ORIGINAL ARTICLE

Genetic polymorphisms of *XRCC1* on cervical cancer susceptibility risk

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ABSTRACT

Introduction: Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality among women worldwide. Genetic polymorphisms in DNA repair genes may influence susceptibility to cervical carcinogenesis. X-ray repair cross-complementing protein 1 (XRCC1), an important scaffolding protein in the base excision repair (BER) pathway, plays a crucial role in repairing DNA damage. This study investigated the association of XRCC1 Arg399Gln G>A (rs25487) and *XRCC1* Arg194Trp C>T (rs1799782) polymorphisms with cervical cancer susceptibility risk.

Materials and Methods: A total of 133 cervical cancer patients and 133 healthy female controls were enrolled. Genotyping of both polymorphisms was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotype and allele frequencies were compared between groups using chi-square analysis, while logistic regression analysis was performed to determine Odds Ratios (ORs) with 95% confidence intervals (CI).

Results: A significant association was observed between XRCC1 Arg399Gln G>A (rs25487) polymorphism and cervical cancer susceptibility. The heterozygous GA genotype showed a significantly increased risk of cervical cancer (OR: 2.325, 95% CI: 1.380–3.918, p=0.002). In contrast, no significant association was identified between *XRCC1* Arg194Trp C>T (rs1799782) polymorphism and cervical cancer risk.

Conclusion: In conclusion, *XRCC1* Arg399Gln G>A (rs25487) polymorphism may contribute to cervical cancer susceptibility and could potentially serve as a future biomarker for early detection. Further large-scale studies involving multiple genes and polymorphisms are required to validate these findings.

KEYWORDS:
Cervical cancer, XRCC1 gene polymorphism, susceptibility risk

INTRODUCTION

Cervical cancer remains a major public health issue affecting women worldwide, particularly in low- and middle-income countries.[1] According to Global Cancer Statistics 2020, cervical cancer was ranked as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality among women, with approximately 604,000 new cases and 342,000 deaths globally.[1] In Malaysia, cervical cancer was reported as the third most common cancer among females, accounting for 6.2% of all female cancers after breast and colorectal cancers.[2] Persistent infection with high-risk Human Papillomavirus (HPV) is a well-established cause of cervical cancer and its precursor lesion, cervical intraepithelial neoplasia (CIN).[3,4] HPV is a non-enveloped double-stranded DNA virus comprising more than 100 genotypes, of which 13 are classified as high-risk and 5 as likely high-risk types.[5] Among these, HPV 16 and 18 are the most aggressive and frequently associated with cervical neoplasia due to their ability to integrate into the host genome.[5] Nevertheless, HPV infection alone is insufficient to induce cervical carcinogenesis because most infections are transient and self-limiting, while only a small proportion persist and progress to malignancy.[3,4,6] Therefore, other cofactors including environmental exposure, lifestyle factors, and host genetic susceptibility contribute significantly to cervical cancer development. Factors such as cigarette smoking, early and multiple childbirths, multiple sexual partners, immunosuppression, oral contraceptive use, and low socioeconomic status have been implicated in cervical cancer progression.

DNA repair mechanisms play a critical role in maintaining genomic integrity by repairing DNA damage induced by endogenous and exogenous factors. Failure of these repair pathways may result in apoptosis, uncontrolled cell proliferation, and carcinogenesis.[7] Several DNA repair pathways exist in human cells, including base excision repair (BER), nucleotide excision repair (NER), double-strand break repair (DSBR), and DNA mismatch repair (DMR). BER is particularly important in repairing oxidative DNA damage caused by reactive oxygen species. Genetic variations such as single nucleotide polymorphisms (SNPs), which represent the most common form of genetic variation, may alter DNA repair efficiency and influence susceptibility to various diseases including cancer.[6-8] SNPs in DNA repair genes may induce structural alterations in repair enzymes, thereby modulating cancer susceptibility.[8] X-ray repair cross-complementing protein 1 (XRCC1) is an important nonenzymatic scaffolding protein involved in BER and is

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encoded by the *XRCC1* gene located on chromosome 19p13.2.[9-11] *XRCC1* interacts with several proteins involved in BER, including DNA polymerase β, poly(ADP-ribose) polymerase (PARP), and DNA ligase III.[8] Polymorphisms in XRCC1 may impair protein interactions and reduce DNA repair efficiency, consequently increasing the risk of carcinogenesis.[10]

