RESEARCH ARTICLE

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Sequence Variation in X-ray Cross Complimenting (*XRCC4, XRCC5, XRCC6* and *XRCC7*) Genes and the Risk of Gastrointestinal Cancer in South-Western Maharashtra: A Hospital Based Case-Control Study

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Abstract

Objective: A number of X-ray repair cross complementing group (*XRCC*) genes are found to be involved in the DNA repair by the repair of single strand breaks (SSBs). Variation in these genes may lead to variation in DNA repair capacity, thereby increasing the genetic susceptibility to numerous human cancers. Among the known genetic polymorphisms of the DNA repair genes, there are many functional genetic variants have been identified in the XRCC genes particularly *XRCC4, XRCC5, XRCC6* and *XRCC7* that shows the positive association with the multiple cancers including cancers of GI tract. Therefore, in the present study, polymorphic variants of *XRCC4, XRCC5, XRCC6* and *XRCC7* were chosen to be studied in association with gastrointestinal cancer susceptibility in the south western Maharashtrian population. **Methods:** A total of 200 histologically confirmed cases of gastrointestinal cancer (GI) and 200 hospital-based controls were included in the study. The genotyping for *XRCC4, XRCC5, XRCC6* and *XRCC7* genes was carried out by polymerase chain reaction-restriction fragment length polymorphism. **Results:** We found that tobacco consumption in any form either smoking or chewing (OR=4.03; 95% CI: 2.65-6.11) and alcohol drinking habit (OR=4.45; CI: 2.15–9.22) is strongly associated with gastrointestinal cancer risk. Similarly, data analysis of cases and control group showed that *XRCC4*.2 G1394T is significantly associated with GI cancer risk. Our studies also revealed that fewer repeats (1R/1R, 0R/0R) of *XRCC5* in the promoter region were found to be associated with the increased risk of GI cancer. In case of XRCC7 6721G>T our findings suggest a strong association with development of GI cancer risk in south-western Maharashtrian population. However, we did not find any association of polymorphic variants of *XRCC4*.1 cd247, *XRCC4*.5 Intron-7 and *XRCC6* 61C>G with GI cancer risk in the study population. However, multicentric studies with larger sample size are needed to substantiate the findings.

Keywords: GI Cancer- Gene polymorphism- *PCR-RFLP- XRCC4- XRCC5- XRCC6- XRCC7*

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Introduction

Gastrointestinal (GI) cancer is a collective term used to describe malignant conditions that affect the organs of digestive tract including the sites from the oesophagus to the anus and its accessory organs like pancreas, liver & gall bladder. Among all organ cancers, malignancies of GI tract are the second most common form of cancer in the men and third most common among the females in Asia and Worldwide [1]. In 2020, International agency for research on cancer (IARC), global cancer observatory reported 3,544,225 deaths worldwide from the most common GI cancers which accounts about 36% among all types of cancers, with a further 5,026,243 new GI cases diagnosed, accounting about 26% [2]. The latest publication from the National Cancer Registry Program (NCRP) stated that about 19.7% of all cancers that occurred in 2020 among the Indian population were GI cancer. India points the differences in GI cancer incidence rates, indicating that the cancers of esophagus, liver, gallbladder and stomach are leading in north eastern region as compared to the rest parts of India [3]. The etiology of GI cancer is multifaceted

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and the exact cause of the disease is unknown; however, risk factors like changing life style, dietary habits and various addictions have established to be associated with the development and progression of GI cancer. Besides these modulatory impacts of environmental factors, family history and host genetic factors also confer the risk of GI malignancy [4]. The connections between genes, the environment, and cancer formation provide an attractive research venue. Over the past decade epidemiological research has concentrated on the identification of these genes and an assessment of their role in cancer aetiology.

