J Gynecol Oncol. 2019 Jul;30(4):e52
https://doi.org/10.3802/jgo.2019.30.e52
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Human papillomavirus genotype-specific risk in cervical carcinogenesis

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Received: Aug 21, 2018
Revised: Jan 3, 2019
Accepted: Jan 9, 2019

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ABSTRACT

Objective: To evaluate the risk of genotype-specific human papillomavirus (HPV) infections for the spectrum of cervical carcinogenesis and the distribution of HPV types according to age and different cervical lesions
Methods: This study included HPV-positive women who underwent cervical biopsy at the Cheil General Hospital & Women's Healthcare Center between July 1, 2011 and December 31, 2017. HPV genotyping was conducted using a Cheil HPV DNA chip kit.
Results: The study sample consisted of 400 normal, 399 cervical intraepithelial neoplasia (CIN) 1, 400 CIN 2, 400 CIN 3, and 389 cervical cancer cases. HPV 16 was the most common type found with a prevalence of 9.5% in normal, 6.8% in CIN 1, 15.0% in CIN 2, 44.5% in CIN 3, and 64.3% in cervical cancer. The most common HPV types were 16, 52, 58, 53, 51, 56, 68, and 18 in all study samples. HPV 16, 31, 33, and 58 were more common in CIN 2/3 and cancer, and HPV 39, 51, 53, 56, 66, and 68 were more common in CIN 1 and normal cases ($p<0.001$). In CIN 3 and cervical cancer, HPV 16 was the most common type in all age groups. HPV 52 was the most common type in CIN 2 (all age groups) and in CIN 1/normal (age ≤30 years) cases. Among the high-risk HPV types, 16, 31, 33, 52, and 58 showed significant risk for high-grade disease.
Conclusions: HPV 16, 31, 33, 52, and 58 showed the significant risk of high-grade disease for cervical carcinogenesis.

Keywords: Human Papilloma Virus; Genotype; Cervical Intraepithelial Neoplasia; Cervical Cancer

INTRODUCTION

Cervical cancer is the fourth most commonly diagnosed cancer in females worldwide [1]. In Korea, it was the fifth most common female cancer and the third most common cancer among 15–34-year-old women [2]. Oncogenic human papillomavirus (HPV) infection is a major risk factor for cervical cancer. The overall prevalence of high-risk human papillomavirus (HR-HPV) increases from 12% in normal cytology to 89% in cervical cancer [3]. Globally, HPV 16/18 are the 2 most common genotypes in approximately 70% of invasive cervical cancer cases [4].

Presentation
This study has been presented in the 33rd Annual Meeting of The Korean Society of Gynecologic Oncology.

Funding
This study was supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp.

Conflicts of Interest
Dr. Kim reports grants from Merck Sharp & Dohme Corp., during the conduct of the study. Other authors declare no conflicts of interest.

Author Contributions
Conceptualization: S.K.A. Data curation: S.K.A., H.S.R. Formal analysis: K.Y.J. Funding acquisition: K.T.J. Investigation: K.Y.J., S.H.H. Methodology: S.H.H. Resources: L.I.H., L.K.H., H.S.R. Supervision: L.K.H., K.T.J. Writing - original draft: S.K.A. Writing - review & editing: L.I.H., K.T.J.

The remaining 30% are caused by other HR-HPV types. HPV infections are common among young women and most spontaneously clear within 1–2 years [5]. Persistent infection with HR-HPV is considered essential for the development of cervical cancer [6]. However, the trend of persistent infection differed by HPV genotype and age. The most persistent types are 16, 31, 33, and 52 and the least persistent types are 35, 51, 66, and 68 [7]. The association between age and persistent infection is inconsistent. Previous studies suggested that women over 30 years of age have a higher rate of persistent HPV infection than women under 30 years of age [7,8]. Other studies showed that the persistence of HPV infection was not related to age [9,10].

In addition, HPV type-specific prevalence is different between low-grade squamous intraepithelial lesion (LSIL) and malignancy. HPV 16, 18, and 45 are more frequent in invasive cervical cancer than in any other grade of cervical disease, whereas HPV 51, 52, and 31 are more frequently detected in precancerous lesions than in invasive cervical cancer [11]. However, the risk of individual HPV type and the pattern of age-specific prevalence in cervical carcinogenesis are still not fully understood. A clear understanding of the individual risk according to HPV genotype would provide basic data for the prediction of vaccine effects and the clinical use of cervical cancer prevention. Thus, we performed this study to evaluate the genotype-specific risk for cervical carcinogenesis and the distribution of HPV types according to age in different cervical lesions.

