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Genetic polymorphisms in DNA repair genes and their association with cervical cancer

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ABSTRACT

Background and objective: Carcinoma of cervix is the second most common cancer among women worldwide. The DNA repair network plays an important role in the maintenance of genetic stability, protection against DNA damage and carcinogenesis. Alterations in repair genes *XRCC1, XRCC2* and *XRCC3* and been reported in certain cancers. We hypothesised an association between *XRCC1*+399A/G, *XRCC2*+31467G/A and *XRCC3*+18067C/T polymorphisms and the risk of cervical cancer.

Subjects and methods: This study included 525 subjects (265 controls and 260 cervical cancer cases). Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: Women with GA and AA genotypes of *XRCC1*+399A/G showed 2.4–3.8 fold higher risk of cervical cancer (P = 0.001). The +399A* allele was significantly linked with cervical cancer (P = 0.002). However, *XRCC2*+31479G/A and *XRCC3*+18067C/T polymorphisms did not show any statistically significant associations.

Conclusion: The *XRCC1*+399A/G SNP is linked with cervical cancer. We suggest that this variant can be utilized as a prognostic marker for determination of cervical cancer susceptibility.

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Cervical cancer; genetic polymorphism; PCR-RFLP; repair genes

Introduction

Carcinoma of cervix is the second most common cancer among women worldwide, with approximately 530,000 new cases and 275,000 deaths each year [1]. As a result of early detection screening programmes and treatment of precursor lesions, i.e. cervical intraepithelial neoplasia (CIN), incidence and mortality have substantially reduced. More than 80% of cervical cancer cases occur in developing countries [2]. In India, it was the most common cancer with 132,000 new cases diagnosed annually, out of which 74,000 deaths occurred accounting for a third of global cervical cancer deaths [3].

Epidemiologic studies have shown that most cases of cervical cancer are caused by the Human Papillomavirus (HPV), mainly HPV-16 and HPV-18 [4]. However, not all women infected with HPV develop cervical cancer, indicating roles for additional co-factors such as age, marriage age, number of abortions, young age at first delivery, early and multiple child births, oral contraceptive, multiple sexual partners, heavy cigarette smoking, immune suppression and low socio-economic status. In addition, genetic susceptibility factors are also known to influence the risk of developing cervical carcinoma [5].

The DNA repair network is very important in the maintenance of genetic stability and protection against DNA damage [6]. Genetic variations in DNA repair genes can affect their efficiency and increase the risk of developing cancer [7]. Among various DNA repair pathways, the base excision repair (BER) restores DNA single-strand breaks by eliminating methylation and oxidation of a single base, while homologous recombination repair (HRR) restores DNA double-strand breaks [8]. Variations in these pathways (BER or HRR) might trigger many types of cancer. Previous studies have reported that the X-ray repair cross-complementing group 1 (*XRCC1*) is involved in the BER pathway while *XRCC2* and *XRCC3* function in DNA repair of double-strand breaks by HRR mechanism [9]. Genetic polymorphisms in DNA repair genes may be associated with repair efficiency of damaged DNA and influence cancer risk [10]. Three polymorphisms, Arg194Trp, Arg280His and Arg399Gln in *XRCC1* analyzed in different populations are associated with susceptibility to gastric, lung, oral and breast cancers [11,12]. The Arg188His polymorphism of *XRCC2* plays an important role in carcinogenesis of pancreas and colorectal cancers [13,14]. Similarly, the polymorphism Thr241Met of *XRCC3* has been associated with the risk of lung and skin cancers [14].

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Against this background we hypothesised an impact of SNPs in *XRCC1, XRCC2* and *XRCC3* on susceptibility to cervical cancer.

