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Original Article

Evaluation of clinical usefulness of HPV-16 and HPV-18 genotyping for cervical cancer screening

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ABSTRACT

Objective: High-risk human papillomavirus (HR-HPV) infection is a leading cause of cervical cancer, of which human papillomavirus (HPV)-16 and HPV-18 account for about 70% of cases. Since HPV infection is common, it is important to focus on the HPV genotypes that pose the highest risk for effective cervical cancer screening. In this study, we evaluated the clinical usefulness of HPV-16/HPV-18 genotyping for cervical cancer screening.
Methods: A total of 86,022 women aged 25 years or older was analyzed in this study. Sensitivity, specificity, positive predictive value, and negative predictive value of HPV genotyping and cytology were analyzed. In addition, we subdivided participants into two groups according to cytology results, negative for intraepithelial lesion of malignancy (NILM) and atypical squamous cells of undetermined significance (ASC-US), and analyzed absolute risk (AR) and relative risk (RR) of cervical intraepithelial neoplasia (CIN) 3 or worse according to HPV genotype.
Results: The AR of CIN 3 or worse was 77.0 times higher in HR-HPV-positive compared to HR-HPV-negative. Compared to 12 other HR-HPV-positive, the AR of CIN 3 or worse was 4.2 times higher in HPV-16 and/or HPV-18 positive. This finding was more evident in women with NILM than in women with ASC-US. The RR of CIN 3 or worse was 7.0 in women with NILM and 4.5 in women with ASC-US.
Conclusion: Regardless of the cytology results, the risk of CIN 3 or worse was higher in HPV-16/HPV-18 than in other HR-HPV. HPV-16/HPV-18 genotyping is recommended to screen women with a high risk of cervical cancer.

Keywords: Human Papillomavirus; Genotyping; Screening

Synopsis

In this study, the clinical usefulness of human papillomavirus (HPV)-16/18 genotyping for cervical cancer screening was evaluated. Compared to 12 other high-risk HPV-positive, the risk of cervical intraepithelial neoplasia 3 or worse was higher in HPV-16/18 positive, which was more evident in women with normal cytology. This finding is important for effective cervical cancer screening.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: C.E.H., K.M.J.; Data curation: C.E.H.; Formal analysis: C.E.H.; Investigation: C.E.H.; Methodology: C.E.H., K.M.J.; Supervision: W.H.Y., P.H., K.M.J.; Writing - original draft: C.E.H.; Writing - review & editing: C.E.H., P.M.S., W.H.Y., P.H., K.M.J.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide. In 2020, about 604,000 new cases were diagnosed and 342,000 women died from cervical cancer. Although population-based cervical cancer screening using cytology has reduced the incidence of cervical cancer significantly [1], cytology has some limitations. First, cytology is less effective in vaccinated women because high-grade abnormalities caused by high-risk human papillomavirus (HR-HPV) have decreased [2]. As the vaccination rate increases, this is an important factor in determining the screening policy. In addition, cytology is inefficient in screening adenocarcinoma due to difficulty in sampling [3,4]. Indeed, after adopting cytology as a screening test, the incidence of squamous carcinoma has decreased, while the incidence of adenocarcinoma has increased [5].

Molecular testing for human papillomavirus (HPV) is becoming increasingly important in cervical cancer screening. The American Cancer Society recommends primary HPV testing every 5 years from the age of 25 [6]. In European guidelines published by experts from 11 European countries and International Agency for Research on Cancer (IARC), primary HPV testing is recommended at age 35 or above [7]. Indeed, several countries have adopted primary HPV testing as a cervical cancer screening program with starting age varying from 25 to 34 years depending on cost-effectiveness of each country [8].

HR-HPV infection is a leading cause of cervical cancer, of which HPV-16 and HPV-18 account for about 70% of cases [9]. HR-HPV infection is common with a worldwide prevalence of 12.6%–15.2% [10,11]. Even in women with normal cytology, the prevalence of HPV infection is 7.2%–10.4% [12,13]. Therefore, it is important to focus on the HPV genotypes that pose the highest risk for effective cervical cancer screening. In this study, we retrospectively reviewed the incidence of cervical cancer according to the results of HPV genotyping and evaluated the clinical usefulness of HPV-16/HPV-18 genotyping for screening of cervical cancer.

