Susceptibility of *XRCC3*, *XPB*, and *XPG* Genetic Variants to Cervical Carcinoma

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Key Words

Cervical carcinoma · Single nucleotide polymorphism · *XRCC3* · *XPB* · *XPG*

Abstract

Objective: DNA repair genes play a key role in maintaining genomic stability and integrity. DNA repair gene polymorphisms, such as those of *XRCC3* and xeroderma pigmentosum, complementation group D and G (*XPB*, *XPG*), contribute to carcinogenesis. In this study, we investigated the correlation between cervical carcinoma risk and *XRCC3*, *XPB*, *XPG* genetic variants. **Methods:** A case-control study of 400 cases including 200 carcinoma, 200 cervical intraepithelial neoplasia (CIN) and 200 normal women was performed. Four single nucleotide polymorphisms (SNPs) (*XRCC3* Thr241Met, *XPG* His1104Asp, *XPB* Asp312Asn, and *XPB* Lys751Gln) were genotyped by mismatch amplification polymerase chain reaction. **Results:** Women carrying homozygous Asp1104Asp genotypes had a significantly decreased risk of cervical or cervical squamous cell carcinoma compared to His1104Asp or His1104His genotypes. Similarly, *XPB* Asn312Asn (AA) reduced the risk of cervical or cervical squamous cell carcinoma. No association of *XRCC3* Thr241Met or *XPB* Lys751Gln and cervical carcinoma was found. None of the 4 SNPs influenced

the risk of CIN in our study. **Conclusion:** Our results support the hypothesis that genetic variations in DNA repair genes may contribute to an inherited genetic susceptibility to cervical carcinoma.

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Introduction

Cervical cancer is one of the most common cancers in women. It is well known that the human papillomavirus (HPV) is regarded as a prime etiologic factor of cervical carcinoma and its precursor lesion, cervical intraepithelial neoplasia (CIN). Approximately 30% of women with sexual experience are infected with high-risk HPV. However, only 1% of these women will develop CIN and cervical carcinoma [1]. This indicates that HPV infection is not sufficient to develop CIN or cancer, and other cofactors, such as variations in DNA repair genes, should be considered.

DNA repair genes play a key role in maintaining genomic stability and integrity. It is now thought that an individual's DNA repair capacity is genetically determined, and is the result of a combination of multiple genes that display subtle differences in their activity. Sin-

gle nucleotide polymorphisms (SNPs) may cause subtle structural alterations in repair enzymes, and subsequent modulation of cancer susceptibility. In humans, more than 130 genes are involved in the 5 major DNA repair pathways, including nucleotide excision repair (NER) and homologous recombinational repair [2]. A number of SNPs in DNA repair genes have been identified [3]. Defects in DNA repair pathways are found to be associated with many types of cancer, including cervical carcinoma.

The *XRCC3* gene encodes a protein involved in the homologous recombinational repair pathway of double-strand DNA repair, and plays a key role in maintaining chromosome stability. The most frequent polymorphism in *XRCC3* is a C→T transition (Thr241Met), which may affect the function of the enzyme and/or its interaction with other proteins involved in DNA damage and repair [4, 5]. Molecular epidemiological studies have shown that this *XRCC3* polymorphism is associated with increased risk of breast [5] but not lung cancer [6].

Xeroderma pigmentosum complementation group D and G (*XPD*, *XPG*) are 2 of the more than 20 genes involved in NER. One common nonsynonymous SNP has been identified in its coding region, which causes an amino acid substitution (His1104Asp). The His1104Asp amino acid substitution may influence protein-protein interactions, and consequently predispose individuals with these variants to cancer.

XPD works as an adenosine triphosphate-dependent 5'-3' helicase and is a subunit of the basal transcription factor IIH, which is required for separation of the double helix during both global genomic repair and transcription-coupled repair. Several SNPs have been identified in the *XPD* gene. Two common nonsynonymous SNPs in the coding region of the *XPD* gene have been identified: a G→A substitution causing exon 10 codon 312 Asp (D) to be exchanged for Asn (N), and an A→C substitution causing exon 23 codon 751 Lys (K) to be substituted for Gln (Q) [7]. There have been some studies claiming links between the *XPD* SNPs and cancers of various kinds, including basal cell carcinoma [8], head and neck carcinomas [9], and cancer of the bladder [10], lung [6] and prostate [11].

