**ORIGINAL ARTICLE**

# XRCC1 and XPD polymorphisms: clinical outcomes and risk of prostate cancer in Bangladeshi population

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## Abstract

**Background** In Bangladesh, only a fraction of prostate cancer patients are diagnosed annually due to lack of symptom awareness and screening challenges, resulting in high mortality. Aiming to improve screening methods, we evaluated X-ray cross-complementing gene 1 (XRCC1) Arg194Gln and Xeroderma pigmentosum group D (XPD) Lys751Gln polymorphisms to determine their relevance as potential markers for predicting prostate cancer risk, severity and clinical parameters in Bangladeshi population.

**Methods and results** This study included 132 prostate cancer patients and 135 healthy controls. Genotype analysis was done from blood samples by the PCR-RFLP method. The XRCC1 Trp/Trp genotype was associated with prostate cancer ($OR^{adj}$ = 5.51; 95% CI = 1.13–26.78; $p$-value = 0.03) compared to Arg/Arg genotype. No significant association was found between the XPD variants and prostate cancer risk. The XRCC1 Trp/Trp genotype increased prostate cancer risk in smokers and non-smokers but was statistically non-significant. In individuals without a family history of cancer, the XRCC1 Trp/Trp genotype had a non-significant 4.64-fold higher risk ($OR^{adj}$=4.64; 95% CI = 0.88–24.36; $p$-value = 0.07), while the XPD Gln/Gln had a 2.66-fold non-significant higher risk ($OR^{adj}$=2.66; 95% CI = 0.88–8.10; $p$-value = 0.09). The XRCC1 Trp/Trp variant was associated with hematuria risk, higher mean serum creatinine, and mean prostate-specific antigen (PSA) levels in prostate cancer patients. The XPD Gln/Gln variant was only associated with higher mean serum creatinine levels.

**Conclusion** Our findings suggest that XRCC1 screening may be used as a biomarker for prostate cancer to improve early diagnosis in Bangladesh.

**Keywords** DNA repair genes · Polymorphism · XRCC1 · XPD · Prostate Cancer

**Abbreviations**

| | |
|---|---|
| APEI | Apurinic/apyrimidinic Endonuclease |
| BER | Base excision repair |
| CI | Confidence Interval |
| DRE | Digital Rectal Examination |
| DSB | Double Strand Breaks |
| HDI | Human Development Index |
| NER | Nucleotide Excision Repair |
| OR | Odds Ratio |
| PAH | Polycyclic Aromatic Hydrocarbon |
| PCa | Prostate Cancer |
| PSA | Prostate-Specific Antigen |
| ROS | Reactive Oxygen Species |
| SCE | Sister Chromatid Exchange |
| SNP | Single Nucleotide Polymorphisms |
| SSB | Single-Strand Breaks |
| TFIIH | Transcription factor II |
| UTI | Urinary Tract Infection |

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| XPD | Xeroderma pigmentosum group D |
| XRCC1 | X-ray cross-complementing gene 1 |

## Introduction

Prostate cancer (PCa) remains the second most prevalent carcinoma and the fifth leading cause of male cancer death [1]. Current therapeutic approaches for high-risk non-metastatic PCa patients include the combination of abiraterone with prednisolone and androgen deprivation therapy (ADT) [2]. In the metastatic setting, enzalutamide and abiraterone should not be combined for those starting long-term ADT, as recently reported by Attard et al. (2023) [2]. Despite the excellent outcomes in the trials, there remains concerns regarding the risks of harm from continuous treatment to progression [2]. Thus, novel therapeutic approaches are needed. These advances in therapy also underscore the importance of early detection and proper screening, as available treatment options can significantly improve survival rates if the disease is diagnosed early. The occurrence of PCa in developing countries is much lower, yet survival rates are low [3, 4]. Developing countries account for a significant proportion of PCa incidence and mortality globally [5]. According to the Global Cancer Statistics 2020, PCa ranked second in countries with higher Human Development Index (HDI) following lung cancer and first in countries with lower HDI countries among men [1]. In Bangladesh, out of 1.3–1.5 million PCa patients, only 0.2 million are diagnosed annually due to a lack of symptoms, awareness, and screening techniques [6]. Additionally, most deaths occur due to late diagnosis. While PCa is screened on prostate-specific antigen (PSA) and digital examination, there remains an unmet need for an effective PCa screening method to reduce cancer-related mortality in Bangladesh.

Genetic variations are increasingly implicated in prostate carcinogenesis and its use in PCa prediction and prognosis [7–9]. Abnormalities in DNA repair genes, either germline or somatic, are detected in 19% of primary PCa cases and nearly 23% in advanced castration-resistant PCa cases [10]. For instance, pathogenic variants of BRCA1 have been linked to high Gleason score (aggressive tumor grades), distant metastases, and high chances of recurrence [10]. Polymorphisms of genes involved in DNA repair may alter protein function and an individual's capacity to repair damaged DNA, thus modulating susceptibility to cancer [11]. Base excision repair (BER) is a DNA repair pathway that precisely repairs non-bulky adducts, strand breaks, and endogenous base damage [12]. The X-ray Cross Complementing 1 (XRCC1) protein is an essential enzyme in the BER pathway encoded by the XRCC1 gene on chromosome 19q13.2-13.3 [13, 14]. The protein recognizes and binds to single-strand breaks (SSBs) by complexing with DNA ligase III at its COOH terminus, DNA polymerase β at its $NH_2$ terminus domain, human AP endonuclease (APE1), polynucleotide kinase, and poly(ADP-ribose) polymerase at the repair site [13]. One polymorphism in codon 194 in exon 6 of the XRCC1 gene (at position 26,304 on exon 6, base C to T, amino acid Arg to Trp, rs1799782) resulting in an arginine-to-tryptophan transition has been linked to cancer susceptibility in case-control studies of numerous cancers such as breast cancer [15], lung cancer [16], thyroid [17] and bladder cancer [18]. Data in PCa are much more conflicting across different races [19–22].

