Contents lists available at ScienceDirect

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Research article

The *ECCR1* rs11615, *ERCC4* rs2276466, *XPC* rs2228000 and *XPC* rs2228001 polymorphisms increase the cervical cancer risk and aggressiveness in the Bangladeshi population

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ABSTRACT

Background: Multiple studies around the world revealed that genetic polymorphism in different genes of the DNA repair system might affect the DNA repair capabilities and accelerate the chances of cervical cancer (CC) development. Therefore, we aimed to evaluate the association of DNA repair gene- *ECCR1* rs11615, *ERCC4* rs2276466, *XPC* rs2228000 and rs2228001 polymorphisms and CC susceptibility in the Bangladeshi population.
Methods: A case-control genetic association study was conducted among 210 patients with diagnostically confirmed CC and 200 healthy volunteers. The *p*-value and OR (odds ratios) with 95% CI (confidence interval) were evaluated to get the level of association.
Results: After the individual analysis of all SNPs, we noticed that *ECCR1* rs11615 possessed a significantly lower risk, whereas *ERCC4* rs2276466 possessed a significantly elevated risk of CC in all genetic models ($p < 0.05$). *XPC* rs2228000 showed a significantly lower risk of CC in TC, TC + CC genotypes and allele model (OR = 0.61, $p = 0.025$; OR = 0.61, $p = 0.019$ and OR = 0.67, $p = 0.027$, respectively), whereas *XPC* rs2228001 possessed a significantly elevated risk of CC in CA, CA + AA genotypes and allele model (OR = 1.67, $p = 0.012$; OR = 1.69, $p = 0.009$ and OR = 1.42, $p = 0.022$). Besides, *ERCC4* rs2276466 (Grade III vs. I + II: OR = 4.01, $p = 0.003$) and *XPC* rs2228001 (Grade III vs. I + II: OR = 3.38, $p = 0.003$) were connected with high tumor aggressiveness and *ERCC4* rs2276466 was also showed a lower risk of CC development in the younger population (<45 years).
Conclusion: The findings supported that rs2276466 and rs2228001 polymorphisms increase CC development and aggressiveness, whereas rs11615 and rs2228000 lower the CC risk in the studied population.

1. Introduction

Cervical Cancer (CC), a cancer developed in the female reproductive system, especially in the cervix, is the second most leading female cancer worldwide and in developing countries, it is acting as a very common reason for death among women [1]. Every year, almost half a million patients of CC appear worldwide and 8% of which found in developing countries, where Central, South and Southeast Asian, Caribbean and Africans are possessed the highest amount of incidence rate [2]. In Bangladesh, almost 12000 new CC patients have detected every year, and the mortality rate is 55.05%, which is very worrying [3]. The etiological factors behind this carcinogenesis involve first intercourse at an early age, Human Papillomavirus (HPV) infection, various reproductive

factors, sexual partners or multiple pregnancies, alcohol ingestion, intake of oral contraceptives, diet, smoking and affected by another disease which is transmitted sexually [2]. But in most cases, women who are exposed to previously mentioned factors do not develop CC, revealing that some other factors are engaged in this carcinogenesis. Some potent heritable components are related to CC and these genetic factors can play a significant role in its pathogenicity [4].

DNA repair systems are more important to retain the stability and integrity of the genome, which possess various sophisticated mechanisms to repair any DNA defects. Any error in this repair system can cause different diseases like cancer in the human body, and the importance of this pathway is well accepted to gain protection against carcinogenic diseases [5]. DNA repair pathways are; the nucleotide excision repair

(NER) and base excision repair (BER) for single-strand damage systems; on the other side, homologous recombination (HR) and non-homologous end-joining (NHEJ) for double-strand DNA damage [6]. When DNA got any defects or lesions, several assembling proteins respond here in a stepwise way to the damaged DNA and altered genes started to encode those proteins, which contributes to making the variability of implicated genes more right away that can enhance carcinogenesis risk significantly [7].

