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A Case-Control Study on Combined Effects of Base Excision Repair and Nucleotide Excision Repair Gene Polymorphisms in Gastrointestinal Cancer Susceptibility

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Abstract

Background: Gastrointestinal (GI) cancer constitute a major global health problem influenced by genetic and environmental factors. Genetic variations within base excision repair (BER and) nucleotide exchange repair (NER) pathway genes can impact DNA repair capacity. Investigating the combined effects of *BER* and *NER* pathway genes offers a promising avenue for understanding their impact on cancer susceptibility. This study was aimed to address combined effects of genetic variants in *BER* and *NER* on the risk of developing GI cancer. **Methods:** Genetic polymorphisms within *BER* and *NER* genes were examined in two hundred histologically confirmed GI cancer cases, along with equal number of controls by the PCR-RFLP technique. Odds ratios (OR) with 95% CI and associated p-values were computed to assess an extent of association of these polymorphisms with GI cancer susceptibility, with statistical significance established at $p \leq 0.005$. **Results:** Regression analysis revealed compelling evidence of synergistic effects between specific variant genotypes. Notably, combinations involving variants of *XPG* (rs17655) and *XRCC1* (rs1799782) (OR=2.20; 95% CI: 1.02-4.72; p=0.042) and XRCC1 (rs25487) (OR=2.56; 95% CI: 1.39-4.72; p=0.002) as well as *XPD* (rs238406) and *XRCC1* (rs1799782) (OR=3.02; 95% CI: 1.60-5.70; p=0.0006) and *XCC1* (rs25487) (OR=6.63; 95% CI: 3.63-12.10; p=0.0001) exhibited significant associations with increased GI cancer risk within the study population. **Conclusion:** These findings suggested combined influence of SNPs within *XRCC1, XRCC3*, and *APE1*, in combination with polymorphisms of *XPC* and *XPD*, on the development of GI cancer. Nonetheless, further investigations on larger scale are warranted to validate and expand upon these observations.

Keywords: Gastrointestinal cancer- *BER*- *NER*- genetic polymorphism- cancer risk

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Introduction

Gastrointestinal (GI) cancer is one of the most imperative health concern globally; influenced by interaction of genetic and environmental factors. This multifactorial disease is characterized by accumulation of genetic alterations that disrupt normal individual's cellular functions. A comprehensive knowledge of genetic mechanisms contributing to cancer susceptibility is crucial for understanding disease presentation, progression, and development of preventive and targeted treatment strategies. Among various mechanisms concerned with cancer development, DNA repair pathways play a pivotal role in maintaining genomic stability and integrity thereby preventing the onset of malignancy [1-2]. Two fundamental DNA repair pathways, BER and NER are involved in correcting single strand breaks and bulky helix-distorting lesions [3]. The BER primarily deals with small, non-helix-distorting lesions such as oxidized bases and single-strand breaks, while NER is responsible for removing bulky DNA adducts induced by carcinogens, ultraviolet (UV) radiation, and other environmental factors. Both pathways operate collectively in response to various types of DNA damage, and disruptions in their coordinated function can contribute to genomic instability and carcinogenesis. The interference in one pathway may affect the compensatory capacity of the other, leading to an accumulation of unrepaired DNA lesions and an increased risk of malignant transformation. Interactions between genetic variants within *BER* and *NER* genes and environmental exposures may synergistically impact DNA repair efficiency and predispose individuals to heightened cancer susceptibility [4-6]. Genetic variations, including single nucleotide polymorphisms (SNPs), within the genes encoding proteins involved in *BER* and *NER* have been implicated in altering DNA repair capacity and influencing

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cancer susceptibility.

Several investigations have demonstrated that inhibition of *BER* and *NER* pathway genes can increase cancer susceptibility. Commonly studied polymorphisms associated with different cancers include Arg194Trp, Arg280His, and Arg399Gln of *XRCC1*; Arg188His of *XRCC2;* Thr241Met of *XRCC3*; Ser326Cys of hOGG1; and Asp148Gly polymorphisms of the BER pathway. Similarly, Lys939Gln of XPC, His1104Asp of *XPG*, and Arg156Arg, Asp312Asn, and Lys751Gln of *XPD* polymorphisms are notable in the *NER* pathway genes [7-16]. However, the combined genotype effect and interactive association of SNPs of both *BER* and *NER* pathway genes with cancer susceptibility remains largely unexplored in any ethnic population.

Thus, exploring the interaction between *BER* and *NER* pathway genes and their combined impact on cancer susceptibility can secure significant promise in elucidating the underlying molecular mechanisms of carcinogenesis. The emerging evidences suggest that the interactive relationship within and between *BER* and *NER* pathway genes may help to identify the key genetic determinants and biomarkers associated with altered DNA repair capacity and increased cancer risk. However, the precise mechanisms by which these genetic variants influence cancer risk, and the potential interactions between *BER* and *NER* genes, remain incompletely understood. Thus, by unraveling gene-gene and gene-environment interactions, we decided to identify key genetic determinants associated with altered DNA repair capacity and increased GI cancer risk in the population of South-Western Maharashtra. To address this understanding of possible combined effects of *BER* and *NER* gene polymorphisms and their association with GI cancer risk, we conducted a hospital based case-control study in the population of South-Western Maharashtra. We assessed the association of rs1799782 (exon-6), rs25487 (exon-10) SNPs of *XRCC1*; rs3218536 (exon-3) SNP of of XRCC2; and rs861539 (exon-7) SNP pf *XRCC3* rs1052133 (exon-7) SNP of hOGG1; rs1130409 (exon5) SNP of *APE1* genes and the SNPs of *NER* genes rs2228001 (exon-15) of *XPC* gene; rs17655 (exon-15) of *XPG* gene and rs238406 (exon-6), rs1799793 (exon-10), rs13181 (exon-23) of *XPD* gene with the risk of GI cancer in rural population of south-western Maharashtra