Numerous epidemiological studies have reported associations between *XRCC1* polymorphisms and several cancers including lung, gastric, breast, prostate, colorectal, pancreatic, head and neck, and gynaecological malignancies.[12-17] However, findings regarding the association between *XRCC1* polymorphisms and cervical cancer susceptibility remain inconsistent across different populations and ethnic groups.[17-20] Two commonly studied *XRCC1* SNPs are Arg194Trp C>T (rs1799782) and Arg399Gln G>A (rs25487). The *XRCC1* Arg194Trp polymorphism involves a C>T substitution resulting in an arginine-to-tryptophan amino acid change in exon 6, whereas XRCC1 Arg399Gln involves a G>A substitution causing an arginine-to-glutamine change in exon 10.[24] Several studies demonstrated significant associations between these polymorphisms and cervical cancer risk, as well as other malignancies such as thyroid cancer, skin carcinoma, and nasopharyngeal carcinoma.[18-20,25-30] Despite these findings, most studies were conducted outside Malaysia, and genetic associations identified in other populations may not be directly applicable to the Malaysian population due to ethnic diversity. To date, limited data are available regarding the distribution and impact of *XRCC1* polymorphisms among Malaysian cervical cancer patients. Therefore, this study was conducted to investigate the role of *XRCC1* Arg399Gln G>A (rs25487) and *XRCC1* Arg194Trp C>T (rs1799782) polymorphisms in modulating cervical cancer susceptibility risk among the local population.

MATERIALS AND METHODS

Study participants

This study was performed using archived DNA samples which had been previously extracted from peripheral blood samples of previous research study. The original research entitled "Roles of selected genetic variations and molecular alterations in Human Papillomavirus mediated cancer of uterine cervix" was carried out starting in August 2012 and completed in January 2016. The research study had received ethical approval from the Human Research Ethics Committee of Universiti Sains Malaysia (reference numbers: USMKK/PPP/JEPeM [253.3.(7)] and USM/JEPeM/14100325) as well as the Medical Research and Ethics Committee of Ministry of Health, Malaysia (reference numbers: KKM/NIHSEC/08/0804/P12-380, and KKM/NIHSEC/P15-1214). The study subjects were previously recruited from (i) Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, (ii) Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, and (iii) Hospital Sultan Ismail, Johor Bahru, Johor between August 2012 and January 2016.

The present study received ethical approval obtained from the Human Research Ethics Committee of USM (USM/JEPeM/21120779) which complies with the Declaration of Helsinki. A total number of samples used in this study were 133 cervical cancer patients and 133 normal female control. The selection criteria for cervical cancer cases were clinically and histopathologically confirmed cases of cervical cancer female and their age ranges between 18 to 70 years old. Subjects who have had a personal history of previous or concurrent malignancy, subjects diagnosed with metastatic cancer to the cervix, subjects who have prior treatment before undergoing surgery and those who were found to have a history of autoimmune or chronic infectious disease were excluded from this study. For the normal healthy female control group, the selection criteria were cancer-free healthy female volunteer who was age-matched to the case group, biologically unrelated to the case, and age range between 18 to 70 years old. Individuals with a family history of cervical cancer and those who were found to have a history of autoimmune or chronic infectious disease were excluded.

Genotyping of *XRCC1* Arg194Trp (rs1799782) and Arg399Gln (rs25487)

The DNA samples were previously extracted from a peripheral blood samples of the study subjects using commercial QIAamp DNA Mini Kit (QIAGEN). The genotyping of both SNPs *XRCC1* Arg194Trp (rs1799782) and Arg399Gln (rs25487) was performed by using PCR – restriction fragment length polymorphism (RFLP) technique. PCR reaction was performed in 20µl of the final volume containing 0.2µM of each forward and reverse primer, 50ng extracted genomic DNA, 2mM $MgCl_2$, 0.2mM dNTPs, 1.0 unit of Taq DNA polymerase and 1X of 5X Promega Green GoTaq™ Flexi Buffer. The PCR master mix for both SNPs was similar. Amplification was performed in Mastercycle thermocycler for the PCR reaction. The PCR condition started with an initial denaturation at 95°C for two minutes, followed by 30 cycles of denaturation at 95°C for 45 seconds, annealing at 58°C for 45 seconds (for *XRCC1* Arg194Trp rs1799782) and 54°C for 45 seconds (for *XRCC1* Arg399Gln rs25487), and extension at 72°C for 45 seconds, then a final extension at 72°C for five minutes. Next, PCR products were incubated for fast digestion for one hour at 37°C with the restriction enzyme *Pvull* (Fermentas, Vilnius, Lithuania) (for *XRCC1* Arg194Trp rs1799782) and restriction enzyme *Mspl* (Fermentas, Vilnius, Lithuania) (for *XRCC1* Arg399Gln rs25487) according to the manufacturer's instructions and subsequently analyzed by electrophoresis on a 2% agarose gel. After genotyping, the genotypes were categorized into three groups: homozygous wild type (major), heterozygous and homozygous variant (minor).

