

# Single nucleotide polymorphisms in DNA repair genes and risk of cervical cancer: A case-control study

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**Abstract.** In this report, we describe a case control study in a Chinese population aimed at identifying possible associations between susceptibility to cervical cancer and single nucleotide polymorphisms in *XRCC1* 194C>T, *XRCC1* 280G>A, *XRCC1* 399G>A, *ERCC2* 751A>C, *ERCC2* 156C>A, *ERCC1* 118C>T, *PARP1* 762T>C, *RAD51* 135G>C and *HER2* 655A>G. The cases comprised 154 patients: 80 cervical squamous cell carcinomas (SCCs), 2 adenocarcinomas and 72 cervical intraepithelial neoplasias (CINs). A total of 177 healthy women were recruited as the controls. A significant association was found between *ERCC1* 118C>T and SCC in the additive genetic model [odds ratio (OR)=1.711; 95% confidence interval (CI), 1.089-2.880; p=0.021] and the dominant genetic model (OR=1.947; 95% CI, 1.056-3.590; p=0.033). Among women with a smoking family member, *ERCC1* 118C>T increased SCC risk in the additive model (OR=2.800; 95% CI, 1.314-5.968; p=0.008). For women who had first intercourse before 22 years of age, *XRCC1* 280G>A was found to act as a protective factor for SCC under the additive model (OR=0.228; 95% CI, 0.058-0.900; p=0.035), while *RAD51* 135G>C was a risk factor for CIN (OR=4.246; 95% CI, 1.335-13.502; p=0.014). For women who had first intercourse after 22 years

of age, the additive genetic model showed *RAD51* 135G>C (OR=0.359; 95% CI, 0.138-0.934; p=0.036) and *HER2* 655A>G (OR=0.309; 95% CI, 0.098-0.972; p=0.045) to be protective factors for SCC. *XRCC1* 399G>A increased CIN risk among women who first gave birth before the age of 22 in the additive genetic model (OR=4.459; 95% CI, 1.139-17.453; p=0.032). For those who first gave birth after age 22, *ERCC1* 118C>T was found to be a risk factor for SCC in the additive genetic model (OR=1.884; 95% CI, 1.088-3.264; p=0.024). A significant interaction was observed between *RAD51* 135G>C and age at first intercourse ( $p_{\text{interaction}}=0.033$  for SCC,  $p_{\text{interaction}}=0.021$  for CIN), as well with sexual partner number ( $p_{\text{interaction}}=0.001$  for SCC). The interaction between *HER2* 655A>G and age at first intercourse, *ERCC2* 156C>A and family smoking status and *XRCC1* 280G>A and alcohol consumption were significant, with  $p_{\text{interaction}}=0.023$  for SCC,  $p_{\text{interaction}}=0.021$  for CIN and  $p_{\text{interaction}}=0.025$  for SCC, respectively.

## Introduction

Cervical cancer ranks as the second most common female-related cancer worldwide, following breast cancer. Squamous cell carcinoma (SCC), adenocarcinoma (ADC), and adenosquamous cell carcinoma (ADSC) are the three most common histological subtypes of cervical cancer. Screening programs in developed countries have reduced the incidence and prevalence of cervical cancer in these areas, but developing countries often do not have the resources for these programs (1). The result is that 80% of cervical cancer cases now occur in developing countries (2).

In China, incidence rates of cervical cancer range from 2.4 to 4.6 per 100,000 women (3), and the mortality rates range from 2 to 4 per 100,000 women in urban areas. Various evidence has shown that certain types of the oncogenic virus human papillomavirus (HPV) are closely related to the occurrence of cervical cancer (4) and its precursor lesion cervical intraepithelial neoplasia (CIN) (5). However, only a small portion of women go on to develop cervical cancer following infection with HPV (6), and this suggests that other factors,

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including genetic susceptibility, may also contribute to cervical cancer.

An association between smoking and cervical cancer has been reported (7), as well as smoking-related DNA damage in the cervical epithelium (8). Defects in DNA repair pathways relate to a number of diseases including cancer, and the significance of DNA repair mechanisms in genetic stability maintenance is well accepted in the protection against cancer initiation (9).

There are a number of different types of DNA repair pathways; for single-strand breaks, these include the base excision repair (BER) and nucleotide excision repair (NER) systems and for double-strand DNA breaks, there are two principle mechanisms: homologous recombination (HR) and non-homologous end joining (NHEJ) (10). There are a number of genes known to be involved in these pathways. For example, it is known that the genes, *ERCC1* and *ERCC2*, code for proteins involved in the NER system, removing bulky lesions from DNA caused by things such as toxic chemicals or ultraviolet light (11,12). Two other genes, *XRCC1* and *PARP1*, are crucial to BER systems, which repair DNA damage due to causes such as ionizing radiation. *PARP1* is also known to signal damage to other repair mechanisms (12,13). *RAD51* functions in the DNA repair of double-strand breaks by HR mechanisms (10). It is also notable that these genes have been implicated in response (or non-response) to certain types of chemotherapeutic drugs (14).

A single nucleotide polymorphism (SNP) is a single nucleotide change in a DNA sequence between two individuals. Knowledge of the genes involved in these DNA repair mechanisms is enlightening investigators and enabling the study of the association between SNPs in these genes and the likelihood of developing cancer (15).

The associations of SNPs in DNA repair genes and various types of cancer and tumors have been extensively described. However, the evidence is frequently confusing, with some SNPs increasing the risk of certain types of cancer, but decreasing the risk of others. For example, previous studies have reported that *XRCC1* Arg194Trp C>T (TT) increases the risk of esophageal (16) and bile duct cancer (17), but decreases the risk of gastric carcinoma (18). *XRCC1* Arg280His G>A has been reported as a risk factor for breast cancer (19) and as a protective factor for bile duct cancer (17). Niwa *et al* (20) first reported that the *XRCC1* Arg399Gln G>A polymorphism is related to the increased susceptibility to cervical cancer in a Japanese population.