Excision repair cross-complementation group 1 (*ERCC1*), a critical DNA repair protein and contains 10 exons, is involved with different pathways of DNA-damage repair [8]. *ERCC1* attached to the endonuclease called xeroderma pigmentosum complementation group F (XPF)-one of the common NER genes and also known as excision repair cross-complimentary group 4 (*ERCC4*) gene that encodes ERCC4 protein which is a key enzyme of NER pathway, by the formation of a heterodimeric complex. This ERCC1- ERCC4 endonuclease is a structure-specific complex that catalyzes the incision process around the DNA lesions and contributes a vital role in the DNA repair pathway [9]. rs11615 of *ERCC1* gene is located in exon 4 of 19q13.32 chromosome, and after polymorphism, cytosine (C) of amino acid asparagine is replaced by thymine (T), but the sequence of amino acid, as well as the function of the protein, do not alter because of the silent polymorphism. Howsoever, previous studies suggested that silent mutation can alter the nature of protein folding and, most importantly, can alter the level of gene expression [10]. *ERCC4* gene-plays an important role in 5' incision of the NER pathway, is actively remove interstrand crosslinks of DNA, and stops the breakdown of DNA double-strand. *ERCC4* rs2276466 spans almost 28.2 kb and contains 11 exons, is situated on chromosome 16p13.12, and guanine (G) takes the place of cytosine (C) after polymorphism [11, 12].

Xeroderma pigmentosum complementation group C (*XPC*) gene encodes some protein called XPC protein-contain 940 amino acids, which also has a significant role in the NER mechanism. This protein responsibly recognizes the DNA damaged site very early and starts the repair of defected DNA within the NER pathway. Previous studies found that abnormal expression of XPC protein is associated with cancer progression [13, 14]. The *XPC* gene located in chromosome 3p25.1 contains 15 introns and 16 exons. There are three most common variants of the *XPC* gene, where rs2228000 (C21151T) and rs2228001 (A33512C) are two of them. *XPC* rs2228000 are located in exon 9, and after the substitution mutation of this variant, thymine (T) is converted to cytosine (C) in 499 positions and, at the same time, amino acid alanine is substituted for valine (Ala499Val). Another variant, rs2228001, is situated in the 16th exon, and its 939 positioned amino acid lysine transversed to glutamine (Lys939Gln) after polymorphism [13, 14].

Our selected variants- *ERCC1* rs11615, *ERCC4* rs2276466, *XPC* rs2228000 and *XPC* rs2228001, were studied lots of times upon the different population for multiple diseases like breast cancer, colorectal cancer, prostate cancer, lung cancer [10, 13, 15, 16, 17, 18]. However, very few or almost no evidence was found about their association with cervical cancer development yet. Therefore, the current study observed the dynamic genetic role of all candidate markers on the risk of progression and the aggressiveness of cervical cancer in the Bangladeshi ethnicities. We also investigated the relation of all selected polymorphisms with several clinicopathological parameters of CC cases.

2. Method

2.1. Ethical statement

This research protocol was sanctioned by the ethical committee of the National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka, Bangladesh. Before the investigation, written permission was received from all of the recruited CC patients and healthy volunteers after informing them about the study aim and all experimental procedures. If any subject (cases or controls) denied sharing their data and giving consent were cropped out from this study.

2.2. Study subjects

This study was carried out on a total of 210 CC female patients who were genetically unconnected ethnic Bengalis from different areas of Bangladesh. Cases with histopathologically ensured cervical cancer were consecutively taken from the NICRH between early to mid of 2019. After a proper personal interview and diagnostic procedure, the patients' all clinical (stage of the tumor, histological type, tumor grade and nature of lymph nodes) and physical (age) information were collected by an expert nurse during the presence of a doctor. Again, 200 Bengali women with no family history were recruited from multiple places of Bangladesh as healthy volunteers after matching of age with CC cases. The clinico-pathological properties of all study subjects were documented in a written questionnaire form. We carried out this experiment according to the Helsinki Declaration and its further correction [19]. This genetic experiment was done in the pharmacogenetics laboratory at the Pharmacy department of the University of Asia Pacific, Dhaka, Bangladesh.

2.3. SNP selection

From nearly 1,098 identified SNPs of the NER pathway, the functionally potent SNPs of the investigation were selected according to some criteria from the SNPinfo and dbSNP database of NCBI. These criteria are: (1) the risk allele frequency (RAF) is higher than 0.05 found in non-Hispanic whites or HapMap of different populations and (2) not enlisted in the published genome-wide association studies (GWAS) for CC [20, 21].

2.4. Genotyping

From all selected cases and controls, 3 ml of peripheral blood were taken in EDTA-Na$_2$ containing sterile tubes, and then genomic DNA was extracted by FavorPrepTM Blood Genomic DNA Extraction Kit, Favorgen Biotech Corporation, Taiwan, according to their suggested process. Extracted DNA was stored at -20 °C temperature and then DNA amplification of all variants was performed separately with predesigned four different reverse and forward primers (Table 1) [22]. To genotype the polymorphisms of *ERCC1* rs11615, *ERCC4* rs2276466, *XPC* rs2228000 and *XPC* rs2228001, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) procedure was used (Figure S1–S4). After 2 % agarose gel electrophoresis, 239 bp, 190 bp, 152 bp and 281 bp PCR product found for *ERCC1* rs11615, *ERCC4* rs2276466, *XPC* rs2228000 and *XPC* rs2228001, respectively. Digestion of confirmed PCR products took place with the dedicated restriction enzymes which were BsrD1, NdeI, SacII and PvuII for rs11615, rs2276466, rs2228000 and rs2228001 polymorphisms, respectively for overnight at different temperatures (Table 1) and then visualized on agarose gel (2.5%) after staining with ethidium bromide. We repeated the digestion of 20% of samples where at least one variant carrier was detected, and our two results were 100% consistent.