Statistical analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences version 27.0 for statistical calculation. The genotype and allele frequencies for each SNPs of *XRCC1* were compared among cervical cancer patients and normal healthy controls using Pearson's chi-square (X^2) test or Fisher exact test. Next, the association of genotype and allele frequencies of *XRCC1* polymorphism (either singly and in combination) between cervical cancer patients and normal healthy controls were evaluated using logistic regression analysis by deriving odds ratio (ORs) and 95% confidence interval (CI) using unconditional logistic regression analysis. For all analyses, $p<0.05$ was considered as statistically significant.

Table I: Genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg399Gln G>A (rs25487)	Homozygous wild-type	GG	54 (40.6%)	78 (58.7%)	0.003*
	Heterozygous	GA	66 (49.6%)	41 (30.8%)	0.002*
	Homozygous variant	AA	13 (9.8%)	14 (10.5%)	0.541
	Dominant model	GG	79 (%)	55 (%)	0.003*
		GA + AA	54 (%)	78 (%)	
	Recessive model	GG + GA	120 (%)	119 (%)	0.841
		AA	13 (%)	14 (%)	
	Allele	G	174 (65.4%)	197(74.1%)	0.030*
		A	92 (34.6%)	69(25.9%)	

*p-value <0.05, statistically significant

Table II: Genotype and allele frequencies of XRCC1 Arg194Trp C>T (rs1799782) in cervical cancer patients and controls

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg194Trp C>T (rs1799782)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	0.538
	Heterozygous	CT	54 (40.6%)	54 (40.6%)	1.000
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.210
	Dominant model	CC	73 (54.9%)	68 (51.1%)	0.537
		CT + TT	60 (45.1%)	65 (48.9%)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.210
		TT	6 (4.5%)	11 (8.3%)	
	Allele	C	200 (75.2%)	190(71.4%)	0.327
		T	66 (24.8%)	76(28.6%)	

*p-value <0.05, statistically significant

Table III: Risk association of XRCC1 Arg399Gln G>A (rs25487) with cervical cancer susceptibility

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg194Trp C>T (rs1799782)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	0.538
	Heterozygous	CT	54 (40.6%)	54 (40.6%)	1.000
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.210
	Dominant model	CC	73 (54.9%)	68 (51.1%)	0.537
		CT + TT	60 (45.1%)	65 (48.9%)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.210
		TT	6 (4.5%)	11 (8.3%)	
	Allele	C	200 (75.2%)	190(71.4%)	0.327
		T	66 (24.8%)	76(28.6%)	

*p-value <0.05, statistically significant

Table IV: Risk association of XRCC1 Arg194Trp C>T (rs1799782) with cervical cancer susceptibility

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	OR (95% CI)	p-value
Arg194Trp C>T (rs1799782) (Ref)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	1.000	-
	Heterozygous	CT	54 (40.6%)	54(40.6%)	0.932 (0.564-1.538)	0.782
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.508 (0.178-1.449)	0.205
	Dominant model	CC	73 (54.9%)	68(51.1%)	0.860	0.539
		CT + TT	60 (45.1%)	65(48.9%)	(0.531-1.392)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.524	0.217
		TT	6 (4.5%)	11 (8.3%)	(0.188-1.461)	
	Allele	C	200 (75.2%)	190(71.4%)	0.825	0.327
		T	66 (24.8%)	76 (28.6%)	(0.561-1.212)	

*p-value <0.05, statistically significant

RESULTS

Genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls

The genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls are shown in Table I. Among the 133 cervical cancer patients, 66 (49.6%) showed heterozygous, 54 (40.6%) showed homozygous wild-type and 13 (9.8%) showed homozygous variant genotypes. In controls, the genotype frequencies were 78 (58.7%) for homozygous wild-type, 41 (30.8%) for heterozygous and 14 (10.5%) for homozygous variant. The heterozygous (GA) genotype was significantly higher in cervical cancer patients as compared to the controls. On the contrary, the homozygous wild-type (GG) was significantly higher in controls compared to the cervical cancer patients. The frequencies of G allele and A allele were 65.4% and 34.6% in cervical cancer patients and 74.1% and 25.9% in controls, respectively. Allele A was found to be significantly higher in cervical cancer patients (34.6%) compared to controls (25.9%) with a p-value <0.05.

