Observational Study

Medicine®

OPEN

# Persistent HPV-16 infection leads to recurrence of high-grade cervical intraepithelial neoplasia

Jung Mi Byun, MD, PhD[a,b,*], Dae Hoon Jeong, MD, PhD[a,b,*], Young Nam Kim, MD, PhD[a,b], Eun Jung Jung, MD[a], Kyung Bok Lee, MD, PhD[a,b], Moon Su Sung, MD, PhD[a,b], Ki Tae Kim, MD, PhD[a,b]

**Abstract**

High-grade cervical intraepithelial neoplasia (CIN) is a precancerous lesion of cervical cancer. The aims of this study were to evaluate the risk factors for recurrence of high-grade CIN and to determine if the specific genotype of human papillomavirus (HPV) is a predictor of recurrent high-grade CIN. Between January 2010 and December 2014, 172 patients with CIN 2+ underwent cold knife conization or a loop electrosurgical excision. The HPV DNA chip was used to detect HPV. Recurrent lesions were histologically confirmed and considered to be recurrence of CIN2+. We compared the recurrence rate in patients who did and did not have HPV infection after treatment. One hundred forty-eight (86%) patients had HPV infection before treatment. The first follow-up HPV test was performed on average 4.6 months after treatment and the recurrence rate for high-grade CIN was 3.5%. Fifty-eight patients (33.7%) were found to have HPV infection after treatment; of these, 14 (24.1%) had HPV genotype 16 and/or 18. Eleven patients had persistent HPV16 and/or 18 infection and 3 had new HPV 16 infection after treatment (78.6% and 21.4%, $P = .001$); the HPV 16 genotype was significantly correlated with recurrent disease and persistent infection after treatment ($P = .013$ and $P = .054$, respectively, [OR], 19.4; 95% [CI], 1.89–198.79). Recurrence of high-grade CIN was related to HPV infection after treatment, and persistent HPV16 infection was the most important factor for recurrence. Therefore, HPV vaccination for the HPV16 genotype and regular follow-up with HPV testing after treatment may be useful for preventing recurrent high-grade CIN.

**Abbreviations:** ASCUS = atypical squamous cells of undetermined significance, CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HPV = human papillomavirus, LEEP = loop electrosurgical excision procedure.

**Keywords:** cold knife conization, high-grade cervical intraepithelial neoplasia, human papillomavirus 16 genotype, loop electrosurgical excision procedure, recurrence

## 1. Introduction

High-grade cervical intraepithelial neoplasia (CIN) 2/3 is a precancerous lesion,[1] and 60% to 80% of cases are associated with persistent high-risk human papillomavirus (HPV) infection.[2] HPV is the single most important factor in the pathogenesis of cervical cancer and precancerous lesions of the cervix.[3] The average time interval between infection with a carcinogenic type of HPV and development of cervical cancer is 25 to 30 years.[4] According to the composite data for the natural history of CIN, CIN1 is likely to regress in 60% of cases, persist in 30%, progress to CIN 3 in 10%, and progress to invasion in 1%.[5] However, the rate of progression of CIN 2/3 to invasive cervical cancer is higher, and that of CIN3 has recently been estimated at 31.3% in 30 years.[6] Therefore, CIN 1 and CIN 2/3 lesions are treated differently.

HPV infection is more common in younger women, reaching a peak of approximately 20% in women aged 20 to 24 years, with a subsequent decline in women older than 30 years.[7] The mean age of women with CIN 2/3 lesions is approximately 25 to 30 years, and these women need conservative treatment with either excision or ablation of the transformation zone.[8] Generally, conization using a loop electrosurgical excision procedure (LEEP) is considered appropriate treatment for high-grade cervical intraepithelial lesions. Treatment for CIN 2/3 or carcinoma in situ (CIS) is extremely effective and most patients require no further treatment. Nevertheless, approximately 23.0% of patients develop high-grade CIN after conservative treatment due to either residual or recurrent lesions.[9]

Risk factors for recurrent or residual disease after conization may include age, parity, cytological grade, preoperative and follow-up HPV load, HPV genotype, and cone margin involvement.[10,11] Although not all women with recurrent disease develop invasive cervical cancer, those with residual or recurrent lesions remain at five times greater risk of cancer compared with the general population.[12] Therefore, prevention and early detection of recurrent or residual disease is important. The aims