MATERIALS AND METHODS

1. Study population

Kangbuk Samsung Health Study is a cohort study of Korean men and women who underwent a comprehensive annual or biennial health examination at Kangbuk Samsung Hospital Total Healthcare Centers in South Korea [14]. This study involved a portion of the Kangbuk Samsung Health Study female participants aged ≥25 years who underwent HR-HPV testing as part of a comprehensive health examination from 2016 to 2019 (n=88,989). For these participants, the incidence of cervical intraepithelial neoplasia (CIN) 3 or worse until 2020 was retrieved based on the cancer incidence data from the Korea Central Cancer Registry (KCCR). The KCCR is a nationwide population-based cancer registry that contains the nationwide cancer statistics since 1999 and the completeness of cancer incidence data was estimated to be 98.3% [15,16]. CIN 3 or worse was defined using the International Classification of Diseases, 10th Revision (ICD-10): D06.0, D06.1, D06.7, D06.9, C53.0, C53.1, C53.8, and C53.9. Among 88,989 women, 2,967 who did not have cytology results, had a history of cervical cancer, or were not linked to the cancer incidence data from the KCCR were excluded. Finally, 86,022 women were included (**Fig. 1**). This study was approved by the Kangbuk Samsung Hospital Institutional Review Board (approval number: 2021-11-039).

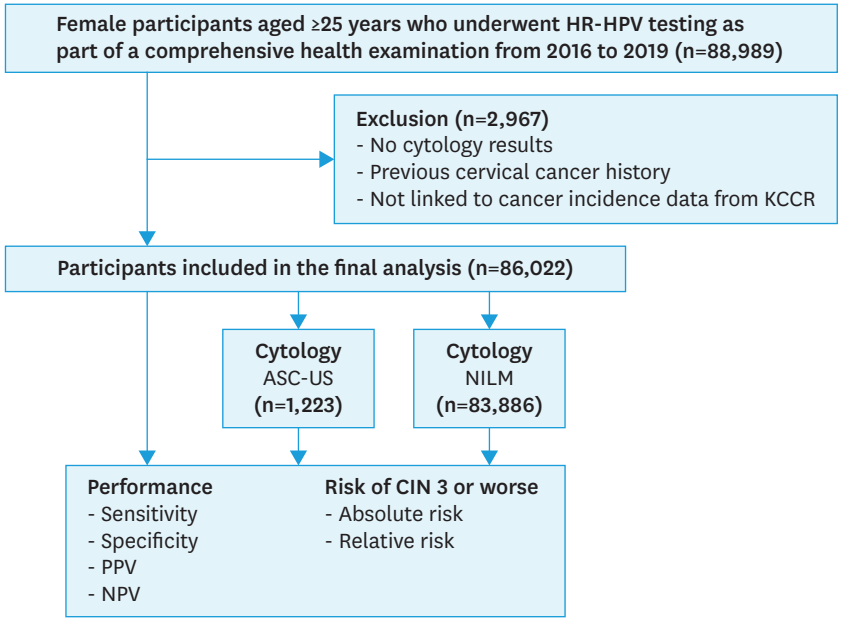

Fig. 1. Schematic diagram for participant selection and statistical analysis.
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus; KCCR, Korea Central Cancer Registry; NILM, negative for intraepithelial lesion of malignancy; NPV, negative predictive value; PPV, positive predictive value.

2. HPV genotyping

HPV genotyping was conducted at Kangbuk Samsung Hospital using the cobas HPV test (Roche Molecular Systems, Pleasanton, CA, USA), which detects 14 HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV-16 and HPV-18 were individually detected, and the 12 other HR-HPVs were detected together. We considered both persistent and transient infection as HR-HPV-positive. HPV-16 and HPV-18 positivity included not only a single infection but also co-infection involving other HR-HPV genotypes. The 12 other HR-HPVs positivity included only those 12 and did not include co-infection with HPV-16 and/or HPV-18.

