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ORIGINAL ARTICLE

Association of DNA repair and xenobiotic pathway gene polymorphisms with genetic susceptibility to gastric cancer patients in West Bengal, India

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Abstract Gastric cancer is one of the most common malignancies in India. DNA repair gene or xenobiotic pathway gene polymorphisms have recently been shown to affect individual susceptibility to gastric cancer. Here, the possible interaction between common polymorphisms in X-ray repair cross complementing group I (*XRCC1*) gene and glutathione *S*-transferase (*GST*) genes (*GSTM1*, *GSTT1* and *GSTP1*), smoking and alcohol consumption and overall survival in gastric cancer patients were evaluated. In this population-based case control study, 70 gastric cancer patients and 82 healthy controls were enrolled. The epidemiological data were collected by a standard questionnaire, and blood samples were collected from each individual. *XRCC1* Arg194Trp, Arg280His and Arg399Gln polymorphisms were determined by polymerase chain reaction and direct DNA sequencing. *GSTM1* and *GSTT1* null polymorphisms and *GSTP1* Ile105Val polymorphism were identified by multiplex polymerase chain reaction and restriction fragment length polymorphism (RFLP), respectively. The risk of gastric cancer was significantly elevated in individuals with *XRCC1* Arg/Gln +Gln/Gln ($p = 0.031$; odds ratio = 2.32; 95 % confidence interval (CI) 1.07–5.06) and *GSTP1* Val/Val genotype ($p = 0.009$; odds ratio = 8.64; 95 % CI 1.84–40.55). An elevated risk for GC was observed in smokers and alcohol consumers carrying *GSTP1* Ile/Val +Val/Val genotype ($p = 0.041$; odds ratio = 3.71; 95 % CI 0.98–14.12; $p = 0.002$; odds ratio = 12.31; 95 % CI 1.71–88.59). These findings suggest that *XRCC1* rs25487 and *GSTP1* rs1695 can be considered as a risk factor associated with gastric cancer and might be used as a molecular marker for evaluating the susceptibility of the disease.

Keywords Gastric cancer · *XRCC1* · *GSTP1* · SNPs

Introduction

Cancer is the biggest cause of mortality worldwide as a single entity securing 8.2 million deaths in 2012 [1]. In India especially, gastric cancer imparts one of the major causes of cancer-related deaths. It contributes a huge socio-economic burden. Around 1 million new cancer cases have been estimated for the year 2015 in India [2]. Gastric cancer (GC) is a complex multifactorial disease, whose pathogenesis and molecular mechanism are poorly understood [3]. This process of carcinogenesis is a multistep phenomenon in which various environmental and host-related factors interact in disease manifestation like dietary habits, gastritis and chemical carcinogens [4], and genetic factors make it even more complex as all individuals who are exposed to these risk factors will not

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develop the disease since inter-individual differences in genetic susceptibility exist [5]. There are several mechanisms along with various genetic factors that are related to the development of gastric cancer, but a large number of evidences indicate that polymorphisms in DNA repair gene and phase 1 and phase 2 genes of xenobiotic pathway increase the cancer susceptibility of individuals [6].

DNA damage repair is a complex, multistep phenomena involving large numbers of proteins and enzymes. So far, four major repair pathways identified in cells are base excision repair (BER), nucleotide excision repair, double strand break repair and mismatch repair [7]. Such DNA repair systems are crucial for maintaining the integrity of the human genome and X-ray repair cross complementing group I gene (*XRCC1*) is an important component of base excision repair (BER) systems. *XRCC1* is independently involved in DNA damage recognition process [8]. There are three genetic polymorphisms in *XRCC1* conserved sites: Arg194Trp, Arg280His and Arg399Gln [9]. The alterations in the conserved protein site might change the BER capacity of *XRCC1* leading to increased DNA damage [9].

Glutathione *S*-transferases (*GST*s) are important phase II metabolizing enzymes of the xenobiotic pathway which detoxifies several cytotoxic and genotoxic compounds, thereby protecting against carcinogenic progression [10]. Therefore, a reduction in the activity of these enzymes increases the carcinogenic susceptibility of individuals. There are mainly three *GST* isoenzymes, *GSTM (mu) 1*, *GSTT (theta) 1* and *GSTP (pi) 1*, which are highly polymorphic and expressed along the gastrointestinal tract of human beings [11]. Among the three isoenzymes, *GSTM1* and *GSTT1* exhibit deletion polymorphism in a large percentage of individuals with major ethnic differences [12, 13]. Worldwide numerous studies have been performed to elucidate the association of *GST*s with GC. In India, several studies were done on deletion polymorphisms and the results were found to be inconsistent [14–16]. On the other hand, *GSTP1* exhibits a single nucleotide polymorphism (SNP) within its coding region leading to amino acid substitution at codon 105 of the gene (Ile > Val), which is associated with reduced activity of the gene [17].