We performed a case-control study, in a Chinese population, of eight SNPs from the DNA repair-related genes, *ERCC1*, *ERCC2*, *XRCC1*, *PRAP1* and *RAD51*, as well as one SNP in *HER2*, which plays essential roles in stabilizing the active protein dimer.

## Materials and methods

**Study subjects.** All subjects were genetically unrelated ethnic Han Chinese from Shanghai in eastern China. Patients diagnosed with histopathologically confirmed cervical cancer or CIN were consecutively recruited between June 2006 and May 2008 at the Margaret Williamson Hospital, Hongkou Maternal and Child Care Service Centre, and the Gynecology Department of Jiangwan Hospital, without restrictions on age

Table I. Primers for single nucleotide polymorphism detection.

rs1136410	5' primer	TGAGCAGACTGTAGGCCAC
	3' primer	TCTGTCTCATTACATGATACCTA
	Ext primer	CGACTGTAGGTGCGTAACTCGTCC
		AGCAGGTTGTCAAGCATTTCC
rs1801200	5' primer	AAACTAGCCCTCAATCCCTG
	3' primer	AAAGACCACCCCAAGAC
	Ext primer	AGAGCGAGTGACGCATACTACGCCCC
		AGCCCTCTGACGTCCRTC
rs1799782	5' primer	TYAGGACCCAYGTTGTCC
	3' primer	ATGAGAGCGCCAACCTCTCT
	Ext primer	AGATAGAGTCGATGCCAGCTTCACCTG
		GRGATGTCTTGTGTGATCC
rs11615	5' primer	TTCGTCCCTCCCCAGAGG
	3' primer	ATGAGAGCGCCAACCTCTCT
	Ext.primer	GTGATTCTGTACGTGTGCGCCTTACGTC
		GCCAAATTCCCAGGGCAC
rs13181	5' primer	CTGTCCCTGCTCAGCCTG
	3' primer	AAGACTCAGGAGTCACCAGGA
	Ext primer	AGGGTCTCTACGCTGACGATGCTAGAA
		TCAGAGGAGACGCTG
rs25489	5' primer	TTGACCCCCAGTGGTGCTA
	3' primer	TGTCAGTCCCCCTGTGC
	Ext primer	GGCTATGATTGCAATGCTTTCTTCTC
		CAGTGCCAGCTCCAATC
rs1801320	5' primer	AACTGCAACTCATCTGGGTT
	3' primer	TCCTCTCTCCAGCAGGCC
	Ext primer	GCGGTAGGTTCCCGACATATGAGTAGA
		GAAGTGAGCGTAAGCCA
rs25487	5' primer	TAAGGAGTGGGTGCTGGA
	3' primer	ATTGCCCAGCACAGGATA
	Ext primer	AGCGATCTGCGAGACCGTATCGCATGC
		GTCGGCGGCTGCCCTCCC
rs238406	5' primer	TATGTGCGGGCGCAGTAC
	3' primer	TCCTGCCTCCCTCCCTCA
	Ext primer	CGTGCCGCTCGTGATAGAATATGACAC
		CAGCCTGCCCACTGCCG
Ext, extension.		

and histology. The exclusion criteria included self-reported cancer history, previous radiotherapy and chemotherapy for unknown disease conditions and a family history of cancer. The controls were recruited during the same period from health examinees at the Hongkou Maternal and Child Care

Table II. Distributions of demographic characters in the study population.

Variable	Controls (n=177) no. (%)	CIN		SCC	
		(n=72) no. (%)	p-value <sup>b</sup>	(n=80) no. (%)	p-value <sup>b</sup>
Age	43 (24-55) <sup>a</sup>	40 (24-59) <sup>a</sup>		44 (26-79) <sup>a</sup>	
Education level					
≤ Junior high school	64 (36.2)	28 (38.9)	0.772	29 (36.2)	1.000
≥ Senior high school	113 (63.8)	44 (61.1)		51 (63.8)	
Smoking status					
No	167 (94.4)	72 (100)	0.067	76 (95.0)	1.000
Yes	10 (5.6)	0		4 (5.0)	
Alcohol consumption					
No	148 (83.6)	63 (87.5)	0.561	73 (91.2)	0.122
Yes	29 (16.4)	9 (12.5)		7 (8.8)	
Family smoking status					
No	61 (34.5)	47 (65.3)	0	46 (57.5)	0.001
Yes	116 (65.5)	25 (34.7)		34 (42.5)	
Number of sexual partners					
≤1	144 (81.4)	50 (73.5)	0.218	62 (81.6)	1.000
>1	33 (18.6)	18 (26.5)		14 (18.4)	
Age at first intercourse					
≤22	37 (20.9)	28 (41.8)	0.002	38 (51.4)	0
>22	140 (79.1)	39 (58.2)		36 (48.6)	
Age at first childbirth					
≤22	24 (13.6)	13 (19.4)	0.317	19 (25.0)	0.030
>22	153 (86.4)	54 (80.6)		57 (75.0)	

<sup>a</sup>Mean (minimum-maximum). <sup>b</sup>Fisher's exact test. CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

Service Centre. The controls were healthy women whose sexual history and age matched the cases, and who were histologically or cytologically diagnosed as having a normal cervix or chronic cervicitis, with no personal or familial history of cancer or other family genetic diseases.

**Questionnaire.** All patients underwent a complete medical history interview at entry. Detailed information regarding demographic factors (including age at diagnosis, education level, number of sexual partners, age at first intercourse and age at first childbirth), occupational history, environmental exposure data (including tobacco smoking status, alcohol consumption and family smoking status) and family history of cancer were also included. Those who had smoked less than one cigarette per day for a period of one year or less were defined as non-smokers, and the rest were considered to have always smoked. Alcohol consumption was defined as 'no' if the participant drank alcohol less than once per week, but otherwise was regarded as 'yes'. Family smoking status was 'no' for participants who had no family member who smoked in the home, but was otherwise regarded as 'yes'. Family history of cancer was defined as any self-reported cancer in first-degree relatives. Following the interview, approximately 2 ml of venous blood was collected from each participant and maintained below -40°C.