We genotyped 4 variants of the 3 DNA repair genes (*XRCC3* Thr241Met, *XPG* His1104Asp, *XPD* Asp312Asn, *XPD* Lys751Gln), and assessed their contributions to CIN and cervical carcinoma susceptibility, and their association with other epidemiological risk factors. We also explored the association of genetic polymorphisms of DNA repair genes with the risk of cervical carcinoma.

Subjects and Methods

Study Subjects

The subjects were unrelated ethnic Chinese women. Patients with histologically confirmed primary cervical carcinoma were recruited from the Hangzhou area from June 2004 to May 2006 at the Women's Hospital School of Medicine Zhejiang University and the Cancer Hospital of Zhejiang Province. Outside of Hangzhou, a collaborative network of gynecology/oncology teams in 3 areas (Lishui, Wenzhou, and Shaoxing) of the Zhejiang Province was established. There were no age, stage, histology and prior therapy restrictions.

Controls were randomly selected from healthy women who requested gynecological examinations at the Women's Hospital School of Medicine Zhejiang University. The criteria for selection included no positive findings during examination, no history of cancer, and age-matching the patients within 5 years. Each participant signed an informed consent, and sexual and reproductive history was obtained using a standardized questionnaire.

A total of 400 eligible patients (200 carcinoma patients and 200 CIN patients) and 200 eligible control women were interviewed, completed the questionnaires, consented to provide blood samples for genotyping and gave cervical brush-off samples for HPV detection.

Genotyping

Genomic DNA was extracted using a routine phenol/chloroform method from peripheral blood lymphocytes. The polymorphisms of the 4 SNPs were detected using mismatch amplification polymerase chain reaction [12] (primers showed in table 1). All samples were tested twice by different technical persons, and the results were concordant for all masked duplicate sets.

HPV Detection

HPV infection was identified using the hybrid capture II assay (Digene Diagnostics Inc., Gaithersburg, Md., USA) with probe B (a pool of full-length RNA probes specific for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) according to the manufacturer's instructions. Cervical sampling for HPV DNA was performed with the Digene Cervical Sampler, and the tests were classified with the relative light unit/positive control ratio.

Statistical Analysis

Differences in the frequencies of the genotypes and alleles between the cases and controls were evaluated by the χ^2 test. We also evaluated the observed genotype frequencies with those calculated from the Hardy-Weinberg equilibrium theory ($p^2 + 2pq + q^2 = 1$, where p is the frequency of the variant allele, and $q = 1 - p$). Univariate and multivariate logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs), respectively, for the association between the genotypes and risk of cervical carcinoma. The association between the frequencies of all the variant genotypes and cervical cancer risk was also evaluated by stratification analyses by subgroups of histological types.

Table 1. Primers and annealing temperature for the SNP mismatch amplification polymerase chain reaction

Gene	Primer sequence	Product length bp	Annealing temp., °C	Reference SNP ID in NCBI
<i>XRCC3</i> Thr241Met	F-1 5'-CTGCAGTCCCCTGGGGGCCAC-3' F-2 5'-CTGCAGTCCCCTGGGGGCCAT-3' R 5'-TGCTCCTCCATGGCCTCTGT-3'	279	62	rs861539
<i>XPG</i> His1104Asp	F-1 5'-TGATGGATCTTCAAGTGATG-3' F-2 5'-TGATGGATCTTCAAGTGATC-3' R 5'-GGTCACGAGGACCATCTTCT-3'	202	60	rs17655
<i>XPB</i> Asp312Asn	F-1 5'-GGCCAACCCCGTGCTGCCTG-3' F-2 5'-GGCCAACCCCGTGCTGCCTA-3' R 5'-GGAGGACACGGCTCTGCATA-3'	345	62	rs1799793
<i>XPB</i> Lys751Gln	F-1 5'-AGAATCAGAGGAGACGCTCA-3' F-2 5'-AGAATCAGAGGAGACGCTCC-3' R 5'-CTGGTGGATAGCTGCCTTCT-3'	213	62	rs13181

NCBI = National Center for Biotechnology Information.