Another DNA repair pathway, nucleotide excision repair (NER), corrects various DNA lesions, including chemically induced bulky adducts, cross-links, and pyrimidine dimers, by excising the short single-stranded DNA segment containing the lesion and then repairing it through DNA synthesis and ligation [23]. Xeroderma Pigmentosum Complementary group D (XPD) is an ATP-dependent 5′-3′ helicase involved in NER, which interestingly, like XRCC1, also maps to chromosome 19q13.3 [24]. The XPD protein, an essential subunit of the transcription factor IIH (TFIIH) complex, unwinds DNA in damaged regions [25]. An XPD variant at position 751 in exon 23 (at position 35,931 on exon 23, base A to C, rs13181) causing a lysine-to-glutamine transition has been associated with non-small cell lung cancer [26], breast cancer [27], bladder cancer [28], and colorectal cancer [29]. However, several studies failed to identify an increased PCa risk with XPD Lys751Gln polymorphism, namely in the Indian population [30], the Taiwanese population [31], and the South Australian population [32]. The precise role of XRCC1 Arg194Trp and XPD Lys751Gln as genetic polymorphisms in PCa risk among men of Bangladesh remains largely unknown.

In this study, we evaluated the associations between these genetic polymorphisms and the risk of PCa in the Bangladeshi population. We also considered their smoking history and family history of cancer. In addition, studies on the Single Nucleotide Polymorphisms (SNPs) association with biochemical parameters and clinical features of PCa patients are relatively scarce. Therefore, we also explored the SNPs' association with the patient's clinical features, including PSA levels, serum creatinine levels, tumor staging, histopathological grading and digital rectal examination (DRE) findings.

## Materials and methods

### Subject selection criteria

A total of 132 PCa patients with histologically diagnosed PCa were recruited from the Department of Urology of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine, and Metabolic Disorders (BIRDEM) General Hospital, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. The control group comprised 135 healthy subjects who were unrelated to the cases from the same geographic area. Participants with a history of other chronic diseases and cancer were excluded from the study.

### Data collection by interview

With informed consent, participant details including age, smoking history, and family history of chronic diseases were obtained using a structured questionnaire. Clinical data were recorded in the presence of the attending physician. Present and former smokers were considered smokers, whereas individuals who had never smoked were classified as non-smokers. The tumor grade was classified as either low grade (Gleason's score < 7) or moderate to the high-grade tumor (Gleason's score ≥ 7). The cancer stage was categorized into two groups: Localized or Organ-confined, which included T1a-c/T2a-b N0 M0, and Locally advanced or metastatic, which had T3a-b/T4/N1/M1, according to TNM classification. The study was conducted following the approval from the Ethical Review Committees of the Faculty of Biological Sciences, University of Dhaka (Ref no. 206/Biol. Scs).

### Sample Collection and DNA extraction

About three milliliters (3.0 mL) of venous blood was drawn from each participant by a phlebotomist. The drawn blood was immediately transferred to EDTA (1.20 mg/mL) tubes. Genomic DNA was extracted from the whole blood samples using FavorPrep™ Blood Genomic DNA Extraction Mini Kit according to the manufacturer's protocol.

### Genotyping

The XRCC1 codon 194 and XPD 751 genotypes were determined using the PCR-RFLP technique. Briefly, two separate PCR assays were used to amplify the XRCC1 codon 194 and XPD codon 751 polymorphisms using primer sequences (Table 1) and PCR conditions following previously published papers [33–35]. Restriction enzymes PvuII for XRCC1 codon 194 and PstI for XPD codon 751 polymorphisms (New England Biolabs, USA) were used for restriction fragment analyses (Supplementary Figure S1 and S2).

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (v20.0; IBM Corp). Using logistic regression models, the relative associations were determined by calculating the odds ratio (OR) with 95% confidence intervals (CIs) and level of significance (p). Graph Pad Prism (v 8.4.2) was used to run the t-tests and Fisher's exact tests. $p$-value < 0.05 was taken as the significance level.

## Results

### Study subjects

Table 2 lists the baseline characteristics and the clinical parameters of the study subjects. The patients age ranged from 49 to 85, with a mean age of 67 years. Controls were between the ages of 47 and 88 years, with a mean age of 65 years. More than half (56.06%) of the cancer patients were between the ages of 60–70, while the least proportion (15.91%) of patients was observed in the < 60-year group. Smoking was more common among the cases compared to the controls (60.61% vs. 38.52%, $p$-value < 0.001).