**Laboratory methods.** Genetic DNA was extracted from peripheral blood by the standard phenol-chloroform procedure. SNP genotyping was conducted with the SNPware 12plex assay using the SNPstream™ system (Beckman Coulter, Inc., Brea, CA, USA). The amplifying and extension primers are shown in Table I. The nine SNPs were: *XRCC1* 194C>T (rs1799782), *XRCC1* 280G>A (rs25489), *XRCC1* 399G>A (rs25487), *ERCC2* 751A>C (rs13181), *ERCC2* 156C>A (rs238406), *ERCC1* 118C>T (rs11615), *PARP1* 762T>C (rs1136410), *RAD51* 135G>C (rs1801320) and *HER2* 655A>G (rs1801200).

Genotyping was performed according to the manufacturer's instructions. Briefly, multiple polymerase chain reaction (PCR) was performed with the following program: 94°C for 1 min, then 94°C for 30 sec, 55°C for 30 sec and 72°C for 1 min, for 39 cycles. The PCR product was used for SNP extension: 96°C for 3 min, then 94°C for 20 sec and 40°C for 11 sec, for 45 cycles. A chip hybridization reaction was conducted at 42°C for 2 h with hybridization solution and hybridization additive solution at the proportion of 18:1. Chip data were scanned and analyzed using the SNPstream machine (Beckman Coulter, Inc.).

**Statistical analysis.** To examine the Hardy-Weinberg equilibrium, a  $\chi^2$  goodness-of-fit test was performed using a web-based program (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>). The frequency distribution of education,

Table III. Analysis of the association between the polymorphisms and risk of SCC/CIN with multivariate logistic regression analysis.

		Control, n (%)	CIN, n (%)	AOR <sup>a</sup>	P <sup>a</sup>	SCC, n (%)	AOR <sup>a</sup>	P <sup>a</sup>
<i>XRCC1</i> rs1799782	CC	87 (49.2)	32 (44.4)	1.000		41 (51.2)	1.000	
	CT	71 (40.1)	33 (45.8)	1.293 (0.717-2.329)	0.393	31 (38.8)	0.932 (0.531-1.635)	0.805
	TT	19 (10.7)	7 (9.7)	0.950 (0.360-2.510)	0.918	8 (10.0)	0.904 (0.365-2.239)	0.827
	Additive			1.076 (0.711-1.628)	0.730		0.944 (0.634-1.404)	0.775
rs25489	GG	142 (80.2)	61 (85.9)	1.000		68 (85.0)	1.000	
	GA	34 (19.2)	10 (14.1)	0.628 (0.288-1.373)	0.244	11 (13.8)	0.680 (0.325-1.426)	0.308
	AA	1 (0.6)	0	-	-	1 (1.2)	2.022 (0.124-32.955)	0.621
	Additive			0.613 (0.284-1.323)	0.213		0.781 (0.400-1.525)	0.470
rs25487	GG	109 (61.9)	38 (52.8)	1.000		43 (53.8)	1.000	
	GA	58 (32.8)	28 (38.9)	1.371 (0.758-2.481)	0.296	31 (38.8)	1.362 (0.776-2.388)	0.281
	AA	10 (5.6)	6 (8.3)	1.668 (0.561-4.961)	0.358	6 (7.5)	1.526 (0.522-4.461)	0.440
	Additive			1.326 (0.853-2.062)	0.210		1.293 (0.846-1.976)	0.236
<i>ERCC1</i> rs11615	CC	105 (60.0)	45 (62.5)	1.000		39 (48.8)	1.000	
	CT	61 (34.9)	22 (30.6)	0.870 (0.473-1.600)	0.654	34 (42.5)	1.501 (0.859-2.623)	0.153
	TT	9 (5.1)	5 (6.9)	1.460 (0.450-4.735)	0.529	7 (8.8)	2.058 (0.714-5.932)	0.181
	Additive			1.026 (0.642-1.638)	0.916		1.465 (0.958-2.241)	0.078
<i>ERCC2</i> rs13181	AA	148 (84.1)	57 (79.2)	1.000		68 (85.0)	1.000	
	CA	27 (15.3)	15 (20.8)	1.452 (0.712-2.958)	0.305	12 (15.0)	0.967 (0.462-2.024)	0.929
	CC	1 (0.6)	0	-	-	0	-	-
	Additive			1.359 (0.683-2.704)	0.383		0.896 (0.440-1.826)	0.762
rs238406	CC	55 (31.6)	22 (30.6)	1.000		29 (36.2)	1.000	
	CA	83 (47.7)	35 (48.6)	1.042 (0.547-1.983)	0.900	36 (45.0)	0.823 (0.453-1.493)	0.521
	AA	36 (20.7)	15 (20.8)	1.014 (0.459-2.237)	0.973	15 (18.8)	0.799 (0.376-1.697)	0.559
	Additive			1.010 (0.683-1.493)	0.960		0.883 (0.609-1.281)	0.514
<i>PARP1</i> rs1136410	TT	54 (30.7)	28 (39.4)	1.000		25 (31.2)	1.000	
	CT	83 (47.2)	28 (39.4)	0.581 (0.305-1.107)	0.099	39 (48.8)	1.017 (0.553-1.868)	0.958
	CC	39 (22.2)	15 (21.1)	0.775 (0.361-1.664)	0.513	16 (20.0)	0.883 (0.417-1.871)	0.745
	Additive			0.836 (0.566-1.234)	0.367		0.947 (0.655-1.370)	0.772

Table III. Continued.