Results

Characteristics of the Population

Of the 200 cancer patients, 134 (67.0%) had squamous cell carcinomas, 48 (24.0%) adenocarcinomas, and 18 (9%) other types, including 15 adenosquamous carcinomas, 1 undifferentiated carcinoma and 2 carcinosarcomas. Of the 200 carcinoma patients, 19 (9.5%) were Ia stage, 81 (40.5%) were Ib stage, 48 (24.0%) were IIa stage, 33 (16.5%) were IIb stage, 16 (8.0%) were III stage and 3 (1.5%) were IV stage. Of the 200 CIN patients, 104 (52.0%) were CIN III, 67 (33.5%) CIN II, and 29 (14.5%) were CIN I. The median ages of the cancer patients, CIN patients and control women were 42 (range 25–81), 41 (range 21–69) and 40 (range 20–65) years, respectively. The frequency matching of age between the cases and controls appeared to be adequate. It seemed that smoking status was not an important factor in this population study since the number of smokers in the carcinoma, CIN and control groups were only 2 (1.0 %), 1 (0.5%) and 0, respectively, so the data were not adjusted or stratified for this factor in further statistical analyses. The sexual and reproductive histories including age of first intercourse, number of sexual partners, and age at the first parity among the carcinoma patients, CIN patients and controls were not significantly different, while the number of parities was significantly different among the three groups ($\chi^2 = 7.129$, $p = 0.028$; table 2).

The Allelic and Genotypic Frequencies

The genotype distributions and the allele frequencies of all 4 SNPs among the carcinoma, CIN and control groups were not significantly different.

Polymorphisms and Risk for Cervical Carcinoma and CIN

Women carrying the *XPG* Asp1104Asp (GG) genotype had a significantly decreased risk for cervical carcinoma (OR = 0.59, 95% CI = 0.36–0.95). Similarly, compared with the *XPB* Asp312Asn (GA) or Asp312Asp (GG) wild-type genotype, homozygous Asn312Asn (AA) carriers were at reduced risk for carcinoma (OR = 0.51, 95% CI = 0.27–0.95). Neither *XRCC3* Met241Met (TT) nor *XPB* Gln751Gln (CC) increased or decreased the risk for cervical carcinoma when using *XRCC3* Thr241Met (CT) or Thr241Thr (CC) and *XPB* Lys751Gln (AC) or Lys751Lys (AA) as a reference, respectively (table 3). None of the variants among these 4 SNPs increased or decreased the risk for CIN or CIN II–III.

A significantly decreased risk was observed for squamous cell carcinoma in *XPG* Asp1104Asp (GG) carriers using *XPG* His1104Asp (GA) or His1104His (GG) as a reference (OR = 0.58, 95% CI = 0.33–0.99). Similarly, compared with *XPB* Asp312Asn (GA) or Asp312Asp (GG) wild-type genotypes, homozygous Asn312Asn (AA) carriers were at reduced risk for squamous cell carcinoma (OR = 0.47, 95% CI = 0.23–0.97). Neither *XRCC3* Met241Met (TT) nor *XPB* Gln751Gln (CC) increased or

Table 2. Frequency distribution of select characteristics by case-control status

		Control (n = 200)	CIN (n = 200)	Carcinoma (n = 200)	χ^2	p
Age	≤40	100 (50.0)	97 (48.5)	96 (48.0)	0.173	0.917
	>40	100 (50.0)	103 (51.5)	104 (52.0)		
Number of sexual partners	≤1	161 (80.5)	153 (76.5)	146 (73.0)	3.149	0.07
	>1	39 (19.5)	47 (23.5)	54 (27.0)		
Age at the first intercourse	≤20 years	57 (28.5)	68 (34.0)	74 (37.0)	3.353	0.187
	>20 years	143 (71.5)	132 (66.0)	126 (63.0)		
Number of parities	≤3	91 (45.5)	77 (38.5)	65 (32.5)	7.129	0.028
	>3	109 (54.5)	123 (61.5)	135 (67.5)		
Age at the first parity	≤22 years	33 (16.5)	41 (20.5)	45 (22.5)	2.348	0.309
	>22 years	167 (83.5)	159 (79.5)	155 (77.5)		
High-risk HPV infection	positive	56 (28.0)	169 (84.5)	172 (86.0)	195.312	0.000
	negative	144 (72.0)	31 (15.5)	28 (14.0)		

Two-sided χ^2 test. Figures in parentheses are percentages. Figures in italics indicate significant difference.