**Table 1** Primer sequences for allele determination, with amplicon size and the resultant digested products size

| Gene Name | Gene Accession Number | dbSNP ID | Primer (5'-3') | Amplicon size | Restriction Digestion Products | Reference |
|---|---|---|---|---|---|---|
| XRCC1 | NM_006297.3 | rs1799782 | FP: GTTCCGTGTGAAGGAGGAGGA RP: CGAGTCTAGGTCTCAACCCTAC TCACT | 138 bp | Arg/Arg: 138 bp Arg/Trp: 138 bp, 75 bp and 63 bp Trp/Trp:75 bp and 63 bp | (Chacko, Rajan, Joseph, Mathew, & Pillai, 2005) |
| XPD | NM_000400.4 | rs13181 | FP: CCCCCTCTCCCTTTCCTCTGTTC RP: GGACCTGAGCCCCCACTAACG | 413 bp | Lys/Lys: 413 bp Lys/Gln: 413 bp, 322 bp and 91 bp Gln/Gln: 322 bp and 91 bp | (Mitra et al., 2009; Nairuz, Bushra, & Kabir, 2021) |

**Table 2** Baseline and clinical characteristics of the study subject

| Baseline and Clinical Characteristics | Control (n = 135) n (%) | Case (n = 132) n (%) | p-value |
|---|---|---|---|
| Age (Year)[a] | 65.13 ± 0.74 | 67.34 ± 0.73 | 0.03 |
| < 60 | 29 (21.48) | 21 (15.91) | |
| 60–70 | 79 (58.52) | 74 (56.06) | 0.23 |
| > 70 | 27 (20) | 37 (28.03) | |
| BMI (kg/m2) | | | |
| < 18.5 | - | 0 (0) | |
| 18.5–24.9 | - | 110 (83.33) | - |
| 25.0-29.9 | - | 22 (16.67) | |
| > 29.9 | - | 0 (0) | |
| Smoking status | | | |
| Non-Smoker | 83 (61.48) | 52 (39.39) | |
| Smoker | 52 (38.52) | 80 (60.61) | < 0.001 |
| Family History of Cancer | | | |
| No | 127 (94.07) | 110 (83.33) | - |
| Yes | 8 (5.93) | 22 (16.67) | < 0.01 |
| Grading of Tumor | | | |
| Gleason score < 7 | - | 78 (59.09) | - |
| Gleason score ≥ 7 | - | 54 (40.91) | - |
| Tumor Staging | | | |
| Localized or Organ-confined | - | 84 (63.64) | - |
| Locally advanced or metastatic | - | 48 (36.36) | - |
| DRE | | | |
| Soft mass with smooth surface | - | 49 (37.12) | - |
| Hard mass with irregular surface | - | 83 (62.88) | - |
| Hematuria | | | |
| Absent | - | 96 (72.73) | - |
| Present | - | 36 (27.27) | - |
| UTI | | | |
| Absent | - | 51 (38.64) | - |
| Present | - | 81 (61.36) | - |
| Creatinine (mg/dl) | | | |
| < 0.70 | - | 0 (0) | - |
| 0.7–1.3 | - | 91 (68.94) | - |
| > 1.3 | - | 41 (31.06) | - |
| PSA (ng/ml) | | | |
| ≤ 6.5 | - | 5 (3.79) | - |
| 6.6–10 | - | 18 (13.64) | - |
| > 10 | - | 109 (82.57) | - |

[a]Mean±SEM; [b]Numbers in parentheses show percentages. Body Mass Index (BMI); Digital rectal examination (DRE); Urinary Tract Infection (UTI); Prostate-specific Antigen (PSA); $p < 0.05$ was taken as the level of significance

Additionally, the cases had a higher prevalence of family history of cancer than the controls (16.67% vs. 3.7%, p-value < 0.05).

Most of the patients had low-grade (Gleason's score < 7) tumors (59.09%) and localized organ-confined tumors (63.64%). Above 60% of patients had UTIs, while only 27.27% had hematuria. Most patients had BMI in the normal range of 18.5–24.9 kg (83.33%) and average serum creatinine levels (0.7–1.3 mg/dl) (68.94%). However, majority (82.58%) had elevated PSA values (> 10 ng/ml).

## Frequency distribution of XRCC1 and XPD polymorphism and PCa risk

The XRCC1 homozygous mutant type (Trp/Trp) genotype increased PCa risk 5.51-fold (OR$^{adj}$ = 5.51; 95% CI = 1.13–26.78; p-value = 0.03) compared to homozygous wild type (Arg/Arg) genotype (Table 3). Heterozygous mutant (Arg/Trp) risk was not associated with PCa (OR$^{adj}$ = 1.21; 95% CI = 0.73–1.98; p-value = 0.46). The recessive model analysis was used to assess the effect of the minor allele (Trp allele) on the association of PCa risk. The recessive model, i.e., carrying two copies of the XRCC1 194 codon Trp allele, was positively associated by 4.88 times with the risk of PCa (OR$^{adj}$ = 4.88; 95% CI = 1.24–22.62.12; p-value = 0.03).

In the analysis of XPD genotypes, the homozygous mutant variants (Gln/Gln) of XPD had 2.25 times the risk of PCa compared to the wild type variant, however, the association was non-significant (OR$^{adj}$ = 2.25; 95% CI = 0.81–6.28; p-value = 0.12). Similarly, carrying two copies of the XPD codon 751 Gln allele was non-significantly associated (2.5-folds) with the risk of PCa (OR$^{adj}$ = 2.55; 95% CI = 1.01–6.67; p-value = 0.07) as observed in the recessive model analysis.

## Combined genotypic effects of XRCC1 and XPD polymorphisms on PCa Risk

Pairwise joint associations of XRCC1 Arg194Trp and XPD Lys751Gln genotypes with PCa risk were all non-significant (Table 4, Supplementary Table S1). The combined effect of XRCC1 Trp/Trp and XPD Lys/Lys has the highest risk of PCa (8.23 folds) but was statistically insignificant (OR = 8.23; 95% CI = 1.33–95.83; p-value = 0.06). No healthy control was homozygous mutant in both genes, so its combined effect could not be compared.