MATERIALS AND METHODS

1. Study population

This study was a retrospective case-control analysis after Institutional Review Board approval (approval No. CGH-IRB-2016-48). Study samples were collected from HPV-positive women who underwent cervical biopsy between July 2011 and December 2017 at the Department of Obstetrics and Gynecology, Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine. A total of 1,988 samples were collected from women with normal (n=400), cervical intraepithelial neoplasia (CIN) 1 (n=399), CIN 2 (n=400), CIN 3 (n=400), cervical cancer (n=399). According to a large meta-analysis and a Korean HPV cohort study the prevalence of the 5 most common HR-HPVs was 7.2%–18.7% in LSIL [12,13]. Therefore 400 samples per disease grade are required to make up at least 30 cases for the five most common HR-HPVs that is needed to be statistically analyzed. Women were screened by cervical cytology and HPV test prior to biopsies. The women with abnormal cervical cytology and/or HR-HPV underwent a cervical biopsy. The pathologic result of chronic inflammation was included in the normal group. The inclusion criteria of this analysis were evidence of HPV infection and biopsy result. Women with previous hysterectomy were excluded from the analysis.

2. HPV DNA testing

The cervical samples were analyzed for HPV genotype using a Cheil HPV DNA chip kit (Cheil General Hospital, Seoul, Korea). HPV genotyping was based on a SYBR Green real-time polymerase chain reaction (RT-PCR) method. RT-PCR for HPV DNA was performed using the Light Cycler 480 (Roche Diagnostics, Rotkreuz, Switzerland). Post-amplification SYBR Green RT-PCR products were mixed with the hybridization buffer, and the mixture was incubated on the Cheil HPV DNA Chip. A total of 36 HPV types were identified using a chip scanner (NimbleGen MS 200; Roche NimbleGen, Vienna, Austria) and analyzed with GenePix® Pro 6.0 software (Axon Instruments, Union, CA, USA). The 36 HPV genotypes included 19 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68a, 68b, 69, and 82) and 17 low-risk types (6, 11, 30, 32, 40, 42, 43, 44, 54, 55, 62, 70, 72, 81, 84, 90, and 91).

Table 1. Rate of HPV infection and age distributions in study samples

Variables	Normal	CIN 1	CIN 2	CIN 3	Cervical cancer	Total
Number	400	399	400	400	399	1,988
Age	31.4±7.5	34.5±10.0	32.9±7.3	32.3±7.0	51.0±13.1	36.3±11.8
HPV infection (%)						
HR-HPV	389 (97.3)	365 (91.5)	398 (99.5)	398 (99.5)	386 (99.2)	1,936 (97.4)
Single	303 (77.9)	257 (70.4)	268 (67.3)	281 (70.6)	356 (92.2)	1,465 (75.7)
Multiple	86 (22.1)	108 (29.6)	130 (32.7)	117 (29.4)	30 (7.8)	471 (24.3)
Only LR-HPV	11 (2.7)	34 (8.5)	2 (0.5)	2 (0.5)	3 (0.8)	52 (2.6)
HR+LR HPV	122 (30.5)	123 (30.8)	109 (27.3)	74 (18.5)	11 (2.8)	439 (22.1)

Values are presented as number of patients (%) or mean ± standard deviation.
HPV, human papillomavirus; HR, high-risk; LR, low-risk.

3. Statistical analysis

The data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were indicated as numbers and percentages. To assess the risk of severe disease associated with HPV genotype, the odds ratio (OR) with 95% confidence interval (CI) was estimated using the χ^2 test. All p-values <0.05 were considered statistically significant.

RESULTS

Among a total of 1,988 patients, normal, CIN 1, CIN 2, CIN 3, and cancer cases accounted for 400, 399, 400, 400, and 389, respectively (**Table 1**). The overall prevalence of HR-HPV infection was 97.4%. The rate of single HR-HPV infection in the cancer group (92.2%) was higher than that in the other groups (67.3%–77.9%). Multiple HR-HPV infection was more frequent in normal and CIN 1/2/3 cases. Except in cervical cancer, multiple HR-HPV infection was more frequent in women <30 years old.