The pathway from environmental carcinogen to cancer is extremely complex. Normally, exogenous agents are metabolized into different reactive states for conjugation and elimination. Phase I enzymes convert carcinogens to a reactive state, and phase II enzymes (*GSTs*) detoxify the reactive intermediates and facilitate their excretion from the body. Genetic alterations in *GSTs* would prevent excretion of reactive intermediates which in turn would result in the formation of harmful DNA adducts which been successfully repaired by DNA repair enzyme *XRCC1* [18] normally. Mutations/polymorphisms harboured in *XRCC1* would increase the risk of a cell going towards cancer [19, 20]. It is the synchronization between these two genes that function one after the other in an implicated pathway to restore the genetic integrity of the cell by removing the activated carcinogens. Thereby, these two genes naturally qualify as potential biomarkers for gastric cancer susceptibility. Various studies have examined the role of polymorphisms in *XRCC1*, *GST*s and gastric cancer, but the results are equivocal [9, 10, 21–24]. In addition, several studies have also investigated the association between these genes and survival in GC patients associated with anticancer drugs [25, 26]. However, in different demographical region like in India, very few studies [14–16, 27] investigated the association between *GST*s and GC risk, but until now, not a single report investigated the potential role of *XRCC1* polymorphisms and intricate association of *XRCC1* and *GSTs* on GC susceptibility in Indian population. In this study, we have tried to evaluate the association between *XRCC1* Arg194Trp, Arg280His and Arg399Gln and *GSTP1* Ile105Val, *GSTM1* and *GSTT1* null polymorphisms with gastric cancer risk in the population of West Bengal, India.

Materials and method

Study subjects

This case control study consists of 70 gastric cancer patients and age- and sex-matched 82 healthy controls. The gastric cancer patients were recruited from the Department of Surgery, Institute of Post Graduate Medical Education & Research (IPGME&R), Kolkata, West Bengal, India. All the cases were newly diagnosed and histopathologically confirmed gastric adenocarcinoma without any other chronic disease. Patients with gastric neoplasm other than adenocarcinoma (MALT lymphoma, stromal or carcinoid tumours), secondary or recurrent GC and previous history of other malignancies were excluded. Tumours were classified according to their histological type [28] as intestinal, diffuse or indeterminate. The controls were selected from the same geographical region, socio-economic status and ethnic group. The controls did not have any previous history of gastric disease or any tumour-related disease detected by physical examination or familial history of gastric cancer or any type of cancer. All the individuals were personally interviewed for their age, gender, ethnicity, occupation, body mass index (BMI), smoking habits, alcohol drinking, history of familial tumour and exposure to carcinogens. All participants of this study had given informed consent. The experimental protocol was approved by the institutional ethics committee of IPGME&R, Kolkata.

DNA extraction and genotyping

Approximately 4–5 mL of peripheral blood samples were collected from both the case and control individuals. Genomic DNA was isolated from the blood leucocytes by using

QIAamp Blood Kit (QIAGEN, Hilden, Germany). The SNPs (rs1799782, rs25489 and rs25487) of *XRCC1* were amplified by PCR using specific primers (Supplementary Table 1). PCR was performed in a thermo cycler (Applied Biosystems, Model No. 9902). The reaction mixture (30 μL) contained 50–100 ng of genomic DNA, 1X PCR buffer, 2 mM $MgCl_2$, 200 μM of each dNTP, 0.5 μM of each primer and 0.5 U of Taq DNA polymerase (Invitrogen, USA). Denaturation at 94 °C for 30 s, annealing at 55–60 °C for 30 s and extension at 72 °C for 60 s × 44 cycles were performed. The PCR products were subjected to direct sequencing using a Taq Dye Deoxy Terminator sequencing kit (Applied Biosystems, Foster City, USA) with an ABI Prism 377 DNA sequencer (Applied Biosystems).

GSTM1 and *GSTT1* null genotypes were determined by multiplex polymerase chain reaction (PCR) using specific primers (Supplementary Table 1). The reaction mixture (30 μL) contained 50–100 ng genomic DNA, 1X PCR buffer, 2 mM $MgCl_2$, 200 μM dNTPs, 0.5 μM of each primer and 0.5 U of Taq DNA polymerase. The amplified products were analysed by electrophoresis on 8 % polyacrylamide gels, resulting in a 219-bp fragment for *GSTM1*, a 560-bp fragment for *GSTT1* and a 268-bp fragment of the *β globin* gene, which was used as an internal control for DNA amplification. The absence of the *GSTM1* and/or *GSTT1* bands indicated the corresponding null genotype, and the presence of the 268 bp *β globin* band ensured that the null genotype was not the result of PCR failure. In addition, the polymorphism in the *GSTP1* gene, for amino acid substitutions at codons 105 (Ile → Val), was genotyped by PCR-restriction fragment length polymorphism (RFLP)-based methods. The *GSTP1* Ile105Val (rs1695) polymorphic site was amplified according to the following parameters: 95 °C for 5 min followed by 35 cycles of 94 °C for 30 s, 55 °C for 30 s, 72 °C for 1 min and a final elongation at 72 °C for 5 min. Ten microlitres of PCR products was digested with 1 unit of BsmAI restriction enzyme (New England Biolabs, Izasa, Barcelona, Spain) for 1 h at 55 °C. The digested products were then electrophoresed on 8 % polyacrylamide gels. On the basis of band pattern, the genotypes were determined. The Ile allele was resistant to digestion by BsmAI; as a result, an undigested band of 176 bp was obtained for Ile/Ile genotype. The valine (Val) allele resulted in two fragments of 91 and 85 bp. The Ile/Val genotype was determined by the presence of three fragments of 176, 91 and 85 bp. The results were further confirmed by forward strand sequencing.