Materials and Methods

Selection of study subjects

This case-control study included 200 clinically confirmed GI cancer cases and equal number of healthy, disease-free controls of similar age and sex. The sample size was determined using the formula: $n = [(p1 \times q1) + (p2 \times q2)] \times (Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2 / (p1 - p2)$, where p1 represents the presence of allele 1, q1 is the absence of allele 1, p2 indicates the presence of allele 2, q2 is the absence of allele 2, α denotes the probability of detecting false results, and β represents the power. All cases, aged between 20 and 85 years (Mean ± SD: 59.0 ± 13.32), were enrolled immediately after diagnosis at Krishna Hospital and Medical Research Centre between 2018 and 2022. Written informed consent was obtained from all eligible participants, including cases and controls, after providing them with detailed information about the study. Demographic and clinical data were collected using a structured questionnaire. Approval for the study protocol (IEC-164/2017-2018) was obtained from the Institutional Ethics Committee of Krishna Institute of Medical Sciences 'Deemed to be University', Karad.

Blood Sample Collection and Genomic DNA Extraction and Purification

After obtaining informed consent, sterile EDTA-containing vacutainers were used to collect five milliliters (mL) of whole blood from each of the 200 patients. Following the manufacturer's instructions, genomic DNA extraction was conducted on peripheral blood samples using the HipurA® Blood genomic DNA miniprep purification kit (Cat no. MB504-250PR) from HiMedia Laboratories. The resulting pure genomic DNA was then utilized for genotyping assays, employing polymerase chain reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) analysis.

Genotyping Assays

The genotyping of BER (*XRCC1, XRCC2, XRCC3, hOGG1, APE1*) and NER (*XPC, XPD,* and *XPG*) isoforms was conducted using PCR-RFLP. In each PCR reaction mixture containing 20 microliters (μL), 0.2 μg of genomic DNA, along with 1X PCR buffer containing Tris HCl (pH 8), KCL, EDTA, DTT, 25mM MgCl2, 0.2 mM each dNTPs, 1U of Taq DNA polymerase (Bangalore GeNei), and 10 picomoles of each forward and reverse primers for *BER* genes including *XRCC1* [C26304T, G28152A], XRCC2 [G31479], *XRCC3* [C18067T], hOGG1 [C1245G], and *APE1* [T1297G]) were used from previous reported studies[17-18]. Similarly, the primers for *NER* genes, including *XPC* (A2920C), *XPD* (C22541A, G23591A, A35931C), and *XPG* (C3507G), were selected from earlier studies [19-20]. The PCR amplifications of *BER* and *NER* genes were performed using a Master Cycler Gradient PCR machine (Eppendorf India Limited). Subsequently, RFLP analysis for the studied genotypes of *XRCC1* (C26304T, G28152A), *XRCC2* (G31479), *XRCC3* (C18067T) were conducted using 1 unit of PvuII, NciI, Hph1, and NlaIII restriction enzymes, respectively. Similarly, 1 unit of BfaI and MboII were employed for the digestion of PCR products of *APE1* (T1297G) and *hOGG1* (C1245G), respectively. The RFLP analysis of *NER* genes, including *XPC* (Lys939Gln) and *XPG* (His1104Asp) genotypes were carried out using appropriate restriction enzymes PvuII and NlaIII, respectively. The PCR products for XPD (Arg156Arg, Asp312Asn, and Lys751Gln) were digested with TfiI, StyI, and PstI restriction endonucleases, respectively, at 37°C for 16 hours. Following the restriction digestion, the digested products were separated on 1-3% low EEO agarose (GeNei, Merck Biosciences) gel, stained with ethidium bromide, and photographed using a gel documentation system. The variant and wild-type genotypes were analyzed based on their restriction digestion pattern.

Statistical Analysis

The relationship between BER and NER genotypes

and the risk of developing GI cancer was examined using Odds Ratio (OR). A logistic regression model was employed to compute the OR and 95% confidence intervals (CI), adjusting for variables to ascertain the GI cancer risk associated with genotypes. All p values were two-sided, and statistical significance was determined for $p \leq 0.05$. Statistical analyses were conducted using SPSS (IBM Version 11.0) software.