Methods and materials

Cervical cancer patients (n = 265) and healthy age-matched controls (n = 260) between 30 and 70 years of age with similar ethnicity enrolled in departments of Radiotherapy, as well as Obstetrics and Gynecology, King George's Medical University (KGMU), Lucknow, India were recruited for the study as per inclusion/exclusion criteria. The exclusion criteria were history of other cancers, previous chemotherapy, radiotherapy or chemoradiotherapy, any co-morbid conditions such as allergy, cardiovascular disease, diabetes, infection and inflammatory response. The healthy controls had no familial history of cancer and were histologically tested to have a normal cervix. All subjects were interviewed extensively regarding age, marriage age, parity and smoking status. Clinical data were collected and interviews were conducted by expert clinicians as per structured proforma. Following interview, 5 ml venous blood was taken in EDTA vials from all subjects after informed consent. This study was ethically approved by Institutional Ethics Committee (No. 94/R.Cell-14 dated 21 April 2014).

Frozen EDTA blood samples were thawed at room temperature and high molecular weight DNA was extracted by salting out method with slight modifications [15]. The DNA quality and quantity was checked by using a biophotometer (Eppendorf, Germany). *XRCC1*+399A/G, *XRCC2*+31479G/A and *XRCC3* +18067C/T SNPs were detected by polymerase chain reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) with specific primer sets designed by Primer 3 online software (F-5′TTGTGCTTTCTCTGTGTC CA3′/R-5′TCCTCCAGCCTTTTCTGATA3′; F-5′TGTAGTCA CCCATCTCTCTGC3′/R-5′AGTTGCTGCCATGCCTTACA3′; F5′GGTCGAGTGACAGTCCAAAC3′/R-5′CTACCCGCAGG AGCCGGAGG3′, respectively). Amplification was performed in a gradient Master Cycler (Eppendorf, Germany) in a reaction volume of 25 µl containing genomic DNA (100–200 ng), 5 pmol of each primer, 200 µM dNTPs and 0.5 U of Taq DNA polymerase (MBI-Fermentas, U.S.A.). The amplification was followed by initial denaturation at 95°C (5 min), followed by 35 cycles at 95°C (30 s), annealing at 56°C (30 s), extension at 72°C (30 s) and final extension at 72°C (10 min). The amplified products were visualised on ethidium bromide (EtBr) stained 2% agarose gels and documented in gel documentation system (Vilber Lourmat, France). The PCR products were digested with 2 units of respective restriction enzymes (*MspI, HphI* and *NlaIII* respectively) at 37°C for 16 h. The digested products were visualized on 12% polyacrylamide gel (PAGE) after staining with EtBr (Figure 1).