The prevalence of HPV genotype is summarized in **Table 2**. The 10 most common HR-HPV types were 16 (27.8%), 52 (16.7%), 58 (12.2%), 53 (9.3%), 51 (9.1%), 56 (7.7%), 68 (6.8%), 18 (6.0%), 39 (5.7%), and 31 (5.2%). Genotype-specific HPV infection varied according to the different grades of disease (**Fig. 1**). The most common HR-HPV genotypes identified were

Table 2. Prevalence of HPV genotypes (n=1,988)

High-risk	No. (%)	Low-risk	No. (%)
16	553 (27.8)	54	89 (4.5)
52	332 (16.7)	84	78 (3.9)
58	242 (12.2)	70	73 (3.7)
53	184 (9.3)	62	60 (3.0)
51	180 (9.1)	81	48 (2.4)
56	152 (7.7)	44	47 (2.4)
68	135 (6.8)	42	43 (2.2)
18	120 (6.0)	6	39 (2.0)
39	113 (5.7)	30	35 (1.8)
31	103 (5.2)	43	30 (1.5)
33	81 (4.1)	55	26 (1.3)
35	64 (3.2)	11	24 (1.2)
59	56 (2.8)	91	23 (1.2)
66	44 (2.2)	72	13 (0.7)
82	44 (2.2)	32	12 (0.6)
45	38 (1.9)	90	5 (0.3)
67	36 (1.8)	40	0
69	5 (0.3)		

HPV, human papillomavirus.

https://doi.org/10.3802/jgo.2019.30.e52

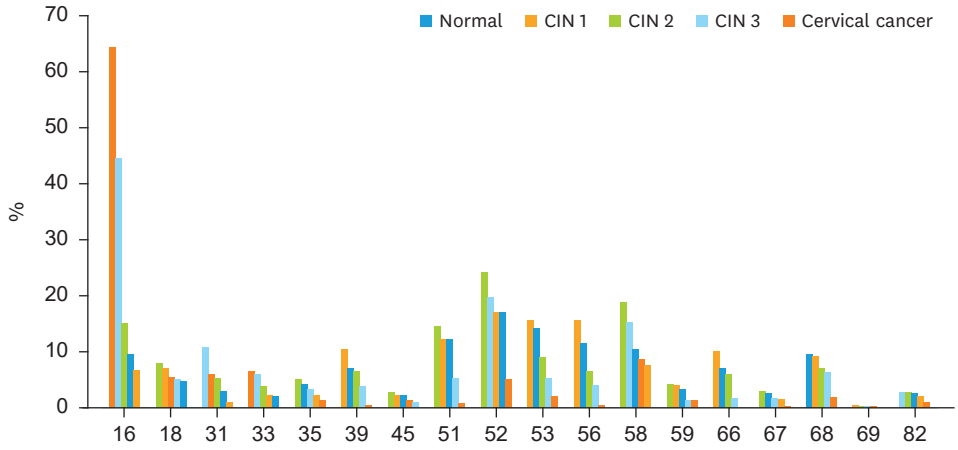

Fig. 1. Genotype-specific prevalence of HR-HPV in different cervical disease grades.
CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus.

16 (64.3%), 58 (8.7%), 33 (6.4%), 31 (5.9%), 18 (5.4%), and 52 (5.1%) in cervical cancer; 16 (44.5%), 52 (20%), 31 (10.8%), 58 (8.7%), and 68 (6.3%) in CIN 3; 52 (24%), 58 (19%), 16 (15%), 51 (15%), and 53 (9%) in CIN 2; 52 (17%), 53 (16%), 56 (16%), 51 (12%), and 39 (11%) in CIN 1; and 52 (17%), 53 (14%), 51 (12%), 56(12%), and 38 (11%) in normal cases.

The distribution of HR-HPV according to age is shown in **Fig. 2**. Three HPV genotypes (16, 52, and 58) were most common in all age groups (≤30 years, n=799; 31–40 years, n=502; ≥41 years, n=653). In addition to HPV 16, 52, and 58, common types were HPV 51 and 53 in those aged ≤30 years; 53 and 68 in those aged 31–40 years; and 18 and 56 in those aged ≥41 years. The prevalence of HR-HPV was analyzed according to age and disease grade (**Fig. 3**). The genotypes showed a similar distribution according to disease grade regardless of age. The most common type was HPV 16 in cervical cancer and CIN 3. Young women with cervical cancer had fewer HPV types than older women. Only 3 types of HR-HPV, 16/31/52 were associated with cervical cancer in women ≤30 years of age. In all age groups, common HR-HPV types in CIN 2 and CIN 1 were 52/58 and 52/53/56, respectively.