3. Statistical analysis

Based on the incidence of CIN 3 or worse from the KCCR, clinical sensitivity, clinical specificity, positive predictive value, and negative predictive value of HPV genotyping and cytology were analyzed. Concordance between HPV genotyping and cytology was assessed using kappa statistics (κ). In addition, we subdivided participants into two groups according to cytology results: negative for intraepithelial lesion of malignancy (NILM) and atypical squamous cells of undetermined significance (ASC-US). Then, we evaluated absolute risk (AR) and relative risk (RR) of CIN 3 or worse according to HPV genotype within each group. AR was calculated as the percentage of participants with CIN 3 or worse among those with positive results in each category of HPV genotyping. RR was calculated by dividing the AR in each group by the AR in the comparison group. R software (version 4.1.2, https://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

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RESULTS

1. Demographics

The mean age was 40.0 years with a standard deviation of 8.2 years (range 25–86 years). A total of 1.4% (1,223/86,002) of women had ASC-US cytology and 97.5% (83,886/86,002) had NILM cytology. Menopause and vaccination status were assessed through self-reported questionnaire, with 9.5% (8,155/86,022) of women reported as postmenopausal, and 32.2% (27,667/86,002) reported as vaccinated.

2. HR-HPV prevalence

In 86,022 women, the prevalence of HR-HPV was 7.8%. Prevalence of HPV-16, HPV-18, and the 12 other HR-HPV genotypes was 0.9%, 0.4%, and 6.5%, respectively (**Table 1**). The prevalence of HR-HPV was highest in women aged 25 to 29 years, followed by women aged 40 to 49 years, women aged 50 to 59 years, women aged 30 to 39 years, and women aged 60 years or older. In 1,223 women with ASC-US, 52.8% were positive for HR-HPV. Prevalence of HPV-16, HPV-18, and the 12 other HR-HPV genotypes was 6.6%, 3.4%, and 43.3%, respectively. In 83,886 women with NILM cytology, 6.3% were positive for HR-HPV. Prevalence of HPV-16, HPV-18, and the 12 other HR-HPV genotypes was 0.7%, 0.4%, and 5.3%, respectively.

3. Distribution of HR-HPV in CIN 3 or worse

Overall, HR-HPV was positive in 7.6% of women without CIN and 86.7% of women with CIN 3 or worse. HPV-16 and/or HPV-18 were positive in 1.2% of women without CIN and 40.4% of women with CIN 3 or worse. The 12 other HR-HPV genotypes were positive in 6.4% of women without CIN and 46.3% of women with CIN 3 or worse (**Fig. 2A**). In women with ASC-US, HR-HPV was positive in 52.2% of women without CIN and 83.3% of women with CIN3 or worse. HPV-16 and/or HPV-18 were positive in 8.9% of women without CIN and 41.7% of women with CIN 3 or worse. The 12 other HR-HPV genotypes were positive in 43.3% of women without CIN and 41.7% of women with CIN 3 or worse (**Fig. 2B**). In women with NILM, HR-HPV was positive in 6.3% of women without CIN and 84.2% of women with CIN3 or worse. HPV-16 and/or HPV-18 were positive in 1.0% of women without CIN and 49.5% of women with CIN 3 or worse. The 12 other HR-HPV genotypes were positive in 5.3% of women without CIN and 34.7% of women with CIN 3 or worse (**Fig. 2C**).

4. Performance of screening methods for detection of CIN 3 or worse

The sensitivity, specificity, positive predictive value, and negative predictive value of HPV genotyping and cytology are presented in **Table 2**. HPV genotyping showed higher sensitivity than cytology, with an increase of 30.7% compared to cytology (86.7% for HPV genotyping vs. 56.0% for cytology). Specificity was higher in cytology than in HPV genotyping (92.4% for HPV genotyping vs. 97.7% for cytology). The concordance rate between HPV genotyping and

Table 1. Prevalence of HR-HPV

Age (yr)	HR-HPV+			HPV-16+			HPV-18+			12 Other HR-HPV+		
	Overall	NILM	ASC-US	Overall	NILM	ASC-US	Overall	NILM	ASC-US	Overall	NILM	ASC-US
25–29	15.30%	11.90%	68.40%	1.70%	1.30%	6.80%	0.70%	0.60%	4.50%	12.80%	10.10%	57.60%
30–39	7.00%	5.70%	55.40%	0.80%	0.60%	8.00%	0.40%	0.30%	3.20%	5.80%	4.70%	44.80%
40–49	7.70%	6.10%	46.40%	0.90%	0.70%	5.30%	0.50%	0.40%	3.60%	6.40%	5.40%	37.70%
50–59	7.40%	6.60%	37.20%	1.10%	1.00%	5.80%	0.40%	0.40%	1.20%	5.90%	5.20%	30.20%
≥60	4.70%	4.20%	47.40%	0.60%	0.60%	0.00%	0.20%	0.20%	0.00%	4.00%	3.50%	47.40%
Overall	7.80%	6.30%	52.80%	0.90%	0.70%	6.60%	0.40%	0.40%	3.40%	6.50%	5.30%	43.30%