2.5. Statistical analysis

For each polymorphism, Hardy–Weinberg equilibrium (HWE) was tested to distinguish the inequality of genotype frequencies between the cancer patients and controls. All clinicopathological data were compared with different genotypes with the Chi-square (χ^2) test. The genetic association of all variants was evaluated by Medcalc software, which is illustrated as 95% confidence intervals (95% CI) with an odds ratio (ORs). $p < 0.05$ was marked as statistically significant.

Table 1. Primers, SAF, PCR conditions, restriction enzymes, and digestion condition for PCR–RFLP.

SNPs	Primers (5′-3′)	SAF (bp)	PCR condition	RE	Expected fregment size (bp)
ERCC1 rs11615	FP: GTGCGAGGAGGCAGGAGGTGTGGG RP: GAGCTCACCTGAGGAACAGG	239	94 °C 30 s 54.5 °C 30 s 72 °C 30 s	BsrD1	CC: 239 CT: 84, 155, 239 TT: 84, 155
ERCC4 rs2276466	FP: ACTTCCTCGTTTCTCAGCTCT RP: ATGAGGAATCACAGGCAGGT	190	94 °C 30 s 59.1 °C 50 s 72 °C 30 s	NdeI	CC: 190 CG: 44, 146, 190 GG: 44, 146
XPC rs2228000	FP: TAAGGACCCAAGCTTGCCCG RP: CCCACTTTTCCTCCTGCTCACAG	152	94 °C 30 s 57.5 °C 30 s 72 °C 30 s	SacII	TT: 152 TC: 21, 131, 152 CC: 21, 131
XPC rs2228001	FP: ACCAGCTCTCAAGCAGAAGC RP: CTGCCTCAGTTTGCCTTCTC	281	94 °C 30 s 60 °C 30 s 72 °C 30 s	PvuII	CC: 131, 150 CA: 131,150, 281 AA: 281

RE: restriction endonuclease.

3. Results

3.1. Clinical distributions of the cases and controls

A total of 210 female cases with cervical cancer and 200 healthy female volunteers were recruited for this case-control study. The mean age of the patients and controls was 57.5 and 52.5 years, respectively. The percentages of cases under the age of 45 and 45–60 years were 33.33% and 58.1%, whereas that were 32.5% and 62.5% in the controls, consecutively. Again, 81 (38.57%) and 51 (24.29%) cases correspondingly suffered from stage IIB and IIIB cervical tumor (Table 2). None of the cases and controls were smokers, and the contraception status, economic status, and the number of pregnancies of the participants were mentioned in Table 2.

3.2. Effect of different genotypes in cervical cancer

The association between all selected genetic variants and the development of cervical cancer was evaluated in this study (Table 3). It allows comparison between different genetic models.

After scrutinizing Table 3 minutely, we found that *ERCC1* rs11615 is significantly associated with the lower risk of cervical cancer in all genetic models when compared to the normal homozygous genotype like CT vs. CC, TT vs. CC, CT + TT vs. CC (dominant model) and allelic model (T vs C) where $p = 0.019, 0.019, 0.003, 0.0007$; OR = 0.58, 0.39, 0.53, 0.55 and 95% CI = 0.37–0.91, 0.17–0.86, 0.35–0.81, 0.39–0.78, respectively. On the other hand, the comparison of the distinct genotypic data of *ERCC4* rs2276466 SNP illustrates a prominent association in all genetic models (for CG vs. CC, GG vs. CC, CG + GG vs. CC and G vs. C by turn, $p < 0.0001, 0.012, <0.0001, <0.0001$; OR = 4.33, 3.00, 4.14, 2.46 and 95% CI = 2.83–6.64, 1.28–7.05, 2.74–6.26, 1.80–3.37). It is visible that the SNP rs2228000 of *XPC* gene indicates a significantly lower association in three models from four, those are TC vs. TT, TC + CC vs. TT and C vs. T ($p = 0.025, 0.019, 0.027$; OR = 0.61, 0.61, 0.67 and 95% CI = 0.39–0.94, 0.41–0.93, 0.47–0.96, in turn) while for rs2228001, three genetic models were associated with an increased cervical cancer risk that were statistically significant (for CA vs. CC, CA + AA vs. CC and A vs. C: $p = 0.012, 0.009, 0.022$; OR = 1.67, 1.69, 1.42 and 95% CI = 1.12–2.49, 1.14–2.51, 1.05–1.92, respectively). However, in case of CC vs TT model of rs2228000 ($p = 0.369$, OR = 0.63 and 95% CI = 0.23–1.73), no significant association observed, whereas AA vs CC of rs2228001 was not associated significantly with higher risk of CC ($p = 0.169$, OR = 2.00 and 95% CI = 0.74–5.40).