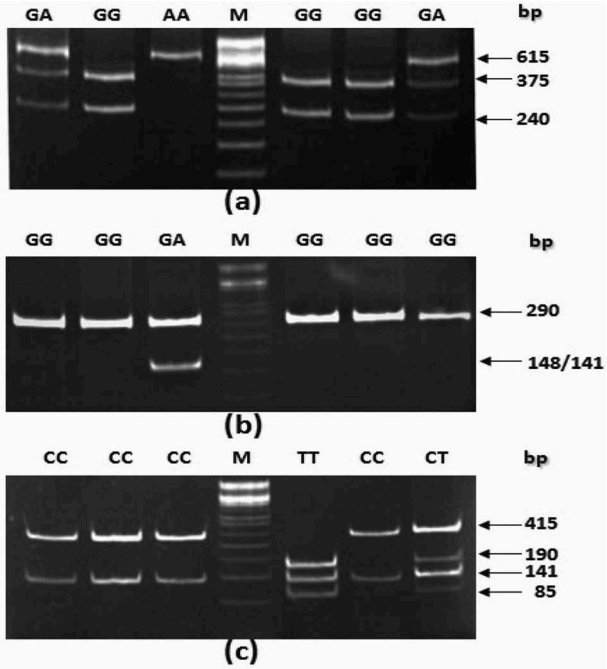

Figure 1. Ethidium bromide stained polyacrylamide gel (12%) showing different genotypes of *XRCC1*+399A/G, *XRCC2* +31479G/A and *XRCC3*+18067C/T polymorphisms. (a) SNP (*XRCC1*+399G/A) showing GG: 375, 240 bp (Wild); GA: 615, 375, 240 bp (Heterozygous); AA: 615 bp (Mutant). (b) SNP (*XRCC2*+31479G/A) showing GG: 290 bp (Wild); GA: 290, 148, 141 bp (Heterozygous). (c) SNP (*XRCC3*+18067C/T) showing CC: 415, 141 bp (Wild); CT: 415, 190, 141, 85 bp (Heterozygous); TT: 190, 141, 85 bp (Mutant). M: 50 bp ladder.

The sample size for each SNP was calculated by QUANTO software (v.online) using minor allele frequency (MAF) and prevalence. Only those SNPs were further analysed whose MAF>0.01. The MAF was calculated after genotyping 100 normal individuals for each SNP. The continuous variables of each group were analysed as mean with SD and compared by Student's t-test after ascertaining the normality by Kolmogorov-Smirmov Z test. Allele frequencies and carriage rate of alleles in both groups were compared using a 2 × 2 contingency table and genotype frequencies in a 2 × 3 contingency table by using Chi-square test and Fisher's exact test. Differences were considered statistically significant for $P < 0.05$. Odds ratio (OR) and 95% confidence intervals (CI) was determined to describe the strength of association between the two SNPs by Logistic Regression Model. All analyses were performed by SPSS (Ver 21.0).

Results

Clinical parameters were compared in controls (n = 265) and cervical cancer cases (n = 260), of whom 93.5% were in stages II/III with 6.5% in stages

I/IV. All 260 cases were histopathologically confirmed in which 12 (4.6%) were adenocarcinoma and 248 (95.4%) were squamous cell carcinoma. There was no significant difference in age distribution between controls and cases: the mean [SD] ages being 47.9 [8.5] and 48.5 [8.3] years respectively ($P = 0.464$).

The raw and adjusted allelic/genotypic frequency distributions and carriage rates of *XRCC1*+399A/G polymorphism among cases and controls are shown in Table1. Compared to the GG genotype, adjusted frequencies of GA, AA and GA+AA genotypes were higher in cases when compared to controls. Compared to the G allele, the A allele frequency was higher in cases as compared to controls. The raw carriage rates of G (+), G (–) and A (+), A (–) showed significant association with cervical cancer when compared to controls, and this association was more significant when adjusted. Results of the *XRCC2*+31479G/A SNP are shown in Table 2 and those of the *XRCC3*+18067C/T SNP as shown in Table 3. None of the genotypes or alleles (raw or adjusted) were linked to cervical cancer.

Discussion

Cervical carcinoma is a serious health problem in both developed and developing countries. Many previous epidemiologic studies have shown that cervical cancer is mainly caused by HPV [4,16]. It is generally accepted that cervical cancer is a complex disease where environmental and genetic factors play important roles in pathogenesis. The genetic factors include inheritance of defective genes or gene variants related to carcinogenesis whereas environmental factors include lifestyle, exposure to tobacco-derived carcinogens, as well as kitchen smoke [17].

DNA-repair systems are necessary for the maintenance of genetic integrity, dysfunction of which will lead to the development of cancer [18]. There are different types of DNA repair system viz. Base-Excision Repair (BER) pathway for single strand breaks (SSBs) and Nucleotide Excision Repair (NER) system for double-strand DNA breaks (DSBs). Principle mechanisms of repair systems are homologous recombination (HR) and non-homologous end joining (NHEJ) [19]. X-ray cross-complementing group 1 (XRCC1) is BER protein that may play an important role to prevent DNA from damaging agents [20]. The important molecules of HRR pathway are RAD51, XRCC2 and XRCC3 [21]. Repair of DSBs is an important component of these genes. Structure and function of *XRCC2* and *XRCC3* genes are related to the *RAD51* gene. RAD51 functional defect results in an increased mutation rate that lead to

Table 1. Genotypic, allelic and carriage rate frequencies of *XRCC1* + 399A/G SNP in controls ($n = 265$) and cervical cancer cases ($n = 260$).