Results

Comparative analysis of genotype frequency distribution of BER and NER genes in GI cancer cases and controls

The frequency distribution analysis of *BER* genes, including *XRCC1, XRCC2, XRCC3, APE1*, and *hOGG1* genotypes and alleles, revealed significant associations in both cases and control groups. Specifically, the A/A genotype of *XRCC1* (rs25487) showed a notable 4.28-fold increase in polymorphism, correlating with a higher risk of GI cancer (OR=4.28; 95% CI: 1.81-10.08; p=0.0009) within the studied population. Conversely, the C/C genotype of T2197G of rs1130409 SNP of *APE1* exhibited a negative association (OR=0.28; 95% CI: 0.12-0.65; p=0.003) with GI risk in our analysis. However, no significant associations were observed between XPC (rs2228001) and *XPG* (rs17655) gene polymorphisms and GI cancer risk. Noteworthy, significant associations were found between the SNPs rs238406 (OR=5.02; 95% CI: 2.52-9.97; p=0.0001) and rs1799793 (OR=3.48; 95% CI: 1.64-7.39; p=0.001) of the *XPD* gene and GI cancer risk.

Combined effects of BER (XRCC1, XRCC2, XRCC, APE1, hOGG1) genotypes with NER (XPC, XPD XPG) gene

Table 1. Distribution and Combined Effects of Genotype Frequencies of base Excision Repair Genes (*XRCC1, XRCC2, XRCC3, hOGG1, APE1*) with Nucleotide Excision Repair Gene (*XPC*) and Their association with Relative Risk of Gastrointestinal Cancer

Gene & Genotype		GI cancer Group N=200 n (%)	Control Group N=200 n (%)	Odds Ratio (OR) 95% CI	p value
XRCC1 codon-194	*XPC* codon-939				
Arg/Arg	Lys/Lys	57 (28.5)	63 (31.5)	1(Reference)	
Arg/Trp+Trp/Trp	Lys/Lys	27 (13.5)	28 (14.0)	1.06 (0.56 – 2.01)	0.845
Arg/Arg	Lys/Gln+Gln/Gln	79 (39.5)	78 (39.0)	1.11 (0.69-1.80)	0.642
Arg/Trp+Trp/Trp	Lys/Gln+Gln/Gln	37 (18.5)	31 (15.5)	1.31 (0.72-2.39)	0.362
XRCC1 codon-399	*XPC* codon-939				
Arg/Arg	Lys/Lys	33 (16.5)	58 (29.0)	1(Reference)	
Arg/Gln+Gln/Gln	Lys/Lys	51 (25.5)	33 (16.5)	2.71 (1.47-5.00)	0.001*
Arg/Arg	Lys/Gln+Gln/Gln	46 (23.0)	65 (32.5)	1.24 (0.70-2.20)	0.453
Arg/Gln+Gln/Gln	Lys/Gln+Gln/Gln	70 (35.0)	44 (22.0)	2.79 (1.28-4.94)	0.0004*
XRCC2 codon-188	*XPC* codon-939				
Arg/Arg	Lys/Lys	67 (33.5)	70 (35.0)	1(Reference)	
Arg/His+His/His	Lys/Lys	17 (8.5)	21 (10.5)	0.84 (0.41-1.74)	0.649
Arg/Arg	Lys/Gln+Gln/Gln	89 (44.5)	82 (41.0)	1.13 (0.72-1.77)	0.583
Arg/His+His/His	Lys/Gln+Gln/Gln	27 (13.5)	27 (13.5)	1.04 (0.55-1.96)	0.891
XRCC3 codon-241	*XPC* codon-939				
Thr/Thr	Lys/Lys	54 (27.0)	64 (32.0)	1(Reference)	
Thr/Met+Met/Met	Lys/Lys	30 (15.0)	27 (13.5)	1.31 (0.69-2.48)	0.394
Thr/Thr	Lys/Gln+Gln/Gln	70 (35.0)	74 (37.0)	1.12 (0.68-1.82)	0.646
Thr/Met+Met/Met	Lys/Gln+Gln/Gln	46 (23.0)	35 (17.5)	1.55 (0.88-2.75)	0.127
hOGG1 codon-326	*XPC* codon-939				
Ser/Ser	Lys/Lys	43 (21.5)	44 (22.0)	1(Reference)	
Ser/Cys+Cys/Cys	Lys/Lys	41 (20.5)	47 (23.5)	0.89 (0.43-1.61)	0.707
Ser/Ser	Lys/Gln+Gln/Gln	49 (24.5)	45 (22.5)	1.11 (0.62-1.99)	0.716
Ser/Cys+Cys/Cys	Lys/Gln+Gln/Gln	67 (33.5)	64 (32.0)	1.07 (0.62-1.84)	0.803
APE1 codon-148	*XPC* codon-939				
Asp/Asp	Lys/Lys	64 (32.0)	58 (29.0)	1(Reference)	
Asp/Glu+Glu/Glu	Lys/Lys	20 (10.0)	32 (16.0)	0.56 (0.29-1.09)	0.092
Asp/Asp	Lys/Gln+Gln/Gln	89 (44.5)	60 (30.0)	1.34 (0.82-2.17)	0.23
Asp/Glu+Glu/Glu	Lys/Gln+Gln/Gln	27 (13.5)	50 (25.0)	0.48 (0.27-0.88)	0.017*

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

Table 2. Distribution and Combined Effects of Genotype Frequencies of Base Excision Repair Genes (*XRCC1, XRCC2, XRCC3, hOGG1, APE1*) with Nucleotide Excision Repair gene (*XPG*) and Their association with Relative Risk of Gastrointestinal Cancer

