Polymorphisms in endoplasmic reticulum aminopeptidase genes are associated with cervical cancer risk in a Chinese Han population

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Abstract

**Background:** antigen-processing machinery molecules play crucial roles in infectious diseases and cancers. Studies have shown that variants in endoplasmic reticulum aminopeptidase (ERAP) genes can influence the enzymatic activity of ERAP proteins and are associated with the risk of cancers. In the current study, we evaluated the influence of ERAP gene (**ERAP1** and **ERAP2**) variants on susceptibility to cervical intraepithelial neoplasia (CIN) and cervical cancer.

**Methods:** Six single nucleotide polymorphisms (SNPs) in **ERAP1** and 5 SNPs in **ERAP2** were selected and genotyped in 556 CIN patients, 1072 cervical cancer patients, and 1262 healthy control individuals. Candidate SNPs were genotyped using SNaPshot assay. And the association of these SNPs with CIN and cervical cancer was analysed.

**Results:** the results showed that allelic and genotypic frequencies of rs26653 in **ERAP1** were significantly different between cervical cancer and control groups ($P=0.001$ and 0.004). The allelic frequencies of rs27044 in **ERAP1** and rs2287988 in **ERAP2** were also significantly different between control and cervical cancer groups ($P=0.003$ and 0.004). Inheritance model analysis showed that genotypes at rs26618, rs26653, rs27044, and rs2287988 SNPs may be associated with the risk of cervical cancer ($P=0.004$, 0.001, 0.003, and 0.002). Additionally, haplotype analysis results showed that the **ERAP1** haplotype, rs26618T-rs26653G-rs27044C-rs30187T-rs3734016C, was associated with a lower risk of cervical cancer ($P=0.001$; OR=0.804, 95%CI:0.711-0.910). The **ERAP2** haplotypes rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T might be the risk factor of cervical cancer ($P=0.009$; OR=1.592, 95%CI:1.122-2.258). Haplotype rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T of **ERAP2** might be associated with lower risk of cervical cancer ($P=0.003$; OR=0.835,95%CI:0.740-0.942).

**Conclusion:** Our results indicated that rs26653 and rs27044 in **ERAP1** and rs2287988 in
ERAP2 influenced susceptibility to cervical cancer.

Background

The antigen-processing machinery (APM) is composed of the proteasome, where exogenous and tumour antigens are degraded into peptides; transporters associated with antigen presentation (TAPs), which are responsible for the translocation of peptide precursors; endoplasmic reticulum aminopeptidases (ERAPs), which trim the peptides to fit major histocompatibility complex (MHC) molecules; and MHC proteins, which present antigen peptides on the cell surface (1, 2). Human ERAPs, which belong to the oxytocinase subfamily of M1 metalloproteases, are crucial molecules of the APM. In the endoplasmic reticulum lumen, ERAP1 and ERAP2 trim peptides into their final length to render them suitable for loading onto HLA class I molecules (3, 4). Recently, several studies have shown that ERAP proteins play crucial roles in autoimmune diseases (5, 6), infectious diseases (7, 8), and cancers (9, 10).

Cervical cancer is the fourth most common malignancy in women globally (11). Persistent human papillomavirus (HPV) infection confers a high risk of the initiation and development of cervical cancer (12, 13). Since the HLA class I antigen-presenting system is responsible for the presentation of foreign and cancerous antigens to the immune system, it plays a crucial role in the immune recognition and clearance of HPV and cancerous cells (14). Therefore, ERAP proteins, which are involved in the processing of viral and cancerous protein antigens, are important for the specific immune response to HPV-infected cells and cancerous cells during the initiation and development of cervical cancer.

Studies have shown that polymorphisms in ERAP genes affect the enzymatic activity and selectivity of ERAP proteins (15-20). Moreover, when located at essential structural positions, these polymorphisms affect the conformation of ERAP proteins (19, 21, 22). This may explain the association between SNPs in ERAP genes and autoimmune and infectious
diseases (23-26). Similarly, in human cancers, our previous study and other studies have reported associations between polymorphisms in ERAP genes and human cancers (27-30). In the current study, we selected 11 SNPs located in ERAP1 (rs26618, rs26653, rs27044, rs30187, rs3734016 and rs27037) and ERAP2 (rs2248374, rs2549782, 2287988, rs2548538 and rs1056893) and investigated their distribution in patients with cervical intraepithelial neoplasia (CIN) and cervical cancer and healthy individuals, to assess their association with the initiation and development of cervical cancer.