## XRCC1 and XPD polymorphism on risk of PCa based on Smoking Status and Family History of Cancer

Smokers with XRCC1 Trp/Trp genotype had a non-significant 5.45 times increased PCa risk (OR$^{adj}$ = 5.45; 95% CI = 0.63–47.39; p-value = 0.13) and XPD Gln/Gln genotype had a non-significant 3-fold increased PCa risk (OR$^{adj}$ = 3.04; 95% CI = 0.59–15.40; p-value = 0.18) (Table 5). Surprisingly, none of the variants of XRCC1 or XPD were significantly associated with PCa risk in

**Table 3** Genotype frequencies of XRCC1 codon 194 and XPD codon 751 using codominant, homozygous dominant, homozygous recessive, and over-dominant models

| Genotype model | Genotype | Control ($n = 135$) n (%) | Case ($n = 132$) n (%) | OR$^{adj}$ (95% CI) | $p$-value$^{adj}$ |
|---|---|---|---|---|---|
| XRCC1 | | | | | |
| Co-dominant model | Arg/Arg | 69 (51.11) | 58 (43.94) | 1 (Ref) | - |
| | Arg/Trp | 64 (47.41) | 65 (49.24) | 1.21 (0.73–1.98) | 0.46 |
| | Trp/Trp | 2 (1.48) | 9 (6.82) | 5.51 (1.13–26.78) | 0.03 |
| Dominant model | Arg/Arg | 69 (51.11) | 58 (43.94) | 1 (Ref) | - |
| | Arg/Trp + Trp/Trp | 66 (48.89) | 74 (56.06) | 1.33 (0.82–2.18) | 0.28 |
| Recessive model | Arg/Arg + Arg/Trp | 133 (98.52) | 123 (93.18) | 1 (Ref) | - |
| | Trp/Trp | 2 (1.48) | 9 (6.18) | 4.88 (1.24–22.62) | 0.03 |
| Over-dominant model | Arg/Arg + Trp/Trp | 71 (52.59) | 67 (50.76) | 1 (Ref) | - |
| | Arg/Trp | 64 (47.41) | 65 (49.24) | 1.06 (0.67–1.74) | 0.82 |
| XPD | | | | | |
| Co-dominant model | Lys/Lys | 68 (50.37) | 64 (48.48) | 1 (Ref) | - |
| | Lys/Gln | 61 (45.19) | 54 (40.91) | 0.91 (0.55–1.51) | 0.72 |
| | Gln/Gln | 6 (4.44) | 14 (10.61) | 2.25 (0.81–6.28) | 0.12 |
| Dominant model | Lys/Lys | 68 (50.37) | 64 (48.48) | 1 (Ref) | - |
| | Lys/Gln + Gln/Gln | 67 (49.63) | 68 (51.52) | 1.08 (0.67–1.75) | 0.81 |
| Recessive model | Lys/Lys + Lys/Gln | 129 (95.56) | 118 (89.39) | 1 (Ref) | - |
| | Gln/Gln | 6 (4.44) | 14 (10.61) | 2.55 (1.01–6.67) | 0.07 |
| Over-dominant model | Lys/Lys + Gln/Gln | 74 (54.81) | 78 (59.09) | 1 (Ref) | - |
| | Lys/Gln | 61 (45.19) | 54 (40.91) | 0.84 (0.51–1.37) | 0.54 |

Adjusted for age in Logistic Regression. Odds ratios (OR) and 95% confidence interval (95%CI); $p < 0.05$ was considered as the level of significance

**Table 4** Combined genotypic effects of XRCC1 Arg194Trp and XPD Lys751Gln and PCa risk

| XRCC1 | XPD | Control ($n = 135$) n (%) | Case ($n = 132$) n (%) | OR (95% CI) | $p$-value |
|---|---|---|---|---|---|
| Arg/Arg | Lys/Lys | 38 (28.15) | 32 (24.24) | 1 (Ref) | - |
| Arg/Arg | Gln/Gln | 2 (1.48) | 5 (3.79) | 2.88 (0.54–15.03) | 0.26 |
| Arg/Trp | Gln/Gln | 4 (2.96) | 9 (6.82) | 2.59 (0.69–8.08) | 0.23 |
| Trp/Trp | Lys/Lys | 1 (0.74) | 7 (5.30) | 8.23 (1.33–95.83) | 0.06 |
| Trp/Trp | Lys/Gln | 1 (0.74) | 2 (1.52) | 2.28 (0.16–36.20) | 0.59 |
| Trp/Trp | Gln/Gln | 0 (0) | 0 (0) | - | - |
| Trp/Trp | Any Gln | 1 (0) | 2 (1.52) | 2.38 (0.26–35.2) | 0.6 |
| Any Trp | Gln/Gln | 4 (2.96) | 9 (6.82) | 2.59 (0.69–8.08) | 0.23 |

Odds ratios (OR) and 95% confidence interval (95%CI); $p < 0.05$ was considered as the level of significance

individuals with a family history of cancer. In those without a family history of cancer, the XRCC1 Trp/Trp genotype had a 4.64-fold higher risk of PCa (OR$^{adj}$=4.64; 95% CI=0.88–24.36; $p$-value=0.07), while the XPD Gln/Gln had a 2.66-fold higher risk (OR$^{adj}$=2.66; 95% CI=0.88–8.10; $p$-value=0.09). Both were statistically insignificant ($p$-value > 0.05).