*Editor: Hua Yang.*

*Funding: This work was supported by 2015 Inje University Busan Paik Hospital research grant.*

*Ethical approval and consent to participate: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board at Inje University Busan Paik Hospital as IRB No.:15-0148. Informed consent was obtained from all individual participants included in the study.*

*The authors have no conflicts of interest to disclose.*

[a] *Department of Obstetrics and Gynecology,* [b] *Paik Institute for Clinical Research, Busan Paik Hospital, Inje University, Busan, Republic of Korea.*

[*] *Correspondence: Jung Mi Byun, Department of Obstetrics and Gynecology, Busan Paik Hospital, Inje University, College of Medicine, 75 Bokji-ro, Busanjin-gu, Busan 473920, Republic of Korea (e-mail: hellojungmi@hanmail.net), Dae Hoon Jeong, Department of Obstetrics and Gynecology, Busan Paik Hospital, Inje University, College of Medicine, 75 Bokji-ro, Busanjin-gu, Busan 473920, Republic of Korea (e-mail: obgynjeong@hanmail.net).*



*Medicine (2018) 97:51(e13606)*

*Received: 14 March 2018 / Accepted: 19 November 2018*

*http://dx.doi.org/10.1097/MD.0000000000013606*

of this study were to evaluate the risk factors for recurrence of high-grade CIN and to determine if the specific HPV genotype is a predictor of recurrent high-grade CIN.

## 2. Patients and methods

### 2.1. Study patients

The study was approved by the Institutional Review Board at Inje University Busan Paik Hospital. Written informed consent was obtained from all women who participated in the study. We recruited patients with high-grade cervical intraepithelial lesions (CIN2/3 or CIS) treated with cold knife conization or LEEP at the Department of Obstetrics and Gynecology, College of Medicine, Inje University Busan Paik Hospital between January 2010 and December 2014 (Fig. 1). During this time, 316 patients underwent conization or LEEP for CIN2/3 or CIS. We excluded 82 patients who did not undergo HPV testing and 62 who were lost to follow-up. Finally, 172 patients with CIN 2, CIN 3, or CIS who received regular follow-up cytology and HPV testing were enrolled in the study. None of these patients was vaccinated before treatment. Patient demographics, including pathologic findings and HPV infection status at the time of their procedure and during follow-up, were identified by hospital chart review. Clinicopathologic data were collected, including patient age, body mass index, type of pathology, strain of HPV, treatment method used, resection margin, follow-up cervical histology, follow-up dates, strain of pretreatment HPV, strain of posttreatment HPV, and recurrence. Follow-up was performed at 3-monthly intervals by cytology in the first year after treatment, at 6-monthly intervals in the following year, and annually thereafter. HPV testing was performed at 6-monthly intervals in the first year after treatment and annually thereafter. Abnormal findings during follow-up were histologically confirmed and considered recurrence of high-grade cervical intraepithelial lesions (CIN2/3 or CIS). The comparison of characteristics according to HPV 16/18 type and non-16/18 HPV types was investigated because HPV type 16/18 were related with 50% of precancerous lesions of cervix and 70% of cervical cancer.[13] And we analyzed the patient characteristics according to preoperative and postoperative HPV infection status and risk factors for recurrence.

### 2.2. HPV detection method

We used the HPV DNA chip (MyHPV chip, Mygene Co., Seoul, Korea), a polymerase chain reaction-based DNA microarray system, as the HPV genotyping method. The HPV DNA chip contains 24 type-specific probes; 15 probes are for the high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68)

