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ORIGINAL RESEARCH

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Predictive value of HPV genotyping for recurrence of CIN2–3 in women treated by LEEP with negative resection margins

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Abstract

The aim of our study was to determine whether the HPV genotype identified by the HPV DNA chip (HDC) test could predict the recurrence of high-grade cervical intraepithelial neoplasia (CIN2–3) in women who had undergone a loop electrosurgical excision procedure (LEEP) and had negative margins. We analyzed the data of 1021 women with CIN2–3 treated by LEEP where histology confirmed negative resection margins. The women were followed up with HDC and endocervical cytology tests at 3, 6, 9, 12, 18 and 24 months during the first 2 years and annually thereafter. Among the 1021 patients, the pre-LEEP HDC test was positive for 992 (97.2%). A total of 90 (8.8%) patients experienced recurrence of CIN2–3 and the post-LEEP follow-up HDC tests were positive, thus demonstrating a persistent high-risk HPV infection of the same genotype, which showed a sensitivity and negative predictive value of 100% in predicting recurrence. We also examined the correlation between pre-LEEP high-risk HPV genotypes and recurrence. The most common subtypes were HPV16, HPV18 and HPV31. Persistence of HPV18 had the highest risk of recurrence of CIN2–3 ($p < 0.05$). Our study suggests that type-specific persistent high-risk HPV infection, particularly the HPV18 subtype, is a significant predictor of recurrence in patients with negative resection margins in the LEEP specimens. Thus, these patients require careful monitoring, and gynecologic oncologists should conduct short-term follow-up tests.

Keywords

Loop electrosurgical excision procedure; High-grade cervical intraepithelial neoplasia; Cone margin; High-risk-human papillomavirus testing

1. Introduction

High-grade cervical intraepithelial neoplasia (CIN2–3) is a premalignant lesion caused by high-risk-human papillomavirus (HPV). Most patients with CIN2–3 are promptly treated with lesion ablation; therefore, studies regarding the natural progression of untreated CIN2–3 are limited. Nevertheless, some studies have estimated that progression rate of cervical dysplasia to cervical cancer as approximately 11.7% [1]. More than 200 HPV genotypes have been identified so far, of which 40 are classified as anogenital HPV because they infect the anogenital mucosa area. The anogenital HPV genotypes are categorized as high-risk (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 62 and 68) and low-risk (HPV6, 11, 42, 43, 44) and the high-risk HPVs are considered to be correlated with malignant or precancerous uterine cervix lesion [2]. The HPV types 16, 18, 31, 33, 45, 52 and 58 are responsible for almost 90% of cervical cancer cases worldwide [3]. Recently, loop electrosurgical excision procedure (LEEP), a minimally invasive cervical conization procedure is being widely used to diagnose and treat CIN2–3 because it can be performed under local anesthesia in a short time with fewer complications on an outpatient basis [4]. However, post-LEEP recurrences or residual lesions occur in approximately 5–30% cases and since it can lead to cervical cancer, the patients should be followed up with caution [5]. Persistent high-risk-HPV infection is significantly associated with CIN2–3 development and testing has recently been proposed during the follow-up examinations of patients being treated for CIN2–3 because of their high sensitivity and negative predictive value (NPV) for detecting residual/recurrent disease as a good index of disease clearance [5]. Therefore, high-risk HPV and cervical cytology co-testing is recommended during the follow-up of post-LEEP patients [6]. However, considering LEEP leads to a relatively higher possibility of the development of post-procedure positive margins, previous studies have examined the correlation between the positive margins and recurrence rates [7]. The positive incisional margins of LEEP specimens are closely associated with the relapse or deterioration of the disease [4]. However, studies regarding patients with negative margins after LEEP are lacking. Thus, the purpose of this study was

to examine the role of HPV genotype determined by the HPV DNA chip (HDC) test in the prediction of recurrent or residual lesions during the post-LEEP follow-up of patients with CIN2–3 who have negative margins.

2. Materials and methods

2.1 Patients

We retrospectively reviewed the medical records of 1342 patients with CIN2–3 after they underwent LEEP in the Department of Obstetrics and Gynecology of the Chonnam National University Hospital between April 2004 and March 2016.