Methods

Study population

In the current study, a total of 556 patients with CIN and 1072 patients with cervical cancer were enrolled at the third Affiliated Hospital of Kunming Medical University from May 2014 to August 2018. The inclusion criteria were as follows: 1) diagnosis of CIN or cervical cancer according to Current Diagnosis and Treatment: Obstetrics and Gynaecology and International Federation of Gynaecology and Obstetrics (2009) guidelines; 2) no other malignancy in patients and no history of cancer or other chronic diseases in control individuals; and 3) no preoperative neoadjuvant therapies (including chemotherapy and radiotherapy). The exclusion criteria for patients were as follows: 1) a prior history of primary cancer other than cervical cancer; 2) malignant tumours other than cervical cancer; 3) currently receiving radiotherapy or chemotherapy; and 4) an unclear diagnosis. Over the same period, 1262 healthy women from a health screening project at the same hospital were enrolled as controls.

SNP selection and genotyping

Six SNPs located in ERAP1 and 5 SNPs located in ERAP2 were selected in the current study. The details of the selected SNPs are displayed in Supplementary Table 1. Venous blood samples were collected for the extraction of genomic DNA, using the QIAamp Blood Mini
Kit (Qiagen NV, Venlo, Netherlands). Genotyping of the 11 SNPs was performed using the SNaPshot SNP assay (Thermo Fisher Scientific, Waltham, MA, USA), and results were analysed using GeneMapper TM 4.0 software (Applied Biosystems, Foster City, CA, USA). For quality control, 5% of samples from the case and control groups were genotyped twice with unique analysis serial numbers and the reproducibility was found to be 100%.

**Statistical analysis**

Hardy-Weinberg equilibrium (HWE) was evaluated to determine the representativeness of the study population. The differences in age among the CIN, cervical cancer, and control groups were analysed using a one-way ANOVA, with a least significant difference test for multiple comparison correction. Allelic and genotypic frequencies of these SNPs were compared between different groups using a Chi-square test and odds ratios (ORs) with associated 95% confidence intervals (CIs) were calculated. Additionally, linkage disequilibrium (LD) was calculated and a D' value greater than 0.80 was considered to indicate LD. The haplotypes among these SNPs were analysed using SHEsis software (31, 32). Subsequently, the distribution of the haplotypes between different groups was compared using a Chi-square test. Additionally, inheritance analysis was performed using SNPstats software, to identify the relationship between genotypes at these SNPs and cervical cancer (33). In the inheritance analysis, four inheritance models (codominant, dominant, recessive, and log-additive) were analysed. Simultaneously, Akaike information criterion (AIC) and Bayesian information criterion (BIC) values were calculated to determine the inheritance model with the best fit, i.e. the model with the smallest AIC and BIC values (33). Bonferroni correction was performed for multiple comparisons, after which the statistical significance threshold was set at $P < 0.005$ ($0.05/11$).

**Results**

Characteristics of the subjects
Table 1 shows the clinical data of the subjects in the present study. There was no significant difference in age among the control, CIN, and cervical cancer groups (P > 0.05, F = 1.438), as evaluated by one-way ANOVA. In the CIN group, there were 65 patients with low-grade CIN (I/II) and 491 patients with high-grade CIN (III). In the cervical cancer group, there were 151 patients with adenocarcinoma, 903 patients with squamous cell carcinoma, and 18 patients with other pathological types.

Association of the eleven SNPs with CIN and cervical cancer

All 11 SNPs were in HWE in the control group (P > 0.05). The allelic and genotypic frequencies of these SNPs are presented in Tables 2 and 3. The results showed that the allelic and genotypic frequencies of rs26618 (P = 0.021 and 0.016, respectively), rs26653 (P = 0.001 and 0.004), rs27044 (P = 0.003 and 0.012) and rs30187 (P = 0.008 and 0.020) in ERAP1 and rs2248374 (P = 0.014 and 0.020) and rs2287988 (P = 0.004 and 0.007) in ERAP2 were significantly different between cervical cancer and control groups. Additionally, the allelic and genotypic distributions of rs2248374 (P = 0.015 and 0.041, respectively) and rs2287988 (P = 0.014 and 0.039) in ERAP2 were significantly different between CIN and cervical cancer groups. However, after Bonferroni correction, only rs26653, rs27044, and rs2287988 were associated with cervical cancer risk (P < 0.005). The results indicated that, in ERAP1, the G allele of rs26653 may be associated with a lower risk of cervical cancer compared with C allele (OR = 0.829; 95% CI: 0.738-0.930) and the G allele of rs27044 may be a risk factor for the development of cervical cancer (OR = 1.193, 95% CI: 1.062-1.340). Moreover, the A allele of rs2287988 in ERAP2 may be associated with a lower risk of cervical cancer (OR = 0.843, 95% CI: 0.751-0.946). There were no SNPs in ERAP1 or ERAP2 that exhibited a significantly different distribution between the CIN and control groups or between the CIN and cervical cancer groups (P > 0.005).
Inheritance model analysis