Table 3. Analysis of association between the *XRCC3*, *XPG*, *XPB* polymorphisms and risk for cervical carcinoma and CIN

Genotypes		Control (n = 200)	All CIN (n = 200)	Adjusted OR	p	Carcinomas (n = 200)	Adjusted OR	p
<i>XRCC3</i> codon 241	Thr/Thr (CC)	182 (91.0)	179 (89.5)	0.99 (0.74–1.32)	0.937	177 (88.5)	0.99 (0.74–1.31)	0.931
	Thr/Met (CT)	17 (8.5)	19 (9.5)	1.12 (0.57–2.22)	0.739	19 (9.5)	1.14 (0.57–2.25)	0.717
	Met/Met (TT)	1 (0.5)	2 (1.0)	2.01 (0.18–22.35)	0.570	4 (1.0)	4.06 (0.45–36.66)	0.212
	Thr/Thr or Thr/Met	199 (99.5)	198 (99.0)	1.00		196 (98.0)	1.00	
<i>XPG</i> codon 1104	His/His (CC)	67 (33.5)	70 (35.0)	1.02 (0.68–1.54)	0.909	71 (35.5)	0.93 (0.62–1.39)	0.720
	His/Asp (CG)	80 (40.0)	80 (40.0)	0.98 (0.67–1.44)	0.918	94 (47.0)	1.06 (0.73–1.54)	0.760
	Asp/Asp (GG)	53 (26.5)	50 (25.0)	0.93 (0.59–1.45)	0.732	35 (17.5)	0.59 (0.36–0.95)	0.031
	His/His or His/Asp	147 (73.5)	150 (75.0)	1.00		165 (82.5)	1.00	
<i>XPB</i> codon 312	Asp/Asp (GG)	79 (39.5)	81 (40.5)	1.02 (0.70–1.49)	0.921	90 (45.0)	1.04 (0.72–1.05)	0.838
	Asp/Asn (GA)	89 (44.5)	88 (44.0)	0.98 (0.68–1.41)	0.926	93 (46.5)	0.97 (0.68–1.38)	0.845
	Asn/Asn (AA)	32 (16.0)	31 (15.5)	0.99 (0.58–1.71)	0.983	17 (8.5)	0.51 (0.27–0.95)	0.034
	Asp/Asp or Asp/Asn	168 (84.0)	169 (84.5)	1.00		183 (91.5)	1.00	
<i>XPB</i> codon 751	Lys/Lys (AA)	164 (82.0)	167 (83.5)	1.01 (0.76–1.36)	0.931	165 (82.5)	0.99 (0.74–1.33)	0.951
	Lys/Gln (AC)	31 (15.5)	29 (14.5)	0.93 (0.54–1.60)	0.796	33 (16.5)	1.05 (0.62–1.78)	0.861
	Gln/Gln (CC)	5 (2.5)	4 (2.0)	0.80 (0.21–3.01)	0.737	2 (1.0)	0.39 (0.08–2.06)	0.269
	Lys/Lys or Lys/Gln	195 (97.5)	196 (98.0)	1.00		198 (99.0)	1.00	

ORs were adjusted for age by binary logistic regression. Figures in parentheses are percentages or 95% CIs. Figures in italics indicate significant difference.

decreased the risk for squamous cell carcinoma when using *XRCC3* Thr241Met (CT) or Thr241Thr (CC) and *XPB* Lys751Gln (AC) or Lys751Lys (AA) as a reference, respectively. No significantly reduced or elevated risk for adenocarcinoma or other types of cancer was found (table 4).