3.3. Correlation of genetic variants with clinicopathological characteristics of the cases

Various clinicopathological parameters, like age, different stages of the tumor, various histological types of tumor, tumor grade and lymph

Table 2. Demographic data of cervical cancer cases and controls and clinico-pathological properties s of the CC-cases.

Variables	Cases (%)	Controls (%)
Number	210	200
Age (Years)		
<45	70 (33.33)	65 (32.5)
45-60	122 (58.1)	125 (62.5)
>60	18 (8.57)	10 (5)
Lymph Nodes		
Negative	190 (90.48)	N/A
Positive	20 (9.52)	N/A
Tumor Grade		
I	72 (34.28)	N/A
II	90 (42.86)	N/A
III	48 (22.86)	N/A
Histological Type		
SQC	97 (46.19)	N/A
Adenocarcinoma	48 (22.86)	N/A
SCC	9 (4.29)	N/A
Endometroid	19 (9.05)	N/A
Other	37 (17.62	N/A
Tumor Stage		
IIA	8 (3.81)	N/A
IIB	81 (38.57)	N/A
IIB1– IIB2	23 (10.95)	N/A
IIIA	30 (14.29)	N/A
IIIB	51 (24.29)	N/A
IVA- IVB	17 (8.1)	N/A
Contraception Use		
Oral pills	118 (56.19)	79 (39.50)
Others[a]	22 (10.48)	34 (17.00)
None	70 (33.33)	87 (43.50)
Economic Status		
Upper class	32 (15.24)	36 (18.00)
Middle class	67 (31.90)	49 (24.50)
Lower class	111 (52.86)	115 (57.50)
Pregnancy		
None	20 (9.52)	15 (7.5)
1	30 (14.29)	35 (17.5)
2	45 (21.43)	50 (25)
3	95 (45.24)	85 (42.5)
>4	20 (9.52)	15 (7.5)
Smoking Status	No	No

SQC Squamous Cell Carcinoma; *SCC* Serous cystadenocarcinoma.

[a] others: Condom (male), barrier (cervical cup, diaphragm, female condom) + intrauterine device (IUD).

Table 3. Statistical presentation of several genotypes of multiple SNPs and their comparative role in cervical cancer development.

Polymorphisms	Genotype	CC Cases (N = 210) (%)	Controls (N = 200) (%)	OR (95% CI)	p-value
ERCC1 rs11615	CC	155 (73.81)	120 (60)	1	-
	CT	45 (21.43)	60 (30)	0.58 (0.37–0.91)	**0.019**
	TT	10 (4.76)	20 (10)	0.39 (0.17–0.86)	**0.019**
	CT + TT	55 (26.19)	80 (40)	0.53 (0.35–0.81)	**0.003**
	C	355 (84.52)	300 (75)	1	-
	T	65 (15.48)	100 (25)	0.55 (0.39–0.78)	**0.0007**
ERCC4 rs2276466	CC	65 (30.95)	130 (65)	1	-
	CG	130 (61.9)	60 (30)	4.33 (2.83–6.64)	**< 0.0001**
	GG	15 (7.14)	10 (5)	3.00 (1.28–7.05)	**0.012**
	CG + GG	145 (69.04)	70 (35)	4.14 (2.74–6.26)	**< 0.0001**
	C	260 (61.9)	320 (80)	1	-
	G	160 (38.1)	80 (20)	2.46 (1.80–3.37)	**< 0.0001**
XPC rs2228000	TT	150 (71.43)	121 (60.5)	1	-
	TC	53 (25.24)	70 (35)	0.61 (0.39–0.94)	**0.025**
	CC	7 (3.33)	9 (4.5)	0.63 (0.23–1.73)	0.369
	TC + CC	60 (28.57)	79 (39.5)	0.61 (0.41–0.93)	**0.019**
	T	353 (84.05)	312 (78)	1	-
	C	67 (15.95)	88 (22)	0.67 (0.47–0.96)	**0.027**
XPC rs2228001	CC	80 (38.10)	102 (51)	1	-
	CA	119 (56.67)	91 (45.5)	1.67 (1.12–2.49)	**0.012**
	AA	11 (5.24)	7 (3.5)	2.00 (0.74–5.40)	0.169
	CA + AA	130 (61.91)	98 (49)	1.69 (1.14–2.51)	**0.009**
	C	279 (66.43)	295 (73.75)	1	-
	A	141 (33.57)	105 (26.25)	1.42 (1.05–1.92)	**0.022**

p < 0.05 was considered statistically significant.