## Association of XRCC1 and XPD polymorphism with clinical parameters of patients

XRCC1 Arg194Trp or XPD Lys751Gln polymorphism was not significantly associated with tumor grade, tumor stage, DRE results, or UTIs ($p$-value > 0.05) (Table 6). However, the XRRC1 Trp/Trp genotype doubled the likelihood of high-grade tumors (Gleason score ≥ 7). Conversely, the XPD

Lys/Gln and Gln/Gln genotypes increased the risk of having locally advanced or metastatic tumors by 3-fold but did not reach statistical significance. The XRCC1 Trp/Trp genotype increased hematuria risk by 12.57 times ($p$-value > 0.05). The homozygous mutant genotypes of XRCC1 and XPD increased the risk of higher serum creatine levels (Table 6). Having the mutant homozygous genotype of XRCC1 also increased the risk of having higher PSA levels in patients.

Mean serum creatinine levels (1.41 mg/dl vs. 1.19 mg/dl) and mean PSA levels (73.2 ng/ml vs. 44.2 ng/ml) were higher in patients with XRCC1 Trp/Trp genotype ($p$-value < 0.05) (Fig. 1). Accordingly, the homozygous mutant Gln/Gln genotype of the XPD gene was also significantly associated with higher creatinine levels in PCa patients (1.34 mg/dl vs. 1.17 mg/dl) ($p$-value = 0.04) (Fig. 2).

**Table 5** XRCC1 and XPD genotype on risk of PCa according to smoking status and family history of cancer

| Variables | Genotype | Control (n = 135) n (%) | Case (n = 132) n (%) | OR$^{adj}$ (95% CI) | p-value$^{adj}$ |
|---|---|---|---|---|---|
| **XRCC1** | | | | | |
| Non-smoker | Arg/Arg | 43 (31.85) | 24 (18.18) | 1 (Ref) | - |
| | Arg/Trp | 39 (28.89) | 26 (19.70) | 1.18 (0.58–2.41) | 0.65 |
| | Trp/Trp | 1 (0.74) | 2 (1.52) | 3.72 (0.32–43.79) | 0.29 |
| Smoker | Arg/Arg | 26 (19.26) | 34 (25.76) | 1 (Ref) | - |
| | Arg/Trp | 25 (18.51) | 39 (29.55) | 1.19 (0.58–2.46) | 0.62 |
| | Trp/Trp | 1 (0.74) | 7 (5.30) | 5.45 (0.63–47.39) | 0.13 |
| No Family History of Cancer | Arg/Arg | 65 (48.15) | 45 (34.09) | 1 (Ref) | - |
| | Arg/Trp | 60 (44.44) | 59 (44.70) | 1.43 (0.84–2.42) | 0.19 |
| | Trp/Trp | 2 (1.48) | 6 (4.55) | 4.64 (0.88–24.36) | 0.07 |
| Have Family History of Cancer | Arg/Arg | 4 (2.96) | 13 (9.85) | 1 (Ref) | - |
| | Arg/Trp | 4 (2.96) | 6 (4.55) | 1.05 (0.30–3.65) | 0.94 |
| | Trp/Trp | 0 (0) | 3 (2.27) | - | - |
| **XPD** | | | | | |
| Non-smoker | Lys/Lys | 40 (29.63) | 26 (19.70) | 1 (Ref) | - |
| | Lys/Gln | 39 (28.89) | 21 (15.91) | 0.77 (0.37–1.62) | 0.49 |
| | Gln/Gln | 4 (2.96) | 5 (3.79) | 1.85 (0.44–7.68) | 0.40 |
| Smoker | Lys/Lys | 28 (20.74) | 38 (28.79) | 1 (Ref) | - |
| | Lys/Gln | 22 (16.30) | 33 (25.00) | 1.09 (0.53–2.27) | 0.81 |
| | Gln/Gln | 2 (1.48) | 9 (6.82) | 3.04 (0.59–15.40) | 0.18 |
| No Family History of Cancer | Lys/Lys | 66 (48.89) | 54 (40.91) | 1 (Ref) | - |
| | Lys/Gln | 56 (41.48) | 44 (33.33) | 0.93 (0.54–1.59) | 0.78 |
| | Gln/Gln | 5 (3.70) | 12 (9.09) | 2.66 (0.88–8.10) | 0.09 |
| Have Family History of Cancer | Lys/Lys | 2 (1.48) | 10 (7.58) | 1 (Ref) | - |
| | Lys/Gln | 5 (3.70) | 10 (7.58) | 0.38 (0.06–2.49) | 0.31 |
| | Gln/Gln | 1 (0.74) | 2 (1.52) | 0.34 (0.02–6.25) | 0.47 |

Adjusted for age in Logistic regression using selection variable. Odds ratios (OR) and 95% confidence interval (95%CI); $p < 0.05$ was considered as the level of significance

# Discussion

Predictive factors can assist clinicians in tailoring treatments for individual patients. Recently, liquid biopsy has emerged as a promising alternative to invasive tissue biopsies, offering minimal invasiveness for prostate cancer diagnoses. Liquid biopsy is used to evaluate several biomarkers in body fluids, including circulating tumor cells (CTCs), extracellular vesicles (EVs), circulating tumor DNA (ctDNA) and RNA (ctRNA), as well as serum biomarkers like miRNA, AR-Vs, bone metabolism, neuroendocrine, and metabolic markers [36, 37]. However, the high cost, the discrepancies in definition, isolation methods and standardization pose challenges to validating these tests and being approved for clinical use. Given the ongoing difficulties in developing liquid biopsy biomarkers for clinical use, SNPs in DNA repair genes emerge as a promising area for developing noninvasive biomarkers with prognostic significance [36]. Identifying gene polymorphisms in PCa-associated pathways could improve early diagnosis, provide selective chemoprevention, and better understand the complexity of biological pathways involved in prostate carcinogenesis [38]. Our present study was a molecular population-based

case-control study examining whether the XRCC1 codon 194 and XPD 751 polymorphisms influence the risk of PCa in the Bangladeshi population.