Stratified Analyses of Cervical Carcinoma Risk in Patients with Different Genotypes and Different High-Risk Exposure Factors

We further evaluated the association of *XPG* His1104Asp and *XPB* Asp312Asn variant genotypes with cervical carcinoma risk stratified by high-risk exposure

Table 4. Analysis of association between the *XRCC3*, *XPG*, *XPB*, *XPD* polymorphisms and risk for different histopathological types of cervical carcinoma

Genotypes		Control (n = 200)	Squamous cell carcinoma (n = 134)	Adjusted OR	p	Adeno- carcinoma (n = 48)	Adjusted OR	p
<i>XRCC3</i> codon 241	Thr/Thr (CC)	182 (91.0)	118 (88.1)	0.98 (0.71–1.35)	0.889	43 (89.6)	0.98 (0.62–1.55)	0.929
	Thr/Met (CT)	17 (8.5)	14 (10.4)	1.24 (0.59–2.60)	0.567	5 (10.4)	1.22 (0.43–3.47)	0.710
	Met/Met (TT)	1 (0.5)	2 (1.5)	3.02 (0.27–33.59)	0.370	0		
	Thr/Thr or Thr/Met	199 (99.5)	132 (98.5)	1.00		48 (100.0)	1.00	
<i>XPG</i> codon 1104	His/His (CC)	67 (33.5)	50 (37.3)	0.99 (0.64–1.54)	0.958	18 (37.5)	0.99 (0.53–1.85)	0.968
	His/Asp (CG)	80 (40.0)	61 (45.5)	1.01 (0.67–1.53)	0.963	22 (45.8)	1.01 (0.56–1.82)	0.972
	Asp/Asp (GG)	53 (26.5)	23 (17.2)	0.58 (0.33–0.99)	0.048	8 (16.7)	0.56 (0.24–1.26)	0.160
	His/His or His/Asp	147 (73.5)	111 (82.8)	1.00		40 (83.3)	1.00	
<i>XPB</i> codon 312	Asp/Asp (GG)	79 (39.5)	62 (46.3)	1.07 (0.71–1.61)	0.737	21 (43.8)	1.06 (0.59–1.92)	0.838
	Asp/Asn (GA)	89 (44.5)	61 (45.5)	0.94 (0.63–1.40)	0.747	21 (43.8)	0.94 (0.53–1.69)	0.846
	Asn/Asn (AA)	32 (16.0)	11 (8.2)	0.47 (0.23–0.97)	0.041	6 (12.4)	0.75 (0.29–1.91)	0.547
	Asp/Asp or Asp/Asn	168 (84.0)	123 (91.8)	1.00		42 (87.6)	1.00	
<i>XPB</i> codon 751	Lys/Lys (AA)	164 (82.0)	105 (78.4)	0.95 (0.68–1.32)	0.741	42 (87.5)	1.04 (0.66–1.65)	0.867
	Lys/Gln (AC)	31 (15.5)	27 (20.1)	1.29 (0.73–2.26)	0.379	6 (12.5)	0.79 (0.31–1.99)	0.612
	Gln/Gln (CC)	5 (2.5)	2 (1.5)	0.59 (0.11–3.09)	0.533	0		
	Lys/Lys or Lys/Gln	195 (97.5)	132 (98.5)	1.00		48 (100.0)	1.00	

ORs were adjusted for age by binary logistic regression. Figures in parentheses are percentages or 95% CIs. Figures in italics indicate significant difference.

factors (table 5). The effect of *XPG* Asp1104Asp (GG) was less evident in women who had multiple partners, early onset of sexual activity and early age of the first parity [adjusted ORs and 95% CIs being 0.57 (0.33–0.99), 0.53 (0.29–0.97), and 0.56 (0.33–1.11), respectively]. Similar results were also observed for Asn312Asn (AA) carriers [adjusted ORs and 95% CIs being 0.45 (0.21–0.95), 0.45 (0.21–0.99), and 0.48 (0.24–0.96), respectively]. However, the effect of *XPG* Asp1104Asp (GG) or *XPB* Asn312Asn (AA) was very similar between the women with parities equal to or less than 3 and the women with parities more than 3. The *XPG* Asp1104Asp (GG) or *XPB* Asn312Asn (AA) genotypes similarly affected women with or without high-risk HPV infection.

