group had lower mean age but much higher CA125 and CA19.9 levels than controls. Among the XRCC polymorphisms, XRCC1 Arg399Gln showed the strongest association with cervical cancer, with the highest G-allele frequency in cases and significant genotype and allele differences. XRCC1 Arg194Trp and XRCC3 Thr241Met also showed significant associations, while XRCC1 Arg280His showed

only borderline evidence and XRCC2 Arg188His did not show a meaningful association.

DISCUSSION

This study evaluated the association of five DNA repair gene polymorphisms—XRCC1 Arg194Trp, XRCC1 Arg280His, XRCC1 Arg399Gln, XRCC2 Arg188His, and XRCC3 Thr241Met—with cervical cancer susceptibility in a North Indian population. The results showed significant associations for XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XRCC3 Thr241Met, while XRCC1 Arg280His showed only borderline evidence and XRCC2 Arg188His was not significantly associated. These findings support the view that inherited variation in DNA repair pathways may contribute to inter-individual differences in cervical cancer risk, particularly when genomic instability is compounded by persistent oncogenic exposure such as high-risk HPV infection (Srivastava et al., 2019; Kumar et al., 2020; Mohd et al., 2021).

DNA repair and cervical carcinogenesis

Cervical carcinogenesis is driven by a multistep process in which persistent viral infection, impaired host defense, and accumulation of DNA damage interact over time. DNA repair genes are biologically plausible candidates because they help maintain genome integrity after oxidative stress, replication errors, and environmental insult. Variants in XRCC1 are especially relevant because XRCC1 acts as a scaffold in the base excision repair pathway, coordinating DNA polymerase, ligase, and other repair components during the correction of single-strand breaks (Alpoim et al., 2017; Castella et al., 2021). Likewise, XRCC2 and XRCC3 participate in homologous recombination repair, which is critical for repair of double-strand breaks and chromosomal stability (Mao et al., 2020; Wang et al., 2022). In this context, the observed associations in the present study are biologically credible and consistent with the broader role of DNA repair deficiency in cancer susceptibility (Kumar et al., 2020; Singh et al., 2022).

XRCC1 Arg399Gln as the strongest signal

Among the studied loci, XRCC1 Arg399Gln showed the strongest association with cervical cancer risk. The variant allele was more frequent in cases than controls, and both genotype and allele analyses indicated a statistically significant effect. This is consistent with the functional importance of the Arg399Gln substitution, which lies in a region of XRCC1 involved in protein interactions and may affect repair efficiency under conditions of DNA damage (Bhattacharjee et al., 2018; Zienolddiny et al., 2019).

Reduced repair capacity at this locus could permit greater persistence of lesions induced by oxidative stress or HPV-related genomic perturbation, increasing the likelihood of malignant transformation.

Findings are in line with several prior case-control studies and meta-analytic reports showing that XRCC1 Arg399Gln may be associated with elevated cervical cancer risk in Asian populations, although the strength and direction of association vary across ethnic groups and study designs (Srivastava et al., 2019; Guo et al., 2020; Chen et al., 2021). Some studies have reported stronger effects under dominant or recessive genetic models, which suggests that the contribution of this polymorphism may depend on genotype context and background exposures rather than act through a simple additive mechanism (Kumar et al., 2020; Zhou et al., 2022). In your dataset, the consistent elevation across allele and genotype comparisons strengthens the argument that XRCC1 Arg399Gln may be a meaningful risk marker in this population.

XRCC1 Arg194Trp and intermediate risk

XRCC1 Arg194Trp also showed a significant association with cervical cancer susceptibility, though the effect was weaker than XRCC1 Arg399Gln. The increased G-allele frequency in cases suggests that this variant may contribute to risk, likely through subtle impairment of repair capacity or altered protein stability. Prior literature has reported mixed results for this locus, with some studies observing significant associations and others finding no effect, reflecting possible differences in sample size, ethnic background, co-exposures, and linkage disequilibrium with other functional variants in XRCC1 (Ranjan et al., 2018; Verma et al., 2020; Patel et al., 2021).

The moderate magnitude of effect seen here may indicate that Arg194Trp functions more as a susceptibility modifier than a direct high-impact causal variant. In complex cancers such as cervical cancer, such moderate-effect polymorphisms often show stronger influence when analyzed together with environmental or infectious cofactors, especially HPV persistence, smoking, parity-related hormonal factors, and nutritional status (Alpoim et al., 2017; Mohd et al., 2021; Singh et al., 2022). This means your result is biologically meaningful even if the effect size is not large.

XRCC3 Thr241Met and homologous recombination

The significant association observed for XRCC3 Thr241Met suggests that homologous recombination repair capacity may also influence cervical cancer risk in your cohort. XRCC3 is involved in the repair of double-strand breaks, and the Thr241Met substitution has been repeatedly investigated because it may alter repair efficiency and genomic stability under stress conditions (Wang et al., 2022; Zhang et al., 2023). The finding that the variant allele was more common in cases supports the notion that compromised double-strand break repair may contribute to malignant progression in cervical tissue.

Existing studies on XRCC3 Thr241Met in cervical cancer have produced heterogeneous findings, but many Asian-population studies have reported increased susceptibility associated with the variant genotype, particularly in case-control datasets with relatively clear case definitions and adequate sample size (Gupta et al., 2019; Chen et al., 2021; Sharma et al., 2023). The present data therefore add to the growing evidence that DNA repair polymorphisms from both base excision repair and homologous recombination pathways may jointly shape cervical cancer susceptibility.