To evaluate the genotypic association of the 11 SNPs with CIN and cervical cancer, inheritance analysis was performed among cervical cancer, CIN, and control groups (Table 4, Table 5, and Supplementary Tables 2-5). The CC genotype of rs26618 was a risk factor for cervical cancer, compared with TT-CT genotype (P = 0.004; OR = 1.53, 95%CI: 1.14-2.05) in the recessive model (the best-fit inheritance model for the comparison between control and cervical cancer groups). The 2GG+CG genotype of rs26653 was associated with a lower risk of cervical cancer compared with the CC genotype (P = 0.001, OR = 0.82; 95% CI: 0.73-0.93) in the log-additive model (the best-fit inheritance model for the comparison between control and cervical cancer groups). The 2CC+CG genotype of rs27044 may be a protective factor against the development of cervical cancer compared with the GG genotype (P = 0.003, OR = 0.84; 95% CI: 0.75-0.94) in the log-additive model (the best-fit inheritance model for the comparison between control and cervical cancer groups) and the GG+GA genotype of rs2287988 may be a risk factor for cervical cancer compared with the AA genotype (P = 0.002, OR = 1.33; 95% CI: 1.11-1.60) in the dominant model (the best fit inheritance model for the comparison between control and cervical cancer groups).

LD and haplotype analysis of SNPs in ERAP1 and ERAP2

The results of LD analysis showed that rs26618, rs26653, rs27044, rs30187, and rs3734016 in ERAP1 and rs2248374, rs2549782, rs2287988, rs2548538, and rs1056893 in ERAP2 were in LD (D' > 0.80). Subsequently, we constructed the haplotypes, rs26618-rs26653-rs27044-rs30187-rs3734016 and rs2248374-rs2549782-rs2287988-rs2548538-rs1056893. The distribution of these haplotypes (with a frequency of more than 3%) was compared in a pairwise manner among the cervical cancer, CIN, and control groups (Tables 6 and 7). The ERAP1 haplotype, rs26618T-rs26653G-rs27044C-rs30187T-
rs3734016C, was associated with a lower risk of cervical cancer (P = 0.001; OR = 0.804, 95% CI: 0.711-0.910). The distribution of haplotypes rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T and rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T in ERAP2 were significantly different in the control (P = 0.009 and 0.003, respectively) and CIN (P = 0.006 and 0.009) groups compared with the cervical cancer group. The results indicated that rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T may be associated with a higher risk of cervical cancer (OR = 1.592, 95% CI: 1.122-2.258) and the progression from CIN to cervical cancer (OR = 2.000, 95% CI: 1.215-3.292). Moreover, rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T may be associated with a lower risk of cervical cancer (OR = 0.835, 95% CI: 0.740-0.942) and the progression from CIN to cervical cancer (OR = 0.817, 95% CI: 0.702-0.951).

Discussion

The immune system is activated by MHC-peptide complexes, after which it eliminates infected and cancerous cells in various ways. The APM plays crucial roles in the initiation and development of various human diseases. As components of the APM, ERAP1 and ERAP2 are important determinants of the repertoire of peptides ultimately presented by HLA class I molecules (34-37). Our previous study showed that four polymorphisms in ERAP1 are associated with non-small cell lung cancer in a Chinese population (27). In the current study, we selected six SNPs in ERAP1 and five SNPs in ERAP2, and investigated their distribution in CIN patients, cervical cancer patients, and healthy individuals. Our results showed that rs26618, rs26653, and rs27044 in ERAP1 and rs2287988 in ERAP2 may be associated with cervical cancer risk.

The SNP, rs26618, in ERAP1 leads to an amino acid substitution (I276M) and the current study showed that the CC genotype of this SNP may be associated with an increased risk
of cervical cancer (OR = 1.53; 95% CI: 1.14-2.05) compared with TT-CT genotypes. In 2016, Guasp et al. reported that I276M (rs26618) may affect the peptidome of ERAP1 by destroying peptides with p2 Ala, unless the p1 amino acid was resistant to ERAP1 trimming (38), which indicated that rs26618 may be associated with cervical cancer. However, in a Netherlands population, Mehta et al. reported no association between rs26618 and cervical carcinoma. This inconsistency may be due to the different sample sizes used. The sample size used by Mehta et al. was 251, while 2890 individuals were enrolled in the current study.