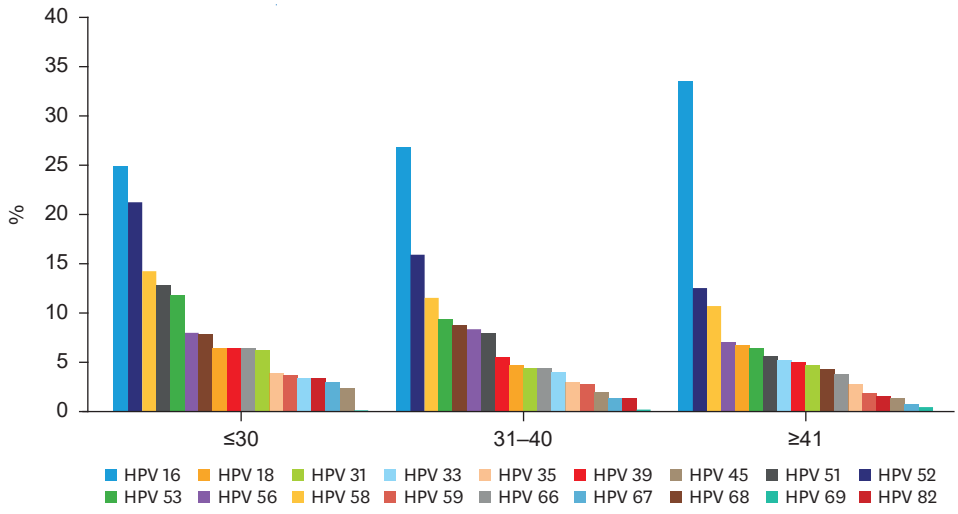

Fig. 2. Genotype-specific distribution of HR-HPV according to age.
HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus.