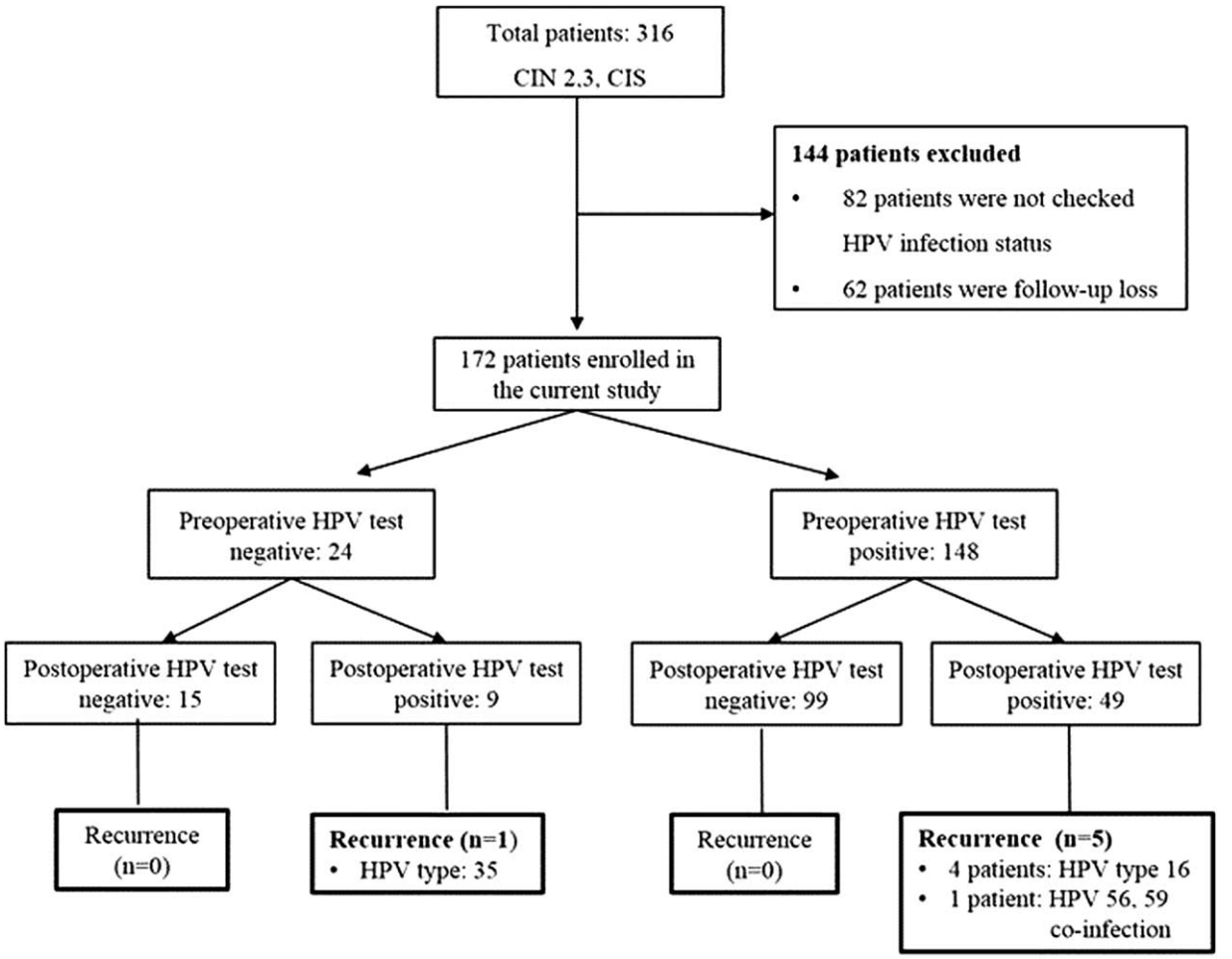


**Figure 1.** Flow chart showing patient recruitment. CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HPV = human papillomavirus.

and 9 are for the low-risk types (6, 11, 34, 40, 42, 43, 44, 54, and 70). Briefly, DNA was isolated from a swab sample using a DNA isolation kit (MyGene Co.). The target L1 region of HPV DNA was then amplified and labeled by a single dye (indocarbocyanine-dUTP; NEN Life Science Products, Inc., Boston, MA). The polymerase chain reaction products of all samples were detected by using electrophoresis with 2.5% agarose gel. The samples were mixed with a hybridization solution (MyGene Co.). Hybridization was performed at 43°C for 90 minutes. The hybridized HPV DNA was visualized using a DNA chip scanner (Scanarray Lite; GSI Lumonics, Ottawa, Ontario, Canada).

### 2.3. Statistical analysis

The statistical analysis was performed using MedCalc version 14.8.1 software (Frank Schoonjans, Ghent University, Belgium). Categorical variables were compared using the Chi-square test or Fisher exact test. The mean, median, and standard deviation were calculated for continuous variables, which were compared using *t* tests and Pearson's correlation coefficients. All tests were 2-sided, and the level of significance was set at $P < .05$.