Discussion

In the current study, the *XPG* Asp1104Asp genotype was associated with a significantly decreased risk of cervical carcinoma compared with the combined His/His and His/Asp genotype. Normal NER function requires the interaction of many DNA repair genes, including the *XPG*, *XPB*, *XPB*, *p62* and *p44* subunits of transcription factor IIH in the incision complex of NER. The His1104Asp polymorphism is located in the *XPG* C-ter-

minus, which is conserved in character rather than sequence, and is very rich in basic amino acids [13]. An amino acid change from an acidic aspartic acid residue to a basic histidine residue may change the protein structure of *XPG*, and therefore influence the protein-protein interactions and the stability of the preincision complex.

Several reports have explored the correlation between the *XPG* Asp1104Asp polymorphisms and risk of lung cancer, and squamous cell carcinomas of the oropharynx, larynx and esophagus. These studies have shown that the Asp1104Asp genotype was associated with a decreased risk of cancer compared to the combination of His1104His and His1104Asp genotypes [14, 15]. Our results were consistent with these studies.

The 2 intriguing SNPs of *XPB* are Asp312Asn and Lys751Gln. Residue 312 is evolutionarily highly conserved, and is located in the seven-motif helicase domain of the RecQ family of DNA helicases [6]. The Asn variant may alter the folding of the resulting protein, and hence the downstream sites of protein interaction and function [6]. The Lys751Gln polymorphism may also be important since it is located in the protein-protein interaction domain [16]. However, it has recently been observed that lymphoblastoid cell lines with homozygous Asn genotypes showed a nearly 2.5-fold higher apoptotic response, representing a direct link between this polymorphism

and its biological significance [17]. Thus, the Asp312Asn polymorphism is considered to be more functionally relevant than the Lys751Gln polymorphism. Our findings regarding the protective role of the Asp312Asn polymorphism in cervical carcinoma are in line with this observation [17]. Many studies have also investigated the functional significance of *XPD* Asp312Asn and *XPD* Lys751Gln [4, 17–19]. However, the majority of these studies inferred that the 312Asn and 751Gln alleles were related to lower DNA repair capacity when compared to the major allele [19, 20] or null results [21]. Our findings suggest a protective effect of the Asn312 allele on the risk of cervical carcinoma. However, we did not find a significant association between the Lys751Gln polymorphism and cervical carcinoma risk. Previous studies have found that the *XPD* 751Gln allele is associated with increased risks for head and neck cancer [9], melanoma skin cancer [22] and lung cancer [19]. However, inconsistent findings were also reported [8, 23].

XRCC3 plays a key role in preventing mutations, chromosomal instability and cancer [24]. Several studies have examined the association between the *XRCC3* Thr241Met polymorphism and risk of cancer [4–6]. *XRCC3* 241Met was reportedly associated with an increased risk for melanoma skin cancer [21, 25], bladder cancer [25] and breast cancer [5]. However, other studies found that the *XRCC3* 241Met variant was not associated with a risk of lung cancer [6, 26]. Therefore, the lack of an association between the *XRCC3* 241Met variant and risk of cervical cancer in our study is not surprising. One possible explanation is that the 241Met variant in this low-penetrance gene may not be an important determinant in the etiology of cervical carcinoma.

In addition, the main effect of both *XPG* Asp1104Asp (GG) and *XPD* Asn312Asn (AA) genotypes was very similar between the women whose parity number was more than or equal to 3 and the women whose parity number was less than 3, indicating that the role of the genotypes was independent of parity status. Moreover, the main effect of both *XPG* Asp1104Asp (GG) and *XPD* Asn312Asn (AA) genotypes was very similar between the women with high-risk HPV infection and the women without high-risk HPV infection, suggesting that the role of these genotypes was independent of high-risk HPV infection status. However, the protective effect of both *XPG* Asp1104Asp (GG) and *XPD* Asn312Asn (AA) genotypes was less evident in women who had multiple sexual partners, early onset of sexual activity and early age of first parity. These results may imply a weak effect of these polymorphisms on cervical carcinoma risk overall.