		Control, n (%)	CIN, n (%)	AOR <sup>a</sup>	P <sup>a</sup>	SCC, n (%)	AOR <sup>a</sup>	P <sup>a</sup>
RAD51 rs1801320	GG	122 (69.7)	46 (64.8)	1.000		58 (72.5)	1.000	
	CG	50 (28.6)	24 (33.8)	1.316 (0.718-2.414)	0.374	20 (25.0)	0.846 (0.461-1.550)	0.587
	CC	3 (1.7))	1 (1.4)	0.782 (0.078-7.871)	0.835	2 (2.5)	1.420 (0.231-8.738)	0.705
	Additive			1.207 (0.699-2.083)	0.499		0.929 (0.546-1.578)	0.784
HER2 rs1801200	AA	131 (74.0)	52 (72.2)	1.000		62 (77.5)	1.000	
	GA	44 (24.9)	20 (27.8)	1.147 (0.611-2.152)	0.670	16 (20.0)	0.766 (0.401-1.463)	0.419
	GG	2 (1.1)	0	-	-	2 (2.5)	2.141 (0.294-15.581)	0.452
	Additive			1.029 (0.565-1.876)	0.925		0.908 (0.517-1.596)	0.738

<sup>a</sup>Adjusted for age - sample number equals to zero. n, number; P, p-value; AOR, adjusted odds ratio.

smoking status, alcohol consumption, family smoking status, number of sexual partners, age at first intercourse and age at first childbirth was compared between the controls and CIN/SCC cases using Fisher's exact  $\chi^2$ -test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by univariate logistic regression analyses and multivariate logistic regression analyses adjusted for age, family smoking status, age at first intercourse and age at first childbirth under the dominant genetic, recessive genetic and additive model. The subjects were stratified according to family smoking status, age at first intercourse, age at first childbirth and disease subtypes, in order to estimate specific ORs and CIs.

Interaction between the nine SNPs and demographic factors (family smoking status, age at first intercourse, age at first childbirth, sexual partner number and alcohol consumption) were estimated. All the regression analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Quanto (version 1.2.4) software was used to calculate the statistical power. All p-values were two-sided, and  $p < 0.05$  was considered to be statistically significant.

## Results

*Characteristics of the study population.* A total of 154 patients (82 carcinomas and 72 CINs) and 177 cancer-free controls were enrolled in the study. Among all carcinomas, two patients were diagnosed with ADC and the rest were diagnosed with SCC. Thus, our study focused on SCC and CIN. The characteristics of the study participants are shown in Table II. There was no significant difference in age between controls and patients with CIN/SCC. Similarly, education level, smoking status, alcohol consumption and the number of sexual partners were not significantly associated with CIN or SCC risk. However, significant differences between the cases and controls were found in family smoking status, age at first intercourse and age at first childbirth. These factors have previously been reported as risk factors for HPV infection, or co-factors for cervical cancer (3).

*Association between SNPs and risk of cervical SCC and CIN.* The genotype distributions of controls were in Hardy-Weinberg equilibrium (data not shown). No SNP was found to be associated with the risk of SCC or CIN in all the subjects in the univariate logistic regression analyses (data not shown). Table III shows the adjusted association of the nine SNPs in the two case groups. In the dominant genetic model, a significantly increased risk of SCC was observed in *ERCC1* 118C>T (OR=1.947; 95% CI, 1.056-3.590;  $p=0.033$ ) when adjusted for age, family smoking status, age at first intercourse and age at first childbirth. The effect was more clear when the additive model was applied (OR=1.771; 95% CI, 1.089-2.880;  $p=0.021$ ).

The statistical powers of the dominant, recessive and additive model were evaluated for each SNP, and the additive model was found to have the highest statistical power in the study (data not shown). Thus, an additive model was used for all the following association analyses.

*Association analysis following stratification.* Significant distribution differences between the controls and cases were found in family smoking status, age at first intercourse and age



Table IV. Analysis of the association between the polymorphisms and risk of SCC/CIN stratified by family smoking status.

		No				Yes			
		CIN		SCC		CIN		SCC	
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>XRCC1</i> rs1799782	CC	1.000		1.000		1.000		1.000	
	CT	1.297 (0.561-2.997)	0.543	0.955 (0.418-2.184)	0.913	1.472 (0.579-3.745)	0.417	0.931 (0.405-2.138)	0.866
	TT	0.645 (0.190-2.196)	0.483	0.360 (0.088-1.466)	0.154	1.156 (0.210-6.375)	0.868	1.928 (0.559-6.646)	0.299
	Additive	0.915 (0.531-1.579)	0.751	0.710 (0.400-1.260)	0.241	1.222 (0.614-2.433)	0.569	1.223 (0.685-2.183)	0.496
	GG	1.000		1.000		1.000		1.000	
rs25489	GA	1.017 (0.323-3.207)	0.977	1.071 (0.340-3.371)	0.907	0.516 (0.166-1.716)	0.281	0.578 (0.202-1.654)	0.307
	AA	-	-	2.263e9	1.000	-	-	-	-
	Additive	1.017 (0.323-3.207)	0.977	1.398 (0.512-3.819)	0.513	0.508 (0.155-1.667)	0.264	0.558 (0.199-1.564)	0.267
	GG	1.000		1.000		1.000		1.000	
	GA	1.579 (0.669-3.728)	0.298	2.463 (1.052-5.766)	0.038	1.515 (0.604-3.799)	0.376	0.783 (0.334-1.834)	0.573
rs25487	AA	1.167 (0.316-4.303)	0.817	0.960 (0.214-4.305)	0.957	1.769 (0.172-18.239)	0.632	2.718 (0.554-13.348)	0.218
	Additive	1.222 (0.689-2.167)	0.493	1.419 (0.777-2.592)	0.255	1.443 (0.666-3.127)	0.352	1.134 (0.591-2.177)	0.705
<i>ERCC1</i> rs11615	CC	1.000		1.000		1.000		1.000	
	CT	0.718 (0.305-1.687)	0.447	1.281 (0.564-2.907)	0.554	1.215 (0.470-3.143)	0.688	2.088 (0.910-4.788)	0.082
	TT	1.343 (0.302-5.978)	0.698	1.009 (0.206-4.947)	0.992	0.954 (0.094-9.655)	0.968	<b>4.913 (1.116-21.634)</b>	<b>0.035</b>
	Additive	0.945 (0.511-1.748)	0.857	1.128 (0.605-2.101)	0.705	1.111 (0.514-2.404)	0.788	<b>2.161 (1.152-4.054)</b>	<b>0.016</b>
	AA	1.000		1.000		1.000		1.000	
<i>ERCC2</i> rs13181	CA	1.500 (0.549-4.101)	0.429	0.569 (0.163-1.991)	0.378	1.494 (0.480-4.649)	0.488	1.730 (0.669-4.472)	0.258
	CC	-	-	-	-	-	-	-	-
	Additive	1.500 (0.549-4.101)	0.429	0.550 (0.158-1.913)	0.550	1.394 (0.466-4.169)	0.552	1.536 (0.623-3.785)	0.351
	CC	1.000		1.000		1.000		1.000	
	CA	0.550 (0.220-1.376)	0.201	0.695 (0.281-1.723)	0.432	2.423 (0.758-7.745)	0.135	0.800 (0.333-1.926)	0.619
rs238406	AA	0.360 (0.116-1.114)	0.076	0.423 (0.133-1.347)	0.145	3.461 (0.913-13.115)	0.068	1.298 (0.459-3.671)	0.623
	Additive	0.595 (0.339-1.046)	0.071	0.655 (0.370-1.159)	0.146	1.843 (0.970-3.500)	0.062	1.093 (0.642-1.859)	0.744
<i>PARP1</i> rs1136410	TT	1.000		1.000		1.000		1.000	
	CT	0.431 (0.179-1.041)	0.062	0.786 (0.325-1.901)	0.593	0.948 (0.326-2.757)	0.923	1.157 (0.473-0.833)	0.749
	CC	0.971 (0.313-3.007)	0.959	1.394 (0.448-4.331)	0.566	1.028 (0.301-3.510)	0.964	0.709 (0.229-2.192)	0.550
	Additive	0.844 (0.486-1.466)	0.547	1.115 (0.638-1.950)	0.702	1.012 (0.545-1.877)	0.971	0.869 (0.510-1.482)	0.607
	AA	1.000		1.000		1.000		1.000	