https://doi.org/10.3802/jgo.2019.30.e52

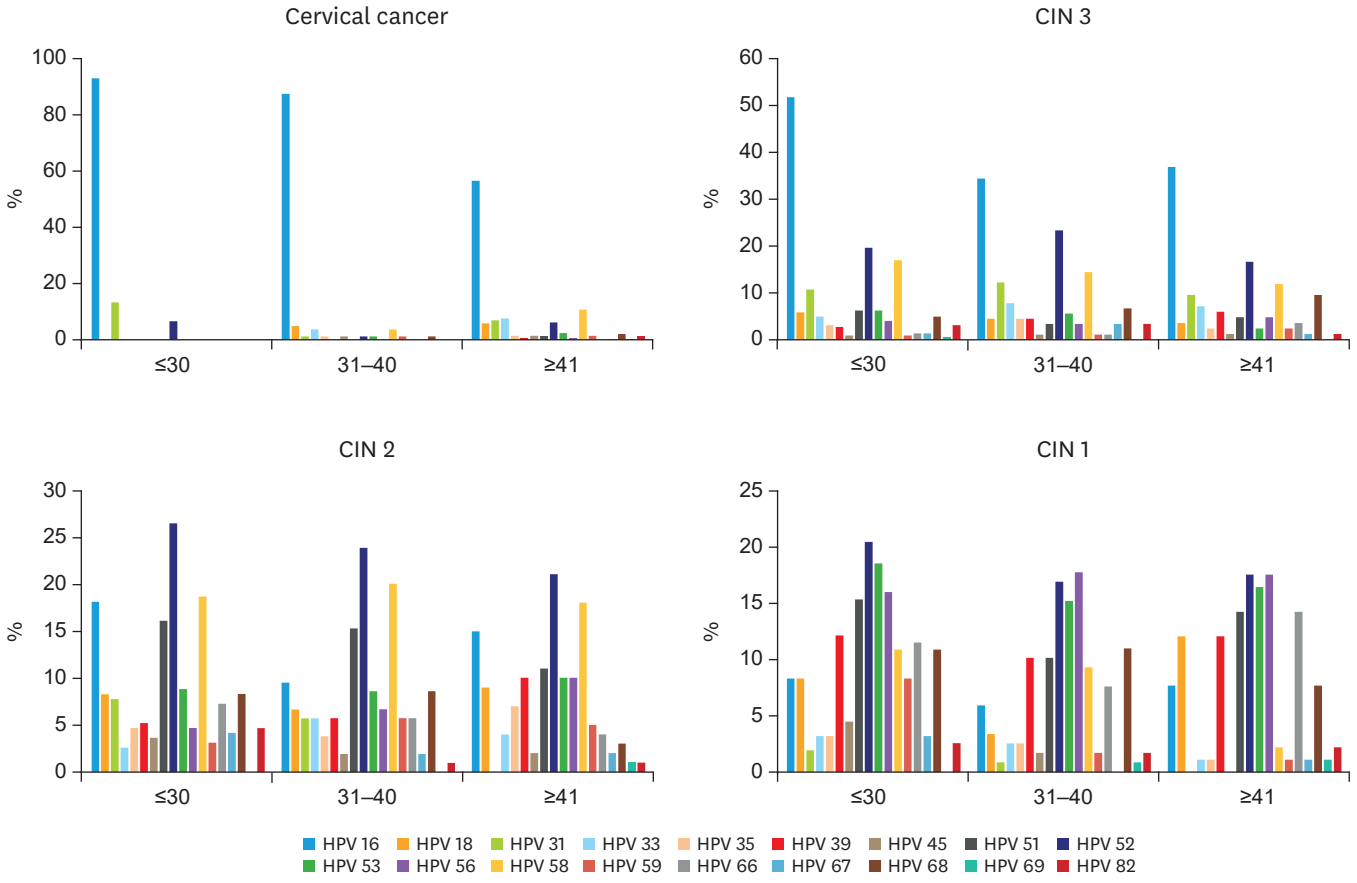

Fig. 3. Prevalence of HR-HPV according to age and disease grades.
CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus.

However, the distribution of genotype-specific HPV according to the severity of cervical lesions showed significant differences (**Table 3**). HPV 16, 31, 33, and 58 were significantly more common in the CIN 2/3/cancer group than in the normal/CIN 1 group. Conversely, HPV 39, 51, 53, 56, 66, and 68 were significantly more common in the normal/CIN 1 group than in the high-grade disease group (p<0.001).

The genotype-specific risks in the CIN 2/3/cancer group in comparison to those in the normal/CIN 1 group are shown in **Table 4**. Compared with the normal group, genotype-specific risk for cancer was found with HPV 16 (OR=17.1; CI=11.6–22.5; p<0.001) and HPV

Table 3. Genotype-specific HPVs according to the severity of cervical lesions

HPV type	Histopathology		p-value
	Normal/CIN 1 (n=799)	CIN 2/3/Cervical cancer (n=1,189)	
16	65 (8.1%)	488 (41.0%)	<0.001
31	16 (2.0%)	87 (7.3%)	<0.001
33	17 (2.1%)	64 (5.4%)	<0.001
58	72 (9.0%)	170 (14.3%)	<0.001
39	70 (8.8%)	43 (3.6%)	<0.001
51	98 (12.3%)	82 (6.9%)	<0.001
53	119 (14.9%)	65 (5.5%)	<0.001
56	108 (13.5%)	44 (3.7%)	<0.001
66	68 (8.5%)	31 (2.6%)	<0.001
68	75 (9.4%)	60 (5.0%)	<0.001

HPV, human papillomavirus.

https://doi.org/10.3802/jgo.2019.30.e52

Table 4. HPV genotype-specific risks of CIN 2/3/Cancer compared with normal/CIN 1

Cervical lesion	Genotype	OR	95% CI	p-value
Cervical cancer vs. Normal	HPV 16	17.1	11.6–25.4	<0.001
	HPV 33	3.4	1.5–7.6	0.002
CIN 3 vs. Normal	HPV 16	7.6	5.2–11.3	<0.001
	HPV 31	3.9	2.0–7.5	<0.001
	HPV 33	3.1	1.4–7.1	0.006
CIN 2 vs. Normal	HPV 58	2.0	1.3–3.0	0.001
	HPV 16	1.7	1.1–2.6	0.023
	HPV 52	1.6	1.1–2.1	0.014
Cervical cancer vs. CIN 1	HPV 16	24.8	15.9–38.6	<0.001
	HPV 31	6.2	2.1–18.1	<0.001
	HPV 33	3.0	1.5–6.6	0.005
CIN 3 vs. CIN 1	HPV 16	11.0	7.1–17.1	<0.001
	HPV 31	11.9	4.2–33.5	<0.001
	HPV 33	2.8	1.3–6.0	0.012
CIN 2 vs. CIN 1	HPV 31	5.5	1.9–16.1	0.001
	HPV 16	2.4	1.5–3.9	<0.001

33 (OR=3.4; CI=1.5–7.6; p=0.002). HPV 16, 31, and 33 were associated with high risk for CIN 3. HPV 58, 16, and 52 were associated with high risk for CIN 2. In contrast to CIN 1, a significantly high risk of cancer was associated with HPV 16 (OR=24.8; CI=15.9–38.6; p<0.001), 31 (OR=6.2; CI=2.1–18.1; p<0.001), and 33 (OR=3.0; CI=1.5–6.6; p=0.005). HPV 16, 31, and 33 were associated with a high risk for CIN 3. HPV 31 and 16 were associated with a high risk for CIN 2.