The inclusion criteria were as follows: (1) pathologically diagnosed CIN2–3 after LEEP, (2) pre-LEEP and post-LEEP HPV infection observed on the HDC test, and (3) follow-up period of 5 years after LEEP, (4) negative margins after LEEP. Based on these, 1021 patients were included in this study. The remaining 321 patients were excluded from the study because they underwent a hysterectomy within 6 months after LEEP, were residual CIN2–3, or were lost to follow-up during the 5-year period. High-risk-HPV test results, histopathologic findings and epidemiologic data were obtained by reviewing the medical records.

LEEP was conducted under local anesthesia on an outpatient basis. Small wire loops heated with electrodes were used to excise the cervical lesions and 10% formalin for pathologic evaluation. All the patients underwent endocervical cytology tests immediately after LEEP. Subsequently, they were followed-up at 3, 6, 12, 18 and 24 months during the first 2 years and annually thereafter. All the patients underwent HDC testing & cytology during the follow-up period. Colposcopic biopsy and endocervical sampling were performed if the HPV test result was positive or the cytology findings indicated a status atypical squamous cells of undetermined significance (ASC-US) or greater. Criteria for residual or recurrent disease were based on positive histology of colposcopy-directed biopsy or endocervical curettage. Patients with histologically-confirmed CIN2–3 at 3 months' follow-up after treatment were considered as having residual disease. Patients diagnosed with CIN2–3 on biopsies at the next follow-up (from 6 months onward) were considered as having recurrent disease. Detection of CIN2–3 on cervical biopsy was considered a positive result and that of CIN1, normal, and other conditions, such as cervicitis, negative.

2.2 HDC assay

HPV genotyping was performed using a DNA chip kit (MyGene Co, Seoul, South Korea) which contains 24 type-specific probes (10 probes for low-risk types 6, 11, 34, 40, 42, 43, 44, 53, 54 and 70 and 14 probes for high-risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). This genotypic test can identify different HPV through reactions on a spotted oligonucleotide chip with HPV-specific sequences. Using the HDC method, DNA isolation, polymerase chain reaction (PCR) amplification, dyeing (MEM Life Science Products, Inc., Boston, MA, USA), hybridization, washing, and scanning were conducted accordingly. After centrifugation of the sample, the supernatant is used for PCR. The labeled PCR sample was hybridized at 43 °C for 90 min, washed with 3× saline-sodium phosphate-ethylene diamine tetraacetic acid (SSPE) for 5 min and with 1× SSPE for 5 min before dehydrating. Finally, chip scanners (Scanarray Lite; GSI Lumonics, Ottawa, Canada) were used to determine each HPV subtypes. The samples which tested positive on HPV PCR gel electrophoresis and negative on the DNA chip scanner were classified as HPV-other-type samples [8], and those that were negative on electrophoresis were regarded as HPV-negative.

2.3 Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). The Student's *t*-test was used analyzing the quantitative variables and correlation between other clinical factors and recurrence of post-LEEP HPV infection. All *p*-values were two-sided and those <0.05 were considered statistically significant.

3. Results

The characteristics of the patients are shown in Table 1. The mean ages of the patients who experienced recurrence and those who did not were 39.2 years (range, 21–74 years) and 40.8 years (range, 23–65 years), respectively. Of the 1021 patients, 920 were in the premenopausal state. The initial cytology results of ASC-US, low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), and high-grade squamous intraepithelial lesion (HSIL) were 134, 77, 77 and 663, respectively. Women with HSIL cytology before LEEP had the highest risk of CIN2–3 recurrence after treatment (9.2%, 61/663). Furthermore, 992 (97.2%, 992/1021) pre-LEEP patients demonstrated positive HDC test results, and all 90 cases (8.8%, 90/1021) of recurrence occurred in this group. The LEEP specimen results showed CIN2 in 220 (21.5%) patients and, CIN3 in 801(78.4%), among who recurrence was observed in 22 and 68 cases, respectively. The result of endocervical cytology performed immediately after LEEP were negative in 981 patients, and positive in 40. The follow-up cytology results were negative in 852 patients and ASC-US and more severe (ASC-US) in 169. Finally, the numbers of post-LEEP patients who demonstrated negative and positive HDC test results were 729 and 292, respectively. All 90 patients with recurrence exhibited positive post-LEEP HDC test. The mean time before recurrence was 21.6 months (range, 6–72 months). Patient age, menopausal status, initial cytology, CIN grade observed on LEEP biopsy, and pre-LEEP HDC test results did not have a statistically significant relationship with recurrence. However, women with abnormal endocervical cytology performed immediately after LEEP, follow-up cytology results showing ASC-US, and positive post-LEEP HDC test results had a significantly higher risk of recurrence of CIN2–3.