The XRCC1 Arg194Trp polymorphism resides in the linker region separating the $NH_2$-terminal domain and the BRCT1 (BRCA1 C-terminus) domain, directly impacting enzymatic function [39]. However, the polymorphism does not cause a complete loss of protein function, as evidenced by the lethal condition observed in mice during embryonic development when XRCC1 is inactivated [40]. In our study, we found that PCa patients with XRCC1 codon 194 Trp/Trp genotype were 5.51 times at higher risk of PCa compared with controls than those carrying the Arg/Arg genotype. Consistent with our result, the genotype 194Trp/Trp was found to be associated with an increased risk of PCa in the Chinese population [19]. In a Japanese population, however, the 194 Arg/Trp genotype instead of the Trp/Trp genotype was significantly more prevalent in PCa patients than in controls [20]. The same study also discovered that having only one Trp allele (Arg/Trp and Trp/Trp genotypes) doubled the chance of developing prostate cancer. Their findings conflict with our dominant model analysis, which indicated that the genotypes Arg/Trp + Trp/Trp did not significantly increase

**Table 6** Association of XRCC1 and XPD polymorphisms with clinical parameters of PCa patients

| Genotype | Clinical Parameters | B | Odds ratio ($e^{\beta}$) | p-value |
|---|---|---|---|---|
| **XRCC1** | | | | |
| Arg/Trp | Gleason Score | -0.15 | 0.86 | 0.81 |
| | Tumor Staging | 0.04 | 1.04 | 0.96 |
| | DRE | -0.4 | 0.67 | 0.51 |
| | Hematuria | -1.03 | 0.36 | 0.08 |
| | UTI | 0.35 | 1.42 | 0.49 |
| | High PSA levels | 0.23 | 1.25 | 0.58 |
| | High serum creatinine | 0.23 | 1.25 | 0.64 |
| Trp/Trp | Gleason Score | 1.09 | 2.96 | 0.33 |
| | Tumor Staging | -0.81 | 0.44 | 0.46 |
| | DRE | 0.59 | 1.81 | 0.71 |
| | Hematuria | 2.53 | 12.57 | 0.06 |
| | UTI | -1.42 | 0.24 | 0.21 |
| | High PSA levels | 0.72 | 2.06 | 0.58 |
| | High serum creatinine | 0.82 | 2.28 | 0.44 |
| **XPD** | | | | |
| Lys/Gln | Gleason Score | -0.42 | 0.66 | 0.52 |
| | Tumor Staging | 1.29 | 3.64 | 0.06 |
| | DRE | 0.32 | 1.38 | 0.6 |
| | Hematuria | -0.89 | 0.41 | 0.14 |
| | UTI | -0.63 | 0.53 | 0.23 |
| | High PSA levels | -0.68 | 0.5 | 0.14 |
| | High serum creatinine | 0.79 | 2.2 | 0.12 |
| Gln/Gln | Gleason Score | 0.34 | 1.4 | 0.75 |
| | Tumor Staging | 1.13 | 3.09 | 0.29 |
| | DRE | -0.68 | 0.51 | 0.52 |
| | Hematuria | -0.56 | 0.57 | 0.58 |
| | UTI | 0.29 | 1.34 | 0.73 |
| | High PSA levels | 0.07 | 1.07 | 0.94 |
| | High serum creatinine | 1.22 | 3.4 | 0.17 |

Multinomial Logistic regression using Arg/Arg as the reference category for XRCC1 and Lys/Lys as the reference category for XPD; Digital rectal examination (DRE); Urinary Tract Infection (UTI); Prostate-specific antigen (PSA); $p < 0.05$ was considered as the level of significance

the risk of PCa. However, the risk of PCa was raised when both copies of the Trp allele were present in comparison to the presence of Arg/Arg and Arg/Trp genotype as suggested by the recessive model (Table 3). Their findings may not apply to us as only patients with a family history of PCa only were included in their study. Contradictory data also exist where codon 194 did not show significant results with PCa risk [21, 22]. The lack of association of the studies may be attributed to variances in ethnicity, geographic and environmental factors. While it is possible that the 194 Arg/Trp or Trp/Trp genotype led to reduces DNA repair capacity and increased tumor progression, the extent to which this polymorphism impairs the DNA repair capacity is uncertain. Alternatively, Rahman & Zein et al. discovered that the wild-type Arg/Arg variation had a larger rise in mean sister chromatid exchange (SCE), a sign of gene damage, in response to the genotoxic chemical than the Arg/Trp varian [41]. These data imply a possible genomic instability associated with the wild-type variant and not with the mutant variants. Due to the lack of participants carrying the rare homozygous mutant Trp/Trp genotype, its effect on SCE could not be studied. Even so, the association between SCP and Arg/Arg genotype was observed in a small study population in their study and did not reach statistical significance. Wang and colleagues also reported significantly more chromosomal breaks in the wild-type Arg/Arg when compared to the homozygous/heterozygous variant group [42], suggesting the wild-type Arg allele, rather than the mutant Trp allele, may be more likely to increase cancer risk in the presence of certain environmental exposures. Since nearly all studies use the wild-type variant as the reference when comparing genotype associations, more functional studies evaluating the DNA repair capacity of XRCC1 codon 194 polymorphism are required to reach a consensus. The disparity in findings could be explained by the likelihood that other cancer SNPs of susceptibility genes in linkage disequilibrium with XRCC1 were present that contribute to higher cancer risk. Moreover, the influence of the polymorphism on DNA repair ability may differ based on the type and degree of DNA damaging insults. It is also possible that some of these outcomes are due to chance.

