Correlation between ER, PR, P53, Ki67 expression, and high-risk HPV infection in patients with different levels of cervical intraepithelial neoplasia

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Abstract
This study was designed to investigate the correlation between high-risk human papillomavirus (HPV) infection and the expression of IHC markers (ER, PR, p53, Ki67) in patients with different grades of cervical intraepithelial neoplasia (CIN). It was a retrospective study, which was conducted from June 2016 to June 2018. 140 specimens of CIN were collected from the pathology department of a certain hospital that included 40 specimens of CIN1, 50 specimens of CIN2 and 50 specimens of CIN3. The expression of ER, PR, P53 and Ki67 were determined by immunohistochemistry. The high-risk HPV infections were detected by PCR fluorescence quantification and were given the correlation analysis. In the 140 specimens, the positive rates of HPV16 and HPV18 in CIN1 specimens were 27.5% and 25.0% respectively, and in CIN2 specimens were 64.0% and 60.0% respectively, and in CIN3 specimens were 90.0% and 92.0% respectively, the difference were statistically significant (p<0.05). There were no significant correlation (p<0.05) between HPV16 and HPV18 positive rate and patient age, tissue differentiation, and tumor size. With the increased of CIN grade, the positive rate of ER, PR, P53 and Ki67 expression in specimen were also increased significantly, and the difference were statistically significant (p<0.05). Pearson correlation analysis showed there were positive correlation (p<0.05) between the positive rates of HPV16 and HPV18 and the positive rates of ER, PR, P53 and Ki67. With the increase of CIN level, the positive rates of high-risk HPV infection as well as ER, PR, P53 and Ki67 are increased, and they have positive correlation.

Keywords
Cervical intraepithelial neoplasia, correlation, HPV infection, Ki67, P53

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low- and medium-risk types and high-risk types. High-risk HPV includes HPV 16, 18, 31, and 33. It can participate in cervical squamous epithelial lesions and cervical cancer to varying degrees.\(^4,5\) Modern studies have shown that the development of cervical squamous epithelial lesions is a multi-step process that develops from normal to inflammatory and develops into tumors, accompanied by multiple genetic changes. In this process, it is associated with changes in various genes such as all oncogenes, tumor suppressor genes, and growth factor genes.\(^6,7\) Estrogen receptor (ER) and progesterone receptor (PR) are present on the surface of hormone target cells and are mainly distributed in targets such as uterus and cervix. It can specifically bind to corresponding hormones and play a role in regulating the occurrence and development of cervical squamous epithelial lesions.\(^8,9\) Ki-67 is a relatively positive sign of nuclear proliferation. It is also an important reference for predicting the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. Its expression can reflect the biological behavior of tumor cells.\(^10,11\)

An imbalance between HPV-induced cell proliferation and apoptosis may be not sufficient for the development of invasive cervical cancer, and several possible cofactors have been identified, including the steroid hormones estrogen and progesterone. Most cervical cancers arise in the transformation zone, an area known as the most estrogen- and progesterone-sensitive region of the cervix. Expression of ERs and PRs has been reported to be a favorable prognostic factor in breast cancer, endometrial carcinoma, ovarian cancer, and cervical adenocarcinoma.\(^12\)

The p53 gene is an important tumor suppressor gene located in human chromosome 17p13.1. Its encoding product p53 protein plays an important role in cell division and differentiation. The normal expression of p53 protein can induce apoptosis and cause cell cycle block. P53 protein mutations can lead to cell transformation and over-proliferation and tumor behavior.\(^12,13\) This article specifically discusses the expression of ER, PR, P53, Ki 67, and the correlation of HPV infection in patients with different levels of cervical squamous epithelial lesions. It is hoped to provide a reference for the study of the pathogenesis of cervical squamous epithelial lesions and to further clarify the relationship between ER, PR, P53, Ki 67 protein expression, and HPV infection.

**Materials and methods**

**Research object**

From June 2016 to June 2018, 140 CIN specimens preserved in the Department of Pathology of our hospital were selected. Minimum age was 26 years, maximum age was 78 years, average age was 47.49 ± 3.39 years, and the age of 90 cases was over 40 years. CIN grading (all sections were independently reviewed by three pathologists with intermediate and above titles, referring to pathological and genetic classification criteria of female reproductive system tumors): 40 cases in grade 1, 50 cases in grade 2, and 50 cases in grade 3; 20 cases in histological differentiation were poorly differentiated, 30 cases in moderate differentiation, and 90 cases in high differentiation.

**Inclusion criteria.** Inclusion criteria were as follows: complete clinical and pathological data; pathological diagnosis of cervical squamous intraepithelial lesions at different levels; all patients were not treated with radiotherapy, chemotherapy, or hormone therapy before operation, 20–80 years old.