## 3. Results

### 3.1. Characteristics according to HPV infection before treatment

Before treatment, patients with HPV infection were younger compared with those without HPV infection (34.8 ± 8.3 vs 39.4 ± 10.7 years, respectively; $P = .018$) and were significantly more likely to have CIN3 or CIS than CIN2 (85.1% vs 14.9%; $P = .001$). There were no significant differences in resection margin involvement, follow-up cytology, or recurrence according to pretreatment HPV infection status.

Nine of the patients with HPV-negative lesions before treatment became HPV-positive during follow-up and 49 of those with HPV-positive lesions before treatment were still HPV-positive at the follow-up after 6 months. Fourteen of the patients who were HPV-positive at follow-up had HPV 16 and/or 18 and 35 had other types of HPV. Of the 49 patients who were HPV-positive before and after treatment, 32 had new HPV infection and 17 had persistent infection with the preoperative HPV type. Eleven of the persistent HPV infections were due to HPV 16 and/or 18, and 6 had other genotypes [HPV 58(1), HPV 33(3), and HPV 39(2)]. Three of the new HPV infections were due to HPV16 and 29 had other types (Table 1).

### 3.2. Characteristics according to HPV infection after treatment

The first follow-up HPV test was performed at an average of 4.6 months after treatment, and 58 patients (33.7%) were found to have HPV infection at this time. Fourteen (24.1%) of the 58 patients had the HPV 16 and/or 18 genotype and 44 (75.9%) had other types of HPV, which included high-risk genotypes (31, 33, 39, 45, 56, 58, 59, 66), low-risk genotypes (6, 11, 40, 42, 43, 44, 54), and others. The data were analyzed according to whether patients were infected with HPV at follow-up after treatment. There were no significant differences in mean age, grade, HPV infection status, or the number of coinfecting HPV types before treatment. At follow-up, 34 patients (19.8%) had abnormal cervical cytology (≥ASCUS) and most had HPV infection after treatment (64.7% vs 35.3%, $P = .001$) (Table 3). In total, 3.5% of patients developed recurrent CIN 2/3 or CIS, and all were HPV-positive on follow-up HPV testing (100% vs 0%, $P = .002$) (Table 2).

When the patients were investigated according to preoperative and postoperative HPV genotype, 56.1% (83/148) were positive

**Table 1**

**Characteristics of patients according to pretreatment HPV infection.**

| | HPV negative (n = 24) | HPV positive (n = 148) | *P* |
|---|---|---|---|
| Age, y | 39.4 ± 10.7 | 34.8 ± 8.3 | .018 |
| BMI, kg/m$^2$ | 22.3 ± 3.8 | 21.3 ± 2.8 | .11 |
| Neoplastic severity | | | .001 |
| CIN 2 | 11 (45.8) | 22 (14.9) | |
| CIN3 or CIS | 13 (54.2) | 126 (85.1) | |
| Method of operation | | | .98 |
| Cold knife conization | 13 (54.2) | 77 (52.0) | |
| LEEP | 11 (45.8) | 71 (48.0) | |
| Follow-up cytology | | | .68 |
| Normal | 18 (75.0) | 120 (81.1) | |
| Abnormal (≥ASCUS) | 6 (25.0) | 28 (18.9) | |
| Follow-up HPV test (>6 mo after treatment) | | 0.85 | |
| Negative | 15 (62.5) | 99 (66.9) | |
| Positive | 9 (37.5)* | 49 (33.1)† | |
| Margin involvement | | | .56 |
| No | 19 (15.3) | 105 (84.7) | |
| Yes | 5 (10.4) | 43 (89.6) | |
| Mean f/u period, mo | 35.4 ± 18.1 | 33.6 ± 20.3 | .69 |
| Recurrence | | | 1.00 |
| No | 23 (95.8) | 143 (96.6) | |
| Yes | 1 (4.2) | 5 (3.4) | |

Data are mean ± standard deviation or number (%).

ASCUS = atypical cells of undetermined significance, CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, f/u = follow-up, HPV = human papillomavirus, LEEP = loop electrosurgical excision procedure.

* HPV genotypes: 42, 43, 44, 35, 58, 6, other types.

† HPV genotypes: 35 patients had other types (22, 31, 33, 35, 39, 40, 42, 45, 54, 56, 58, 59, 66, 68, 6, and 11) and 14 patients had HPV 16/18 type.