node status of tumor in cases, were compared with the data of variant carriers (HE + MH) and wild types (NH) (Table 4 and Table 5). Table 4 illustrates the data of *ERCC1* rs11615 and *ERCC4* rs2276466, as well as Table 5, is for *XPC* rs2228000 and rs2228001. In the case of the ERCC1 variant, no statistically significant correlation was observed of any genotype with any clinicopathological characteristics. Again, with two different parameters of patients-age and grade of the tumor, an important correlation was obtained in the case of *ERCC4* rs2276466 variant. Patients with lower age range (under 45 years) were found to possess a lower number of HE + MH in comparison with the older cases (above 45 years) (OR = 0.49 and 95% CI = 0.27–0.89, p = 0.02) that describes that young patients are at lower risk than the older patients for developing CC. The HE + MH carrier cases *ERCC4* rs2276466 showed an association with higher histologic tumor grade (III) in comparison with grade I and combination of grades I + II tumor containing cases (Grade III vs. Grade I, OR = 4.20, 95%CI = 1.58–11.18, p = 0.004; Grade III vs. Grade I + II: OR = 4.01, 95%CI = 1.61–9.99, p = 0.003, respectively) that were statistically significant. On the other side, *XPC* rs2228001polymorphism was also associated with higher histological tumor grade (Grade III vs. Grade I, OR = 2.92, 95%CI = 1.23–6.94, p = 0.02; Grade III vs. Grade I + II: OR = 3.38, 95%CI = 1.54–7.44, p = 0.003, by turn). But there was no significant association determined of variant *XPC* rs2228000 with all clinicopathological characteristics of the selected cases in this study.

4. Discussion

Cervical cancer, a complex disease, is a strong burdening issue for Bangladesh with higher risk factors and a higher prevalence rate [3]. Previous evidence revealed that although HPV is an essential factor in developing cervical cancer, CC does not develop in the greater number of HPV infected women [4]. Human genomic instability and accumulation of injured DNA can act as a potent carcinogenic factor for the development of any type of cancer [23]. If any carcinogens are exposed during the growth and differentiation of cells, sufficient repairing activity of DNA only can ensure the fidelity and stability of the genome [24]. In this

case-control study, we investigated the correlation between the progression of cervical cancer and four different potential SNPs (rs11615, rs2276466, rs2228000 and rs2228001) of three different DNA repair genes (*ERCC1*, *ERCC4* and *XPC*) in the Bangladeshi population. These SNPs were studied for various types of cancer and other diseases, but there are very few studies carried out over those SNPs to find out their role in CC development. However, after the investigation, we found that *ERCC4* rs2276466 and *XPC* rs2228001 polymorphisms increase cervical cancer development risk and aggressiveness, whereas *ERCC1* rs11615 and *XPC* rs2228000 lower the CC risk in the studied population.

The *ERCC1* protein, one of 16 proteins included in the NER pathway and encoded by the *ERCC1* gene, involves improving the excision repair deficiency of NER program, which helps to remove defects from DNA strand. After the polymorphism in *ERCC1* gene (rs11615, C > T), mRNA translation rate for protein formation is downregulated, which reduces the expression level of *ERCC1* mRNA, then decreases the repair rate of damaged DNA and enhance the injured DNA accumulation as well as cancer formation [25, 26, 27].

The C and T allele frequencies of rs11615 polymorphism in cases were 84.5% and 15.5% and in controls were 75% and 25%, respectively. Furthermore, we found a reduced risk of *ERCC1* rs11615 in both CT vs. CC and TT vs. CC model (OR = 0.58, p = 0.019 and OR = 0.39, p = 0.019, respectively) and also in dominant model (OR = 0.53, p = 0.003) with cervical cancer in the Bangladeshi cases. Zhang et al. initially investigated the connection of *ERCC1* rs11615 SNP with cervical squamous cell carcinomas (SCC) in Chinese patients, and they found a significant association in their all additive (p = 0.021) and dominant (p = 0.033) models [28]. With other malignancies like ovarian, lung and colorectal cancer, rs11615 of *ERCC1* gene polymorphism showed a prominent association in numerous previous analyses [29, 30, 31]. A study showed that rs11615 polymorphism could influence the overall survival of non-small cell lung cancer patients with cisplatin-based treatment [32]. Another analysis found an association between *ERCC1* rs3212986 polymorphisms and gastrointestinal toxicities in cervical cancer (p = 0.038) [33]. Furthermore, a meta-analysis observed a considerable correlation

Table 4. Correlation of ERCC1 rs11615 and ERCC4 rs2276466 polymorphism with clinicopathological properties of the cases.