Table IV. Continued.

		No			Yes		
		CIN		SCC	CIN		SCC
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>RAD51</i> rs1801320	GG	1.000		1.000		1.000	
	CG	1.233 (0.551-2.760)	0.611	0.819 (0.349-1.921)	0.646	0.853 (0.283-2.573)	0.778
	CC	-	-	2.729 (0.234-31.843)	0.423	1.875 (0.152-23.055)	0.624
	Additive	1.085 (0.504-2.335)	0.835	1.026 (0.496-2.119)	0.946	1.027 (0.424-2.490)	0.953
<i>HER2</i> rs1801200	AA	1.000		1.000		1.000	
	GA	0.970 (0.422-2.228)	0.943	0.544 (0.218-1.359)	0.192	0.974 (0.320-2.967)	0.963
	GG	-	-	-	-	-	-
	Additive	0.970 (0.422-2.228)	0.943	0.544 (0.218-1.359)	0.192	0.823 (0.294-2.305)	0.712

<sup>a</sup>Adjusted for age - sample number equals to zero. n, number; P, p-value; AOR, adjusted odds ratio. Bold numbers indicate statistical significance.

at first childbirth (Table II). Thus, stratification was performed by these three factors. Table IV shows the association using multivariate logistic regression analysis, stratified by family smoking status. Using the additive model where the family member smoking status was 'yes', the SNP *ERCC1* 118C>T had an increased risk of SCC (OR=2.800; 95% CI, 1.314-5.968; p=0.008). Meanwhile, *ERCC2* 156C>A tended to act as a risk factor for CIN under the additive model (OR=1.949; 95% CI, 0.951-3.944; p=0.068) if the family member smoking status was 'yes'. However, *ERCC2* 156C>A tended to be a protective factor for CIN under the additive model (OR=0.616; 95% CI, 0.347-1.095; p=0.099) if the family member smoking status was 'no'. The different effects of the *ERCC2* 156C>A polymorphism between CIN and SCC suggest that its function may depend on exposure to tobacco smoke.

Among women having their first intercourse after the age of 22, there was no significant association for CIN using multivariate logistic regression analysis (Table V). However, the additive model showed that *RAD51* 135G>C (OR=0.359; 95% CI, 0.138-0.934; p=0.036) and *HER2* 655A>G (OR=0.309; 95% CI, 0.098-0.972; p=0.045) may be protective factors for SCC. In the subgroup who had their first intercourse before age 22, *XRCC1* 280G>A showed a protective effect for SCC (OR=0.228; 95% CI, 0.058-0.900; p=0.035) under the additive model. Meanwhile, *RAD51* 135G>C was related to increased susceptibility to CIN under the additive model (OR=4.246; 95% CI, 1.335-13.502; p=0.014).

Using the additive model, *XRCC1* 399G>A increased susceptibility to CIN in the subgroup who first gave birth before age 22 (OR=4.459; 95% CI, 1.139-17.453; p=0.032), and *ERCC1* 118C>T was found to be a risk factor for SCC (OR=1.884; 95% CI, 1.088-3.264; p=0.024) among those who first gave birth after age 22.

**Interaction between SNPs and demographic factors.** *RAD51* 135G>C decreased the CIN risk in combination with first intercourse at a later age (OR=0.217; 95% CI, 0.059-0.798; p=0.021), and increased CIN risk in combination with a greater number of sexual partners (OR=12.260; 95% CI, 2.874-52.305; p=0.001). *ERCC2* 156C>A increased the CIN risk in combination with family smoking status (OR=2.639; 95% CI, 1.157-6.020; p=0.021).

*HER2* 655A>G and *RAD51* 135G>C decreased the SCC risk when combined with first intercourse at a later age (OR=0.179; 95% CI, 0.041-0.790; p=0.023; and OR=0.250; 95% CI, 0.070-0.893; p=0.033; respectively). When combined with alcohol consumption, *XRCC1* 280G>A increased the SCC risk (OR=7.117; 95% CI, 1.274-39.754; p=0.025).

## Discussion

DNA repair genes have been frequently studied as significant determinants of cancer risk. Associations between SNPs in these genes and various types of cancer have been well documented but the picture remains complex, with often inconsistent data pointing to both increased and decreased risks (16-19). An association between the SNP *XRCC1* Arg399Gln G>A and an increased susceptibility to cervical cancer has been shown in the Japanese population (20), in contrast to a decreased risk, but an increased persistence of HPV infection, in a population

Table V. Analysis of the association between the polymorphisms and risk of SCC/CIN stratified by age at first intercourse.