In human genome, DNA repair genes are the major components in DNA repair system which help in restoration altered DNA structure, caused by endogenous and environmental agents with the means of different mechanisms thus maintaining the genomic integrity of the cell. A number of X-ray repair cross complementing group (*XRCC*) genes are found to be involved in the DNA repair of single strand breaks (SSBs) and are thereby associated with various cancer related pathways in humans [5]. There are few core genes viz. *XRCC4, XRCC5, XRCC6* and *XRCC7* which plays a key role in non homologous end joining (NHEJ) pathway for DNA double strand break repair (DSBs). Widely cited evidences suggest that genetic variations in these NHEJ genes reduces DNA repair capacity of the cell and thereby inflicting predisposition to several types of cancers, including skin [6], breast [7-9], stomach [10], bladder [11], oral [12], RCC [13] and cervical [14] cancer. Though there are numerous studies revealing the association of SNPs with the risk of different cancers, several more genetic determinants are yet to be illustrated thoroughly. Similarly few of Indian studies have studied the role of SNPs in few of NHEJ genes with the risk of Cervical [14], breast [15] head and neck [16] and Prostate [17] cancer in various populations. However the regarding the association of these polymorphisms and the risk of GI cancer have not been entirely consistent. In this hospital-based case–control study, we hypothesized that the polymorphism in these DNA repair genes viz. *XRCC4*, *XRCC5, XRCC6* and *XRCC7* may also contribute to the development of GI cancer and therefore, we tried to investigate the association of polymorphism within these with the risk for development of GI cancer among the south western Maharashtrian population.

Materials and Methods

Study subjects

The present case-control study included 200 histologically confirmed GI cancer patients and 200 healthy age and gender matched hospital based controls from Krishna Hospital and medical research centre, Karad,. All cases ranged in age from 20-80 years were enrolled immediately after being diagnosed during the year 2018-2019 from Department of Oncology and Department of General Surgery of Krishna Hospital & Medical Research Centre, Karad. The demographic information including age, sex, economic status, place of residence, dietary habits, family history, tobacco and alcohol consumption status and other confounding risk factors were collected from personal interviews in the form of structured questionnaire. Informed consent was obtained from all voluntary participants.

Genomic DNA isolation from whole blood

Genomic DNA extraction was carried out from 2-5 milliliter of whole blood samples of cases and controls collected in sterile EDTA containing vacutainer by laboratory designed method. The extraction was carried out by salting out method where the Red blood cells were processed with red blood cell lysis buffer (10mM tris -HCl pH-7.6, 320mM sucrose, 5mM MgCl2, 1% triton X-100, pH 7.6), thereafter the sample was treated with the nucleic lysis buffer (10mM Tris- HCl, 11.4mM sodium citrate, 1mM EDTA, 1% SDS, pH-8.0). The sample was further treated with the 20mg/ml of proteinase K at 550C for 1 hour and subsequently RNase A (20mg/ml) at 370C for 30 mins to obtain the purified DNA after precipitation with the ethanol. The purified DNA was checked on 1% agarose gel for its quality and quantity. The DNA was used for further genotyping by polymerase chain reaction (PCR) and Restriction fragment Length Polymorphism (RFLP).

Genotyping assays

Single nucleotide polymorphisms (SNPs) in *XRCC4*.1, *XRCC4.2, XRCC4.3, XRCC5*, *XRCC6* and *XRCC7* genes were studied by PCR-RFLP method. Each PCR reaction was carried out separately in 20 µl of reaction mixture containing 100 nanogram (ng) of purified genomic DNA template, 1X PCR buffer,0.2 mM each dNTP, 1U Taq DNA polymerase (Genei, merck Biosciences) and 10 picomole (pmol) primes. The primers were selected to amplify the regions of DNA that contain polymorphic sites of interest as shown in the Table 1.

After performing PCR programme for each of the gene, the PCR products were analyzed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer using 1.5% agarose. The agarose gels were stained with ethidium bromide and visualized under UV Transilluminator and photographed in gel documentation system (BioRad Laboratories). After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme as shown in Table 1 for genotyping. 10 µl of the PCR products were digested at 37°C overnight with specific restriction enzymes in 20 µl reaction mixtures containing buffer supplied with each restriction enzyme. After the overnight incubation, digestion products were then separated on a 2-3% low EEO agarose (sigma) gel at 100 V for 30 min stained with ethidium bromide and photographed in Gel Documentation System.