Characteristics	Cases (%)	ERCC1 rs11615				ERCC4 rs2276466			
		HE + MH	*NH*	*OR (95% CI)*	*p value*	*HE + MH*	*NH*	*OR (95% CI)*	*p value*
Age (Years)									
<45	70	16	54	0.77 (0.39–1.49)	0.44	41	29	0.49 (0.27–0.89)	**0.02**
45–60	122	31	91	0.88 (0.51–1.53)	0.66	93	29	1.11 (0.63–1.95)	0.72
>60	18	8	10	2.07 (0.76–5.63)	0.15	11	7	0.54 (0.20–1.51)	0.24
45-60 + >60	140	39	101	Ref.	-	104	36	Ref.	-
Tumor Stage									
IIA	8	2	6	Ref.	-	4	4	Ref.	-
IIB	81	20	61	0.98 (0.18–5.27)	0.98	63	18	3.50 (0.8–15.4)	0.1
IIB1– IIB2	23	7	16	1.31 (0.21–8.18)	0.77	12	11	1.1 (0.22–5.45)	0.92
IIIA	30	9	21	1.29 (0.22–7.63)	0.78	17	13	1.31 (0.27–6.24)	0.74
IIIB	51	11	40	0.83 (0.15–4.67)	0.83	39	12	3.25 (0.7–15)	0.13
IVA - IVB	17	6	11	1.64 (0.25–10.77)	0.61	10	7	1.43 (0.26–7.74)	0.68
Histological Type									
SQC	97	23	74	Ref.	-	73	24	Ref.	-
Adenocarcinoma	48	12	36	1.07 (0.48–2.4)	0.86	32	16	0.66 (0.31–1.40)	0.28
SCC	9	2	7	0.92 (0.18–4.74)	0.92	5	4	0.41 (0.10–1.66)	0.21
Endometroid	19	5	14	1.15 (0.37–3.53)	0.81	12	7	0.56 (0.2–1.59)	0.28
Other	37	13	24	1.74 (0.77–3.96)	0.19	23	14	0.54 (0.24–1.21)	0.14
Grade									
I	72	18	54	Ref.	-	45	27	Ref.	**-**
II	90	24	66	1.09 (0.54–2.22)	0.81	58	32	1.09 (0.57–2.07)	0.80
III	48	13	35	1.11 (0.49–2.56)	0.80	42	6	4.20 (1.58–11.18)	**0.004**
1 + II	162	42	120	Ref.	-	103	59	Ref.	-
III	48	13	35	1.06 (0.51–2.20)	0.87	42	6	4.01 (1.61–9.99)	**0.003**
Lymph Nodes									
Negative	190	42	148	Ref.	-	131	59	Ref.	-
Positive	20	8	12	2.35 (0.90–6.12)	0.08	14	6	1.05 (0.38–2.87)	0.92

HE heterozygous; *MH* mutant homozygous; *NH* normal homozygous; *SQC* Squamous Cell Carcinoma; *SCC* Serous cystadenocarcinoma $P < 0.05$ is significant; Bold values are indicating statistical significance.

between *ERCC1* rs11615 and the response rate of esophageal cancer patients to neoadjuvant therapy [34]. These findings are not consistent with our observations. This apparent discrepancy in the association of ERCC1 rs11615 polymorphism with CC suggested that the *ERCC1* rs11615 variant may be geographical location and ethnicity-specific. However, in a study of ovarian cancer patients, no significant correlation was detected between overall survival and the *ERCC1* polymorphism [35].