Gene & Genotype		GI cancer Group N=200 n (%)	Control Group N=200 n (%)	Odds Ratio (OR) (95% CI)	p value
XRCC1 codon-194	*XPG* codon-1104				
Arg/Arg	His/His	99 (49.5)	96 (48.0)	1(Reference)	
Arg/Trp+Trp/Trp	His/His	37 (18.5)	45 (22.5)	0.79 (0.47-1.33)	0.391
Arg/Arg	His/Asp+Asp/Asp	39 19.5)	48 (24.0)	0.78 (0.47-1.30)	0.357
Arg/Trp+Trp/Trp	His/Asp+Asp/Asp	25 (12.5)	11 (5.5)	2.20 (1.02-4.72)	0.042*
XRCC1 codon-399	*XPG* codon-1104				
Arg/Arg	His/His	53 (26.5)	92 (46.0)	1(Reference)	
Arg/Gln+Gln/Gln	His/His	30 (15.0)	31 (15.5)	1.67 (0.91-3.07)	0.093
Arg/Arg	His/Asp+Asp/Asp	80 (40.0)	52 (26.0)	2.67 (1.64-4.34)	0.0001*
Arg/Gln+Gln/Gln	His/Asp+Asp/Asp	37 (18.5)	25 (12.5)	2.56 (1.39-4.72)	0.002*
XRCC2 codon-188	*XPG* codon-1104				
Arg/Arg	His/His	102 (51.0)	108 (54.0)	1(Reference)	
Arg/His+His/His	His/His	53 (26.5)	43 (21.5)	1.30 (0.80-2.11)	0.281
Arg/Arg	His/Asp+Asp/Asp	35 17.5)	37 (18.5)	1.05 (0.62-1.79)	0.832
Arg/His+His/His	His/Asp+Asp/Asp	10 (5.0)	12 (6.0)	0.88 (0.36-2.13)	0.78
XRCC3 codon-241	*XPG* codon-1104				
Thr/Thr	His/His	83 (41.5)	102 (51.0)	1(Reference)	
Thr/Met+Met/Met	His/His	41 (2.05)	35 (17.5)	1.43 (0.84-2.46)	0.182
Thr/Thr	His/Asp+Asp/Asp	54 (27.0)	44 (22.0)	1.52 (0.92-2.46)	0.101
Thr/Met+Met/Met	His/Asp+Asp/Asp	22 (11.0)	19 (9.5)	1.42 (0.72-2.80)	0.308
hOGG1 codon-326	*XPG* codon-1104				
Ser/Ser	His/His	62 (31.0)	88 (44.0)	1(Reference)	
Ser/Cys+Cys/Cys	His/His	30 (15.0)	30 (15.0)	1.41 (0.77-2.58)	0.253
Ser/Ser	His/Asp+Asp/Asp	74 (37.0)	58 (29.0)	1.81 (1.12-2.90)	0.013*
Ser/Cys+Cys/Cys	His/Asp+Asp/Asp	34 (17.0)	24 (12.0)	2.01 (1.08-3.72)	0.026*
APE1 codon-148	*XPG* codon-1104				
Asp/Asp	His/His	103 (51.5)	66 (33.0)	1(Reference)	
Asp/Glu+Glu/Glu	His/His	50 (25.0)	24 (12.0)	1.33 (0.75-2.37)	0.326
Asp/Asp	His/Asp+Asp/Asp	36 (18.0)	77 (38.5)	0.29 (0.18-0.49)	<0.0001*
Asp/Glu+Glu/Glu	His/Asp+Asp/Asp	11 (5.5)	33 (16.5)	0.21 (0.10-0.45)	0.0001*

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

polymorphisms for their association with GI cancer risk

In our assessment of the combined effects of variant genotypes of *BER* genes with the XPC Lys939Gln (rs2228001) polymorphism, we found that the combination of variant genotypes of *XRCC1* Arg399Gln (rs25487) and the homozygous variant genotype of XPC (C/C) significantly increased the risk of GI cancer by 2.79 times (OR=2.79; 95% CI: 1.28-4.94; p=0.0004). Conversely, the variant genotype of *APE1* T2197G of rs1130409 SNP in combination with XPC A2920C of rs2228001 showed a negative association with GI risk (OR=0.48; 95% CI: 0.27-0.88; p=0.017). These findings highlight the combined effects of genotypes of *BER* and *XPC* genes with codon 939, and their association with GI cancer risk, are summarized in Table 1. In our analysis we investigated the combined effects of variant genotypes of XPG at codon-1104 (rs17655) with variant genotypes of *XRCC1* at codon-194 (rs1799782) (OR=2.20; 95% CI: 1.02-4.72; p=0.042) and codon-399 (rs25487) (OR=2.56; 95% CI: 1.39-4.72; p=0.002) showed a significant positive association with GI cancer risk. However, the variant genotypes of XPG 1104 alone did not exhibit any association with cancer risk in the studied population. Furthermore, the G/G genotype of XPG (rs17655) was positively associated with GI cancer risk when combined with the G/G genotype of hOGG1 at codon 326 (rs1052133) (OR=2.01; 95% CI: 1.08-3.72; p=0.026). Conversely, the same XPG genotype was ngatively associated with GI cancer risk when combined with the C/C genotype of the *APE1* gene (T2197G) (rs1130409) with OR=0.21; 95% CI: 0.10-0.45; p=0.0001) (Table 2). The combinations of XPD at codons 156, 312, and 751 with variant genotypes of base excision repair genes, we identified a significant association of C22541A and G23591A of XPD when combined with variant genotypes of *XRCC1* at codons 194 and 399. Similarly, variant