Statistical analysis

χ^2 and Fisher exact tests were used to test the allelic and genotypic associations of each SNP wherever applicable. Hardy–Weinberg equilibrium of each SNP in case and control individuals were also examined using a χ^2 test. To calculate any statistically significant difference of continuous independent variables within the control and patient groups like age and BMI, we used the Student *t* test. We analysed non-parametric variables by Mann–Whitney *U* test. All tests were done using GraphPad InStat software (GraphPad InStat software, San Diego, CA) and SNPassoc version 1.8-1 software [29]. Odds ratio and 95 % confidential intervals were also calculated using the same software, and Haploview 4.2 software was used to analyse linkage disequilibrium (LD) pattern of SNPs and calculation of haplotype. Survival curves were obtained according to Kaplan–Meier model. Overall survival was measured from the date of surgery to the date of most

Table 1 Clinical characteristics of gastric cancer patients and controls

Characteristics	Control (n = 82)	Case (n = 70)	Odds ratio (95 % CI)	*p* value
Age (years ± SD)[a]	51 ± 6.72	53.01 ± 10.97		0.085
Sex				
Male	62	55		0.666
Female	20	15		
BMI (kg/m^2)[a]	22.21 ± 2.14	20.41 ± 2.90		*<0.0001*
Histological subtypes of tumour				
Intestinal	–	33		
Diffuse	–	14		
Indeterminate	–	23		
Alcohol consumption				
Ever	25	34	2.15 (1.11–4.18)	*0.023*
No	57	36		
Cigarette/bidi smoking				
Ever	28	51	5.18 (2.58–10.39)	*<0.001*
No	54	19		

P value less than 0.05 and gene name is denoted in italic along with the "*p*" of *p* value (according to convention)

[a] At diagnosis

recent follow-up or death (up to 3 years). SPSS 16.0 was used to perform this test.

Result

Characteristics of study subjects

This study has been performed with total 70 gastric cancer patients (55 male and 15 female) with mean age of 53.01 ± 10.97 years, including gastric adenocarcinomas of intestinal type in 33 patients (47 %), diffuse type in 14 patients (20 %) and indeterminate type in 23 patients (33 %). The clinical and demographic characteristics of GC patients and controls have been shown in Table 1. Our study population is balanced in terms of age and sex (Table 1). The BMI is significantly different between control and case groups (control 22.21 ± 2.14, case 20.41 ± 2.90, p value <0.0001). We found 26 GC patients (37 %) were underweight, whereas only two patients (3 %) were overweight in our study. We did not document any association with GC risk for overweight and obesity as more than one third of adults are thin (39 % women and 35 % men) and only 6.1 % of males and 11 % of females are found to be overweight or obese in West Bengal [30]. Also, at the time of diagnosis, most of the patients presented with weight loss and this reduction of weight may be due to late diagnosis of the disease (II to III stage) of cancer. Analysis of the exposure status clearly indicated that alcohol and smoking habits were significantly different between case and control groups and found to be risk factors for the development of GC (Table 1).

XRCC1 and *GST* gene polymorphisms

The associations between *XRCC1* gene polymorphisms (rs1799782: Arg194Trp, c.580C>T; rs25489: Arg280His, c.839G>A; rs25487: Arg399Gln, c.1196G>A), *GSTM1* null, *GSTT1* null genotype and *GSTP1* A>G (rs1695: Ile105Val, c.313A>G) polymorphism and risk of GC were evaluated in this study. The distribution of the genotypes fitted the Hardy–Weinberg equilibrium. The allelic frequency and genotypic frequency of Arg194Trp, Arg280His and Arg399Gln of *XRCC1* and Ile105Val of *GSTP1* are summarized in Table 2. No linkage disequilibrium was observed among the three SNPs of *XRCC1* (Fig. 1). The frequency of the codon 194-T allele for cases and controls were 19 and 15 %, respectively. The frequency of 194-TT genotype for case was 8.5 % and TT genotype was absent in controls. We did not find any association for Arg194Trp polymorphism with GC risk. In the case of Arg280His, the codon 280-A allele frequency was 19 % in case and 26 % in controls. The AA genotype frequency of Arg280His was very similar in cases and controls (cases 10 %; controls 9.7 %), and we did not get any association between Arg280His and GC. As for c.1196G>A (Arg399Gln), the allele frequencies of cases (G 64 %; A 36 %) were significantly different from controls (G 77 %; A 23 %; $p = 0.013$). Our results suggested that for Arg399Gln, A allele is the risk allele ($p = 0.013$; odds ratio = 1.88; 95 % confidence interval (CI) 1.14–3.11) towards the increased risk of GC (Table 2). Simultaneously, when we combined the variant GA genotype with the AA genotype (i.e. GA+AA), assuming a dominant genetic model, we observed twofold increased risk with the combined genotype GA+AA compared with the GG genotype ($p = 0.031$; odds ratio = 2.32; 95 % CI 1.07–5.06).