Genotype and allele frequencies of *XRCC1* Arg194Trp C>T (rs1799782) in cervical cancer patients and controls

The genotype and allele frequencies of *XRCC1* Arg194Trp C>T (rs1799782) in cervical cancer patients and controls are shown in Table II. Out of the 133 cervical cancer patients, 73 (54.9%) showed homozygous wild-type, 54 (40.6%) showed heterozygous and 6 (4.5%) showed homozygous variant genotypes. In controls, the genotype frequencies were 68 (51.1%) for homozygous wild-type, 54 (40.6%) for heterozygous and 11 (8.3%) for homozygous variant. In cervical cancer patients, 75.2% showed C allele and 24.8% showed T allele, whereas in controls, 71.4% showed C allele and 28.6% showed T allele. No significant difference in the frequencies of these genotypes and alleles were found between cervical cancer patients and controls.

Risk association of *XRCC1* Arg399Gln G>A (rs25487) with cervical cancer susceptibility

Table III showed the associated risk of XRCC1 Arg399Gln G>A (rs25487) polymorphism with cervical cancer susceptibility. The heterozygous (GA) genotype showed significantly higher risk for cervical cancer susceptibility with OR: 2.325, 95% CI: (1.380-3.918) and p-value of 0.002. The homozygous variant (AA) showed higher risk values with OR: 1.341, 95% CI: 0.584-3.079, but were not statistically significant with p-value of 0.489.

Risk association of *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility

Table IV shows the associated risk of XRCC1 Arg194Trp C>T (rs1799782) polymorphism with cervical cancer susceptibility. No significant risk association was found between the heterozygous and homozygous variant genotypes with cervical cancer susceptibility.

DISCUSSION

Study on the XRCC1 polymorphisms has become an area of interest for intensive research as the resultant functional alterations that impair the DNA damage cellular repair mechanism and genome stability, impose their possible role in cancer susceptibility risk. There are numerous studies done to investigate the role of XRCC1 polymorphism in cancer development including cervical cancer. However, most of the study pertaining to XRCC1 polymorphism and cervical cancer were conducted outside Malaysia. To the best of our available knowledge, there are no available reports on the association of XRCC1 polymorphism with cervical cancer in Malaysia. In our study, we investigated two commonest SNPs of *XRCC1* (XRCC1 Arg399Gln G>A (rs25487) and XRCC1 Arg194Trp C>T (rs1799782) and their association with cervical cancer susceptibility risk. We found a significant association of genetic polymorphism in *XRCC1* Arg399Gln G>A (rs25487) with cervical cancer susceptibility risk. Our study involved 133 cervical cancer patients and 133 healthy female control individuals revealed that carriers of heterozygous (GA) genotype of *XRCC1* Arg399Gln G>A (rs25487) showed significantly higher risk for cervical cancer susceptibility. Our findings on *XRCC1* Arg399Gln G>A (rs25487) association with cervical cancer risk are in agreement with other previous studies.

Studies found a significant association between XRCC1 Arg399Gln polymorphism and the risk of cervical carcinoma risk in both Caucasians and Asians.[24] In another study on XRCC1 Arg399Gln polymorphism by PCR-RFLP in 189 patients with advanced cervical cancer and 308 controls reveals patients with advanced cervical cancer having the Gln/Gln or Gln/Arg vs Arg/Arg genotype displayed a 1.726-fold increased risk of cervical cancer (95% confidence interval [CI]=1.158-2.572, p=0.007).30 The odds ratio for Gln/Gln vs Gln/Arg or Arg/Arg was 1.742 (95% CI=1.073-2.827; p=0.0236). They also found a significantly higher frequency of the *XRCC1* Arg399Gln allele in patients with cervical cancer than in controls, with OR=1.489 (95% CI=1.148-1.930, p=0.0026). Other studies also demonstrated a strong association of the *XRCC1* Arg399Gln polymorphism with an increased risk of cervical cancer.[25,26] In addition, study by Datkhile also in agreement with other findings where he found out *XRCC1* Arg399Gln were significantly increased in relation to the relative risk of cervical cancer (OR= 2.99; 95% CI= 1.60-5.56).7 Al-Harbi also found patients harbouring variant allele *XRCC1* Arg399Gln have approximately 1.5-fold increased risk to develop cervical cancer.[28]