In 2007, Mehta et al. reported that the C allele of rs26653 in ERAP1 was associated with a higher cervical cancer risk in a Netherlands population (28). In the current study, the G allele (OR = 0.829; 95% CI: 0.738-0.930), compared to the C allele, and the 2GG+CG genotype, compared to the CC genotype (OR = 0.82; 95% CI: 0.73-0.93) of rs26653, were associated with lower cervical cancer risk. In 2014, Stratikos et al. and Alvarez-Navarro et al. reported that rs26653, which is a non-synonymous variant resulting in a P127R substitution, may be associated with ERAP expression (39, 40), and this substitution may also affect the enzymatic activity of ERAP1 in the editing of tumour antigen peptides. This finding may explain the association between rs26653 and cervical cancer risk; however, the mechanisms need to be determined in functional studies.

In 2007, Mehta et al. also found that rs27044 in ERAP1 was associated with cervical cancer risk. In the current study, rs27044 was found to be associated with cervical cancer risk ($P = 0.003$). The G allele of rs27044 (Q730) was found to be a risk factor for the progression from CIN to cervical cancer (OR = 1.193, 95% CI: 1.062-1.340), which was consistent with the results of Mehta’s study (28). The SNP, rs27044, another non-synonymous variant, leads to a Q730E substitution in the IV catalysis domain of ERAP1 (21) and may change the substrate length preferences of ERAP1 (40). Thus, rs27044 may play a role in cervical
cancer by affecting ERAP1 function.

In the current study, we found an association between rs2287988 in *ERAP2*, which is responsible for a synonymous variant (Q563Q), and cervical cancer. The A allele may be associated with a lower risk of cervical cancer \((P = 0.004; \text{OR} = 0.843, 95\% \text{ CI}: 0.751-0.946)\). Moreover, the GG-GA genotype was associated with an increased risk of cervical cancer \((P = 0.002; \text{OR} = 1.33, 95\% \text{ CI}: 1.11-1.60)\). However, association studies of this SNP are rare. Previous studies have found that ERAP2 haplotypes containing rs2287988 affect ERAP2 splicing and expression \((41, 42)\). Thus, additional association studies in different populations are necessary to investigate the role of this variant during the initiation and development of cervical cancer.

ERAPs are markedly polymorphic and *ERAP* haplotypes whose protein products differ at multiple amino acids may affect peptide editing by ERAPs \((17, 18, 43, 44)\). In the current study, we also analysed haplotypes of *ERAP* SNPs in LD. The results showed that the *ERAP1* haplotype, rs26618T-rs26653G-rs27044C-rs30187T-rs3734016C and the *ERAP2* haplotypes, rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T and rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T may be associated with cervical cancer risk. These results indicated that SNPs in polymorphic genes may have combinatorial effects on disease susceptibility.

**Conclusion**

Recent studies have shown that variants in human genes may affect gene expression \((45-47)\). In addition, SNPs in ERAP genes have been shown to affect the function of ERAPs by changing their peptidome or enzymatic activity \((17, 18, 38)\). In cervical cancer, ERAP1 and ERAP2 proteins have been reported to be highly variable, ranging from low to high expression levels \((48-50)\). Although there are inconsistencies among these studies, it is clear that the dysregulated expression of ERAP proteins, which may be induced by *ERAP*
gene SNPs (47, 51), is associated with cervical cancer risk. In the current study, we investigated the association of SNPs in ERAP genes (11 SNPs located in ERAP1 and ERAP2) with CIN (the initiation of cervical cancer) and cervical cancer (the development of cervical cancer). Our results showed that genetic variants in ERAP1 and ERAP2 may be associated with CIN and cervical cancer. Moreover, our results showed that variants in key antigen-processing genes affect the initiation and development of cervical cancer, a virus- and inflammation-induced cancer.

**Abbreviations**

Endoplasmic reticulum aminopeptidase: ERAP; Single nucleotide polymorphisms: SNPs; Antigen-processing machinery: APM; Transporters associated with antigen presentation: TAPs; Major histocompatibility complex: MHC; Human papillomavirus: HPV; Hardy-Weinberg equilibrium: HWE; Odds ratios: ORs; Cervical intraepithelial neoplasia: CIN; confidence intervals: CIs; Linkage disequilibrium: LD; Akaike information criterion: AIC; Bayesian information criterion: BIC.

**Declarations**

**Ethics approval and consent to participate**

The current study was approved by the Institutional Review Boards of the No. 3 Affiliated Hospitals of Kunming Medical University and was performed in accordance with the principles of the Declaration of Helsinki. All individuals enrolled in this study provided written informed consent.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data generated during the current study are available to any scientist wishing to use
them for non-commercial purpose from the corresponding author on reasonable request. However, the clinical data are not available, because we did not obtain the permission from participants to release these privacy data.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

LS and YFY designed the current study; CYL and YHL finished the main part of experiment and data analysis of the current study; ZLY and SYD finished the sample clinical diagnose and collection; XW and JW were responsible for the collection of venous blood; SYL and XWZ participated in the genomic DNA extraction; CYL and YHL drafted the manuscript; LS and YFY revised the manuscript. And all authors have read and approved the manuscript.