Statistical analysis

Chi-square test was used to compare the frequency distribution of the genotypes among the selected demographic variables and frequencies of allele and genotype of polymorphism between the cases and controls .The risk of developing GI cancer in association with *XRCC4.1, XRCC4.2 XRCC4.3, XRCC5, XRCC6* and *XRCC7* polymorphisms was studied by logistic regression model by calculating the odds ratio (OR) with 95% confidence intervals (CI) after adjustment of variables to determine the cancer risk associated with genotypes. All

Table 1. Details of PCR and RFLP Procedure and Their Expected Product

Gene	FP/RP	PCR condition	PCR product	Restriction enzyme	Restriction site
XRCC4.1 codon 247	5'-gct aat gag ttg ctg cat ttt a-3' 5'-ttt cta ggg aaa ctg caa tct gt-3	95^{0}C- 5 min, 30 cycles of 95^{0}C- 30 sec, 55^{0}C- 30 sec, 72^{0}C- 30 sec, 72^{0}C- 5 min	308 bp	1U BbsI	WT: C/C: 308 bp VT:A/A: 204bp, 104bp
XRCC4-2 (G1394T)	5'-gat gcg aac tca aag ata ctg a-3' 5'- tgt aaa gcc agt act caa act t -3'	95^{0}C- 5 min, 30 cycles of 95^{0}C- 30 sec, 53^{0}C- 30 sec, 72^{0}C- 30 sec, 72^{0}C- 5 min	300 bp	1U HincII	WT : T/T: 300 bp VT:G/G: 200bp, 100bp
XRCC4.4 intron7	5'- ttc act tat gtg tct ctt ca -3' 5'- aac ata gtc tag tga aca tc -3'	95^{0}C- 5 min, 30 cycles of 95^{0}C- 30 sec, 48^{0}C- 30 sec, 72^{0}C- 30 sec, 72^{0}C- 5 min	237 bp	1U Tsp509I	WT: G/G: 237 bp VT: A/A: 158bp, 79bp
XRCC5 2R/1R/0R	5'- agg cgg ctc aaa cac cac ac -3' 5'- caa gcg gca gat agc gga aag -3'	95^{0}C- 5 min, 30 cycles of 95^{0}C- 30 sec, 62^{0}C- 30 sec, 72^{0}C- 30 sec, 72^{0}C- 5 min	2R/2R: 266 bp 1R/1R:245 bp 0R/0R: 224bp	--	--
XRCC6 61 (C>G)	5'-tct cca ctc ggc ttt tct tcc a -3' 5'-tct ccc tcc gct tcg cac tc - 3	95^{0}C- 5 min, 35 cycles of 95^{0}C- 30 sec, 56^{0}C- 30 sec, 72^{0}C- 30 sec, 72^{0}C- 5 min	320 bp	1U BanI	WT C/C: 262bp, 58bp VT G/G:182bp,80bp,58bp
XRCC7 6721 (G>T)	5'-cgg ctg cca acg ttc ttt cc -3' 5'-tgc cct tag tgg ttc cct gg - 3'.	95^{0}C- 5 min, 30 cycles of 95^{0}C- 30 sec, 58^{0}C- 30 sec, 72^{0}C-30 sec, 72^{0}C- 5 min	368 bp	1U PvuII	WT G/G: 368bp VT T/T: 274bp,94bp

statistical analyses were performed using SPSS software (Version 11.0).

Results

Characteristics of study population

200 untreated GI cancer patients and 200 cancer free controls were included in the study. The demographic characteristics of the study subjects are summarized in the Table 2. Based on the demographic characteristics it was observed that there were no statistically significant differences between age (p=0.012) of the cases and control group, where the Mean±SD age in years was 59±13.33 for cases and 57.46±10.73 for controls. Similarly the data analysis of the cases and control group did not show significant relationships between gender (p=0.19) and age-related differences (p=0.012). However, it was observed that there is a significant relationship between tobacco chewing habit [OR: 4.03, CI: 2.65-6.11, p<0.0001] and drinking habit of alcohol [OR: 4.45, CI: 2.15-9.22, p<0.0001] with the increased risk of GI cancer (Table 2).

Analysis of XRCC4.1 Ala247Ser codon247 (rs3734091)

The frequencies of CC/CC and AA/AA genotype at codon247 of *XRCC4* were 90.5% and 9.5% in GI cancer cases and 76.0% and 24.0% in controls respectively (Table 3). With the CC/CC genotype as the reference group, the odds ratio for AA/AA genotype was (OR: 0.33; CI: 0.18-0.58; p :< 0.0001), suggesting that this genotype might be a protective for GI cancer.