		≤22				>22			
		CIN		SCC		CIN		SCC	
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>XRCC1</i> rs1799782	CC	1.000		1.000		1.000		1.000	
	CT	2.040 (0.711-5.852)	0.185	1.131 (0.382-3.349)	0.825	0.991 (0.463-2.121)	0.982	0.996 (0.468-2.121)	0.992
	TT	3.122 (0.438-22.263)	0.256	5.071 (0.795-32.331)	0.086	0.786 (0.232-2.658)	0.699	0.197 (0.024-1.591)	0.127
	Additive	1.888 (0.850-4.194)	0.119	1.743 (0.824-3.690)	0.146	0.920 (0.540-1.568)	0.760	0.700 (0.390-1.258)	0.233
	GG	1.000		1.000		1.000		1.000	
rs25489	GA	0.284 (0.071-1.142)	0.076	<b>0.242 (0.063-0.930)</b>	<b>0.039</b>	1.068 (0.414-2.757)	0.892	0.991 (0.367-2.677)	0.986
	AA	-	-	-	-	-	-	4.508 (0.270-75.395)	0.295
	Additive	0.284 (0.071-1.142)	0.076	<b>0.242 (0.063-0.930)</b>	<b>0.039</b>	1.002 (0.401-2.501)	0.997	1.239 (0.537-2.861)	0.615
	GG	1.000		1.000		1.000		1.000	
	GA	1.945 (0.681-5.559)	0.214	0.975 (0.352-2.701)	0.961	1.052 (0.483-2.296)	0.898	1.737 (0.799-3.779)	0.164
rs25487	AA	6.132 (0.524-71.825)	0.149	0.775 (0.044-13.594)	0.862	1.053 (0.258-4.301)	0.942	1.601 (0.389-6.597)	0.514
	Additive	2.151 (0.901-5.133)	0.084	0.944 (0.392-2.276)	0.899	1.038 (0.586-1.837)	0.899	1.442 (0.817-2.547)	0.207
<i>ERCC1</i> rs11615	CC	1.000		1.000		1.000		1.000	
	CT	1.258 (0.411-3.851)	0.688	1.685 (0.599-4.736)	0.323	0.653 (0.294-1.450)	0.295	1.341 (0.611-2.942)	0.464
	TT	4.608 (0.432-49.149)	0.206	2.476 (0.216-28.394)	0.466	0.814 (0.159-4.183)	0.806	2.478 (0.663-9.267)	0.178
	Additive	1.643 (0.704-3.833)	0.251	1.640 (0.692-3.885)	0.261	0.755 (0.400-1.423)	0.384	1.478 (0.834-2.620)	0.181
	CC	1.000		1.000		1.000		1.000	
<i>ERCC2</i> rs13181	AA	2.066 (0.623-6.857)	0.236	1.082 (0.297-3.948)	0.905	1.252 (0.484-3.237)	0.643	0.917 (0.319-2.636)	0.872
	CA	-	-	-	-	-	-	-	-
	CC	2.066 (0.623-6.857)	0.236	1.082 (0.297-3.948)	0.905	1.156 (0.464-2.877)	0.756	0.855 (0.309-2.365)	0.762
	Additive	2.066 (0.623-6.857)	0.236	1.082 (0.297-3.948)	0.905	1.156 (0.464-2.877)	0.756	0.855 (0.309-2.365)	0.762
	CC	1.000		1.000		1.000		1.000	
rs238406	CA	0.749 (0.241-2.324)	0.617	0.511 (0.164-1.590)	0.247	1.049 (0.458-2.403)	0.909	1.061 (0.466-2.415)	0.888
	AA	1.404 (0.354-5.565)	0.629	1.494 (0.388-5.758)	0.560	0.908 (0.327-2.521)	0.852	0.596 (0.189-1.876)	0.377
	Additive	1.125 (0.569-2.224)	0.735	1.112 (0.578-2.141)	0.751	0.961 (0.583-1.585)	0.877	0.819 (0.485-1.383)	0.455
	CC	1.000		1.000		1.000		1.000	
	CA	0.749 (0.241-2.324)	0.617	0.511 (0.164-1.590)	0.247	1.049 (0.458-2.403)	0.909	1.061 (0.466-2.415)	0.888
<i>PARP1</i> rs1136410	TT	1.000		1.000		1.000		1.000	
	CT	0.585 (0.188-1.820)	0.355	0.493 (0.162-1.503)	0.214	0.552 (0.235-1.294)	0.172	1.202 (0.504-2.862)	0.678
	CC	0.573 (0.140-2.347)	0.439	0.661 (0.176-2.481)	0.539	1.019 (0.399-2.601)	0.969	1.150 (0.406-3.257)	0.792
	Additive	0.733 (0.363-1.478)	0.385	0.773 (0.401-1.490)	0.443	0.956 (0.583-1.566)	0.857	1.080 (0.648-1.799)	0.768
	CC	1.000		1.000		1.000		1.000	



Table V. Continued.

		≤22				>22			
		CIN		SCC		CIN		SCC	
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>RAD51</i> rs1801320	GG	1.000		1.000		1.000		1.000	
	CG	<b>3.241 (1.050-10.005)</b>	<b>0.041</b>	1.915 (0.603-6.082)	0.270	0.877 (0.393-1.955)	0.748	0.592 (0.248-1.416)	0.239
	CC	3.408e9	NA	1.696e9	NA	-	-	-	-
	Additive	<b>3.524 (1.208-10.286)</b>	<b>0.021</b>	2.347 (0.836-6.589)	0.105	0.764 (0.362-1.614)	0.481	0.540 (0.235-1.237)	0.145
<i>HER2</i> rs1801200	AA	1.000		1.000		1.000		1.000	
	GA	1.724 (0.538-5.523)	0.359	1.687 (0.529-5.375)	0.377	1.194 (0.544-2.623)	0.658	0.344 (0.114-1.042)	0.059

<sup>a</sup>Adjusted for age - sample number equals to zero. n, number; P, p-value; AOR, adjusted odds ratio. Bold numbers indicate statistical significance.

in Costa Rica (21). These data have been partially confirmed in this study where we observed an association between *XRCC1* Arg399Gln G>A and an increased CIN risk among women who first gave birth before the age of 22. However, other changes in *XRCC1*, such as *XRCC1* Arg194Trp C>T showed no significant association with CIN/SCC, and among women who had their first intercourse before 22 years of age, there was a significant association between *XRCC1* Arg280His G>A and a decreased susceptibility to SCC. Although no previous study has reported an association between alcohol consumption and cervical cancer, we observed an interaction between *XRCC1* 280G>A and alcohol consumption ( $p_{\text{interaction}} < 0.05$ ), which may suggest that alcohol is involved in the development of cervical cancer.