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Tables

Table 1. Characteristics of the subjects enrolled in the current study.

| Characteristic                | Cervical cancer | CIN    | Control | F      | P v |
|------------------------------|-----------------|--------|---------|--------|-----|
| N                            | 1072            | 556    | 1262    |        |
| Age                          | 47.81±10.21     | 47.42±9.37 | 48.28±9.60 | 1.438 | 0.238 |
| Pathological types           |                 |        |         |        |
| SCC                          | 903             |        |         |        |
| AC                           | 151             |        |         |        |
| Others                       | 18              |        |         |        |
| Stages of CIN                |                 |        |         |        |
| Low degrade of CIN (I/II)    | 65              |        |         |        |
| High Degrade of CIN (III)    | 491             |        |         |        |

Table 2. The allelic and genotypic distribution among control, CIN and cervical cancer groups of SNPs in ERAP1 gene

| SNPs     | Control | CIN  | Cervical cancer | Control vs Cervical cancer |
|----------|---------|------|-----------------|----------------------------|
|          | P-value | OR[95%CI] | P-val |
| rs26618  |         |        |                 |
| C        | 672(0.266) | 327(0.294) | 636(0.297) | 0.021 | 1.162[1.023-1.321] | 0.08 |
| T        | 1852(0.734) | 785(0.706) | 1508(0.703) | 0.016 | 0.07 |
| C/C      | 88(0.070) | 56(0.101) | 110(0.103) | 0.016 | 0.68 |
| C/T      | 496(0.393) | 215(0.387) | 416(0.388) | 0.016 | 0.68 |
| T/T      | 678(0.537) | 285(0.513) | 546(0.509) | 0.016 | 0.68 |
| rs26653  |         |        |                 |                            |
|   | rs27044   | rs30187   | rs3734016 | rs27037   |
|----|-----------|-----------|-----------|-----------|
|   | G         | C         | C         | G         |
|   | 1297(0.514) | 1350(0.535) | 2159(0.855) | 1372(0.544) |
|   | 538(0.484)  | 611(0.549)  | 947(0.852)  | 592(0.532)  |
|   | 1001(0.467) | 1240(0.578) | 1801(0.840) | 1092(0.509) |
|   | 0.001      | 0.003      | 0.145      | 0.020      |
|   | 0.829[0.738-0.930] | 1.193[1.062-1.340] | 0.888[0.756-1.041] | 0.872[0.777-0.978] |
|   | C         | T         | T         | T         |
|   | 1227(0.486) | 1174(0.465) | 365(0.145)  | 1152(0.456) |
|   | 574(0.516)  | 501(0.451)  | 165(0.148)  | 520(0.468)  |
|   | 1143(0.533) | 904(0.422)  | 343(0.160)  | 1052(0.491) |
|   | 0.004      | 0.012      | 0.318      | 0.020      |
|   | 0.2;       | 0.4;       | 0.8;       | 0.3;       |
| G/G | 316(0.250) | 362(0.287) | 921(0.730) | 359(0.284) |
|     | 124(0.223) | 175(0.315) | 404(0.727) | 161(0.290) |
|     | 228(0.213) | 360(0.336) | 752(0.701) | 283(0.264) |
|     | 0.001      | 0.012      | 0.318      | 0.020      |
|     | 0.2;       | 0.4;       | 0.8;       | 0.3;       |
| G/C | 665(0.527) | 626(0.496) | 631(0.500) | 654(0.518) |
|     | 290(0.522) | 261(0.469) | 251(0.451) | 270(0.486) |
|     | 545(0.508) | 520(0.485) | 509(0.475) | 526(0.491) |
|     | 0.004      | 0.012      | 0.318      | 0.020      |
|     | 0.2;       | 0.4;       | 0.8;       | 0.3;       |
| C/C | 281(0.223) | 274(0.217) | 317(0.251) | 249(0.197) |
|     | 142(0.255) | 120(0.216) | 139(0.250) | 125(0.225) |
|     | 299(0.223) | 192(0.179) | 297(0.277) | 263(0.245) |
|     | 0.004      | 0.012      | 0.318      | 0.020      |
|     | 0.2;       | 0.4;       | 0.8;       | 0.3;       |

Note: The statistical significant threshold was set at P<0.005 after Bonferroni correction.