**Exclusion criteria.** Exclusion criteria were as follows: past history of cervical cancer, immunodeficiency disorders, absence of clinical and pathological data.

**Immunohistochemical method**

Mouse anti-human p53 monoclonal antibody, mouse anti-human PR monoclonal antibody, mouse anti-human Ki67 monoclonal antibody, and mouse anti-human ER monoclonal antibody were purchased from Santa Cruz Biotechnology Company; immunohistochemical universal staining kit, phosphate-buffered saline (PBS) buffer, 3,3’-diaminobenzidine (DAB) staining kit were purchased from Beijing Zhongshan Biotechnology Co., Ltd. All tissue specimens were sectioned continuously in wax with a thickness of 2 μm. Xylene and ethanol were used for transparency and dehydration. The tissue sections were stained with hematoxylin for 15–30 s and sealed with neutral gum.

**Detection of high-risk HPV DNA**

The specimens were rinsed with sterile water and fixed with 95% ethanol for 15 min. The cervical secretions of the specimens were dissolved with lysate. Sterile ophthalmic shears were used to cut
the tissue to about 1 mm³ size, add 0.25% trypsin, and digest it in 37°C water bath. The tissue suspension was filtered by 200-mesh stainless-steel mesh and then transferred into the test tube. After 5 min of centrifugation, the supernatant was discarded. Cell precipitation was washed 2–3 times with Hanks solution to obtain single-cell suspension. Fully automatic nucleic acid extractor produced by Jiangsu Shuoshi Biotechnology Co., Ltd. was used to operate according to the scheduled scheme. Specific primers of HPV-16 and HPV-18 were designed and amplified according to NCBI BLAST sequence.

**Statistical method**

SPSS22.00 software was selected to analyze the measurement data and counting data of this study. The measurement data describing the normal distribution were expressed by mean ± standard deviation. The counting data were expressed by frequency. The comparison was t test, chi-square test, and variance analysis. Pearson correlation analysis was used for correlation analysis, and the test level was a = 0.05. Power calculation was made for sample size determination via using G*Power software.

**Results**

*Immunohistochemical results*

The results for immunohistochemical tissue specimen were observed under optical microscope. Positive control group was set up in each section; positive control group was cervical cancer tissue, and negative control group was PBS instead of primary antibody. Each slice was randomly observed in five high-power microscopic fields. ER and PR were positive for brown granules in the nucleus. Ki-67 was mainly positive in the nucleus. The positive signals of p53 staining were brown and yellow and were strictly located in the nucleus. The pathologists made immunohistochemical grading diagnosis of cervical squamous intraepithelial lesions according to the combined grading criteria. The negative staining intensity was 0, weak but stronger than negative control was 1, the clear staining was 2, and the strong staining was 3; the number of positive cells < 10% was 0, 10%–30% was 1, 31%–60% was 2, and > 60% was 3. The above two scores were added up: 0–1 was (−, negative), 2 was (+, weak positive), 3–4 was (+++, medium positive), 5–6 was (+++++, strong positive), and (+++++++) was positive.

*Results for high-risk HPV DNA*

The forward sequence of HPV-16 primers was 5′-GAATCCATGCTATGATAA-3′, the reverse sequence was 5′-GATETGCAACAAGACATACAT-3′; the forward sequence of HPV-18 primers was 5′-CACGGEAGCTAAGCTACC-3′, the reverse sequence was 5′-TGCAGEACGCAGCTAAGCTA CC-3′. The cycling conditions of polymerase chain reaction (PCR) fluorescence method were 95 for 5 min, 55 for 30 s, 72 for 1 min, 40 and 72 cycles for 1 min. The products of PCR digestion were sent to Shanghai Biotechnology Service Co., Ltd. for DNA sequencing and compared with NCBI gene sequence.

*Comparison of high-risk HPV positive rates*

In 140 samples, the positive rates of HPV16 and HPV18 were 27.5% and 25.0% in low-grade squamous intraepithelial lesion (LSIL), 64.0% and 60.0% in high-grade squamous intraepithelial lesion (HSILa), 90.0% and 92.0% in HSILb, respectively. The difference was statistically significant (P < 0.05). The data are shown in Table 1.

*The correlation between high-risk HPV positive rate and clinical characteristics*

The positive rates of HPV16 and HPV18 were not significantly correlated with age and tissue differentiation (P < 0.05). Results are summarized in Table 2.

*Comparison of positive rates of ER, PR, P53, and Ki67 expression*

The positive rates of ER, PR, P53, and Ki67 in specimens were also significantly increased with the increase in CIN grading (P < 0.05). Findings are presented in Table 3 and Figures 1–3.

*Correlation analysis*

Pearson correlation analysis showed that the positive rates of HPV16 and HPV18 were positively correlated with the positive rates of ER, PR, P53, and Ki67 (P < 0.05). Data are depicted in Table 4.