We also examined haplotype frequencies of these three polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) of *XRCC1* gene in controls and cases. The Haploview program predicted eight different haplotypes. Of the eight, three haplotypes occurring with a frequency of ≤5 % (control) were excluded from the haplotype analysis. The haplotype distribution of controls and cases is shown in Table 3. The three common haplotypes (CGG, CGA and CAG) were estimated to account for over 80 % of all haplotype. The result from haplotype analysis revealed that CAG (194Arg, 280His, 399Arg) haplotype appeared to be associated with significant reduction in GC risk ($p = 0.012$; odds ratio = 0.40; 95 % CI 0.19–0.83). Therefore, individuals carrying this haplotype have decreased risk of GC. The haplotype CGA was more prevalent in the cases (25.8 %) than in controls (16.6 %). This haplotype appeared to be a marginal risk haplotype for GC (odds ratio = 1.59; 95 % CI 0.87–2.89).

Our result showed 22 (26.8 %) controls and 24 (34.4 %) cases carry the *GSTM1* null genotype. This *GSTM1* null genotype did not show any association with GC risk in our study group ($p = 0.196$; odds ratio = 1.74; 95 % CI 0.75–4.02). In the case of *GSTT1* null genotype, we found 15 (18.3 %) controls and 10 (14.3 %) cases carry the null genotype, but no association stated between *GSTT1* null genotype and GC risk ($p = 0.377$; odds ratio = 0.63; 95 % CI 0.22–1.78). For the Ile105Val (A>G) change in *GSTP1*, G allele and GG genotype frequency of cases and controls was 28 and 15 % and 14.2 and 3.6 %, respectively. Consequently, our results showed G allele to be a risk allele ($p = 0.006$; odds ratio = 2.20; 95 % CI 1.25–3.88) and GG genotype as a risk genotype ($p = 0.009$; odds ratio = 8.64; 95 % CI 1.84–40.55) towards the development of GC (Table 2). Individuals carrying GG genotype have more than eightfold increased risk for the development of GC. Similarly, when we considered recessive model of genotyping (AA+AG vs. GG), nearly sevenfold increased risk was observed for GC ($p = 0.005$; odds ratio = 6.96; 95 % CI 1.57–30.93).

Combined effect of *XRCC1* Arg399Gln and *GSTP1* Ile105Val polymorphism with GC risk

To evaluate the combined risk of these two SNPs, we compared individuals carrying both risk alleles (A of rs25487 and

Table 2 Allele and genotype frequencies of *XRCC1* and *GSTP1* gene and association with gastric cancer risk

	SNP	Allele	Allele frequency		Odds Ratio (95 % CI)	*p* value	Genotype	Case (n = 70)	Control (n = 82)	Odds ratio (95 % CI)[a]	*p* value
			Case	Control							
XRCC1	rs1799782 Arg194Trp c.580C>T	C	0.81	0.85	1.33 (0.73–2.43)	0.353	CC	50	58	Reference	
		T	0.19	0.15			CT	14	24	CC vs CT, 0.91 (0.36–2.32)	0.069
							TT	6	0	CC vs CT+TT, 1.27 (0.53–3.04)	0.597
	rs25489 Arg280His c.839G>A	G	0.81	0.74	0.67 (0.39–1.15)	0.147	GG	50	48	Reference	
		A	0.19	0.26			GA	13	26	GG vs GA, 0.57 (0.23–1.43)	0.640
							AA	7	8	GG vs AA, 0.98 (0.29–3.31)	0.476
										GG+GA vs AA, 1.14 (0.35–3.77)	0.828
										GG vs GA+AA, 0.68 (0.31–1.51)	0.342
	rs25487 Arg399Gln c.1196G>A	G	0.64	0.77	1.88 (1.14–3.11)	*0.013*	GG	28	48	Reference	
		A	0.36	0.23			GA	33	30	GG vs GA, 2.16 (0.96–4.88)	0.086
							AA	9	4	GG vs AA, 3.35 (0.75–14.89)	0.083
										GG+GA vs AA, 2.35 (0.56–9.86)	0.230
										GG vs GA+AA, 2.32 (1.07–5.06)	*0.031*
GSTP1	rs1695 Ile105Val c.313A>G	A	0.72	0.85	2.20 (1.25–3.88)	*0.006*	AA	41	61	Reference	
		G	0.28	0.15			AG	19	18	AA vs AG, 1.88 (0.72–4.91)	0.227
							GG	10	3	AA vs GG, 8.64 (1.84–40.55)	*0.009*
										AA+AG vs GG, 6.96 (1.57–30.93)	*0.005*
										AA vs AG+GG, 2.78 (1.16–6.64)	*0.018*

Chi-square test was used to compare the genotype and allele frequencies between cases and controls