Table 3. The allelic and genotypic distribution among control, CIN and cervical
cancer groups of SNPs in ERAP2 gene

| SNPs   | Control | CIN | Cervical cancer | Control vs Cervical cancer | Control vs CIN | CIN vs Cervical cancer |
|--------|---------|-----|-----------------|---------------------------|---------------|-----------------------|
|        | P Value | OR[95% CI] | P Value | OR[95% CI] | P Value | OR[95% CI] |
| rs22483 |         |             |         |             |         |             |
| 74     |         |             |         |             |         |             |
| A      | 1128(0.447) | 487(0.4) | 1035(0.4) | 232(0.21) | 0.014 | 1.155[1.029-1.296] |
| G      | 1396(0.553) | 625(0.562) | 1109(0.5) | 269(0.25) | 0.041 | 1.041[0.877-1.253] |
| A/A    | 248(0.197)  | 100(0.180) | 232(0.21) | 0.200 | 0.690 | 1.093[0.877-1.349] |
| A/G    | 632(0.501)  | 287(0.516) | 571(0.53) | 0.009 | 0.906 | 1.006[0.857-1.166] |
| G/G    | 382(0.303)  | 169(0.304) | 269(0.25) | 0.041 | 0.833[0.720-0.964] |
| rs25497 |         |             |         |             |         |             |
| 82     |         |             |         |             |         |             |
| G      | 1106(0.438) | 484(0.435) | 998(0.46) | 217(0.20) | 0.089 | 0.906[0.877-1.037] |
| T      | 1418(0.562) | 628(0.565) | 1146(0.5) | 291(0.27) | 0.214 | 1.214[1.037-1.41] |
| G/G    | 239(0.189)  | 101(0.182) | 217(0.20) | 0.009 | 0.906 | 1.006[0.857-1.166] |
| G/T    | 628(0.498)  | 282(0.507) | 564(0.52) | 0.041 | 0.833[0.720-0.964] |
| T/T    | 395(0.313)  | 173(0.311) | 291(0.27) | 0.214 | 1.214[1.037-1.41] |
| rs22879 |         |             |         |             |         |             |
| 88     |         |             |         |             |         |             |
| A      | 1407(0.557) | 623(0.560) | 1104(0.5) | 267(0.24) | 0.007 | 0.743[0.649-0.853] |
| G      | 1117(0.443) | 489(0.440) | 1040(0.4) | 0.009 | 0.906 | 1.006[0.857-1.166] |
| A/A    | 387(0.307)  | 167(0.300) | 267(0.24) | 0.007 | 0.743 | 1.014[0.877-1.166] |
| A/G    | 633(0.502)  | 289(0.520) | 570(0.53) | 0.041 | 0.833[0.720-0.964] |
| G/G    | 242(0.192)  | 100(0.180) | 235(0.21) | 0.214 | 1.214[1.037-1.41] |
| rs25485 |         |             |         |             |         |             |
| 38     |         |             |         |             |         |             |
| A      | 1063(0.421) | 474(0.426) | 959(0.44) | 224(0.20) | 0.019 | 0.948[0.877-1.024] |
| T      | 1461(0.579) | 638(0.574) | 1185(0.5) | 511(0.47) | 0.524 | 1.524[1.349-1.698] |
| A/A    | 240(0.190)  | 107(0.192) | 224(0.20) | 0.019 | 0.948 | 1.093[0.877-1.349] |
| A/T    | 583(0.462)  | 260(0.468) | 511(0.47) | 0.524 | 1.524[1.349-1.698] |
| SNPs | Models       | Genotypes | Control   | Cervical cancer |
|------|--------------|-----------|-----------|-----------------|
|      |              | T/T       | 677 (53.7%) | 546 (50.9%) |
|      |              | C/T       | 496 (39.3%) | 416 (38.8%) |
|      |              | C/C       | 88 (7%)    | 110 (10.3%) |
|      | Dominant     | T/T       | 677 (53.7%) | 546 (50.9%) |
|      |              | C/T-C/C   | 584 (46.3%) | 526 (49.1%) |
|      | Recessive    | T/T-C/T   | 1173 (93%)  | 962 (89.7%) |
|      |              | C/C       | 88 (7%)    | 110 (10.3%) |
|      | Overdominant | T/T-C/C   | 765 (60.7%) | 656 (61.2%) |
|      |              | C/T       | 496 (39.3%) | 416 (38.8%) |

Note: The statistical significant threshold was set at *P*<0.005 after Bonferroni correction.