XRCC1+399A/G						
Genotypes/Alleles	Controls (%)	Cases (%)	Unadjusted OR (95% CI)	*P* value	Adjusted[a] OR (95% CI)	*P* value
GG	141 (53.2)	109 (41.9)	1.0 (Ref.)		1.0 (Ref.)	
GA	102 (38.5)	112 (43.1)	1.42 (0.98–2.05)	0.061	2.42 (1.47–3.99)	0.001
AA	22 (8.3)	39 (15.0)	2.30 (1.28–4.09)	0.005	3.84 (1.77–8.32)	0.001
GA+AA	124 (46.8)	151 (58.1)	1.74 (1.21–2.50)	0.003	2.67 (1.66–4.29)	<0.0001
G* allele	384 (72.5)	330 (63.5)	1.0 (Ref.)			
A* allele	146 (27.5)	190 (36.5)	1.51 (1.17–1.97)	0.002		
Carriage rate						
G (+)	243 (91.7)	221 (85.0)	1.0 (Ref.)		1.0 (Ref.)	
G (–)	22 (8.3)	39 (15.0)	2.64 (1.01–6.92)	0.048	2.49 (1.21–5.12)	0.013
A (+)	124 (46.8)	151 (58.1)	1.0 (Ref.)		1.0 (Ref.)	
A (–)	141 (53.2)	109 (41.9)	0.58 (0.40–0.83)	0.003	0.37 (0.23–0.60)	<0.0001

CI = confidence interval; OR = odds ratio; [a]Adjusted for age, marriage age, parity and smoking; 1.0 (Reference), Alleles*, total number of chromosomes in controls = 530 and cases = 520.

Table 2. Genotypic, allelic and carriage rate frequencies of *XRCC2*+31479G/A SNP in controls ($n = 265$) and cervical cancer cases ($n = 260$).

XRCC2+31479G/A						
Genotypes/Alleles	Controls (%)	Cases (%)	Unadjusted OR (95%CI)	*P* value	Adjusted[a] OR (95% CI)	*P* value
GG	210 (79.2)	206 (79.2)	1.0 (Ref.)		1.0 (Ref.)	
GA	49 (18.5)	53 (20.8)	1.10 (0.71–1.70)	0.66	1.53 (0.85–2.75)	0.152
AA	6 (2.3)	1 (0.4)	0.20 (0.02–1.42)	0.102	0.27 (0.03–2.52)	0.253
GA+AA	55 (20.8)	54 (20.8)	1.00 (0.66–1.53)	0.997	1.40 (0.77–2.37)	0.299
G* allele	469 (88.5)	465 (89.4)	1.0 (Ref.)			
A* allele	61 (11.5)	55 (10.6)	0.91 (0.62–1.34)	0.63		
Carriage rate						
G (+)	259 (97.7)	259 (99.6)	1.0 (Ref.)		1.0 (Ref.)	
G (–)	6 (2.3)	1 (0.4)	0.17 (0.02–1.39)	0.098	0.25 (0.03–2.31)	0.223
A (+)	55 (20.8)	54 (20.8)	1.0 (Ref.)		1.0 (Ref.)	
A (–)	210 (79.2)	206 (79.2)	1.00 (0.65–1.52)	0.997	0.74 (0.42–1.30)	0.299

CI = confidence interval; OR = odds ratio; [a]Adjusted for age, marriage age, parity and smoking; 1.0 (Reference), Alleles*, total number of chromosomes in controls = 530 and cases = 520.

Table 3. Genotypic, allelic and carriage rate frequencies of *XRCC3*+18067C/T SNP in controls (n = 265) and cervical cancer cases (n = 260).