XPD, which maps close to XRCC1 on chromosome 19, is a probable cancer susceptibility gene in linkage disequilibrium with XRCC1. Therefore, the polymorphism in codon 751 affects the COOH-terminal domain of the XPD protein, an essential domain for TFIIH function. Mutations in the XPD gene may affect its interactions with other subunits, reducing XPD DNA helicase activity in TFIIH and defects in NER [43, 44]. However, it has been speculated that TFIIH transcriptional activity is relatively tolerant of amino acid alterations in the XPD protein. The 751 residue lies near the C-terminal end of the polypeptide, well past the point where disease-associated mutations have been observed [45]. Accordingly, we observed no statistically significant association between the XPD codon 751 genotype and PCa risk. A positive association was observed for XPD codon 751 Gln/Gln with PCa risk compared to wild type variant, but the link did not reach statistical significance (Table 3). Our findings align with some previous studies of XPD codon 751 polymorphism and PCa conducted in other countries [30, 31]. We also investigated the combined effect of the two SNPs that may have a collective impact on DNA repair outcomes (Table 4), but the results are not statistically significant. The lack of statistically significant association may be due to the selection of DNA repair genes of two different pathways. No healthy control was homozygous mutant in both genes, so its combined effect could not be compared.
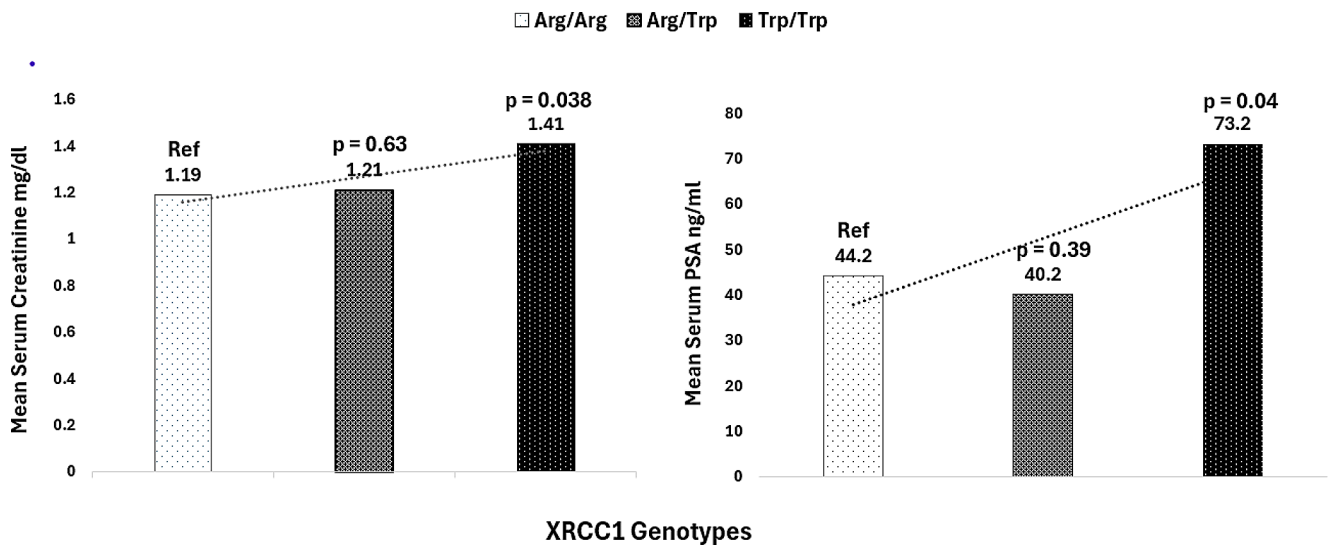
**Fig. 1** Association of XRCC1 codon 194 polymorphism with biochemical parameters in PCa patients
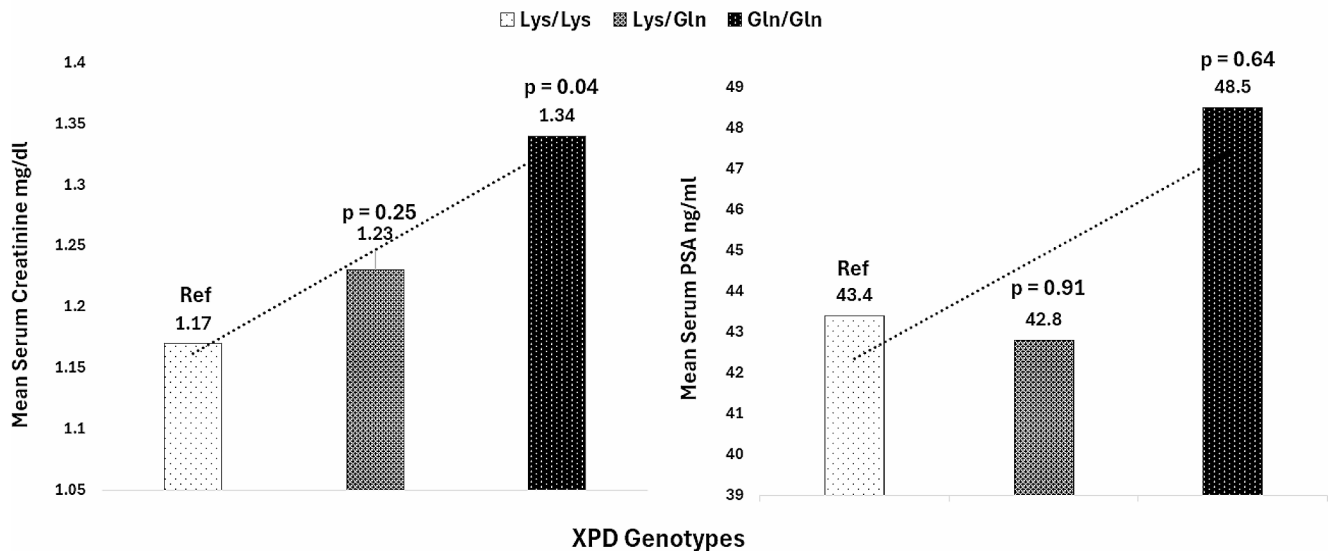