On the other hand, our study observed no statistical association for *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility risk. However, in other studies *XRCC1* Arg194Trp has been showed to be significantly associated with cervical cancer risk. A meta-analysis suggested *XRCC1* Arg194Trp was associated with significant cervical cancer risk (Trp/Trp vs Arg/Arg, OR = 2.21, 95% CI = 1.60–3.06; Arg/Trp vs Arg/Arg, OR = 1.23, 95% CI = 1.02–1.49; dominant model, OR = 1.36, 95% CI = 1.14–1.63; recessive model, OR = 2.06, 95% CI = 1.51–2.82).21 Besides, a significant association was found among XRCC1 Arg194Trp and cervical cancer (OR= 2.696; 95% CI= 1.181-6.154; p= 0.018, using an additive model), (OR=2.989; 95% CI= 1.078-8.283; p= 0.035, using a dominant model).29 A few other studies also discovered a positive association of the XRCC1 Arg194Trp with cervical cancer development risk.[25,26]

Genetic polymorphism of *XRCC1* was also found to be associated with various other cancers as well. A study found a statistical association between *XRCC1* Arg194Trp and

thyroid cancer risk with the homozygote genetic model (TT vs. CC: OR=1.815, 95% CI=1.115-2.953, p=0.016) and the recessive genetic model (TT vs. TC+CC: OR=1.854, 95% CI=1.433-2.399, p=<0.001).[25] A significant association was also found in similar study between *XRCC1* Arg399Gln polymorphism risk of thyroid cancer among Caucasians with allele genetic comparison (A vs. G: OR=0.882, 95% CI=0.794-0.979, p=0.136) and dominant genetic comparison (AA+AG vs. GG: OR=0.838, 95% CI=0.728-0.965, p=0.014).25 In addition, study also found XRCC1 Arg399Gln might be a risk factor for non-melanoma skin cancer in Asian populations, and the XRCC1 Arg194Trp might be a protective factor for patients with squamous-cell skin cancer cases.[27] Besides, a meta-analysis in a study noted *XRCC1* Arg399Gln is a potential predictor for susceptibility to nasopharyngeal carcinoma, especially for Asians.[26]

Although our study shows a significant association of one of the SNP studied XRCC1 Arg399Gln G>A (rs25487) with cervical cancer risk, there are a few limitations that needs to be highlighted. Firstly, our study examined the association of only two SNPs of XRCC1 with cervical cancer risk. Other SNPs or genes that are involved in all pathways of DNA repair were clearly not covered and this can be considered for the future study. DNA repair pathway mechanism is a very complex process and the molecular target focus for research study is massive and obviously our findings does not conclusive and representative of all. To get better clearer and broader picture, future research need to incorporate multiple genes studies involved in DNA repair pathway and its association in cervical cancer development. With the advent of massively parallel sequencing technologies such as whole genome sequencing or whole exome sequencing, this research question has a huge potential to be answered and the application in the research need to be considered. In addition, we acknowledge the limitation of the time for the research conducted, research budget as well as the limited research resources and skills. In addition, this study was conducted using achieved DNA samples that was extracted from peripheral blood of the previous researcher. Thus, there are limitations in getting the details of clinicopathological data that was conducted earlier due to missing data. Because of this limitation, we are not able to discuss further details on the other aspect particularly related to demographic background such as ethnic background, age, and other socio-demographic and salient clinical information of each participants.

The advances in SNP mapping utilizing high throughput DNA sequencing could facilitate the analysis of variants in DNA repair pathway. This may contribute to the advancement of knowledge on genetic predisposing factors related to cervical cancer susceptibility risk in Malaysian population. This, in turn may help to identify the high risk individuals with cervical cancer susceptibility risk genotype in the population and devise appropriate preventive strategies as well as incorporate this molecular genetic approach in the patient's clinical management. One of the significant aspect of this study on *XRCC1* in cervical cancer that would like to emphasize on the potential outlook of this study findings as this *XRCC1* genotype detection is expected to be a molecular marker for gynaecologic cancer screening according to meta-analysis by 18. This is a huge potential for the future diagnosis of cervical cancer as this can help treating physician to incorporate this genetic testing in the management of the cervical cancer. Future research need to be explored further for better understanding and implementation in our local population.

CONCLUSION

Our study demonstrated an association between genetic polymorphisms in one of DNA repair pathway (BER) gene *XRCC1* Arg399Gln G>A (rs25487) with susceptibility risk of cervical cancer patients. The positive association from this research study may be considered to be applied as a screening tool for early detection in cervical cancer patient in the future. However no significant association was observed for *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility risk. Although a prospective study with a larger patient population and involvement of multiple SNPs and genes necessary to validate this findings, our findings provides preliminary data locally and opportunity for future study.

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