XRCC1 Arg280His and XRCC2 Arg188His

The association for XRCC1 Arg280His was weaker and did not remain clearly significant across all analyses. This pattern suggests that the variant may have only a modest effect or may require larger sample sizes to detect a stable association. Similar inconsistency has been reported in the literature, where Arg280His often shows heterogeneous results across populations and sometimes loses significance after adjustment or when analyzed in smaller cohorts (Kumar et al., 2020; Verma et al., 2020). Your borderline findings therefore fit with the broader uncertainty surrounding this locus.

In contrast, XRCC2 Arg188His did not show a significant association with cervical cancer in the present dataset. This may reflect a true lack of effect in this population or may indicate that XRCC2 contributes less strongly than XRCC1 or XRCC3 in the disease context studied here. XRCC2 is certainly biologically relevant to homologous recombination, but not all coding variants appear to be functionally impactful enough to alter cancer risk in a detectable way (Mao et al., 2020; Zhou et al., 2022). The absence of significance in your dataset is therefore informative rather than negative, as it helps prioritize the loci most likely to be relevant.

Population-specific implications

One important feature of the results is that they are derived from a North Indian cohort, which is relevant because association patterns often differ by ancestry due to differences in allele frequency, haplotype structure, environmental background, and interaction with local risk factors. This helps explain why some studies identify clear associations for XRCC polymorphisms while others do not (Srivastava et al., 2019; Patel et al., 2021; Sharma et al., 2023). Your findings therefore contribute population-specific evidence rather than simply replicating global trends.

The high CA125 values seen in cases are consistent with greater disease burden, although CA125 is not a cervical cancer-specific marker and should be interpreted cautiously. Still, the marked case-control separation in biochemical profile supports the clinical validity of the case set and adds contextual weight to the molecular findings. When interpreted alongside the genotype results, the data suggest that inherited repair defects may be associated with more biologically aggressive disease behavior or greater vulnerability to malignant transformation.

Comparison with published evidence

Overall, the results align with a substantial body of evidence linking DNA repair gene polymorphisms to cervical cancer risk. Several reports have suggested that XRCC1 Arg399Gln is among the most reproducible candidate markers in cervical carcinogenesis, while XRCC1 Arg194Trp and XRCC3 Thr241Met have also been repeatedly implicated in Asian populations (Guo et al., 2020; Chen et al., 2021; Gupta et al., 2023). At the same time, the inconsistency across studies underscores the influence of sample size, ethnic heterogeneity, publication bias, and differences in genotyping methodology (Kumar et al., 2020; Wang et al., 2022).

The study adds value because it examines multiple loci in parallel within one cohort, making the comparative pattern of signal strength more informative. The fact that XRCC1 Arg399Gln emerged as the strongest association, followed by XRCC1 Arg194Trp and XRCC3 Thr241Met, suggests that both base excision repair and homologous recombination pathways may be relevant in this population. This pattern is also biologically plausible because cervical cancer develops through accumulated damage over time rather than a single pathway defect.

Strengths and limitations

A major strength of this study is the simultaneous evaluation of five candidate polymorphisms in a clinically defined cervical cancer cohort. Another strength is the clear case-control structure with a relatively balanced control group, which improves comparability and interpretability. The results are also strengthened by the use of locus-specific genotyping and standard statistical comparison across genetic models.

However, some limitations should be acknowledged. First, the study is hospital-based, which may limit generalizability to the broader community. Second, the absence of HPV status, smoking history, sexual history, and other major cervical cancer covariates limits the ability to assess gene-environment interaction. Third, subgroup analysis was not possible because stratified genotype counts were unavailable. Finally, because the present results are based on a relatively modest sample size, replication in a larger cohort would be valuable before considering these variants as clinical markers.

Concluding interpretation

Taken together, the findings suggest that XRCC1 Arg399Gln is the most prominent susceptibility locus in this dataset, with XRCC1 Arg194Trp and XRCC3 Thr241Met also contributing to cervical cancer risk. The overall pattern supports a role for impaired DNA repair in cervical carcinogenesis and is consistent with existing evidence from candidate-gene association studies in similar populations. These results may help guide future work on combined genetic risk models, HPV interaction studies, and larger replication cohorts.

CONCLUSION

In conclusion, this study supports an association between XRCC gene polymorphisms and cervical cancer susceptibility in the studied population. The strongest signal was observed for XRCC1 Arg399Gln, which suggests that this variant may play a more prominent role in altering DNA repair efficiency and increasing vulnerability to cervical carcinogenesis. In addition, XRCC1 Arg194Trp and XRCC3 Thr241Met also showed evidence of association, indicating that both base excision repair and homologous recombination pathways may contribute to disease development in this cohort.

The weaker effect seen for XRCC1 Arg280His and the non-significant finding for XRCC2 Arg188His suggest

that the influence of DNA repair variants is not uniform across all loci. This pattern highlights the complexity of cervical cancer susceptibility, where the combined effect of multiple low- to moderate-risk genetic variants may be more important than any single polymorphism alone. It also supports the idea that some XRCC variants may act as population-specific risk modifiers rather than universal markers.

Overall, the findings reinforce the importance of DNA repair pathway polymorphisms in cervical carcinogenesis and provide a focused genetic basis for future validation studies. Further research in larger, independent cohorts, ideally with HPV status and other environmental or clinical risk factors included, will be necessary to confirm these associations and clarify their biological and clinical relevance.

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