Table 2 shows the association between various characteristics and persistent HPV infection. Menopausal status and, initial cytology were not significantly associated with persistent HPV infection ($p = 0.798$ and 0.227, respectively). Results of endocervical cytology performed immediately after

TABLE 1. Patient characteristics.

	No recurrence (%) N = 931	Recurrence (%) N = 90	*p*
Age (yr)			
Mean ± SD	39.2 ± 8.8	40.8 ± 8.4	0.10
Range	21–74	23–65	
Menopause			
No	839 (90.1)	81 (90)	0.97
Yes	92 (9.9)	9 (10)	
Initial cytology			
ASC-US	118 (12.7)	16 (17.8)	0.49
LSIL	68 (7.3)	9 (10.0)	
ASC-H	73 (7.8)	4 (4.4)	
HSIL	602 (64.7)	61 (67.8)	
CIN at LEEP			
CIN2	198 (21.3)	22 (24.4)	0.48
CIN3	733 (78.7)	68 (75.6)	
Pre-LEEP HDC			
Negative	29 (3.1)	0 (0)	0.09
Positive	902 (96.9)	90 (100)	
Endocervical cytology at LEEP			
Negative	901 (96.8)	80 (88.9)	<0.01
Positive	30 (3.2)	10 (11.1)	
Follow-up cytology			
Negative	843 (90.5)	9 (10)	<0.01
ASC-US	88 (9.5)	81 (90)	
Post-LEEP HDC			
Negative	729 (78.3)	0 (0)	<0.01
Positive	202 (21.7)	90 (100)	

SD, standard deviation; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells of cannot exclude high-garde squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; HDC, HPV DNA chip test.

LEEP showed no significant association with persistent HPV infection ($p = 0.513$). The CIN grade obtained from LEEP and recurrence of CIN2–3 were related to persistent HPV infection ($p < 0.01$). All 90 patients with recurrence were positive for the same HPV subtype, and those with persistent HPV infection having a different subtype showed no recurrence.

Table 3 represents sensitivity, specificity, positive predictive value (PPV), and NPV of various tests (endocervical cytology, follow-up cytology, post-LEEP HDC test, and same-type high-risk HPV genotype observed on the HDC test) in diagnosing recurrent CIN2–3. The sensitivity, specificity, PPV and NPV of endocervical cytology were 11.1%, 96.8%, 25.0% and 91.8%, respectively and those of follow-up cytology were 90.0%, 90.6%, 47.9% and 98.9%, respectively. The sensitivity, as well as NPV of post-LEEP HDC test and same-type high-risk HPV genotype observed on the HDC test were all 100%, which signified negative post-LEEP HDC test results. The different-type high-risk HPV genotype group exhibited no recurrence (Table 3).

Table 4 shows the relationship between high-risk HPV genotypes and recurrence of CIN2–3 in the initial 992 HPV-positive cases. Single-type high-risk HPV genotype infection was observed in 792 patients, and 200 exhibited multiple high-risk HPV genotype infection. Among the 90 patients with recurrence, single and multiple high-risk HPV genotype infections were observed in 71 and 19 patients, respectively. HPV16 (44.3%, 351/792) was the most common single infection type; it was also the most common subtype in the recurrence group (31.1%, 28/90). The second and third most common single infection types were HPV18 (7.4%, 59/792) and HPV31 (6.7%, 53/792). HPV18 showed the highest correlation with CIN2–3 recurrence ($p < 0.05$).

TABLE 2. Comparison of the two groups divided according to HR-HPV genotype infection after a LEEP.