**Table 2**

**Characteristics of patients according to posttreatment HPV infection.**

| | HPV positive (n = 58) | HPV negative (n = 114) | *P* |
|---|---|---|---|
| Age, y | 35.1 ± 8.8 | 35.6 ± 8.9 | .76 |
| Neoplastic severity | | | .88 |
| CIN 2 | 12 (36.4) | 21 (63.6) | |
| CIN3 or CIS | 46 (33.1) | 93 (66.9) | |
| Follow-up cytology | | | .001 |
| Normal | 36 (26.1) | 102 (73.9) | |
| Abnormal | 22 (64.7) | 12 (35.3) | |
| HPV infection before treatment | | | .85 |
| No | 9 (37.5) | 15 (62.5) | |
| Yes | 49 (33.1) | 99 (66.9) | |
| Concordance of HPV infection status | | | .001 |
| New infection | 41 (70.7) | 0 (0) | |
| Persistent infection | 17 (29.3) | 0 (0) | |
| Negative | 0 (0) | 114 (100) | |
| Number of positive HPV before treatment | | 0.21 | |
| 0 | 9 (37.5) | 15 (62.5) | |
| 1 | 39 (30.5) | 89 (69.5) | |
| ≥2 (n = 20) | 10 (50.0) | 10 (50.0) | |
| Recurrence | | | .002 |
| No | 52 (31.3) | 114 (68.7) | |
| Yes | 6 (100) | 0 (0) | |

Data are mean ± standard deviation or number (%).

CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HPV = human papillomavirus.

**Table 3**

**Comparison of characteristics according to pretreatment and posttreatment HPV genotyping results*.**

| Variable | Pretreatment HPV genotype (n = 148) | | | Posttreatment HPV genotype (n = 58) | | |
|---|---|---|---|---|---|---|
| | HPV 16/18 (n = 83) | Non-HPV 16/18 (n = 65) | *P* | HPV 16/18 (n = 14) | Non-HPV 16/18 (n = 44) | *P* |
| Mean age, y | 33.2 ± 8.0 | 36.8 ± 8.3 | .009 | 35.6 ± 9.0 | 34.9 ± 8.8 | .81 |
| Neoplastic severity | | | .39 | | | 1.00 |
| CIN 2 | 10 (45.5) | 12 (54.5) | | 3 (25.0) | 9 (75.0) | |
| CIN3 or CIS | 73 (57.9) | 53 (42.1) | | 11 (23.9) | 35 (76.1) | |
| Follow-up cytology | | | .24 | | | .12 |
| Normal | 64 (53.3) | 56 (46.7) | | 6 (16.7) | 30 (83.3) | |
| Abnormal | 19 (67.9) | 9 (32.1) | | 8 (36.4) | 14 (63.6) | |
| Margin involvement | | | .89 | | | 1.00 |
| No | 58 (55.2) | 47 (44.8) | | 10 (24.4) | 31 (75.6) | |
| Yes | 25 (58.1) | 18 (41.9) | | 4 (23.5) | 13 (76.5) | |
| HPV infection before treatment | | 0.09 | | | | |
| No | — | — | | 0 (0.0) | 9 (100.0) | |
| Yes | — | — | | 14 (28.6) | 35 (71.4) | |
| Concordance of HPV infection status | 0.001 | | | | | |
| New infection | — | — | | 3 (7.3) | 38 (92.7) | |
| Persistent infection | — | — | | 11 (64.7) | 6 (35.3) | |
| Recurrence | | | .06 | | | .026 |
| No | 78 (54.5) | 65 (45.5) | | 10 (19.2) | 42 (80.8) | |
| Yes | 5 (100.0) | 0 (0.0) | | 4 (66.7) | 2 (33.3) | |

Data are mean ± standard deviation or number (%).

CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HPV = human papillomavirus.

* HPV16/18 type (+) includes HPV-16 (+) or HPV-18 (+); non-16/18 HPV types (+) includes HPV-16 (−) and HPV-18 (−), other HPV type (+).

for HPV 16/18 type before treatment and 24.1% (14/58) were positive for HPV 16/18 type after treatment (Table 4). Before treatment, the patients who were positive for HPV 16/18 type were significantly younger compared with the HPV-positive patients with other genotypes (mean 33.2 ± 8.0 years vs 36.8 ± 8.3 years, $P = .009$). There was no significant difference in severity of disease, follow-up cytology, margin involvement, or positive HPV genotypes between before and after treatment. However, on the basis of the HPV infection status, 41 patients (70.7%) were newly HPV-positive and 17 (29.3%) were persistently HPV-positive. Of the 14 patients with posttreatment HPV 16/18 positivity, 11 (78.6%) had persistent HPV 16/18 positivity and 3 (21.4%) were newly infected with HPV 16 type after treatment ($P = .001$). Patients with postoperative HPV 16/18 positivity were more likely to develop recurrence than those with other types of HPV positivity (66.7% vs 33.3%, $P = .026$) (Table 3).