ASC-US, atypical squamous cells of undetermined significance; HR-HPV, high-risk human papillomavirus; NILM, negative for intraepithelial lesion of malignancy.

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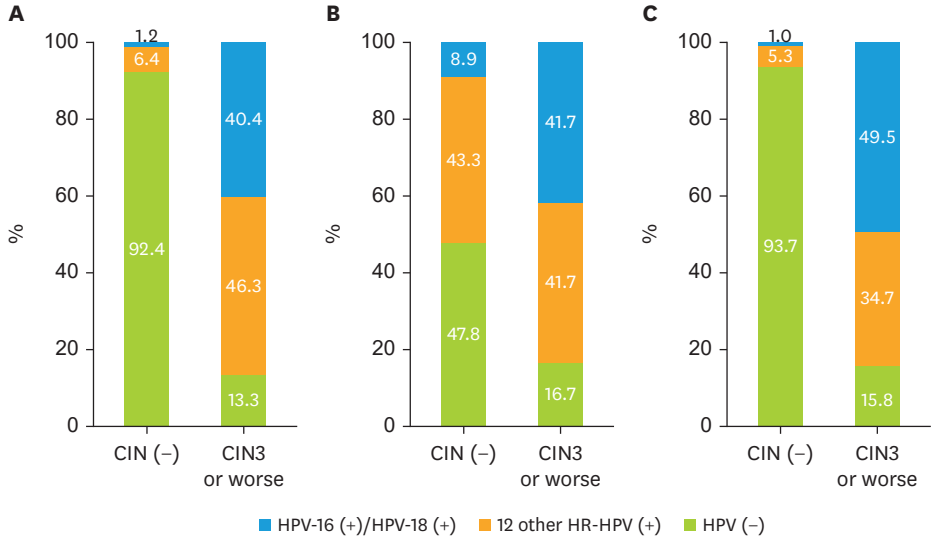

Fig. 2. Distribution of HPV genotype in CIN 3 or worse in total participants (A), women with atypical squamous cells of undetermined significance (B), and women with negative for intraepithelial lesion of malignancy (C). CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

cytology was 92.8% with a kappa value of 0.272. Most discrepancies were caused by positive HPV genotyping and negative cytology.

5. Absolute risk of CIN 3 or worse according to HR-HPV genotype

The overall AR of CIN 3 or worse was 0.25%. In HR-HPV positivity and negativity, the AR was 2.8% and 0.04%, respectively. The AR was higher in women with HPV-16 and/or HPV-18 positive than in those with 12 other HR-HPV genotypes (7.6% for HPV-16 and/or HPV-18 positive vs. 1.8% for the 12 other HR-HPV-positive), as was the case in women with ASC-US or NILM. The AR in women with NILM positive for HPV-16 and/or HPV-18 was higher than in women with ASC-US positive for the 12 other HR-HPV genotypes (**Table 3**).

Table 2. Performance of HPV genotyping and cytology for CIN 3 or worse

Performance	HPV genotyping	Cytology
Sensitivity (95% confidence interval)	86.7 (81.5–90.9)	56.0 (49.1–62.7)
Specificity (95% confidence interval)	92.4 (92.2–92.6)	97.7 (97.6–97.8)
PPV (95% confidence interval)	2.8 (2.4–3.2)	5.7 (4.8–6.8)
NPV (95% confidence interval)	99.96 (99.95–99.98)	99.89 (99.86–99.91)
Concordance rate	92.8 (92.6–93.0)	
Kappa value	0.272 (0.266–0.277)	

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Absolute risk of CIN 3 or worse according to HPV genotype