The enzyme PARP1 (encoded by the gene of the same name) plays a role in repairing single-stranded DNA breaks. The *PARP1* Val762Ala T>C polymorphism located in the catalytic domain has been shown to interact with *XRCC1*. *In vitro*, this polymorphism markedly reduces the enzymatic activity of *PARP1*, and has also been linked to cancer susceptibility (22). An increased risk of smoking-related lung cancer has also been reported (23). There are no previous reports evaluating the correlation of *PARP1* Val762Ala T>C with cervical cancer as yet. Our analysis showed no significant association between the polymorphism and CIN/SCC risk.

The proteins, ERCC1 and ERCC2, are two of 16 proteins involved in NER systems, where they help to excise lesions from the DNA strand (11,24). The proteins are encoded by the genes *ERCC1* and *ERCC2*, respectively. In *ERCC1*, a polymorphism at *ERCC1* 118C>T has been shown to decrease the rate of mRNA translation to the protein (25). It is possible that a decreased level of *ERCC1* mRNA expression influences the repair efficiency of DNA damage, which then contributes to cancer susceptibility. Studies have also shown an association between the polymorphism and malignancies such as lung, ovarian and colorectal cancer (26-29), although no previous association with cervical cancer has been shown. Our study showed that *ERCC1* 118C>T may be a potential risk factor for SCC. Among the Chinese population, a homozygous CC polymorphism in *ERCC2* at position 751A>C is related to a decreased DNA repair capacity in patients with lung cancer (30). In addition, there are data linking an *ERCC2* polymorphism and glioblastoma (31). Our data indicate that *ERCC2* 751A>C and *ERCC2* 156C>A have no significant association in CIN/SCC. Furthermore, among women who first gave birth after 22 years of age, *ERCC1* 118C>T may be a risk factor for SCC.

The association between cervical cancer and smoking (and second-hand smoke) has already been established (7,32). The hypothesis is that the carcinogens in smoke initiate DNA damage, and then activate the DNA repair process; with polymorphisms in the DNA repair genes either increasing or decreasing the risk of cancer in the areas affected. In the case of cervical cancer, it is thought that smoke may have a directly carcinogenic effect by acting through the polycyclic aromatic hydrocarbon-DNA adduct in the cervix (33). When we looked at associations between family smoking status and SNPs, we found that *ERCC1* 118C>T, a potential risk factor for SCC, became more significantly associated with this outcome in women who live with family members who smoke.

Table VI. Analysis of the association between the polymorphisms and risk of SCC/CIN stratified by age at first giving birth.

		≤22				>22			
		CIN		SCC		CIN		SCC	
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>XRCC1</i> rs1799782	CC	1.000		1.000	1.000				
	CT	1.260 (0.313-5.069)	0.745	0.516 (0.117-2.282)	0.383	1.326 (0.685-2.569)	1.000	1.018 (0.536-1.936)	0.956
	TT	-	-	0.632 (0.085-4.723)	0.655	0.898 (0.294-2.736)	0.849	0.585 (0.178-1.923)	0.377
	Additive	0.784 (0.247-2.494)	0.680	0.713 (0.279-1.820)	0.479	1.069 (0.671-1.703)	0.780	0.863 (0.538-1.384)	0.541
rs25489	GG	1.000		1.000	1.000				
	GA	0.427 (0.067-2.739)	0.370	0.491 (0.088-2.725)	0.416	0.756 (0.318-1.796)	0.526	0.707 (0.299-1.670)	0.429
	AA	-	-	-	-	-		3.165 (0.190-52.685)	0.422
	Additive	0.427 (0.067-2.739)	0.370	0.491 (0.088-2.725)	0.416	0.727 (0.312-1.692)	0.459	0.872 (0.409-1.859)	0.722
rs25487	GG	1.000		1.000	1.000				
	GA	8.522 (1.671-43.448)	0.010	2.588 (0.583-11.487)	0.211	1.016 (0.515-2.005)	0.963	1.158 (0.601-2.230)	0.662
	AA	6.389 (0.296-137.767)	0.237	2.215 (0.118-41.529)	0.595	1.554 (0.479-5.040)	0.463	1.646 (0.507-5.340)	0.406
	Additive	4.766 (1.266-17.943)	0.021	1.965 (0.622-6.201)	0.250	1.144 (0.697-1.876)	0.595	1.227 (0.755-1.993)	0.410
<i>ERCC1</i> rs11615	CC	1.000		1.000	1.000				
	CT	1.384 (0.290-6.611)	0.684	1.639 (0.393-6.835)	0.498	0.702 (0.350-1.408)	0.319	1.521 (0.798-2.900)	0.203
	TT	2.540 (0.273-23.633)	0.413	1.144 (0.118-11.128)	0.908	1.182 (0.283-4.934)	0.818	2.682 (0.774-9.297)	0.120
	Additive	1.531 (0.556-4.219)	0.410	1.242 (0.458-3.369)	0.671	0.853 (0.491-1.484)	0.574	1.581 (0.960-2.603)	0.072
<i>ERCC2</i> rs13181	AA	1.000		1.000	1.000				
	CA	1.788 (0.293-10.932)	0.529	3.559 (0.573-22.112)	0.173	1.423 (0.639-3.172)	0.388	0.905 (0.379-2.164)	0.823
	CC	-	-	-	-	-	-	-	-
	Additive	1.788 (0.293-10.932)	0.529	3.559 (0.573-22.112)	0.173	1.315 (0.608-2.844)	0.487	0.853 (0.367-1.986)	0.713
rs238406	CC	1.000		1.000	1.000				
	CA	0.758 (0.142-4.044)	0.746	1.012 (0.243-4.218)	0.986	1.032 (0.504-2.113)	0.931	0.726 (0.360-1.464)	0.371
	AA	2.364 (0.393-14.208)	0.347	0.488 (0.039-6.032)	0.576	0.856 (0.345-2.127)	0.738	0.913 (0.398-2.094)	0.829
	Additive	1.508 (0.604-3.766)	0.379	0.803 (0.280-2.297)	0.682	0.937 (0.602-1.459)	0.775	0.929 (0.609-1.416)	0.732
<i>PARP1</i> rs1136410	TT	1.000		1.000	1.000				
	CT	0.615 (0.140-2.692)	0.518	0.862 (0.192-3.881)	0.847	0.607 (0.287-1.284)	0.192	0.919 (0.457-1.850)	0.814
	CC	-	-	1.260 (0.191-8.324)	0.810	1.129 (0.498-2.559)	0.772	0.838 (0.351-2.001)	0.690
	Additive	0.358 (0.109-1.179)	0.091	1.087 (0.426-2.768)	0.862	1.028 (0.670-1.575)	0.901	0.916 (0.597-1.406)	0.688