Table 3. Distribution and Combined Effects of Genotype Frequencies of Base Excision Repair Genes (*XRCC1, XRCC2, XRCC3, hOGG1, APE1*) with Codon 156 of Nucleotide Excision Repair gene (*XPD*) and Their association with Relative Risk of Gastrointestinal Cancer

Gene & Genotype		GI cancer Group N=200 n (%)	Control Group N=200 n (%)	Odds Ratio (OR) 95% CI	p value
XRCC1 codon-194	*XPD* codon-156				
Arg/Arg	Arg/Arg	51 (25.5)	83 (41.5)	1(Reference)	
Arg/Trp+Trp/Trp	Arg/Arg	85 (42.5)	58 (29.0)	2.38 (1.47-3.86)	0.0004*
Arg/Arg	Arg/Arg+Arg/Arg	25 (12.5)	38 (19.0)	1.07 (0.57-1.97)	0.827
Arg/Trp+Trp/Trp	Arg/Arg+Arg/Arg	39 (19.5)	21 (10.5)	3.02 (1.60-5.70)	0.0006*
XRCC1 codon-399	*XPD* codon-156				
Arg/Arg	Arg/Arg	29 (14.5)	74 (37.0)	1(Reference)	
Arg/Gln+Gln/Gln	Arg/Arg	49 (24.5)	49 (24.5)	2.55 (1.42-4.57)	0.001*
Arg/Arg	Arg/Arg+Arg/Arg	44 (22.0)	47 (23.5)	2.38 (1.31-4.32)	0.004*
Arg/Gln+Gln/Gln	Arg/Arg+Arg/Arg	78 (34.0)	30 (15.0)	6.63 (3.63-12.10)	0.0001
XRCC2 codon-188	*XPD* codon-156				
Arg/Arg	Arg/Arg	59 (19.5)	90 (45.0)	1(Reference)	
Arg/His+His/His	Arg/Arg	97 (48.5)	61 (30.5)	2.42 (1.53-3.83)	0.0002*
Arg/Arg	Arg/Arg+Arg/Arg	17 (8.5)	31 (15.5)	0.83 (0.42-1.64)	0.605
Arg/His+His/His	Arg/Arg+Arg/Arg	17 (8.5)	18 (9.0)	1.44 (0.68-3.01)	0.333
XRCC3 codon-241	*XPD* codon-156				
Thr/Thr	Arg/Arg	52 (26.0)	82 (41.0)	1(Reference)	
Thr/Met+Met/Met	Arg/Arg	72 (36.0)	56 (28.0)	2.02 (1.23-3.31)	0.004*
Thr/Thr	Arg/Arg+Arg/Arg	24 (12.0)	39 (19.5)	0.97 (0.52-1.79)	0.923
Thr/Met+Met/Met	Arg/Arg+Arg/Arg	52 (26.0)	23 (11.5)	3.56 (1.95-6.50)	0.0001*
hOGG1 codon-326	*XPD* codon-156				
Ser/Ser	Arg/Arg	36 (18.0)	53 (26.5)	1(Reference)	
Ser/Cys+Cys/Cys	Arg/Arg	58 (29.0)	36 (18.0)	2.37 (1.31-4.29)	0.004*
Ser/Ser	Arg/Arg+Arg/Arg	38 (19.0)	68 (34.0)	0.82 (0.46-1.46)	0.509
Ser/Cys+Cys/Cys	Arg/Arg+Arg/Arg	68 (34.0)	43(21.5)	2.32 (1.31-4.11)	0.003*
APE1 codon-148	*XPD* codon-156				
Asp/Asp	Arg/Arg	55 (27.5)	72 (36.0)	1(Reference)	
Asp/Glu+Glu/Glu	Arg/Arg	98 (49.0)	46 (23.0)	2.78 (1.69-4.57)	0.0001*
Asp/Asp	Arg/Arg+Arg/Arg	21 (10.5)	49 (24.5)	0.56 (0.30-1.04)	0.067
Asp/Glu+Glu/Glu	Arg/Arg+Arg/Arg	26 (13.0)	33 (16.5)	1.03 (0.55-1.92)	0.922