### 3.3. Risk factors for recurrent disease

Table 4 shows the demographic and clinicopathologic variables in relation to recurrent high-grade CIN after cold knife conization or LEEP. Six patients relapsed with CIN 3 (n = 3) or CIS (n = 3), and the recurrence rate was 3.5%. Three patients with recurrent disease were treated with hysterectomy, 2 underwent LEEP, and 1 had cold knife conization. Women with recurrence were older compared with those without recurrence, but not significantly so. All the patients with recurrent disease were HPV-positive after treatment, and this finding was statistically significant (100% vs 0%, $P = .002$). Four of these patients were HPV 16-positive and 2 were positive for other types of HPV. HPV 16 infection after treatment was associated with recurrent disease ($P = .013$). The 4 patients with recurrent disease and persistent HPV infection after treatment ($P = .054$) had the HPV 16 genotype.

In the 58 patients who had HPV infection after treatment, the most important factor affecting recurrence after treatment is persistent HPV 16 infection. Patients with persistent HPV 16 infection after treatment had a significantly higher risk for recurrence after conization compared to patients with non-16 HPV types infection (odd ratio [OR], 19.4; 95% confidence interval [CI], 1.89–198.79) (Table 5).

## 4. Discussion

In this study, 86% of patients with high-grade cervical CIN had HPV infection, and 56% of these patients had HPV 16/18 type. After a mean follow-up duration of 34 months, 6 patients had relapsed with CIN 3 or CIS and had HPV infection after treatment. Although the majority of patients with HPV infection were HPV-negative before treatment, 33.1% were still HPV-positive after treatment (Table 1), indicating that conization do not necessarily clear HPV infection rapidly. Therefore, follow-up of CIN after treatment is important for early detection of recurrence. At the follow-up HPV test 6 months after treatment, one-third of the positive HPV genotypes were HPV 16 and/or 18. This finding indicates that HPV 16 and/or 18 were not rapidly cleared after surgical treatment. A study by Kristina et al showed that although the clearance of HPV DNA was rapid and usually occurred within 3 months of treatment, the type of HPV contributed to differences in the clearance rate.[4] These authors suggested that HPV testing could be used as an important intermediate endpoint in follow-up after treatment of CIN. Several reports have suggested that successful conization also eradicates HPV infection effectively in most patients with CIN,[11,12] and that the persistence of high-risk HPV infection at follow-up is a significant predictor of residual or recurrent CIN after conization. In our study, the patients who were HPV-positive after treatment had abnormal cytology at follow-up and they were recurred. During follow-up, 70.7% of HPV infections were new and 29.3% were persistent, indicating a need to prevent reinfection after treatment and to regular follow-up for persistent HPV infection (Table 2).

**Table 4**

**Correlation between patient demographic and histologic characteristics and recurrence after initial treatment.**

| Variable | No recurrence (n = 166) | Recurrence (n = 6)† | P |
|---|---|---|---|
| Age, y | 35.4 ± 8.8 | 36.1 ± 8.2 | .84 |
| Parity, no. | 1 (0–8) | 2 (0–5) | .79 |
| Method of operation | | | .43 |
| Cold knife conization | 88 (53.0) | 2 (33.3) | |
| LEEP | 78 (47.0) | 4 (66.7) | |
| Neoplastic severity | | | 1.00 |
| CIN 2 | 32 (19.3) | 1 (16.7) | |
| CIN3 or CIS | 134 (80.7) | 5 (83.3) | |
| Cytology before treatment* | | | .69 |
| Minor abnormality | 78 (47.0) | 2 (33.3) | |
| Major abnormality | 88 (53.0) | 4 (66.7) | |
| Margin involvement | | | .67 |
| No | 120 (72.3) | 4 (66.7) | |
| Yes | 46 (27.7) | 2 (33.3) | |
| Glandular involvement | | | .40 |
| No | 70 (42.2) | 1 (16.7) | |
| Yes | 96 (57.8) | 5 (83.3) | |
| HPV infection before treatment | | | .69 |
| No | 23 (13.9) | 1 (16.7) | |
| Yes | 143 (86.1) | 5 (83.5) | |
| HPV infection after treatment | | | .002 |
| No | 114 (68.7) | 0 (0.0) | |
| Yes | 52 (31.3) | 6 (100)† | |
| HPV genotype after treatment (n = 58) | | | 0.013 |
| 16 (12, 20.7%) | 8 (15.4) | 4 (66.7) | |
| Others (46, 79.3%) | 44 (84.6) | 2 (33.3) | |
| HPV infection status after treatment (n = 58) | | | 0.054 |
| New infection (41, 70.7%) | 39 (75.0) | 2 (33.3) | |
| Persistent infection (17, 29.3%) | 13 (25.0) | 4 (66.7) | |