	Persistent HR-HPV infection		*p*
	Different subtype (%) N = 73	Same subtype (%) N = 219	
Menopause			
No	68 (93.2)	202 (92.2)	0.798
Yes	5 (6.8)	17 (7.8)	
Initial cytology			
ASC-US	25 (34.2)	50 (22.8)	0.227
LSIL	3 (4.1)	17 (7.8)	
ASC-H	5 (6.9)	16 (7.3)	
HSIL	40 (54.8)	136 (62.1)	
CIN at LEEP			
CIN2	31 (42.5)	44 (20.1)	<0.01
CIN3	42 (57.5)	175 (79.9)	
Positive endocervical cytology at LEEP			
Negative	69 (94.5)	202 (91.2)	0.513
Positive	4 (5.5)	17 (7.8)	
Recurrence	0 (0)	90 (41.1)	<0.01

HR, high risk; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells of cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

TABLE 3. Sensitivity, specificity, and predictive values of the different tests in predicting recurrent CIN2–3.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Endocervical cytology	11.1 (2.8–19.4)	96.8 (95.3–98.2)	25.0 (7.9–42.1)	91.8 (89.7–94.0)
Follow-up cytology	90.0 (82.1–97.9)	90.6 (88.2–92.9)	47.9 (38.3–57.5)	98.9 (98.1–99.8)
Post-LEEP HDC	100.0 (100.0–100.0)	83.4 (80.3–86.4)	36.7 (29.0–44.4)	100.0 (100.0–100.0)
Same HR-HPV genotype by HDC	100.0 (100.0–100.0)	86.1 (83.3–89.0)	41.1 (32.8–49.4)	100.0 (100.0–100.0)

PPV, positive predictive value; NPV, negative predictive value; HR, high risk; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; HDC, HPV DNA chip test; CI, confidence interval.

4. Discussion

Patients who receive LEEP are at a higher risk of cervical cancer within 10 years of the procedure than the general population [7]. Specifying the predictors of recurrent CIN2–3 or cervical cancer after LEEP would enable taking appropriate action depending on the risk factors in individual patients, thereby reducing patient anxiety and overtreatment. Preterm birth can be induced depending on the cervical excision range; therefore, it is important to maintain the equilibrium between accurate therapy and iatrogenic complications, such as incompetent internal os of the cervix (IIOC) [9, 10].

According to the American Society for Colposcopy and Cervical Pathology Consensus (ASCCP) guidelines [11], after histologic treatment for HSIL, HPV and cytology co-testing at 12, 24 months are recommended when excision margin is negative. And if CIN2 is identified at the margins of an excisional procedure or post-procedure ECC (endocervical curettage), colposcopy and ECC at 6 months or repeat excision are acceptable. Hysterectomy is recommended if re-excision is not feasible. Although the relative risk of persistent or recurrent histologic HSIL is approximately 5 times higher after excisional treatment with positive margins than that associated with negative margins, only 56% of persistent/recurrent precancers were predicted by a positive margin status. Therefore, margin status is a poor predictor of persistent/recurrent precancer, which is a point against differentiating follow-up testing based on margin status alone. Nevertheless, the success rate of HPV-based testing in predicting persistent/recurrent histologic HSIL was 91%, and this did not differ significantly between patients with positive and negative margins.

In previous studies, the recurrence rate in patients with positive margins and negative margins were approximately 17–29.8% [12, 13], and 2.8–7% [12–15], respectively. Our study revealed that the recurrence rate in patients with negative margins was 8.8%, which conforms to that observed in other studies. Women with HSIL cytology before LEEP had the highest risk of CIN2–3 recurrence after treatment

TABLE 4. The correlation between pre-LEEP HR-HPV genotypes by HDC and disease recurrence.

	No recurrence N = 931	Recurrence N = 90	Total N = 1021
None (N = 29)	29	0	29
Single infection (N = 792)			
16	323	28	351
18*	49	10	59
31	47	6	53
33	39	4	43
35	16	0	16
39	5	1	6
45	8	0	8
51	12	2	14
52	67	5	72
56	10	3	13
58	112	8	120
Other types†	33	4	37
Multiple infection (N = 200)			
16 + 18	13	1	14
16 + 58	13	0	13
Other mixed types	155	18	173

*LEEP, loop electrosurgical excision procedure; HR, high risk; HPV, human papillomavirus; HDC, HPV DNA chip test. *Significantly higher than the results for other HR-HPV genotype infection (chi-square test; $p < 0.05$). †High risk human papillomavirus types 53, 59, 66 and 68.*