XRCC3+18067C/T						
Genotypes/Alleles	Controls (%)	Cases (%)	Unadjusted OR (95%CI)	*P* value	Adjusted[a] OR (95% CI)	*P* value
CC	145 (54.7)	157 (60.4)	1.0 (Ref.)		1.0 (Ref.)	
CT	93 (35.1)	88 (33.8)	0.87 (0.60–1.26)	0.474	0.84 (0.51–1.38)	0.494
TT	27 (10.2)	15 (5.8)	0.51 (0.26–1.01)	0.051	0.52 (0.22–1.22)	0.134
CT+TT	120 (45.3)	103 (39.6)	0.80 (0.56–1.12)	0.189	0.77 (0.48–1.22)	0.257
C* allele	383 (72.3)	402 (77.3)	1.0 (Ref.)			
T* allele	147 (27.7)	118 (22.7)	0.77 (0.58–1.01)	0.06		
Carriage rate						
C (+)	238 (89.8)	245 (94.2)	1.0 (Ref.)		1.0 (Ref.)	
C (-)	27 (10.2)	15 (5.8)	0.54 (0.28–1.04)	0.065	0.56 (0.24–1.28)	0.167
T (+)	120 (45.3)	103 (39.6)	1.0 (Ref.)		1.0 (Ref.)	
T (-)	145 (54.7)	157 (60.4)	1.26 (0.89–1.78)	0.189	1.31 (0.82–2.08)	0.257

CI = confidence interval; OR = odds ratio; [a]Adjusted for age, marriage age, parity and smoking; 1.0 (Reference), Alleles*, total number of chromosomes in controls = 530 and cases = 520.

accumulation of DNA damage and subsequently increased cancer risk [22].

Several studies have demonstrated that *XRCC1* +399A/G (Arg399Gln) SNP is linked to susceptibility to breast, lung, gastric cancer and other types of cancers [23]. Studies showed that *XRCC1*+399A/G (Arg399Gln) was not associated with cervical cancer in Japanese and Chinese populations [24,25]. However, in our population the frequency of GA and AA genotypes, and the A allele, of *XRCC1* +399A/G are significantly greater in cases compared to controls, showing higher risk of cervical cancer. Some genetic polymorphisms of *XRCC2* and *XRCC3* have been related to human cancers. Individuals with GA genotype of *XRCC2*+31479G/A polymorphism carry a small but significant risk of colorectal [26] and breast cancer [27]. Another relevant genetic variant is *XRCC3*+18067C/T, which is associated with breast cancer [28]. However, we found no link between *XRCC2*+31479G/A and *XRCC3* +18067 and cervical cancer.

We recognise the limitation of small numbers in our study, and indeed note that several significances were borderline (p = 0.051–0.065), but in adjustment these became less significant. Molecular genetics are playing an increasingly important part in cancer of the cervix [5,24]. Recently, SNPs in genes for certain antioxidants were found to be linked to protection from the side-effects of chemoradiotherapy in cervical cancer [29]. We contribute to this data, showing that the risk of cervical cancer linked to the GA, AA and GA+AA genotypes becomes more significant after adjusting for age, marriage age, parity and smoking, as in the case of GA, this moves the risk from not significant to significant. We therefore recommend all cancers linked to the reproductive system in women also be adjusted for these factors.

This work represents an advance in biomedical science because it links the genetic polymorphism *XRCC1*+399A/G with cervical cancer, and so may be a potential prognostic marker for determination of cervical cancer susceptibility.

Summary table

What is known about this subject:

- Cervical cancer is second most common cancer among women worldwide and the commonest cancer in Indian women.
- The DNA repair network is very important in maintenance of genetic stability, protection against DNA damage and plays an important role in carcinogenesis.
- SNPs in repair genes *XRCC1+399A/G, XRCC2+31467G/A* and *XRCC3 +18067C/T* are linked to certain cancers.

What this paper adds:

- The *XRCC1*+399A/G SNP is significantly associated with cervical cancer risk.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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