**Fig. 2** Association of XPD codon 751 polymorphism with biochemical parameters in PCa patients

Tobacco smoke is a rich source of various potent carcinogens and Reactive Oxygen Species (ROS), including Polycyclic Aromatic Hydrocarbon (PAHs), aromatic amines, and N-nitroso compounds which can produce DNA bulky adducts, base damage, and SSBs and Double Strand Breaks (DSBs) [46, 47]. The formation of PAH-DNA adducts in the prostate caused by cigarette smoke exposure has been demonstrated to differ between races, implying that genetic differences in the DNA repair genes contribute to individual susceptibility to cancer risk [47, 48]. The mutant homozygous Trp/Trp variant of XRCC1 and Gln/Gln variant of XPD was positively associated with PCa in smokers in this study, although not statistically significant (Table 5). While

previous studies have also shown similar findings about XPD as our study [30], another study showed an association of XRCC1 Arg/Trp and Trp/Trp genotype with PCa risk in smokers [19], suggesting a strong gene-environment interaction in PCa susceptibility. In the same study, the XRCC1 Arg/Trp and Trp/Trp genotypes were found to raise PCa risk in individuals with no family history of cancer. Our study observed a statistically insignificant association between homozygous mutant genotypes of both genes with PCa in individuals without a family history of cancer. Inconsistencies in results across epidemiological studies could be explained by the varying distributions of genetic and

environmental factors in the study cohort, which may influence the effects of any particular genetic variant.

Finally, we explored the association of the SNPs with clinical features and biochemical parameters with genotypes of PCa patients. We found that these polymorphisms did not affect tumor grade, tumor aggressiveness, DRE results, or UTIs ($p$-value > 0.05) (Table 6). Only the XRCC1 Trp/Trp genotype significantly increased hematuria risk by 12.6 times ($p$-value < 0.05). The XRCC1 Trp/Trp genotype was also significantly associated with higher serum creatinine levels and PSA compared to patients having the wild type (Arg/Arg) genotype (Fig. 1). The effect on serum creatine levels was also seen in patients with XPD Gln/Gln genotype (Fig. 2). Serum creatinine level is an independent predictor of high-risk PCa prognosis; low and high serum creatinine levels have a significantly higher prognostic risk of PCa [49]. Most patients (68.94%) included in our study had serum creatinine levels within the normal range of 0.7–1.3 mg/dL. Survival rates were not evaluated in our study, and the prognostic risk was, therefore, outside the scope of our investigation. Although the association of XRCC1 and XPD polymorphisms with PCa risk has been studied, it is unclear how SNPs affect clinical factors such as tumor stage, tumor grade, creatinine, and PSA levels. Hematuria and high creatinine levels are indicators of compromised kidney function. The association of XRCC1 homozygous wild-type Trp/Trp genotype with increased hematuria risk and serum creatinine levels suggests that patients with this genotype are particularly at risk of kidney function impairment. Vacher and colleagues [50] found that renal insufficiency is highly prevalent in PCa patients even when serum creatinine levels are normal. Even though most of the patients in our study had normal serum creatinine levels, the renal function of patients with the Trp/Trp genotype and PCa should be evaluated.

One of the merits of our study is that our control group included both hospital-based and non-hospital-based participants, eliminating the possibility of a selection bias. Moreover, by excluding tribal or other ethnic groups from the study groups, we achieved a homogeneous genetic background of the subject. We did, however, assess the reproducibility of results by repeating genotype assays on 10% of the samples chosen at random, and the replicates showed 100% concordance.

# Conclusion

Our study suggested a prospective connection between genetic polymorphisms and increased PCa susceptibility. We found that the Trp/Trp variant at codon 194 of XRCC1 is associated with the PCA risk; however, XPD Lys751Gln gene polymorphism did not show a statistically significant association with an increased risk of developing PCa in the Bangladeshi population. XRCC1 Trp/Trp variant appears to be linked to hematuria risk, higher mean serum creatinine, and mean serum PSA levels. At the same time, XPD Gln/Gln is associated with only higher mean serum creatinine levels in PCa patients. Additional studies using a bigger sample size are required to explore the relationship of these polymorphisms with serum creatinine and PSA levels.

**Author contributions** Y.K. and M.H. conceptualized the research idea and provided overall supervision and project administration throughout the study. N.A. designed the methodology, curated the data, engaged in the investigation process, and contributed to data visualization. M.A.I. refined the methodology, secured essential resources, conducted formal analysis and validated the results. N.A. wrote the original draft. All authors reviewed, edited and revised the final draft.

**Data availability** No datasets were generated or analysed during the current study.

# Declarations

**Informed consent and ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by The Ethical Review Committees of the Department of Biochemistry and Molecular Biology, University of Dhaka, Bangladesh.

**Consent to participate** Informed consent was obtained from all participants before the sample and data collection.

**Consent to publish** The authors affirm that human research participants provided informed consent for publication of their clinical data.

**Competing interests** The authors declare that they have no conflicting interests. All authors declare they have no financial interests.

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