[a] Odds ratio was adjusted for age, sex, BMI, alcohol and smoking status

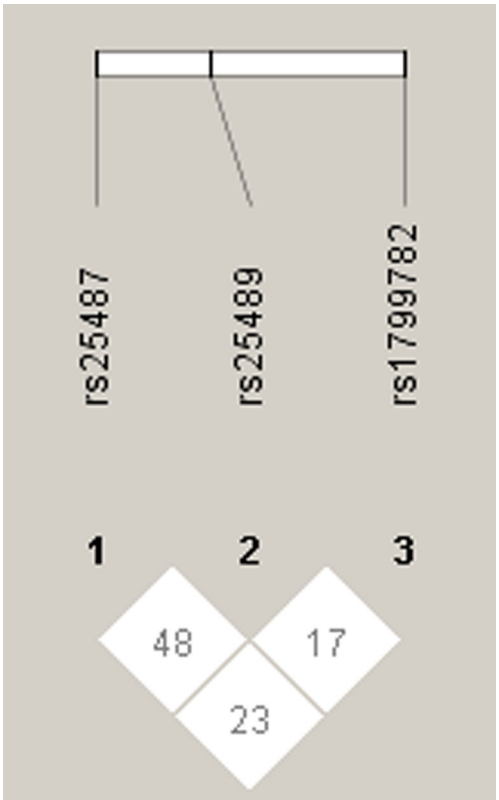

Fig. 1 Linkage disequilibrium (LD) pattern of the three SNPs in *XRCC1* in case and control groups. SNPs are measured as r^2 and shown in the *diamond* at the intersection of the diagonals from each SNP. $r^2 = 0$ is shown as *white*

G of rs1695) with individuals carrying single risk allele and no risk allele. Our result suggested that individuals carrying both risk alleles showed twofold (approximately) increased risk ($p = 0.08$; odds ratio = 1.8; 95 % CI 0.73–4.40) compared to individuals carrying single risk allele and individuals carrying both risk alleles showed fourfold increased risk ($p = 0.003$; odds ratio = 3.92; 95 % CI 1.5–10.26) compared to individuals having no risk allele for the development of GC (Table 4).

Association between *XRCC1* Arg399Gln, *GSTP1* Ile105Val polymorphisms and exposure status

We further assessed interaction between the *XRCC1* Arg399Gln (c.1196G>A), *GSTP1* Ile105Val (c.313A>G) polymorphisms and exposure status, i.e. smoking and alcohol. There was no evidence of interaction between Arg399Gln with either smoking ($p = 0.152$; odds ratio = 2.19; 95 % CI 0.74–6.54) or alcohol status ($p = 0.151$; odds ratio = 2.78; 95 % CI 0.66–11.61) or both ($p = 0.614$; odds ratio = 1.55; 95 % CI 0.28–8.50) (Table 5). On the contrary, the c.313A>G-AG+GG genotype was significantly associated with smoking and alcohol consumption. We found smokers carrying the AG+GG genotype have significantly fourfold (approximately) increased GC risk ($p = 0.041$; odds ratio = 3.71; 95 % CI 0.98–14.12) (Table 5). Similarly, alcohol consumers carrying the AG+GG genotype showed threefold increased risk of GC ($p = 0.033$; unadjusted odds ratio = 3.26;

Table 3 Association analysis between *XRCC1* haplotype and gastric cancer risk

Arg194Trp	Arg280His	Arg399Gln	Controls	Case	OR ratio	*p* value
C→T	G→A	G→A	No. of chr, 164 (100 %)[a]	No. of chr, 140 (100 %)[a]	(95 % CI)	
C	G	G	76 (46.4)	64 (45.4)	Reference[b]	
C	G	A	27 (16.6)	36 (25.8)	1.59 (0.87–2.89)	0.129
C	A	G	36 (21.8)	12 (8.5)	0.40 (0.19–0.83)	*0.012*
T	G	A	9 (5.6)	7 (4.8)	0.88 (0.31–2.52)	0.818
T	G	G	9 (5.7)	7 (4.7)	0.83 (0.29–2.37)	0.724

Haplotype occurring with a frequency of ≤5 % was excluded from the haplotype analysis

[a] Number of chromosome

[b] The haplotype combining the most frequent alleles at each site is chosen as the reference haplotype (CGG)

95 % CI 1.08–9.83), but when OR was adjusted for age, sex, BMI, alcohol status and smoking status, we found 12-fold increased risk ($p = 0.002$; odds ratio = 12.31; 95 % CI 1.71–88.59) for GC (Table 5). It was also observed that the individuals who are both smokers and alcohol consumers carrying valine amino acid at codon 105 have fivefold (approximately) increased risk for GC ($p = 0.038$; odds ratio = 5.19; 95 % CI 0.94–28.56) (Table 5).

Patient survivability with *XRCC1* Arg399Gln and *GSTP1* Ile105Val polymorphisms

The average survivals of all GC patients were 10.8 months, and the median overall survival was 6.5 months. The mortality in GC patients with *XRCC*1 rs25487 risk genotype GA+AA was 81 versus 78 % in the GC patients with non-risk genotype GG. Hence, Kaplan–Meier survival analysis did not show any association between rs25487 and patient survivability (GG vs GA $p = 0.710$; GG vs AA $p = 0.590$) (Fig. 2a). In the case of *GSTP1* rs1695, the mortality of risk genotype AG+GG and non-risk genotype AA was 79 and 80 % that is almost the same; therefore, no association was found (AA vs AG $p = 0.796$; AA vs GG $p = 0.540$) (Fig. 2b).