(9.2%, 61/663), which corresponds with that of other studies [5, 12]. Moreover, all the 90 patients with recurrence exhibited positive pre-LEEP HDC test results. Various factors including, patient age, menopausal status, initial cytology, CIN grade observed on LEEP, and pre-LEEP HDC test result were not statistically related with recurrence. Nonetheless, the presence of abnormal endocervical cytology obtained immediately after LEEP, follow-up cytology indicating ASC-US, and positive results on post-LEEP HDC tests were significantly associated with the risk of CIN2–3 recurrence after treatment ($p < 0.01$). Previous studies revealed that the recurrence rate among patients exhibiting positive result on endocervical cytology performed immediately after LEEP and abnormal result on follow-up cytology test were 19.0–44.2% [5, 12] and 16.3–61.5% [5, 12, 16–18], respectively, which are similar to our study findings (25% (10/40), 47.9% (81/169)). In this study, patients with persistent high-risk HPV infection exhibited a 30.8% (90/292) recurrence rate, while none of the patients with negative post-LEEP HDC test results experienced recurrence.

Seventy-eight percent (219/292) of persistent high-risk HPV-positive patients had the same subtype HPV. There was no notable difference between the same and different persistent high-risk HPV genotypes among patients who exhibited CIN2 in LEEP, whereas this difference was significant among those who exhibited CIN3 in LEEP. This signifies the correlation between CIN3 detected by LEEP and recurrence. All the 90 patients with recurrence had persistent same subtype high-risk HPV infection.

In our study, we examined the sensitivity, specificity, PPV and NPV of various factors (endocervical cytology observed in LEEP, follow-up cytology result, post-LEEP HDC test result, and same genotype high-risk HPV) in predicting recurrent CIN2–3. Post-LEEP HDC test results and persistent high-risk HPV infection of same genotype determined by HDC testing revealed sensitivity and, NPV of 100%. Thus, persistent same-subtype high-risk HPV infection may be regarded as a meaningful diagnostic tool for predicting recurrence. Previous studies also showed that persistent high-risk HPV infection is significantly associated with early detection of recurrence and recurrence itself [15–17].

The most common HPV subtypes that cause cervical cancer are HPV16 and HPV18. However, our study revealed that the most common subtypes in the order of decreasing prevalence were HPV16, HPV58, HPV52, HPV18 and HPV31. HPV18 and HPV45 might have been less which corresponds with the findings of other studies that examined the HPV prevalence in CIN2–3 rather than cancer [3, 19]. In our study, while HPV16 was most prevalent, the difference was not statistically significant. Single or multiple high-risk HPV infections were also not meaningfully related to recurrence. Although the prevalence of HPV18 is low, it was found to be more strongly associated with recurrence of CIN2–3 than other subtypes. As a result, patients with persistent HPV18 infection should receive close monitoring.

Positive margins after LEEP are traditionally regarded as treatment failure [7]. Nevertheless, negative margins after

LEEP do not always guarantee complete lesion excision because CIN2–3, which represents minimal colposcopic changes and frequent extension into the endocervical canal, makes it difficult to determine the limits of lesion excision; the possibility of AIS occurrence also exists [6, 7, 16]. On average, about 8.0–17.0% of post-LEEP patients demonstrated histologic margin involvement [4, 7, 12].

The main strength of our study is the long-term follow-up of patients with CIN2–3 who exhibited negative margins after LEEP. Detailed histologic diagnoses based on follow-up cytology-results and the identification of each high-risk HPV genotype also helped understand to the natural progression of HPV. However, the limitation of our study was that although the HDC test in which cervical swabs are used to identify different HPV types, it has not yet been approved by the United States Food and Drug Administration (FDA).

5. Conclusions

In conclusion, our findings indicate that the type-specific persistence of high-risk HPV infection, particularly HPV18, is a valuable predictor of the recurrence of CIN2–3 after treatment. Our study demonstrates that the persistence or clearance of high-risk HPV in patients with negative resection margins in LEEP specimens is a crucial indicator of the risk of recurrence. Our study shows that HPV genotyping test is more effective than cytology alone and performs with lower costs than HPV and cytology co-testing. Further research is necessary to standardize the polymerase chain reaction (PCR) technique for HPV detection. However, based on our results, we recommend that patients with persistent high-risk HPV, particularly HPV18 and high-risk HPV of the same subtype observed on LEEP, should be monitored carefully with short-term follow-up tests, even if their post-LEEP margin is negative.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

IYJ, WDK, UCJ and SMK—designed the research study. IYJ and WDK—performed the research and analyzed the data; wrote the manuscript. UCJ and SMK—provided help and advice on the data analyzation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital (CNUHH-2022-212).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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