HPV genotype	Absolute risk (95% confidence interval)		
	Overall	NILM	ASC-US
HR-HPV+	2.8 (2.4–3.2)	1.5 (1.2–1.9)	3.1 (2.0–4.8)
HPV-16+/HPV-18+	7.6 (6.2–9.3)	5.2 (3.9–6.9)	8.5 (4.4–15.5)
HPV-16+	8.1 (6.4–10.3)	5.3 (3.8–7.5)	7.4 (3.0–16.0)
HPV-18+	6.5 (4.3–9.5)	5.1 (3.0–8.3)	9.8 (3.2–24.1)
12 other HR-HPV+	1.8 (1.5–2.2)	0.7 (0.5–1.0)	1.9 (1.0–3.6)
HR-HPV−	0.04 (0.02–0.05)	0.02 (0.01–0.03)	0.7 (0.2–1.9)
Overall	0.25 (0.22–0.29)	0.11 (0.09–0.14)	2.0 (1.3–3.0)

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus; NILM, negative for intraepithelial lesion of malignancy.

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6. Relative risk of CIN 3 or worse according to HR-HPV genotype

The AR of CIN 3 or worse was 77.0 times higher in HR-HPV positivity compared to HR-HPV negativity. The RR compared to HR-HPV negativity was higher in HPV-16 and/or HPV-18 positivity than in those positive for the 12 other HR-HPV genotypes (207.8 for HPV-16 and/or HPV-18 positive vs. 49.8 for 12 other HR-HPV-positive). Compared to women positive for the 12 other HR-HPV genotypes, the AR of CIN 3 or worse was 4.2 times higher in HPV-16 and/or HPV-18 positivity (**Table 4**). This finding was more evident in women with NILM than in women with ASC-US, with an RR of 7.0 in women with NILM and of 4.5 in women with ASC-US.

DISCUSSION

We analyzed the risk of CIN 3 or worse according to HPV genotype in 86,022 women aged 25 or older. Overall, the AR of CIN 3 or worse was 2.8% in HR-HPV-positive women. Regardless of cytology result, AR was higher in HPV-16 and/or HPV-18 positivity than in those positive for the 12 other HR-HPV genotypes, which was more evident in women with NILM than in women with ASC-US.

In this study, overall prevalence of HR-HPV was 7.8% and prevalence in women with NILM and ASC-US was 6.3% and 52.8%, respectively. The overall prevalence was relatively low compared with previous studies in the Korean population [17,18]. It might be due to the fact that most of the study population live in metropolitan areas and might not be representative of the entire Korean population. Indeed, previous study have shown that HPV vaccination rate was higher in metropolitan areas, which might contribute to the low prevalence [19]. Regardless of cytology result, the prevalence of 12 other HR-HPV genotypes was the highest compared to that of HPV-16 and HPV-18, which is consistent with previous studies [20-23]. Distribution of HPV genotype showed clinical significance for HPV-16 and HPV-18. Overall, HPV-16 and/or HPV-18 accounted for 40.4% of women with CIN 3 or worse. In women with ASC-US, the proportion of HPV genotype in CIN 3 or worse was the same at 41.7% in HPV-16 and/or HPV-18 and 12 other HR-HPV. On the other hand, in women with NILM, HPV-16 and/or HPV-18 and the 12 other HR-HPV accounted for 49.5% and 34.7% of CIN 3 or worse, respectively. This can be useful information for establishing a strategy for cervical cancer screening that minimizes unnecessary colposcopy.

Overall, the AR of CIN 3 or worse was 0.25%. In women with ASC-US and NILM, AR was 2.0% and 0.11%, respectively. Compared with women with the same cytology result, the

Table 4. Relative risk of CIN 3 or worse according to HPV genotype

HPV genotype	Relative risk (95% confidence interval)		
	Overall	NILM	ASC-US
HR-HPV+ vs. HPV–	77.0 (52.2–113.8)	77.7 (44.8–134.8)	4.5 (1.5–13.0)
HPV-16+/HPV-18+ vs. HPV–	207.8 (137.2–314.9)	270.0 (151.5–481.0)	12.3 (3.9–38.6)
HPV-16+ vs. HPV–	222.8 (144.6–343.2)	279.9 (152.8–512.7)	10.7 (3.1–37.1)
HPV-18+ vs. HPV–	176.7 (104.5–298.8)	267.5 (133.4–536.4)	14.1 (3.7–54.2)
12 other HPV+ vs. HPV–	49.8 (33.0–75.1)	38.6 (21.0–71.0)	2.7 (0.9–8.6)
HPV-16+/HPV-18+ vs. 12 other HPV+	4.2 (3.2–5.5)	7.0 (4.5–10.9)	4.5 (1.9–10.6)
HPV-16+ vs. 12 other HPV	4.5 (3.3–6.1)	7.2 (4.5–11.6)	3.9 (1.5–10.5)
HPV-18+ vs. 12 other HPV	3.6 (2.3–5.4)	6.9 (3.9–12.4)	5.2 (1.7–15.7)