Analysis of XRCC4.2 promoter G1394T (rs6869366)

For SNP rs6869366, variant TT/TT genotype was more frequent in GI cancer cases (38.5%) as compared to controls (26.0%) and was significantly associated with increased risk of GI cancer when compared with wildtype GG/GG genotype (OR:1.78; CI:1.16-2.72; p:0.007).

Analysis of XRCC4.4 intron-7 (rs1805377)

The variant AA/AA genotype at intron-7 was less frequent in GI cancer cases (25.0%) as compared to controls (32.5%) however; the genotypic frequency for wildtype GG/GG was 75.0% in GI cancer cases and 67.5% in controls. The further logistic regression analysis of the genotype does not show statistical significant association with the risk of GI cancer (OR: 0.69; CI: 0.44-1.07; p: 0.097).

Analysis of XRCC5 VNTR, (rs6147172)

In our study *XRCC5* 2R/1R/0R were selected to investigate the association between gene polymorphism and risk of GI cancer. The frequency distribution of 2R/2R, 1R/1R & 0R/0R genotypes differed significantly between cases and controls which were 27.0%, 49.0% & 24.0% respectively in GI cancer patients, and 75.5%, 11.5% & 13.0% respectively among controls. As shown in Table 2 the 1R/1R, 0R/0R and combined 1R/1R +0R/0R are more common in cases than the controls. For the VNTR *XRCC5* polymorphism, in comparision with 2R/2R genotype, 1R/1R (OR:11.91; CI:6.87-20.65; p:<0.0001), 0R/0R (OR:5.16; CI:2.92-9.12; p:<0.0001) and combined ratio of 1R/1R +0R/0R genotype (OR:8.33; CI:5.31-13.05; p:<0.0001) conferred an increased risk of GI cancer.

Analysis of XRCC6 promoter G61C (rs2267437)

For XRCC6 61C>G polymorphism the frequencies of the CC, CG and GG genotypes were 52.0%, 42.0% & 6.0% in GI cancer cases and 78.5%, 9.0% and 12.5% among controls. The logistic regression analysis revealed that compared with wild type CC homozygote, subjects carrying heterozygous CG genotype had increased risk of developing the GI cancer (OR:7.04; CI:3.99-12.41; p:<0.0001), however the subjects carrying variant genotype GG did not show any significant difference (OR:0.72; CI:0.34-1.56; p:0.38). It can be noted that subjects having at least one G allele (CG+GG) were

Table 2. Distribution of Selected Demographic Variables of GI Cancer Cases and Healthy Cancer Free Controls

Variable		Cases (n=200)	Controls (n=200)	Chi-Square Value	p-value based on X^2
Age (Mean±SD) yrs		59±13.33	57±10.73		
Age	<= 50 yrs	51 (25.5%)	42 (21.0%)	10.98	0.012
	51- 60 yrs	50 (25.0%)	81 (40.5%)		
	61- 70 yrs	67 (33.5%)	53 (26.5%)		
	>= 71 yrs	32 (16.0%)	24 (12.0%)		
Gender	Male	113 (56.5%)	100 (50%)	1.69	0.19
	Female	87 (43.5%)	100 (50%)		
Diet	Vegetarian	36 (18%)	49 (24.5%)	2.52	0.11
	Mixed	164 (82%)	151 (75.5%)		
Economic Status	Rich	2 (1.0%)	50 (25.0%)	100.8	<0.0001
	Middle Class	39 (19.5%)	85 (42.5%)		
	Poor	159 (79.5%)	65 (32.5%)		
Chewing Habit	Yes	134 (67%)	67 (33.5%)	44.89	<0.001*
	No	66 (33%)	133 (66.5%)		
Drinking Habit	Yes	38 (19%)	10 (5%)	18.56	<0.001*
	No	162 (81%)	190 (95%)		
Education	illiterate	77 (38.5%)	29 (14.5%)	52.03	<0.001
	SSC	85 (42.5%)	85 (42.5%)		
	HSC	26 (13.0%)	28 (14.0%)		
	graduate	12 (6%)	58 (29.0%)		

*indicates significant p<0.05, p value determined based on x2

found to be at higher risk to be patient compared with the reference group (OR:3.3; CI:2.17-5.21; p:<0.0001).