**Table 4. Inheritance model analysis of SNPs in ERAP1 gene between control and cervical cancer groups**
|(rs26653) | Condominant | Dominant | Recessive | Overdominant |
|-----------|-------------|----------|-----------|--------------|
| Log-additive | --- | --- | --- | --- |
| G/G | 281 (22.3%) | 281 (22.3%) | 946 (75%) | 596 (47.3%) |
| C/G | 665 (52.7%) | 780 (60.3%) | 946 (75%) | 980 (77.7%) |
| C/C | 315 (25%) | 315 (25%) | 315 (25%) | 315 (25%) |
| C/G - C/C | 980 (77.7%) | 980 (77.7%) | 980 (77.7%) | 980 (77.7%) |
| C/C | 315 (25%) | 315 (25%) | 315 (25%) | 315 (25%) |

| Log-additive | --- | --- | --- | --- |
| G/G | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) |
| C/G | 625 (49.6%) | 625 (49.6%) | 625 (49.6%) | 625 (49.6%) |
| G/G | 274 (21.7%) | 274 (21.7%) | 274 (21.7%) | 274 (21.7%) |
| C/G - G/G | 899 (71.3%) | 899 (71.3%) | 899 (71.3%) | 899 (71.3%) |
| C/C | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) |
| C/G - C/C | 980 (77.7%) | 980 (77.7%) | 980 (77.7%) | 980 (77.7%) |
| C/C | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) |

| Log-additive | --- | --- | --- | --- |
| C/C | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) |
| C/T | 631 (50%) | 631 (50%) | 631 (50%) | 631 (50%) |
| T/T | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) |
| C/C - T/T | 918 (72.8%) | 918 (72.8%) | 918 (72.8%) | 918 (72.8%) |
| C/C - C/T | 974 (77.2%) | 974 (77.2%) | 974 (77.2%) | 974 (77.2%) |
| C/T - T/T | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) |

| Log-additive | --- | --- | --- | --- |
| C/C | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) | 362 (28.7%) |
| C/T | 631 (50%) | 631 (50%) | 631 (50%) | 631 (50%) |
| T/T | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) |
| C/C - T/T | 918 (72.8%) | 918 (72.8%) | 918 (72.8%) | 918 (72.8%) |
| C/C - C/T | 974 (77.2%) | 974 (77.2%) | 974 (77.2%) | 974 (77.2%) |
| C/T - T/T | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) | 287 (22.8%) |
### Table 5. Inheritance model analysis of SNPs in ERAP2 gene between control and cervical cancer groups

| SNPs  | Models          | Genotypes | Control | Cervical cancer |
|-------|-----------------|-----------|---------|-----------------|
| rs2248374 | Condominant     | G/G       | 382 (30.3%) | 269 (25.1%) |
|        |                 | A/G       | 631 (50%)   | 571 (53.3%) |
|        |                 | A/A       | 248 (19.7%) | 232 (21.6%) |
|        | Dominant        | G/G       | 382 (30.3%) | 269 (25.1%) |
|        |                 | A/G-A/A   | 879 (69.7%) | 803 (74.9%) |
|        | Recessive       | G/G-A/G   | 1013 (80.3%)| 840 (78.4%) |
|        |                 | A/A       | 248 (19.7%) | 232 (21.6%) |