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

genotypes of *XRCC3* (C18067T), Thr241Met (rs861539) exhibited significant associations with GI cancer risk when combined with variant genotypes of *XPD* at codons 156 and 312 in the studied population. Specifically, the genotype distribution of *XPD* C22541, Arg156Arg (rs238406) combined with the variant Trp/Trp genotype of *XRCC1* Arg194Trp showed a significant association with GI cancer risk (OR=3.02; 95% CI: 1.60-5.70; p=0.0006). Similarly, when combined with the Gln/Gln variant genotype of *XRCC1* at codon 399, a significant association was observed (OR=6.63; 95% CI: 3.63-12.10; p=0.0001). Additionally, the combination of variant genotypes of *XRCC3* at codon 241 and *XPD* at codon 156 also showed significant association with GI cancer risk (Table 3). The analysis of genotype distribution of *APE1* and *hOGG1* genes together with *XPD* codon 156 revealed a significant association. Specifically, the combined variant genotypes (Ser/Cys+Cys/Cys) of hOGG1 codon 326 and the variant Arg/Arg genotype of *XPD* at codon 156 were positively associated with GI cancer risk. Individuals carrying a combination of variant genotypes (Asp/Asn+Asn/Asn) of *XPD* codon 312 along with variant genotypes (Arg/Trp+Trp/Trp) of *XRCC1* codon 194 (OR=3.92; 95% CI: 2.08-7.35; p=0.0001), (Arg/Gln+Gln/Gln) genotype of *XRCC1* codon 399 (OR=9.24; 95% CI: 4.65-18.36; p<0.0001), and (Arg/His+His/His) genotype of XRCC2 at codon 188 (OR=2.81; 95% CI: 1.48-5.31; p=0.001) combined with (Thr/Met+Met/Met) genotype of *XRCC3* (OR=4.72; 95% CI: 2.50-8.92; p<0.0001) exhibited an increased risk of GI cancer (Table 4). Expounding on the results, the combination of variant genotypes of XPD A35931C, Lys751Gln (rs13181) with *BER* genes did not contribute to an increased risk of GI cancer. However, the combination of variant Asp/Glu+Glu/Glu genotype of *APE1* at codon 148 showed a negative association with GI cancer when combined with the variant (Lys/Gln+Gln/

Table 4. Distribution and Combined Effects of Genotype Frequencies of Base Excision Repair Genes (*XRCC1, XRCC2, XRCC3, hOGG1, APE1)* with Codon 312 of Nucleotide Excision Repair Gene (*XPD*) and Their association with Relative Risk of Gastrointestinal Cancer

Gene & Genotype		GI cancer Group N=200 n (%)	Control Group N=200 n (%)	Odds Ratio (OR) (95% CI)	p value
XRCC1 codon-194	*XPD* codon-312				
Arg/Arg	Asp/Asp	25 (12.5)	70 (35.0)	1 (Reference)	
Arg/Trp+Trp/Trp	Asp/Asp	111 (50.5)	69 (34.5)	4.50 (2.60-7.78	0.0001*
Arg/Arg	Asp/Asn+Asn/Asn	15 (7.5)	26 (13.0)	1.61 (0.73-3.53	0.229
Arg/Trp+Trp/Trp	Asp/Asn+Asn/Asn	49 (24.5)	35 (17.5)	3.92 (2.08-7.35	0.0001*
XRCC1 codon-399	*XPD* codon-312				
Arg/Arg	Asp/Asp	15 (7.5)	54 (27.0)	1 (Reference)	
Arg/Gln+Gln/Gln	Asp/Asp	64 (32.0)	69 (34.5)	3.33 (1.71-6.49)	0.0004*
Arg/Arg	Asp/Asn+Asn/Asn	26 (13.0)	40 (20.0)	2.34 (1.09-4.98)	0.027*
Arg/Gln+Gln/Gln	Asp/Asn+Asn/Asn	95 47.5)	37 (18.5)	9.24 (4.65-18.36)	<0.0001*
XRCC2 codon-188	*XPD* codon-312				
Arg/Arg	Asp/Asp	32 (16.0)	75 (37.5)	1 (Reference)	
Arg/His+His/His	Asp/Asp	124 (62.0)	75 (37.5)	3.87 (2.34-6.41)	<0.0001*
Arg/Arg	Asp/Asn+Asn/Asn	8 (4.0)	20 (10.0)	0.93 (0.37-2.34)	0.89
Arg/His+His/His	Asp/Asn+Asn/Asn	36 (18.0)	30 (15.0)	2.81 (1.48-5.31)	0.001*
XRCC3 codon-241	*XPD* codon-312				
Thr/Thr	Asp/Asp	25 (12.5)	60 (30.0)	1 (Reference)	
Thr/Met+Met/Met	Asp/Asp	99 (49.5)	79 (39.5)	3.00 (1.73-5.22)	<0.0001*
Thr/Thr	Asp/Asn+Asn/Asn	15 (7.5)	30 (15.0)	1.20 (0.55-2.60)	0.645
Thr/Met+Met/Met	Asp/Asn+Asn/Asn	61 (30.5)	31 (15.5)	4.72 (2.50-8.92)	<0.0001*
hOGG1 codon-326	*XPD* codon-312				
Ser/Ser	Asp/Asp	43 (21.5)	40 (20.0)	1 (Reference)	
Ser/Cys+Cys/Cys	Asp/Asp	45 (22.5)	50 (25.0)	0.83 (0.46-1.50)	0.554
Ser/Ser	Asp/Asn+Asn/Asn	19 (9.5)	54 (27.0)	0.32 (0.16-0.64)	0.001*
Ser/Cys+Cys/Cys	Asp/Asn+Asn/Asn	93 (46.5)	56 (28.0)	1.54 (0.89-2.66)	0.116
APE1 codon-148	*XPD* codon-312				
Asp/Asp	Asp/Asp	69 (34.5)	57 (28.5)	1 (Reference)	
Asp/Glu+Glu/Glu	Asp/Asp	77 (38.5)	61 (30.5)	1.04 (0.64-1.69)	0.865
Asp/Asp	Asp/Asn+Asn/Asn	15 (7.5)	40 (20.0)	0.30 (0.15-0.61)	0.0009
Asp/Glu+Glu/Glu	Asp/Asn+Asn/Asn	39 (19.5)	42 (21.0)	0.76 (0.43-1.34)	0.352

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

Gln) genotype of XPD at codon 751 (OR=0.46; 95% CI: 0.25-0.83; p=0.011) (Table 5).