Discussion

Genetic polymorphisms leading to inter-individual genetic difference in carcinogen susceptibility are considered to be important factors in the development of cancer [31]. The polymorphisms in DNA repair gene and xenobiotic pathway gene plays a crucial role in human carcinogenesis. Thus, we carried out a case control study to evaluate whether polymorphisms in selected DNA repair gene and *GST* genes modulate the risk of GC in the population of West Bengal, India. We found that subjects carrying *XRCC1* rs25487 A allele (GA+AA) and *GSTP1* rs1695 GG genotype have increased risk of GC, whereas individuals having CAG haplotype of *XRCC1* gene have decreased risk of GC. In addition, a significant interaction between *GSTP1* rs1695 polymorphism and exposure status was found. To the best of our knowledge, this is the first report regarding the association between *XRCC1* gene polymorphisms and the risk of gastric cancer from India.

In this context, *XRCC1* gene polymorphisms (rs1799782: Arg194Trp, c.580C>T; rs25489: Arg280His, c.839G>A; rs25487: Arg399Gln, c.1196G>A) and GC risk were evaluated. Our result revealed that Arg194Trp and Arg280His change is not associated with GC risk; at the same time, Arg399Gln is significantly associated with GC risk. In agreement with our result, Ratnasinghe et al., Jin et al., Lee et al., Yan et al. and Xue et al. [20, 32–35] did not report any association between *XRCC1* Arg194Trp and GC risks in Asian population. Similarly, in the Brazilian population, Duarte et al. did not show any interaction between Arg194Trp and GC [36], which is consistent with our result. In contrast, multiple studies [7, 21, 37, 38] have shown positive association between *XRCC1* Arg194Trp and GC risk in the Chinese population. A recent meta-analysis suggested that Asians with Arg194Trp (Arg/

Table 4 Analysis of combined effect of rs25487 and rs1695 polymorphism with gastric cancer risk

	Control (n)	Case (n)	Odds ratio (95 % CI)	*p* value
Individuals having single risk allele[a]	35	35	Reference	0.08
Individuals having both risk alleles[b]	10	18	1.8 (0.73–4.4)	
Individuals having no risk allele	37	17	Reference	*0.003*
Individuals having both risk alleles[b]	10	18	3.92 (1.5–10.26)	

[a] A of rs25487 or G of rs1695

[b] A of rs25487 and G of rs1695

Table 5 Interaction between *XRCC1* Arg399Gln and *GSTP1* Ile105Val polymorphisms and smoking and alcohol consumption in gastric cancer

	Exposure	Status	Genotypes	Control (n)	Case (n)	Odds ratio (95 % CI)[a]	*p* value
XRCC1 Arg399Gln	Smoking	Non-smoker	GG	33	8	Reference	0.141
			GA+AA	21	11	2.40 (0.73–7.88)	
		Smoker	GG	15	20	Reference	0.152
			GA+AA	13	31	2.19 (0.74–6.54)	
XRCC1 Arg399Gln	Alcohol	Non-alcoholic	GG	33	15	Reference	0.112
			GA+AA	24	21	2.14 (0.83–5.52)	
		Alcoholic	GG	15	13	Reference	0.151
			GA+AA	10	21	2.78 (0.66–11.61)	
XRCC1 Arg399Gln	Smoking + alcohol	No addiction	GG	23	8	Reference	0.474
			GA+AA	17	8	1.60 (0.44–5.85)	
		Both alcohol and smoking	GG	5	5	Reference	0.614
			GA+AA	6	5	1.55 (0.28–8.50)	
GSTP1 Ile105Val	Smoking	Non-smoker	AA	38	10	Reference	0.263
			AG+GG	16	9	1.97 (0.60–6.50)	
		Smoker	AA	23	31	Reference	*0.041*
			AG+GG	5	20	3.71 (0.98–14.12)	
GSTP1 Ile105Val	Alcohol	Non-alcoholic	AA	43	26	Reference	0.410
			AG+GG	14	10	1.58 (0.53–4.73)	
		Alcoholic	AA	18	15	Reference	*0.002*
			AG+GG	7	19	12.31 (1.71–88.59)	
GSTP1 Ile105Val	Smoking + alcohol	No addiction	GG	29	9	Reference	0.283
			GA+AA	11	7	2.08 (0.54–7.92)	
		Both alcohol and smoking	GG	9	14	Reference	*0.038*
			GA+AA	2	17	5.19 (0.94–28.56)	