*Discussion*

Cervical squamous intraepithelial lesions are malignant tumors that seriously threaten women’s
health. The etiology of cervical squamous intraepithelial lesions has not been fully understood. Relevant studies have shown that the incidence of cervical squamous intraepithelial lesions is related to factors such as early marriage, sexual disorder, prolificacy, economic status, premature sexual life, economic status, and race. Persistent infection of high-risk HPV is also an important factor.14–16

HPV is a common pathogen of female genital tract infection. So far, more than 200 kinds of HPV have been found. Epidemiological investigation showed that HPV16 accounted for about 50% of cervical squamous cell carcinoma and HPV18 accounted for about 15%.17 The results showed that the positive rates of HPV16 and HPV18 were 27.5% and 25.0% in LSIL, 64.0% and 60.0% in HSILa, 90.0% and 92.0% in HSILb, respectively. The difference was statistically significant ($P < 0.05$). The positive rates of HPV16 and HPV18 were not significantly correlated with age and histological differentiation of patients ($P < 0.05$), leading role in change. Current studies have shown that overexpression of E6 and E7 proteins in HPV promotes the release of P53 and pRB proteins and immortalizes host cells, leading to cervical epithelial neoplasia and canceration.18

Although HPV is a necessary condition for the occurrence of cervical squamous intraepithelial lesions, HPV infection does not always lead to the occurrence of cervical squamous intraepithelial lesions. The majority of HPV-infected people are subclinical or latent viral infections. 19 HPV infection alone is not enough to cause cervical squamous intraepithelial lesions or cervical cancer. The development from HPV infection to cervical squamous intraepithelial lesions depends on the synergistic effect of other factors.20 Current studies have shown that the occurrence of cervical squamous

### Table 1. Comparison of high-risk HPV positive rates in cervical squamous intraepithelial lesions of different grades (n).

| Group      | Case (n) | HPV16 positive | Positive rate | HPV18 positive | Positive rate |
|------------|----------|----------------|---------------|----------------|---------------|
| LSIL       | 40       | 11             | 27.5%         | 10             | 25.0%         |
| HSILa      | 50       | 32             | 64.0%         | 30             | 60.0%         |
| HSILb      | 50       | 45             | 90.0%         | 46             | 92.0%         |
| F          |          |                | 37.224        | 42.169         |               |
| $P$ value  |          |                | 0.000         | 0.000          |               |
| Total      | 88       |                | 62.9%         | 86             | 61.4%         |

HPV: human papillomavirus; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

### Table 2. Correlation between high-risk HPV positive rate and clinical features of cervical squamous intraepithelial lesions (n = 140).

| Clinical features                           | Case (n) | HPV16 positive rate (n = 88) | $F$ or 2 | $P$ value | HPV18 positive rate (n = 86) | $F$ or 2 | $P$ value |
|---------------------------------------------|----------|-----------------------------|----------|-----------|-----------------------------|----------|-----------|
| Age- ⩾ 40                                   | 90       | 80 (88.9%)                  | 73.144   | 0.000     | 78 (86.7%)                  | 67.745   | 0.000     |
| Age- < 60                                   | 50       | 8 (16.0%)                   | 8 (16.0%)|           |                             |          |           |
| Histological differentiation                |          |                            |          |           |                             |          |           |
| Highly differentiated                        | 90       | 55 (61.1%)                  | 12.336   | 0.002     | 53 (58.9%)                  | 14.549   | 0.001     |
| Moderately differentiated                    | 30       | 14 (46.7%)                  |          |           | 15 (50.0%)                  |          |           |
| Poorly differentiated                        | 20       | 19 (95.0%)                  |          |           | 20 (100.0%)                 |          |           |

HPV: human papillomavirus.

### Table 3. Positive rates of ER, PR, P53, and Ki67 expression in cervical squamous intraepithelial lesions of different grades (n = 140).

| Group      | Case (n) | ER positive rate | PR positive rate | P53 positive rate | Ki67 positive rate |
|------------|----------|------------------|------------------|-------------------|-------------------|
| LSIL       | 40       | 16 (40.0%)       | 15 (37.5%)       | 17 (42.5%)        | 16 (40.0%)        |
| HSILa      | 50       | 35 (70.0%)       | 34 (68.0%)       | 37 (74.0%)        | 41 (82.0%)        |
| HSILb      | 50       | 48 (96.0%)       | 48 (96.0%)       | 50 (100.0%)       | 49 (98.0%)        |
| F          | 33.670   | 35.797           | 38.466           | 42.326            |                   |
| $P$ value  | 0.000    | 0.000            | 0.000            | 0.000             |                   |

ER: estrogen receptor; PR: progesterone receptor; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.
Figure 1. Expression of ER, PR, P53, and Ki67 in CIN1 sample.