Table 5. Stratified analyses between the *XPG*, *XPD* genotypes and cervical carcinoma risk in different lifestyle subgroups or HPV infection status

High-risk exposure	XPG His1104Asp			p	Adjusted OR ¹	XPD Asp312Asn			p	Adjusted OR ¹	p	
	controls					carcinoma cases						
	CC or CG	GG	GG			CC or CG	GG	GG				GG or GA
Number of sexual partners												
≤1	118 (73.3)	43 (26.7)	25 (17.1)	0.045	136 (84.5)	25 (15.5)	133 (92.5)	11 (7.5)	0.45 (0.21–0.95)	0.036		
>1	29 (74.4)	10 (25.6)	10 (18.5)	0.411	32 (82.1)	7 (17.9)	48 (88.9)	6 (11.1)	0.57 (0.18–1.86)	0.352		
Age at the first intercourse												
≤20 years	43 (75.4)	14 (24.6)	14 (18.9)	0.436	48 (84.2)	9 (15.8)	67 (90.5)	7 (9.5)	0.56 (0.19–1.60)	0.277		
>20 years	104 (72.7)	39 (27.3)	21 (16.7)	0.039	120 (83.9)	23 (16.1)	116 (92.2)	10 (7.9)	0.45 (0.21–0.99)	0.046		
Number of parities												
≤3	66 (72.5)	25 (27.5)	12 (18.5)	0.195	77 (84.6)	14 (15.4)	60 (92.3)	5 (7.7)	0.46 (0.16–1.34)	0.155		
>3	81 (24.3)	28 (25.7)	23 (17.0)	0.100	91 (83.5)	18 (16.5)	123 (91.1)	12 (8.9)	0.49 (0.23–1.08)	0.075		
Age at the first parity												
≤22 years	24 (72.7)	9 (27.3)	9 (20.0)	0.319	28 (84.8)	5 (15.2)	41 (91.1)	4 (8.9)	0.55 (0.14–2.22)	0.397		
>22 years	123 (73.7)	44 (26.3)	26 (17.8)	0.039	140 (83.8)	27 (16.2)	142 (91.6)	13 (8.4)	0.48 (0.24–0.96)	0.037		
High-risk HPV infection												
Negative	107 (73.6)	38 (26.4)	24 (85.7)	0.186	121 (84.0)	23 (16.0)	26 (92.9)	2 (7.1)	0.41 (0.09–1.82)	0.239		
Positive	40 (73.2)	15 (26.8)	31 (18.0)	0.140	47 (83.9)	9 (16.1)	157 (91.3)	15 (8.7)	0.50 (0.21–1.21)	0.125		

Figures in parentheses are percentages or 95% CIs. Figures in italics indicate significant difference. ¹ Adjusted for age at reference.

Figures in parentheses are percentages or 95% CIs. Figures in italics indicate significant difference. ¹ Adjusted for age at reference.

We found that the risk associated with *XPG* Asp1104Asp (GG) and *XPB* Asn312Asn (AA) genotypes was decreased for cervical carcinoma patients with squamous cell carcinomas but not adenocarcinomas, suggesting that different histopathological types may have different biological mechanisms and etiologies. Moreover, cofactors associated with the development of squamous cell carcinomas and adenocarcinomas are distinct, not only in relation to environmental risk factors but also in genetic susceptibility [27, 28].

Cervical carcinoma is known to develop from precursor CIN lesions through a multistep process [29]. However, we did not observe a similar association between the 2 SNPs and the risk for CIN. It implied that the gene was associated with the period of carcinogenesis from CIN to carcinoma.

In summary, our findings offer evidence of the association between polymorphisms [*XPG* Asp1104Asp (GG)

and *XPB* Asn312Asn (AA)] and decreased risk for cervical carcinoma or cervical squamous cell carcinoma. In addition, the effect of genotypes was less evident in those women with multiple partners, early age of sexual activity and early age of first parity. Our results support the hypothesis that genetic variations in DNA repair genes may contribute to an inherited genetic susceptibility to cervical carcinoma.

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