[a] Odds ratio was adjusted for age, sex, BMI, alcohol and smoking status

Trp+Trp/Trp) genotype had a higher GC risk [39]. This discrepancy might be due to different genetic backgrounds between ethnic groups and associated environmental factors. A wide variation of the Trp allele frequencies of control resources in Asians (0.269), Indians (0.200), Caucasians (0.077) and Africans (0.082) [40] clearly supported our prediction. Additionally, we did not find any association between 280His and GC risk which is consistent with previous published worldwide studies [7, 20]. The 399Gln allele and 399Arg/Gln+Gln/Gln genotype of Arg399Gln polymorphism were found to be associated with increased risk of GC in our study group. This amino acid change Arg to Gln at 399 is located in the -COOH terminal site of poly(ADP-ribose) polymerase (PARP)-interacting domain within BRCT1 (BRCA1 C terminus) domain [41]. BRCT domains mediate specific protein–protein interactions and are present in various DNA damage response proteins [42]. Therefore, alterations of this amino acid may inhibit the interaction pattern of *XRCC1* protein which ultimately may reduce the functional efficacy. An earlier report stated that the 399Gln allele was significantly associated with higher levels of DNA adduct formations and increased frequency of sister chromatid exchange [43]. The Gln allele of Arg399Gln polymorphism was associated with an increased risk of various cancers, namely oesophageal cancer, breast cancer, prostate cancer, colorectal cancer, lung cancer and hepatocellular cancer [44–49]. Engin et al. suggested that 399Gln allele was associated with 2.54 times higher risk of gastric cancer in Turkish population [50] and similarly 399 Gln allele was associated with increased risk of gastric atrophy among Caucasians [51], which is in line with our result. A recent meta-analysis exhibited the association between breast cancer and prostate cancer with Arg399Gln polymorphism in Indian population [52]. Further, a previous study from South India showed association between Arg399Gln polymorphism and lung cancer [53], whereas studies reported from northern and north-eastern part of India did not show any association between Arg399Gln polymorphism and colorectal cancer and lung cancer [54, 55]. The results are complex and contradictory with each other. But majority of the reports considered this to be a cancer risk factor in various populations.

The haplotype analysis results of these three polymorphisms revealed that Arg194-His280-Arg399 (CAG) haplotype have reduced risk against GC. Individually, A allele or 280His amino acid of His280Arg change is associated with reduced risk of different cancers [56–58] as it is related with increased repair activity [56] and reduced chromosomal aberration [57]. Interestingly, we did not find 280His alone to be protective but in combination with Arg194 and Arg399, the haplotype showed reduction of GC risk. Previously Hong

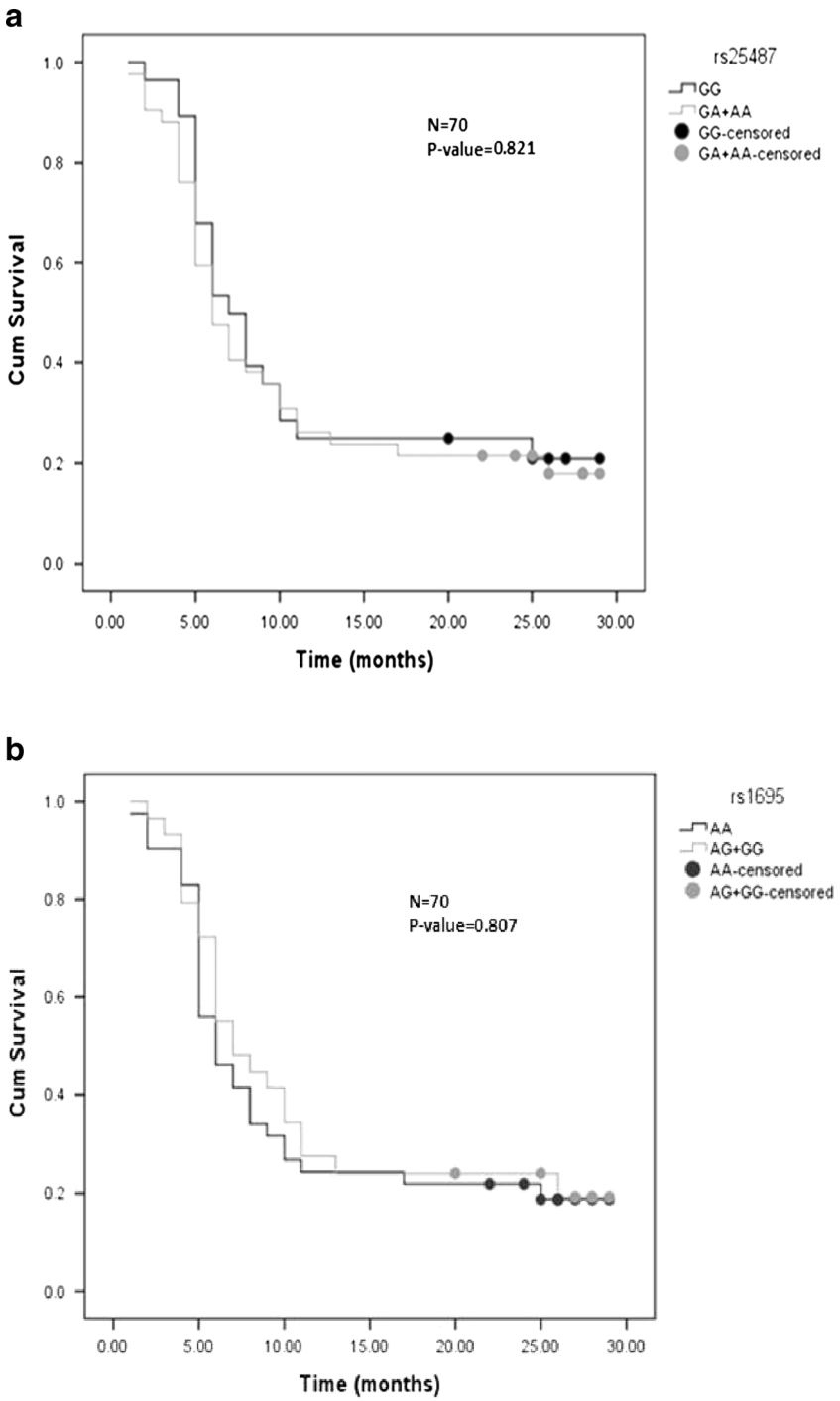

Fig. 2 **a**, **b** Kaplan–Meier 3-year survival probability curves with survival of GC patients by genotype status of *XRCC1* rs25487 (GG vs GA $p = 0.710$; GG vs AA $p = 0.590$) and *GSTP1* rs1695 (AA vs AG $p = 0.796$; AA vs GG $p = 0.540$). Survival time was defined as the time from surgery to patient's death or last time the patient was known to be alive. Statistical analysis was performed by the log-rank test