Figure 2. Expression of ER, PR, P53, and Ki67 in CIN2 sample.
intraepithelial lesions is a complex process involving multiple stages and factors. It is also a disorder of the balance between cell proliferation, differentiation, and apoptosis. ER and PR are located in the nucleus and mainly exist in the tissue cells of female reproductive system. The binding of receptors and hormones can induce gene activation and regulate cell proliferation and apoptosis. Current studies have shown that estrogen can induce ER and PR production at the level of DNA replication and transcription during endometrial cell proliferation, while progesterone has antagonistic effect on estrogen, which can make dysplasia cells mature and downregulate at the level of transcription and post-transcription. Some studies have shown that ER and PR are most expressed in normal endometrium, but less expressed in cancer. ER and PR may participate in abnormal proliferation and inhibit normal cell apoptosis. P53 gene abnormality is closely related to the carcinogenesis of cervical epithelial cells. P53 gene mutation exists in cervical squamous intraepithelial lesions. As an important tumor suppressor gene, P53 inactivation plays an important role in the occurrence and development of cervical squamous intraepithelial lesions. High-risk HPV E6 proto-oncogene–coding protein can bind to p53 protein and degrade it. Wild-type P53 can participate in the regulation of cell growth, development, and differentiation through P53-dependent or P53-independent pathways. Current studies have also shown that P53 can prevent cells from entering S phase from G1 phase, thereby inhibiting cell proliferation and mediating cell cycle. Overexpression of P53 has been proved to be significantly related to the initiation of HP-HPV transformation infection. Ki-67 is a definite marker of nuclear proliferation at present. Its half-life is short. It can be quickly interpreted as a
marker to detect the proliferation activity of cancer cells after it is detached from cell cycle. HPV infection can accelerate cell proliferation and increase the number of Ki-67 positive nuclei, and the number of Ki-67 positive nuclei increases with the grade of cervical lesions.27,28 This study showed that the positive rates of ER, PR, P53, and Ki67 expression in cervical squamous intraepithelial lesions increased significantly with the grade of cervical squamous intraepithelial lesions ($P < 0.05$). These results indicate that ER, PR, P53, and Ki67 are of great value in predicting the occurrence and development of cervical squamous intraepithelial lesions and have guiding significance for the treatment and prognosis of cervical squamous intraepithelial lesions.

Cervical squamous intraepithelial lesions are the result of interaction between environmental factors and genetic factors. Cell atypia is prone to occur on the basis of abnormal gene expression and viral infection.29 Especially, HPV infection is not the only pathogenic factor of cervical squamous intraepithelial lesions. The functional changes of oncogenes and tumor suppressor genes also play a key role in the occurrence and development of cervical squamous intraepithelial lesions.30 In 140 samples, Pearson correlation analysis showed that the positive rates of HPV16 and HPV18 were positively correlated with the positive rates of ER, PR, P53, and Ki67 ($P < 0.05$). Current studies have shown that E6 proteins of HPV16 and HPV18 can bind to wild-type P53 proteins, and with the participation of E6-related proteins, promote the degradation of P53 proteins, eventually leading to the reduction of P53-induced G1 phase arrest in cell cycle, thus completing DNA synthesis and promoting cell proliferation.15,31 HPV infection also destroys normal sex hormone function, which weakens the anti-estrogen effect of progesterone in endometrial lesions and increases the malignant transformation of cells.32 HPV can induce the cell cycle activity of Ki67 positive cells. With the increase of Ki67 expression level, the number of HPV copies also increased significantly.33,34 This study also has some shortcomings: the number of experimental cases is relatively small, relatively limited, and there is no healthy population, there can be some research bias, and there will be in-depth analysis in the next step. Two limitations of this study include the following: (1) the probability of CIN progression is considered greater with the persistence of HPV infection and age, p53 polymorphism, hormone-induced cervical cancer by ER and PR; however, in cervical cancer, increased bcl-2 and Bax immunoreactivity is generally associated, and in this study, bcl-2 and Bax expression has not been studied. (2) We did not consider the points of developing CIN, persisting CIN, and regressing CIN.

**Conclusion**

In conclusion, with the increase in the grade of cervical squamous intraepithelial lesions, the positive rate of high-risk HPV infection increased, along with the increased positive rate of ER, PR, P53, and Ki67 expression, which had a positive correlation.

Our study suggests that coexpression of ER and PR may be a useful tool in identifying the CIN lesions with low risk of progression to cervical cancer.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

The study was approved by the ethics review committee of Tianjin Medical University.

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**Informed consent**

Written informed consent was obtained from all subjects before the study and in some cases written informed consent was obtained from legally authorized representatives before the study.

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