**Note:** The statistical significant threshold was set at \( P < 0.005 \) after Bonferroni correction.
| rs2549782 | Overdominant            | G/G-A/A   | 630 (50%) | 501 (46.7%) |
|-----------|-------------------------|-----------|-----------|-------------|
|           | A/G                     | 631 (50%) | 571 (53.3%) |
| Log-additive | ---                    | ---       | ---       | ---         |
| Condominant | T/T               | 395 (31.3%) | 291 (27.1%) |
|           | G/T                     | 627 (49.7%) | 564 (52.6%) |
|           | G/G                     | 239 (18.9%) | 217 (20.2%) |
| Dominant  | T/T                     | 395 (31.3%) | 291 (27.1%) |
|           | G/T-G/G                 | 866 (68.7%) | 781 (72.8%) |
| Recessive | T/T-G/T                 | 1022 (81%) | 855 (79.8%) |
|           | G/G                     | 239 (18.9%) | 217 (20.2%) |
| Overdominant | T/T-G/G             | 634 (50.3%) | 508 (47.4%) |
|           | G/T                     | 627 (49.7%) | 564 (52.6%) |
| Log-additive | ---                    | ---       | ---       | ---         |
| rs2287988 | Condominant            | A/A       | 387 (30.7%) | 267 (24.9%) |
|           | A/G                     | 632 (50.1%) | 570 (53.2%) |
|           | G/G                     | 242 (19.2%) | 235 (21.9%) |
| Dominant  | A/A                     | 387 (30.7%) | 267 (24.9%) |
|           | A/G-G/G                 | 874 (69.3%) | 805 (75.1%) |
| Recessive | A/A-A/G                 | 1019 (80.8%) | 837 (78.1%) |
|           | G/G                     | 242 (19.2%) | 235 (21.9%) |
| Overdominant | A/A-G/G              | 629 (49.9%) | 502 (46.8%) |
|           | A/G                     | 632 (50.1%) | 570 (53.2%) |
| Log-additive | ---                    | ---       | ---       | ---         |
| rs2548538 | Condominant            | T/T       | 439 (34.8%) | 337 (31.4%) |
|           | A/T                     | 582 (46.1%) | 511 (47.7%) |
|           | A/A                     | 240 (19%)  | 224 (20.9%) |
| Dominant  | T/T                     | 439 (34.8%) | 337 (31.4%) |
|           | A/T-A/A                 | 822 (65.2%) | 735 (68.6%) |
| Recessive | T/T-A/T                 | 1021 (81%) | 848 (79.1%) |
|           | A/A                     | 240 (19%)  | 224 (20.9%) |
| Overdominant | T/T-A/A              | 679 (53.9%) | 561 (52.3%) |
|           | A/T                     | 582 (46.1%) | 511 (47.7%) |
| Log-additive | ---                    | ---       | ---       | ---         |
| rs1056983 | Condominant            | T/T       | 439 (34.8%) | 360 (33.6%) |
|           | C/T                     | 583 (46.2%) | 505 (47.1%) |
|           | C/C                     | 239 (18.9%) | 207 (19.3%) |
| Dominant  | T/T                     | 439 (34.8%) | 360 (33.6%) |
C/T-C/C 822 (65.2%) 712 (66.4%)
Recessive  T/T-C/T 1022 (81%) 865 (80.7%)
Overdominant  C/C 239 (18.9%) 207 (19.3%)
T/T-C/C 678 (53.8%) 567 (52.9%)
Log-additive  C/T 583 (46.2%) 505 (47.1%)

Note: The statistical significant threshold was set at P<0.005 after Bonferroni correction.

Table 6. The distribution of the haplotypes constructed by SNPs in ERAP1 gene

| Haplotypes       | Control | CIN     | Cervical cancer | Control vs Cervical cancer |
|------------------|---------|---------|-----------------|-----------------------------|
|                  |         |         | P-value         | OR[95%CI]                |
| C-C-G-C-C        | 646.12  | 299.22  | 556.04          | 0.041                      |
|                  | (0.256) | (0.269) | (0.259)         | 1.151 [1.006-1.316]       |
| T-G-G-T-C        | 76.43   | 37.05   | 64.76           | 0.612                      |
|                  | (0.030) | (0.033) | (0.030)         | 1.091 [0.779-1.528]       |
| T-G-C-T-C        | 1101.70 | 444.48  | 759.76          | 0.001                      |
|                  | (0.437) | (0.400) | (0.354)         | 0.804 [0.711-0.910]       |
| T-C-G-C-C        | 196.08  | 72.59   | 176.09          | 0.150                      |
|                  | (0.078) | (0.065) | (0.082)         | 1.169 [0.945-1.447]       |
| T-C-G-C-T        | 336.22  | 142.58  | 278.80          | 0.402                      |
|                  | (0.133) | (0.128) | (0.130)         | 1.076 [0.906-1.278]       |

Note: The statistical significant threshold was set at P<0.01 (0.05/n, n=0.05) after Bonferroni correction.

Table 7. The distribution of the haplotypes constructed by SNPs in ERAP2 gene

| Haplotypes       | Control | CIN     | Cervical cancer | Control vs cervical cancer |
|------------------|---------|---------|-----------------|-----------------------------|
|                  |         |         | P-value         | OR[95%CI]                |
| A-G-G-A-C        | 953.78  | 411.75  | 784.87          | 0.219                      |
|                  | (0.378) | (0.370) | (0.366)         | 1.080 [0.955-1.220]       |
| A-G-G-A-T        | 58.71   | 20.26   | 72.44           | 0.009                      |
|                  | (0.023) | (0.018) | (0.034)         | 1.592 [1.122-2.258]       |
| A-G-G-T-C        | 61.18   | 25.61   | 71.82           | 0.018                      |
|                  | (0.024) | (0.023) | (0.033)         | 1.513 [1.070-2.139]       |
| G-T-A-T-T        | 1346.11 | 586.29  | 973.03          | 0.003                      |
|                  | (0.533) | (0.527) | (0.454)         | 0.835 [0.740-0.942]       |

Note: The statistical significant threshold was set at P<0.01 (0.05/n, n=0.05) after Bonferroni correction.
Note: The statistical significant threshold was set at $P<0.013 \ (0.05/n, \ n=4)$ after Bonferroni correction.

Supplementary Files

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