Analysis of XRCC7 intron8 (rs7003908)

On analyzing *XRCC7* 6721 G>T for frequency

Table 3. The Genotype Frequencies of *XRCC* Gene Variants and Their Association with Untreated Gastrointestinal Cancer Patients and Healthy Controls

Gene	Genotype	Cases (n=200)	Controls (n=200)	Odds Ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
XRCC 4.1 cd247	C/C	181 (90.5%)	152 (76.0%)	1(Reference)		1 (Reference)	
	A/A	19 (9.5%)	48 (24.0%)	0.33 (0.18-0.58)	<0.0001	0.24 (0.102-0.60)	0.002
XRCC 4.2 G1394T	G/G	123 (61.5%)	148 (74.0%)	1(Reference)		1 (Reference)	
	T/T	77 (38.5%)	52 (26.0%)	1.78 (1.16-2.72)	0.007	1.91 (1.04-3.50)	0.03*
XRCC 4.5 Intron-7	G/G	150 (75.0%)	135 (67.5%)	1 (Reference)		1 (Reference)	
	A/A	50 (25.0%)	65 (32.5%)	0.69 (0.44-1.07)	0.097	0.85 (0.45-1.61)	0.63
XRCC 5 2R/1R/0R	2R/2R	54 (27.0%)	151 (75.5%)	1 (Reference)		1 (Reference)	
	1R/1R	98 (49.0%)	23 (11.5%)	11.91 (6.871-20.65)	<0.0001*	5.98 (2.82-12.68)	<0.0001*
	0R/0R	48 (24.0%)	26 (13.0%)	5.16 (2.92-9.12)	<0.0001*	0.42 (0.18-0.95)	0.038
	1R/1R+ 0R/0R	146 (73%)	49 (24.5%)	8.33 (5.31-13.05)	<0.0001*	0.09 (0.05-0.17)	<0.0001*
XRCC 6 61C>G	C/C	104(52.0%)	157 (78.5%)	1 (Reference)		1 (Reference)	
	C/G	84 (42.0%)	18 (9.0%)	7.04 (3.99-12.41)	<0.0001*	0.60 (0.21-1.65)	0.32
	G/G	12 (6.0%)	25 (12.5%)	0.72 (0.34-1.56)	0.38	0.16 (0.05-0.50)	0.002
	C/G+G/G	96 (48%)	43 (21.5%)	3.3 (2.17-5.21)	<0.0001*	0.45 (0.25-0.82)	0.009
XRCC 7 6721G>T	G/G	44 (22.0%)	151 (75.5%)	1 (Reference)		1 (Reference)	
	G/T	96 (48.0%)	23 (11.5%)	14.32 (8.13-25.21)	<0.0001*	8.55 (4.10-17.83)	<0.0001*
	T/T	60 (30.0%)	26 (13.0%)	7.9 (4.48-14.0)	<0.0001*	0.57 (0.26-1.25)	0.165
	G/T+T/T	156 (78%)	49 (24.5%)	10.92 (6.86-17.38)	<0.0001*	0.07 (0.42-0.14)	<0.0001*

*indicates significant p<0.05, p value determined based on x^2

distribution our results show 22.0% for GG genotype, 48.0% for GT genotype and 30.0% for TT genotype in cases, while in control group the frequency was 75.5% for GG, 11.5% for GT and 13.0% for TT. The difference in the TT alleles frequencies between cases and controls was statistically significant (p :< 0.0001). Further logistic regression model analyses showed that variant TT genotype (OR:7.97; CI:4.48-14.0; p:<0.0001) and heterozygous GT genotype (OR:14.32; CI:8.13-25.21; p:<0.0001) were significantly associated with the elevated risk of developing the GI cancer when compared with homozygous wildtype genotype GG. Similarly a combination of homozygotes and heterozygotes of TT genotypes were found to be significantly associated with increased risk of GI cancer (OR: 10.92; CI: 6.86-17.38; p :< 0.0001).

Discussion

The single nucleotide polymorphisms (SNPs) are the most common form of variations in DNA. These SNPs are presumed to modulate different genes associated with the DNA repair capacity of the cell and hence associated with the altered cancer risk. Association studies play an important role in identification of genetic markers that may help in presymptomatic diagnosis of a disease state, including cancer. Even though numerous SNPs have been accounted to be associated with the risk of gastrointestinal cancers around the world, the studies on genetic polymorphism and their association with gastric carcinoma in the rural parts of India are very rare. Therefore, this hospital based case-control study was initiated with the objective to examine the polymorphism in some important candidate genes of DNA repair genes viz *XRCC4.1 cd247, XRCC 4.2 G139T, XRCC 4.5* Intron-7, *XRCC5, XRCC 6, XRCC 7* in GI cancer cases and healthy controls to explain whether the polymorphic variants determine the risk of GI cancer in the unexplored population of South-western Maharashtra of India.