et al. reported that 194Arg-280Arg-399Gln of *XRCC1* was significantly related to an elevated risk of colorectal cancer [59], but in our study, we found different patterns of haplotype among which CAG haplotype has decreased risk against GC. The difference may be due to ethnic differences between the two studied population and cancer type.

In our study, neither the *GSTM1* nor the *GSTT1* gene deletions were associated with GC risk. Our results are in contrast with a study reported by Saadat et al. [60], who showed that individuals with deletions in both genes have significantly increased GC risk. A similar result was observed in a meta-analysis conducted by Boccia et al. [61]. A recent meta-analysis of 45 studies from Asia and Europe suggested significant association between the *GSTM1* deletion and GC risk in Asians [62]. However, *GSTM1* and *GSTT1* gene deletions were not associated with GC risk in Chinese, Korean, American and Caucasian population [11, 22, 63, 64] which support our result. In India, a study from Kashmir Valley

reported *GSTM1* null genotype as a significant risk factor for GC, while no association was observed between *GSTT1* null polymorphism and GC [14]. In contrast, Yadav et al. suggested *GSTT1* null genotype was associated with GC risk in the north-east Indian population but no such association was observed for *GSTM1* null genotype [15]. The regional, ethnic and geographical differences and exposure to different risk factors or lifestyles of studied populations might be the probable reason for the inconsistent results obtained from the same country.

The polymorphism of *GSTP1* gene results in an amino acid substitution from isoleucine (wild type) to valine in the active site of the enzyme introducing conformational changes due to the bulky side chain of valine. It might be probable that the *GSTP1* enzyme containing valine which metabolizes various carcinogens with lower activity could be associated with an increased risk of developing cancer [17]. Our study revealed that the *GSTP1* Ile105Val polymorphism particularly Val/Val is a risk factor for the development of GC. This result is in consistence with several population-based studies in Asia in other cancer scenario [23, 65–67]. A similar result was shown by Bao et al. [68] by pooling data from 20 different studies. *GSTP1* Ile/Val or Val/Val was reported as a risk factor for GC in the Lucknow Region of North India [16] and for lung cancer in the South Indian population [69]. In contrast, studies from Kashmir Valley and north-eastern India did not show any association [14, 15]. This interesting variation in the same country may be due to several factors, such as the diverse Indian population with different socio-cultural traditions, different genetic backgrounds between ethnic groups and different environmental factors.

In the present study, we also examined gene–gene interaction to explore the combined effect of *XRCC1* Arg399Gln and *GSTP1* Ile105Val polymorphism towards the risk of GC. Our findings revealed that the GC risk is increased significantly if both the risk alleles namely 399Gln and 105Val were present together. A fourfold increased risk among individuals carrying these two risk alleles compared with individuals having no risk allele suggests that cross talk between DNA repair gene *XRCC1* and xenobiotic pathway gene *GSTP1* might modulate susceptibility towards GC. This finding might provide a link between these genetic variants and their potential role in predictive genetic testing with respect to GC.

Furthermore, we have also tested whether the plausible contribution of *XRCC1* and *GSTP1* polymorphisms to GC risk could be modified by other environmental risk factors, namely smoking and alcohol consumption. Our results did not show any association between alcohol consumption or smoking and *XRCC1* Arg399Gln polymorphism, suggesting that smoking or alcohol consumption did not modify the association between *XRCC1* Arg399Gln polymorphism and GC risk. The results from Shen et al. and Duarte et al. have differential conclusion regarding this association [21, 36]. The lack of association may be due to the small sample size. Accordingly, large population-based studies are required to clarify the interrelationship between Arg399Gln with smoking and alcohol consumption on gastric cancer. On the contrary, smokers and alcohol consumers carrying Val allele of *GSTP1* Ile105Val polymorphism are approximately at fourfold and 12-fold increased risk, respectively. This result is in accordance with the study on Chinese population that showed significant increase in the risk of GC development for combined effect of *GSTP1* Val allele with smoking and alcohol consumption [23]. These findings suggested that the risk of GC was greatly dependent upon smoking exposure, alcohol consumption and susceptibility gene.

In conclusion, our findings indicate that c.1196G>A: Arg399Gln of *XRCC1* gene and c.313A>G: Ile105Val of *GSTP1* gene could be a useful marker for the susceptibility of gastric cancer in West Bengal, India. Moreover, *GSTP1* Val allele significantly increased the risk of gastric cancer associated with tobacco smoking and alcohol consumption. Future studies with larger sample size might help in further validation of the current findings.

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Compliance with ethical standards

Conflicts of interest None

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