ERCC4 gene is a well-known part of NER mechanism-the most versatile system of DNA repair, but besides this, it is uniquely involved with the repairing system of broken double-stranded DNA and inter-strand crosslinking of DNA [36, 37]. Some previous study suggested that when polymorphism occurs in *ERCC4* gene, the expression of ERCC4 protein is upregulated, and different types of cancer are associated with this. The uncontrolled expression of the *ERCC4* gene can dramatically reduce the ability of NER pathway, which helps to enhance the risk of different diseases like cervical or other types of cancer [38]. It was demonstrated that variations in the *ERCC4* gene are associated with various human inherited disorders [39]. The chance of cancer formation (colorectal, breast and other cancer) due to some SNPs in *ERCC4* gene has been reported where an association was found [40]. On the other side, Jennifer et al. conducted a case-control study in USA to provide informative data about the association of endometrial cancer risk with *ERCC1* gene polymorphism, but they didn't find any significant correlation [41]. Again, Pawlak-Adamska et al. conducted another case-control study between two different SNPs, including rs3136176 and rs1799798 of *ERCC4* gene and cervical squamous cell carcinoma risk upon Polish Caucasians, where they reported the association [42].

Although the interrelation of certain *ERCC4* gene polymorphisms with the risk of CC development has been studied before, the association of *ERCC4* rs2276466 gene polymorphism with CC has never yet been studied in any ethnicities. Herein, for the very first time, we investigated to explore whether *ERCC4* genes rs2276466 SNP could associate with the susceptibility of CC in Bangladeshi women or not. The ultimate findings after analysis displayed that this SNP of *ERCC4* gene predisposed to increase the risk of cervical cancer in a significant manner in all genetic models. The polymorphism showed a notable association in GG vs. CC model (OR = 3.00, p = 0.012), but very strong association was found in CG vs. CC (OR = 4.33, p < 0.0001), CG + GG vs. CC model (OR = 4.14, p < 0.0001) and G vs. C model (OR = 2.46, p < 0.0001). We have also found that major allele (C) frequencies were higher in both cases and controls (61.9% and 80%, respectively) compared to minor allele (G) frequencies (38.1% and 20%, consecutively).

Moreover, the effect of *ERCC4* rs2276466 polymorphism on age and tumor aggressiveness was found when various clinicopathological properties were compared between the carrier and non-carrier cases of the minor allele. This polymorphism showed that patients under 45 years are at lower risk for cervical cancer in Bangladeshi ethnicity (OR = 0.49, p = 0.02). Furthermore, it was also observed that patients carrying variant allele showed a significantly higher aggressiveness when compared higher grade (grade III) with the grade I and combination of grade I + II (for grade III vs. I: OR = 4.20, p = 0.004 and grade III vs. I + II: OR = 4.01, p = 0.003).

XPC protein-a necessary damage recognition protein encoded by the *XPC* gene, is another essential component of NER process and involves with the global genome repair system uniquely. It makes a complex formation after the interaction with HR23B that can recognize and easily

Table 5. Correlation of rs2228000 and rs2228001 polymorphism of XPC gene with clinicopathological properties of the cases.

Characteristics	XPC rs2228000				XPC rs2228001			
	HE + MH	NH	OR (95% CI)	p value	HE + MH	NH	OR (95% CI)	p value
Age (Years)								
<45	45	25	0.6 (0.32–1.12)	0.11	41	29	0.81 (0.45–1.46)	0.48
45–60	93	29	1.07 (0.61–1.88)	0.82	78	44	1.02 (0.61–1.68)	0.95
>60	12	6	0.67 (0.23–1.91)	0.45	11	7	0.90 (0.33–2.47)	0.84
45-60 + >60	105	35	Ref.	-	89	51	Ref.	-
Tumor Stage								
IIA	6	2	Ref.	-	4	4	Ref.	-
IIB	65	16	1.35 (0.25–7.35)	0.73	52	29	1.79 (0.42–7.71)	0.43
IIB1– IIB2	12	11	0.36 (0.06–2.19)	0.27	12	11	1.09 (0.22–5.45)	0.92
IIIA	18	12	0.5 (0.09–2.9)	0.44	16	14	1.14 (0.24–5.44)	0.87
IIIB	39	12	1.08 (0.19–6.09)	0.93	35	16	2.19 (0.48–9.87)	0.31
IVA - IVB	10	7	0.48 (0.07–3.09)	0.44	11	6	1.83 (0.33–10.1)	0.49
Histological Type								
SQC	70	27	Ref.	-	64	33	Ref.	-
Adenocarcinoma	34	14	0.94 (0.44–2.01)	0.87	28	20	0.72 (0.35–1.47)	0.37
SCC	6	3	0.77 (0.18–3.31)	0.73	5	4	0.64 (0.16–2.56)	0.53
Endometroid	13	6	0.84 (0.29–2.42)	0.74	10	9	0.57 (0.21–1.55)	0.27
Other	27	10	1.04 (0.44–2.44)	0.93	23	14	0.85 (0.39–1.86)	0.68
Grade								
I	19	53	Ref.	-	43	29	Ref.	-
II	24	66	1.01 (0.50–2.05)	0.97	48	42	0.77 (0.41–1.44)	0.42
III	17	31	1.53 (0.69–3.37)	0.29	39	9	2.92 (1.23–6.94)	**0.02**
1 + II	43	119	Ref.	-	91	71	Ref.	-
III	17	31	1.52 (0.76–3.02)	0.23	39	9	3.38 (1.54–7.44)	**0.003**
Lymph Nodes								
Negative	138	52	Ref.	-	116	74	Ref.	-
Positive	12	8	0.57 (0.22–1.46)	0.24	14	6	1.49 (0.55–4.05)	0.44