Demographic variables and GI cancer risk

Consumption of alcohol in any form is an important and potential risk factor for GI cancer and is found to be associated with esophageal, gastric, hepatocellular, colorectal and pancreatic cancer. Our study showed a significant association between the alcohol consumption and the risk of GI cancer. In agreement to our findings some Indian studies conducted in Hyderabad [18] and Chennai [19] on gastric cancer patients identified the alcohol intake as an independent risk factor for the development of the GI cancer. Similarly a study from northeastern region of India shows a strong association between the intake of alcohol and hepatocellular carcinoma [20]. In several western countries alcohol consumption has became a major risk factor for GI cancer. A study conducted in Russia including 448 cases and 610 controls provided a strong support to our findings [21]. Another Korean study conduted by Park et. al in 2015 also provides a supporting data in gastric cancer [22]. The findings from Shanghai, Venenzula and Thailand provides a supporting evidence to our results that alcohol and tobacco consumption increases the risk of gastric cancer among their study population [23-25]. However, a study carried out in Poland to assess potential risks due to smoking and alcohol consumption showed no significant association on gastric cancer risk [26]. In opposition, a meta-analysis performed by Tramacere et.al involving 20 case-control and 4 cohort studies, that includes 5500 cases shows no association between alcohol drinking and esophageal and gastric cancer risk [27].

Tobacco chewing in the form of mishri or betel nut is common habit among South- Maharashtrian population; we found a positive association with the development of GI cancer among the study population. A prospective study conducted in the rural parts of Maharashtra, India also shows use of tobacco in any form to cause increasing trends of GI malignancy [28]. Our studies were in line with the studies performed in Mizoram [29] and Manipal [30], India which showed a significant association of tobacco use in any form smoking and chewing increased the risk of stomach cancer. In line with the previous studies carried out in Coimbatore, India implicated that Alcoholism, smoking, and chewing of tobacco are factors predisposing to esophageal cancer in south India population [31]. On a contrary some studies conducted in different regions of India reported that the habits of drinking alcohol and chewing tobacco did not emerge as risk factors for stomach cancer among the south Indian population [19, 32-35]. In support to our finding a study from Japan, China and Korea confirms that smoking was associated with increased risk of gastric cancer [36, 37].

X-ray cross complimenting (XRCC 4) gene polymorphism and GI cancer risk

We have investigated three SNPs of *XRCC4*: i) codon247 (rs3734091) ii) G1394T (rs6869366) iii) Intron-7 (rs1805377) in GI cancer patients and healthy controls and their association with the risk of the disease. Our investigations revealed that C→A polymorphism *XRCC4* codon247 plays a protective role, by decreasing the risk of developing the GI cancer among the subjects. As for *XRCC 4 codon247* gene, many reports suggested no association of the gene with the gastric, colorectal, lung cancers [10, 38, 39]. However some studies revealed possible association of *XRCC4.1* with the liver cancer [40] and oral cancer [41]. The studies conducted on breast cancer in the population of west India, suggest strong association with *XRCC4 cd247* [42].

Furthermore in present study, we found that *XRCC4 G1394T* gene polymorphism had a substantial association with the increased risk of GI Cancer. Other studies on *XRCC4.2* from Taiwan, China and Iran suggest that *G1394T* gene polymorphism increase the risk of colorectal cancer in support to our findings [10, 43, 44]. Another research mentioning *XRCC4.2* polymorphism suggested association with gastric carcinogenesis in Taiwanese population [10]. Together with our findings, these results suggest that *XRCC 4.2* genetic variants involved in DNA repair pathways are indeed involved in GI cancer etiology. The *XRCC4.2 G1394T* is also positively related