Fisher exact test. Data are mean standard deviation or number (%).

ASC-H = atypical squamous cells with possible high-grade squamous intraepithelial lesion, ASCUS = atypical cells of undetermined significance, CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, HPV = human papillomavirus, HSIL = high-grade squamous intraepithelial lesion, LEEP = loop electrosurgical excision procedure, LSIL = low-grade squamous intraepithelial lesion, SCC = squamous cell carcinoma.

* Minor abnormalities included ASCUS + LSIL; major abnormalities included ASC-H + HSIL + SCC.

† Six patients: 4 had persistent infection (HPV 16 type), 2 had new infection (multiple infections: one with HPV 35, 42, and 44 types; the other with HPV 56 and 59 types).

Many risk factors for recurrent dysplasia after conization have been known, but in our study, age, parity, preoperative HPV infection status, major abnormal cytology, treatment modality, margin and gland involvement, and severity of disease were not significant risk factors. Although Ku et al[14] reported that the high-risk HPV 18 genotype is related to resection margin involvement, this was not the case in our study. However, our patients who developed recurrent disease were HPV 16-positive after treatment and had persistent infection. New infection posttreatment contributed to some recurrent disease, but persistent infection was more significantly associated with recurrence ($P = .054$). The most reliable risk factor for recurrence was HPV infection posttreatment and the factor most strongly associated with recurrence was persistent HPV16 infection. According to multivariate analysis of factors affecting recurrence, the persistent HPV16 infection is a predictor of recurrence.

**Table 5**

**Multivariate evaluation of factors affecting recurrence after treatment (n = 58).**

| Variable | Odds ratio (95% CI) | P |
|---|---|---|
| Margin involvement | 2.03 (0.19–21.32) | .553 |
| Method of operation | 1.35 (0.16–11.74) | .783 |
| HPV 16 infection after treatment | 19.4 (1.89–198.79) | .012 |
| Number of HPV infection after treatment | 13.34 (0.84–210.94) | .065 |

CI = confidence interval, HPV = human papillomavirus.

Nagai et al[15] reported that the persistence rate of HPV infection after conization for HPV-positive CIN 3 was approximately 20%, and 46% of these patients with persistent HPV infection developed recurrence of CIN at 4 to 10 months after treatment. In our study, the rate of persistent or new HPV infection after treatment for HPV-positive high-grade CIN was 25.7%, and while treated women were likely to have newer HPV infection than persistent HPV infection (41 vs 17), 66.7% of recurrent disease following treatment occurred in women with persistent HPV16 infection.

Several reports had suggested that the presence of oncogenic types of HPV after treatment is a risk factor for posttreatment CIN2/3.[16] CIN2 caused by HPV16 positivity seems less likely to regress than CIN2 caused by other high-risk HPV genotypes and CIN 2 that is HPV16-negative.[17] Therefore, the initial step for preventing recurrence of CIN 2/3 or CIS is prevention of HPV infection. HPV vaccination is established in the prevention of CIN and its efficacy is known.[18] Aiméeet et al mentioned that women with disease recurrence would not have benefited from prophylactic HPV vaccine if administered after the initial treatment because all disease recurrence is attributable to the presence of infection before treatment.[19] Therefore, the most important step for prevention of recurrent disease is to confirm the patient's HPV infection status at follow-up after treatment; if persistent high-risk HPV infection is found, close colposcopic follow-up and cytology are mandatory.[19] According to a recent published report, administration of the quadrivalent HPV vaccine after treatment may be considered for the prevention of recurrence of CIN 2/3. The efficacy of vaccination after treatment of CIN should now be investigated.[20]

There are several limitations in our study including small sample size, retrospective design and limited long-term follow-up. The sample size could have been expanded by collection of the data and further research with assessing the recurrence of CIN 2/3 can complete of the limitations.