Table VI. Continued.

		≤22				>22			
		CIN		SCC		CIN		SCC	
		AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>	AOR <sup>a</sup>	P <sup>a</sup>
<i>RAD51</i> rs1801320	GG	1.000		1.000		1.000		1.000	
	CG	1.342 (0.243-7.423)	0.736	1.349 (0.204-8.936)	0.756	1.307 (0.668-2.560)	0.435	0.891 (0.451-1.761)	0.740
	CC	-	-	1.829e9	N/A	0.902 (0.089-9.119)	0.930	0.802 (0.081-7.973)	0.851
	Additive	1.342 (0.243-7.423)	0.736	1.991 (0.438-9.051)	0.372	1.207 (0.665-2.190)	0.537	0.892 (0.486-1.638)	0.713
<i>HER2</i> rs1801200	AA	1.000		1.000		1.000		1.000	
	GA	3.294 (0.580-18.718)	0.179	1.736 (0.295-10.213)	0.542	0.932 (0.457-1.901)	0.846	0.735 (0.352-1.535)	0.412
	GG	-	-	-	-	-	-	1.259 (0.109-14.543)	0.853
	Additive	3.294 (0.580-18.718)	0.179	1.726 (0.295-10.213)	0.542	0.843 (0.428-1.663)	0.623	0.807 (0.417-1.564)	0.526

<sup>a</sup>Adjusted for age - sample number equals to zero. n, number; P, p-value; AOR, adjusted odds ratio.

Although not statistically significant, *ERCC2* 156C>A tended to be a risk factor among patients who have smoking family members, but tended to play a protective role in women whose families did not smoke. Tsai *et al* (32) previously showed that non-smoking women exposed to second-hand cigarette smoke had a significantly greater risk of developing CIN than unexposed non-smokers. Our data indicate that *ERCC2* 156C>A may play a role in the association between second-hand smoke and CIN.

The gene *RAD51* plays a significant role in DNA repair of double-strand breaks via HR (34). Previous studies, although not looking at functional evidence, have shown that the polymorphism *RAD51* 135G>C is related to breast cancer susceptibility (35). No *RAD51* polymorphisms related to cervical cancer have been reported as yet. In this study, we observed that *RAD51* 135G>C may increase the risk of CIN in women who first had intercourse before the age of 22, but may be a protective factor for SCC in women who first had intercourse after the age of 22. Studies examining SNPs in *HER2* have mostly focused on *HER2* 655A>G in breast cancer (36), and no previous association has been shown in cervical cancer. In our analysis, *HER2* 655A>G showed a decreased susceptibility to SCC in women who had first intercourse after the age of 22.

The interaction analysis in our study shows a consistent result with epidemiological data of cervical cancer. Women who have multiple sexual partners or a younger age at first sexual intercourse had a significantly higher risk of HPV infection (3) as well as an increased risk of cervical cancer (37). While our study indicates that polymorphisms in *HER2* 655A>G and *RAD51* 135G>C and the age of first intercourse are related, it is worth noting that the age we used as a cut-off (22 years) is an arbitrary age that is open to some debate. There is evidence that in certain countries as many as 50% of women have their first intercourse between the ages of 13 and 19 years (37). Altering the age cut-off in our interaction analyses may affect the outcome and correlations between cervical cancer and the selected SNPs, and these analyses will need to be performed before any more firm conclusions can be drawn.

It is also worth noting that the sample size of our study was relatively small, which limits the statistical power, and, hence, the conclusions that may be drawn. Other studies examining associations in other types of cancer, such as lung or breast cancer have recruited larger numbers of patients, and this larger number of data points has enhanced the robustness of the findings. Cervical cancer patients however, are fewer in number compared with other types of cancer, and therefore we were limited as to the number of patients we could recruit to our study. Our study of 154 patients (82 carcinomas and 72 CINs) compares favorably with other recently published case-control studies in the same geographical area (38-40), but clearly there is a need for further research with larger sample sizes across diverse populations.

In addition, the data presented in this study were gained using an additive genetic model. Although the additive and dominant models are often highly correlated, there is debate as regards which is the most appropriate, and there are also cases where these tests are not appropriate, particularly if testing traits that turn out to be recessive (41). Further explo-

ration of different models is required, particularly if larger sample sizes are used.

In conclusion, this is the first association study between cervical cancer and SNPs in *ERCC1*, *ERCC2*, *RAD51* and *HER2*. Interaction analysis suggests that sexual behavior, second-hand smoke and alcohol consumption are co-factors combined with SNPs, and further research is required to confirm these findings.

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