to breast, [45] oral [12] cancer and childhood leukemia [46]. In oppose to our findings, some Indian studies shows no association between *XRCC 4.2* polymorphism and breast [42], cervical cancer [14], while other studies from Indian population on bladder [47] and oral [16] cancer also supported our findings. Moreover, it is noteworthy that our data on *XRCC4* G>A polymorphism in intron-7 is consistent with previously published data showing no association of *XRCC 4.4* polymorphism with the risk of GI cancer [10, 38, 41]. Our findings were further supported by Mittal et al. [47], genotyped a case-control study on bladder cancer proving no association between *XRCC4.4* polymorphism and bladder cancer risk [14]. Similarly a meta-analysis performed using 23 studies containing 9,433 cancer patients and 10,337 healthy controls showed that there was no association between *XRCC4.4* rs1805377 and the risk of cancer except for gastric antrum adenocarcinoma [48]. On the contrary other meta analysis performed by Shao et al. [49] genotyped a 31 comprehensive case-control studies investigating 8 SNPs in *XRCC4* and identified an association of rs1805377 in subgroup analysis with bladder cancer. Considering the variations in the current results, more efforts are needed to explore the role of *XRCC4* mutations in the occurrence of cancer.

X-ray cross complimenting (XRCC 5) gene polymorphism and GI cancer risk

Our studies revealed that fewer repeats (1R/1R, 0R/0R) of *XRCC5* in the promoter region enhance the transcriptional activity and were associated with the increased risk of GI cancer. Our findings were supported by other research studies in gastric [50], esophageal [51] and colorectal [52] cancer. Some findings from Indian studies also provide support to our data [16]. These consistent results indicate that our findings on GI cancer risk are unlikely to be false positive. On contrary, the studies carried out by Datkhile et al. [14] on association of *XRCC5* with the risk of cervical cancer reveals no association.

X-ray cross complimenting (XRCC 6) gene polymorphism and GI cancer risk

In the reported study, the other investigated polymorphism, 61C>G in 5'-flanking region of *XRCC6* gene was not associated with the occurrence of GI cancer. Similar results have been reported on gastric [53] and lung [54] cancer. Contradictory to our results the findings from north china suggest that *XRCC6* 61C>G is associated with the esopharangeal cancer [55]. Similarly other studies on renal cell carcinoma [56] and hepatocellular carcinoma [57] validate the association of *XRCC6* with the risk of cancer, whereas another study conducted on Belgian population revealed a protective role of this SNP on breast cancer [7]. The studies intend to explore the association of *DSBR* genes i.e. *XRCC6* and *XRCC7* with susceptibility and survival in North Indian lung cancer patients revealed positive association [58]. These conflicting results may be due to differences in the ethnic groups.

X-ray cross complimenting (XRCC 7) gene polymorphism and GI cancer risk

Regarding another candidate gene for association with GI cancer risk, SNP in *XRCC7* 6721G>T have been interrogated in this study. Our study revealed *XRCC7* 6721G>T is associated with GI cancer risk. Study carried out in Iranian population on colorectal cancer validates our study where both single variant GT and double variant TT pose a statistically significant risk towards CRC [59]. The findings of the present work are in concordance with studies from Indian population in other cancer such as breast, [15] bladder [60] and prostate cancer [61] Among international studies on Gastric antrum adenocarcinoma [62] and glioma [63] also provide support to our data. On the contrary, the studies from North India does not support our finding [58]. Hsieh et al. [64] suggested that the GG and GT genotypes of *(XRCC7) G6721T* had no effect on HCC risk to the whole population, but had protective role among males, these finding were again supported by the studies carried out on lung cancer by Hsia et al. [65] Whereas, other studies on this polymorphism does not show any significant association in breast, [66] acute myeloid leukemia [67] and colorectal [68] cancer. Thus, the literature reports that there is significant difference between ethnicity and susceptibility to cancers in relation to polymorphisms associated with DSB pathway.

In conclusion, from the present study we concluded that genetic polymorphisms within the examined DNA repair pathway genes may be associated with the probability of developing GI cancer in the South-western Maharashtrian population.

However, a larger multicentric study with an increased sample size is necessary to enhance the statistical power to validate the precise genetic relevance of DNA-repair pathways in gastrointestinal carcinogenesis.

Additionally, the study may be limited by potential confounding factors such as environmental influences, dietary habits, and other genetic variations that were not adequately controlled for, which could affect the observed relationships between the genetic variants and GI cancer risk.

Author Contribution Statement

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

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Ethical Clearance

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyalay, Karad. (164/2017-2018).

Conflicts of interest

None declared.

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