HE heterozygous; *MH* mutant homozygous; *NH* normal homozygous; *SQC* Squamous Cell Carcinoma; *SCC* Serous cystadenocarcinoma P < 0.05 is significant; Bold values are indicating statistical significance.

binds to the DNA damaged site. It also plays a specific role in the activation of tumor suppressor gene p53 and controlling cell-cycle [43]. When the most common two SNPs of *XPC* gene (rs2228000 and rs2228001) get mutated, two modified proteins (by turn, valine and glutamine) are formed due to sequence variation, which can modify DNA repair capacity and then induce genetic instability as well as carcinogenicity.

Many studies were conducted earlier between candidate SNPs of *XPC* and different types of cancer like lung cancer, breast cancer, colorectal cancer, bladder cancer and others [44]. However, only two studies were carried out just in India (Lucknow and Maharashtra) that observed the role of these SNPs in the outgrowth of cervical carcinogenesis [2, 45]. In this study, it is clear that SNP rs2228000 revealed a lower association with cervical cancer risk, whereas rs2228001 showed a significantly higher association. For *XPC* rs2228000 polymorphism, three genetic models showed a decreased but significant association (TC vs. TT, TC + CC vs. TT and T vs. C allele: OR = 0.61, p = 0.025; OR = 0.61, p = 0.019 and OR = 0.67, p = 0.027, respectively), whereas Patil et al. found strong association of rs2228000 with the etiology of CC (p = 0.0001, OR = 4.26) in the population of Maharashtra after a case-control study which is inconsistent with our findings [2]. The frequencies of major allele were higher in both cases and controls (84% and 78%) than minor allele (16% and 22%).

At the other hand, in the case of *XPC* rs2228001 polymorphism, the frequency distribution of alleles shows that C allele frequencies were 66.43% and 73.75% in both cases and controls, respectively, whereas minor allele A constitutes 33.57% and 26.25%, respectively. The genetic models including CA vs. CC, CA + AA vs. CC, A vs. C models showed a higher risk for the development of cervical cancer (OR = 1.67, p = 0.012; OR = 1.69, p = 0.009 and OR = 1.42, p = 0.022, respectively) although

no association was observed in the population of Maharashtra. However, Gangwar et al. got the association of rs2228001 (p = 0.036, OR = 2.15) in another regional (Lucknow) population of India with CC development that is consistent with our study findings [2, 45].

No association was noticed after analyzing the effect of *XPC* rs2228000 polymorphism on various clinicopathological data of CC cases, whereas the effect of *XCP* rs2228001 polymorphism was associated significantly with the increased tumor aggressiveness. Cases with poorly differentiated tumor (grade III) were obtained to hold a notable number of HE + MH genotype when compared with well and well + moderately differentiated tumor (grade I and I + II) containing patients that signify the high tumor aggressiveness (OR = 2.92, 3.38, 95% CI = 1.23–6.94, 1.54–7.44 and p = 0.02, 0.003, respectively).

The present research demonstrates certain strengths and limitations. The most important strength is that this is the first genetic association study of these SNPs in the Bangladeshi population. Another strength is the age-matched groups, which substantially decrease the impact of limitations on research outcomes. Finally, an RFLP method was developed for detecting the *ERCC4* rs2276466 polymorphism. There are also some drawbacks to this study that should be taken into account. Firstly, We use a small number of samples, which therefore has limited statistical power. Secondly, there is no collection of certain clinical evidence, such as the lack of specific environmental variables like HPV, which should be tested in the future.

5. Conclusion

In summary, this case-control study proposes that rs2276466 and rs2228001 polymorphisms increase the risk of cervical cancer development, whereas rs11615 and rs2228000 lower the risk in the studied

population. Moreover, rs227646 and rs2228001 showed high tumor aggressiveness in the Bangladeshi population. More extensive studies are needed to reproduce the findings.

Declarations

Author contribution statement

S. Das: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

T. Aka and L. Naher: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Aziz and S. Shabnaz: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Shahriar: Analyzed and interpreted the data; Wrote the paper.

M. Islam: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2021.e05919.

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