Discussion

In contemporary medicine, understanding cancer genetics is paramount for effective management of the disease. Advanced knowledge of point mutations in various pathway genes leading to SNPs is crucial in understanding cancer susceptibility. Numerous epidemiological studies and meta-analyses have underscored the significant role of SNPs in the progression of carcinogenesis. The DNA repair pathway is essential for mammalian cell DNA repair, addressing damage from both endogenous and exogenous agents, thereby preserving genomic stability and integrity [21]. In this hospital-based case-control study, we aimed to investigate the combined genotypic effects of both *BER* and *NER* pathway genes and their susceptibility towards gastrointestinal cancer risk in a representative rural population of Southwestern Maharashtra, India. A notable correlation emerged between the homozygous Gln/Gln variant genotype of the Arg399Gln polymorphic locus within the *XRCC1* gene and the susceptibility to GI cancer (OR = 4.28; 95% CI = 1.81-10.08; p=0.0009) in the studied population. These results align with previous findings that underscore the importance of *XRCC1* gene polymorphisms in relation to cancer risk [22-24]. Additionally, in the same population, the presence of 249Met genotype of Thr241Met SNP within XRCC3 demonstrated a negative correlation with the risk of GI cancer (OR = 0.32; 95% CI = 0.11-0.91; p=0.03). Similarly, studies examining cancer risk associated with *XRCC3* gene polymorphisms have consistently revealed significant associations with cancer susceptibility, further validating earlier reports of

Table 5. Distribution and Combined Effects of Genotype Frequencies of Base Excision Repair Genes (*XRCC1, XRCC2, XRCC3, hOGG1, APE1*) with Codon 751 of Nucleotide Excision Repair Gene (*XPD*) and Their association with Relative Risk of Gastrointestinal Cancer

Gene & Genotype		GI cancer Group N=200 n (%)	Control Group N=200 n (%)	Odds Ratio (OR) (95% CI)	p value
XRCC1 codon-194	XPD codon-312				
Arg/Arg	Asp/Asp	25 (12.5)	70 (35.0)	1 (Reference)	
Arg/Trp+Trp/Trp	Asp/Asp	111 (50.5)	69 (34.5)	4.50 (2.60-7.78	0.0001*
Arg/Arg	Asp/Asn+Asn/Asn	15 (7.5)	26 (13.0)	1.61 (0.73-3.53	0.229
Arg/Trp+Trp/Trp	Asp/Asn+Asn/Asn	49 (24.5)	35 (17.5)	3.92 (2.08-7.35	0.0001*
XRCC1 codon-399	*XPD* codon-312				
Arg/Arg	Asp/Asp	15 (7.5)	54 (27.0)	1 (Reference)	
Arg/Gln+Gln/Gln	Asp/Asp	64 (32.0)	69 (34.5)	3.33 (1.71-6.49)	0.0004*
Arg/Arg	Asp/Asn+Asn/Asn	26 (13.0)	40 (20.0)	2.34 (1.09-4.98)	0.027*
Arg/Gln+Gln/Gln	Asp/Asn+Asn/Asn	95 47.5)	37 (18.5)	9.24 (4.65-18.36)	<0.0001*
XRCC2 codon-188	*XPD* codon-312				
Arg/Arg	Asp/Asp	32 (16.0)	75 (37.5)	1 (Reference)	
Arg/His+His/His	Asp/Asp	124 (62.0)	75 (37.5)	3.87 (2.34-6.41)	<0.0001*
Arg/Arg	Asp/Asn+Asn/Asn	8 (4.0)	20 (10.0)	0.93 (0.37-2.34)	0.89
Arg/His+His/His	Asp/Asn+Asn/Asn	36 (18.0)	30 (15.0)	2.81 (1.48-5.31)	0.001*
XRCC3 codon-241	*XPD* codon-312				
Thr/Thr	Asp/Asp	25 (12.5)	60 (30.0)	1 (Reference)	
Thr/Met+Met/Met	Asp/Asp	99 (49.5)	79 (39.5)	3.00 (1.73-5.22)	<0.0001*
Thr/Thr	Asp/Asn+Asn/Asn	15 (7.5)	30 (15.0)	1.20 (0.55-2.60)	0.645
Thr/Met+Met/Met	Asp/Asn+Asn/Asn	61 (30.5)	31 (15.5)	4.72 (2.50-8.92)	<0.0001*
hOGG1 codon-326	*XPD* codon-312				
Ser/Ser	Asp/Asp	43 (21.5)	40 (20.0)	1 (Reference)	
Ser/Cys+Cys/Cys	Asp/Asp	45 (22.5)	50 (25.0)	0.83 (0.46-1.50)	0.554
Ser/Ser	Asp/Asn+Asn/Asn	19 (9.5)	54 (27.0)	0.32 (0.16-0.64)	0.001*
Ser/Cys+Cys/Cys	Asp/Asn+Asn/Asn	93 (46.5)	56 (28.0)	1.54 (0.89-2.66)	0.116
APE1 codon-148	*XPD* codon-312				
Asp/Asp	Asp/Asp	69 (34.5)	57 (28.5)	1 (Reference)	
Asp/Glu+Glu/Glu	Asp/Asp	77 (38.5)	61 (30.5)	1.04 (0.64-1.69)	0.865
Asp/Asp	Asp/Asn+Asn/Asn	15 (7.5)	40 (20.0)	0.30 (0.15-0.61)	0.0009
Asp/Glu+Glu/Glu	Asp/Asn+Asn/Asn	39 (19.5)	42 (21.0)	0.76 (0.43-1.34)	0.352

OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

the importance of *XRCC1* gene polymorphisms in breast [25-26], cervical [27], ovarian [28], head and neck cancer risk [29]. Furthermore, upon investigating the association between other *BER* genes, such as *APE1* and hOGG1, and cancer risk, the findings indicated that 148Glu genotype (OR = 0.28; 95% CI = 0.121-0.65; p=0.003) and the presence of C allele (OR = 0.45; 95% CI = 0.31-0.65; p<0001) within Asp148Glu polymorphism of *APE1* were inversely correlated with the risk of GI cancer in the examined population and these results corroborated with previous reports [30-31]. Similarly, in our investigation into *NER* gene polymorphisms and their correlation with GI cancer susceptibility, our findings revealed a noteworthy correlation between the Arg156Arg (OR = 5.02; 95% CI = 2.52-9.97; p<0.0001) and Asp312Asn (OR = 3.48; 95% CI = 1.64-7.39; p=0.001) polymorphisms of *XPD* gene and the risk of GI cancer.

The combined influence of these polymorphisms had a notable effect on the susceptibility to GI cancer within the studied Maharashtrian population. These findings highlight the importance of considering genetic variations of *XRCC1* gene when assessing GI cancer risk, emphasizing the potential for customized risk assessment and targeted interventions in this population. Limited studies have confirmed the significance of polymorphisms in *XRCC1*, *hOGG1*, *APE1*, *XPC*, and *XPD* genes in cancer risk. However, inadequate information is available regarding the association between combined effects of *BER* and *NER* gene polymorphisms and susceptibility to GI cancer. When we studied the combination of Arg/Gln+Gln/Gln genotypes of *XRCC1* (Arg399Gln) with the wild type (Lys/Lys) genotype (Lys939Gln) (OR = 2.71; 95% CI = 1.47-5.00; p=0.001), along with the heterozygous variant genotype (Lys/Gln+Gln/Gln) of XPC, exhibited significant association with GI cancer risk (OR = 2.79; 95% CI = 1.28-4.94; p=0.004). Similarly,

combined effect of XPG (His1104Asp) with heterozygous variant genotype (His/Asp+Asp/Asp), when assessed alongside *BER* genes, demonstrated a noteworthy correlation with an increased risk of GI cancer within the studied population. To the best of our knowledge, the combined effects of SNPs of base excision repair and nucleotide excision repair genes have not been reported in any cancer except cervical cancer in Indian scenario [24]. Thus, this analysis of the combined effects of SNP-SNP interaction between *BER* and *NER* genes reaffirmed the significance of genotype combinations in predisposing the studied population to the risk of GI cancer. Robust correlation observed between the combination of the *XPD* gene and the Asp312Asn polymorphism, along with variant genotypes of *BER* genes such as *XRCC1* (Arg194Trp, Arg399Gln), XRCC2 (Arg188His), and XRCC3 (Thr241Met), highlights significant associations with GI cancer risk. These findings underscore the intricate interplay of genetic variations in influencing susceptibility to GI cancers, emphasizing the necessity of comprehending these relationships in cancer research. Nevertheless, further studies with larger sample size are warranted to validate these findings, given the scarcity of literature pertaining to SNP-SNP combinations between different pathway genes and their association with cancer in specific populations.

In conclusion, this study demonstrates a significant association between heterozygous variant genotypes of XPC (Lys939Gln) and XPD (Arg156Arg, Asp312Asn), in conjunction with polymorphic variants of *XRCC1* (Arg194Trp, Arg399Gln) and *XRCC3* (Thr241Met), and an elevated risk of gastrointestinal cancer in the Maharashtrian population. However, the interpretation of these findings is constrained by the limited number of SNPs and sample size analyzed. Therefore, further large-scale studies are warranted to confirm these associations and to better elucidate gene–gene interactions contributing to GI cancer susceptibility.

Author Contribution Statement

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

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The study protocol was approved by protocol committee of Krishna Vishwa Vidyapeeth (Deemed to be University).

Ethics Committee Approval

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyapeeth (Deemed to be University), Karad.

Declaration of Conflict of interest

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

Abbreviations

GI Cancer: Gastrointestinal cancer

BER: Base excision repair

NER: Nucleodie excision repair

XRCC: X-ray repair cross-complementing group 1

XPD: Xeroderma pigmentosum, complementation group D

XPC: Xeroderma pigmentosum, complementation group C

APE1: Apurinic/apyrimidinic endonuclease 1

hOGG1: human 8-oxoguanine DNA N-glycosylase 1

DNA: Deoxyribose Nucleic acid

PCR-RFLP: Polymerase chain reaction: Restriction Fragment Length Polymorphism

SNP: Single nucleotide polymorphism

OR: Odds Ratio

CI: Confidence Interval

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