In conclusion, the recurrence of high-grade CIN in our study was related to HPV infection after treatment, and persistent HPV 16 infection was the most important risk factor for recurrence. The majority of our patients who were positive for HPV 16 type after treatment had persistent infection. Therefore, HPV vaccination for HPV 16 type may be useful in preventing recurrence of CIN2/3 and CIS. Patients with persistent HPV infection after treatment should be regularly investigated with HPV testing and cytology. In our study, patients who were HPV-negative after treatment were newly infected with the same or another type of HPV. Therefore, patients who are HPV-positive before treatment and found to be HPV-negative at a follow-up HPV test should still undergo long-term follow-up HPV testing to detect recurrent disease.

## Author contributions

**Conceptualization:** Jung Mi Byun, Dae Hoon Jeong.

**Data curation:** Jung Mi Byun, Young Nam Kim, Eun Jung Jung, Kyung Bok Lee, Moon Su Sung, Ki Tae Kim.

**Formal analysis:** Jung Mi Byun, Dae Hoon Jeong, Young Nam Kim, Eun Jung Jung, Kyung Bok Lee, Moon Su Sung.

**Investigation:** Jung Mi Byun, Young Nam Kim, Eun Jung Jung, Kyung Bok Lee, Moon Su Sung, Ki Tae Kim.
**Methodology:** Ki Tae Kim.
**Project administration:** Jung Mi Byun, Dae Hoon Jeong.
**Supervision:** Dae Hoon Jeong.
**Validation:** Jung Mi Byun, Young Nam Kim.
**Writing – original draft:** Jung Mi Byun.
**Writing – review & editing:** Jung Mi Byun, Dae Hoon Jeong.

## References


[1] Pinto AP, Crum CP. Natural history of cervical neoplasia: defining progression and its consequence. Clin Obstet Gynecol 2000;43:352–62.
[2] Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am J Obstet Gynecol 2004;191:105–13.
[3] Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9.
[4] Elfgren K, Jacobs M, Walboomers JM, et al. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. Obstet Gynecol 2002;100(5 Part 1):965–71.
[5] Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12:186–92.
[6] Vesco KK, Whitlock EP, Eder M, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011
[7] Martin CM, O'Leary JJ. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract Res Clin Obstet Gynaecol 2011;25:605–15.
[8] Wright TCJr, Cox JT, Massad LS, et al. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. Am J Obstet Gynecol 2003;189:295–304.
[9] Ghaem-Maghami S, Sagi S, Majeed G, et al. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol 2007;8:985–93.
[10] Lu CH, Liu FS, Kuo CJ, et al. Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. Obstet Gynecol 2006;107:830–5.
[11] Serati M, Siesto G, Carollo S, et al. Risk factors for cervical intraepithelial neoplasia recurrence after conization: a 10-year study. Eur J Obstet Gynecol Reprod Biol 2012;165:86–90.
[12] Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer 2006;118:2048–55.
[13] Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer 2012;131:2349–59.
[14] Ku CH, Lee SH, Lee SP. Effect of human papillomavirus genotype on severity and prognosis of cervical intraepithelial neoplasia. Obstet Gynecol Sci 2014;57:37–43.
[15] Nagai Y, Maehama T, Asato T, et al. Persistence of human papillomavirus infection after therapeutic conization for CIN 3: is it an alarm for disease recurrence? Gynecol Oncol 2000;79:294–9.
[16] Hernádi Z, Szőke K, Sápy T, et al. Role of human papillomavirus (HPV) testing in the follow-up of patients after treatment for cervical precancerous lesions. Eur J Obstet Gynecol Reprod Biol 2005;118:229–34.
[17] Castle PE, Schiffman M, Wheeler CM, et al. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol 2009;113:18–25.
[18] Kahn JA. HPV vaccination for the prevention of cervical intraepithelial neoplasia. N Engl J Med 2009;361:271–8.
[19] Kreimer AR, Schiffman M, Herrero R, et al. Long-term risk of recurrent cervical human papillomavirus infection and precancer and cancer following excisional treatment. Int J Cancer 2012;131:211–8.
[20] Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol Oncol 2013;130:264–8.