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus; NILM, negative for intraepithelial lesion of malignancy.

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AR was higher in case of HPV-16 and/or HPV-18 positivity than in those positive for the 12 other HR-HPV genotypes. Even compared with women with different cytology results, the AR in women with NILM who were positive for HPV-16 and/or HPV-18 was higher than that in women with ASC-US who were positive for the 12 other HR-HPV genotypes. According to the 2019 American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines, the threshold for colposcopy was 4% risk of immediate CIN grade 3 or more [24]. According to the threshold, the 2019 ASCCP guidelines recommended colposcopy in women with HPV-16 and/or HPV-18 even when cytology results are negative [24]. In this study, AR in women with NILM positivity for HPV-16 and/or HPV-18 was 5.2%, which exceeded the threshold. Therefore, this finding supports the 2019 ASCCP guidelines and emphasizes the importance of HPV genotyping. The 2019 ASCCP guidelines also recommended colposcopy in women with HR-HPV-positive ASC-US [24]. However, in this study, the AR in women with HR-HPV-positive ASC-US was 3.1%, which does not exceed the colposcopy threshold. Only HPV-16 and/or HPV-18 positivity showed an AR higher than the threshold. As we used the cancer incidence data up to 2020, analysis of later data could show a higher AR in women with HR-HPV-positive ASC-US.

Several countries have adopted primary HPV testing as a cervical cancer screening program, and the use is expected to increase. If cytology is the primary screening method, women with NILM may experience underestimation of the risk of cervical cancer because they do not have information about the HPV genotype. In this study, women with NILM showed different risk according to HPV genotype. The RR compared to HR-HPV-negative was 270.0 in HPV-16 and/or HPV-18 and 38.6 in women with the 12 other HR-HPV genotypes. Compared to women with 12 other HR-HPV genotypes, the AR of CIN 3 or worse was 7.0 times higher in HPV-16 and/or HPV-18 positivity. Therefore, HPV genotyping can be useful for identifying women at high risk and for improving the sensitivity of cervical cancer screening. Indeed, in this study, HPV genotyping was more sensitive than cytology, which is consistent with a previous study [25]. A total of 44.0% of women who had CIN 3 or worse had NILM, showing 56.0% sensitivity. Sensitivity of HPV genotyping was 86.7%, which was an increase of 30.7% compared to cytology. It might explain the finding that most discrepancies were caused by positive HPV genotyping and negative cytology. Therefore, HPV genotyping is more appropriate as a primary screening method than cytology. Considering that cytology is less effective in vaccinated women, it is more evident in populations with a high vaccination rate.

This study has considerable strengths. First, this study included a large sample size of women who underwent both cytology and HPV genotyping. Second, the incidence of CIN 3 or worse was retrieved from the cancer incidence data from KCCR. Therefore, no matter which medical center diagnosed it, the incidence of CIN 3 or worse was identified. This study also has some limitations. First, the period between HPV genotyping and incidence of CIN 3 or worse was short, ranging from one year to up to four years. Therefore, there might be unidentified cases of CIN 3 or worse that were not registered in the cancer incidence. Second, the incidence of CIN 3 or worse was identified using cancer incidence data, not colposcopy results. Therefore, it was not possible to identify whether the women who were not diagnosed with cancer had normal findings on colposcopy or did not undergo colposcopy.

In conclusion, the risk of CIN 3 or worse was higher in women with HPV-16/18 than in those with the 12 other HR-HPVs regardless of the cytology results. Considering the prevalence of HR-HPV genotypes and the risk of CIN 3 or worse in each genotype, HPV-16/18 genotyping is recommended to screen women with a high risk of cervical cancer.

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