DISCUSSION

This study analyzed the genotype-specific risk for the spectrum of cervical carcinogenesis and investigated genotype-specific age distribution for different grades of cervical disease. Although the distributions of HPV infections are different according to geographical region, our results are in agreement with previous studies, with a point prevalence of HPV 16 [3,14]. HPV 16 was the most common type, especially in CIN 3 and cervical cancer. HPV 52, 58, 53, and 51 followed HPV 16 in the top 5. HPV 18 (6.0%) and 45 (1.8%) were not common in this study, consistent with the less common types in East Asia [15]. HPV genotypes 16, 52, and 58 were the most common in all age groups according to cervical disease grade. The prevalence of multiple infections was approximately 30% in this study. Multiple HR-HPV infections were more frequent in precancerous lesion and more common in women <30 years old. Several previous studies reported a multiple infection rate of 20%–40% [16,17]. Multiple infections present more frequent in younger women with high-grade CIN and the infection rate decline with increasing age [11]. The potential significance of multiple infections is their common presence in young women and women with multiple sexual partners, and in specimens with abnormal cytology [16,18].

HPV 16/31/33/58 types were more frequently detected in women with high-grade CIN and cervical cancer, whereas HPV 39/51/53/56/66/68 were more frequently detected in women with normal and low-grade CIN. Several HR-HPV types (HPV 53/56/51/39/66/68) were prominent in low-grade CIN but disappeared in high-grade CIN and cancer. The results suggest that there is genotype-specific risk of HR-HPV developing into high-grade CIN and cancer by causing persistent infection. Indeed, these HR-HPV types belong to alpha-9 species (HPV 16/31/33/35/52/58/67) and are likely to have biological properties similar to those of HPV

https://doi.org/10.3802/jgo.2019.30.e52

16 [19]. HPV types in the alpha-9 species are more persistent and more likely to progress to CIN 3 or worse, compared with HPV types in the alpha-5 (HPV 51), 6 (HPV 53/56/66) and 7 (HPV 18/39/45/59/68) groups [20].

This study estimated genotype-specific risks. HPV 16, 31, and 33 were associated with higher risk of CIN 2/3 and cervical cancer compared with normal and CIN 1 cases. HPV 52 and 58 were only associated with higher risk for CIN 2 compared with the normal group. The results showed that relative carcinogenic potential varied. HPV 16/31/33 infection may be a consistent and strong risk for carcinogenesis. Carcinogenic risk of HPV 31 and 33 has been reported [7,21,22]. A 12-year follow-up study in Denmark showed that the absolute risk of CIN 3 or worse among those infected with HPV 31 was 14.3% (CI=9.1–19.4), with 14.9% for HPV 33 (CI=7.9– 21.1) [20]. HPV 52 and 58 are among the 5 most common types associated with cervical cancer in Eastern and Southeastern Asia [13,14,23]. In this study, overall prevalence of HPV 52 and 58 infections was more common than HPV 31/33 infection (28.9% vs 9.3%). Therefore, the prevention of HPV 52 and 58 infections is important to reduce the burden of precancerous cervical disease.

Most HPV infections are self-regulated for one to 2 years, and development of cervical cancer may take a long time even in patients with persistent HPV infection. This study is not a prospective study with repeated HPV results in the same patient so that actual progression from normal to cervical cancer for individual HPV types may be an indirect consideration. However, this study has strengths that relatively large sample size including all grades of disease in the cervical carcinogenesis. The cases of each disease group are well balanced. The results of our study provide important information regarding difference in the CIN2/3/cancer and normal/CIN1 prevalence of individual HPV types and different distribution of HR-HPV according to age. The results can be helpful for individualized management with HPV genotype-based screening.

Our study indicates that HPV 16, 31, 33, 52, and 58 infections are associated with significant risk of high-grade disease and might play important roles in the development of cervical cancer. Fortunately, these oncogenic HPV infections can be prevented by vaccination. The quadrivalent and bivalent HPV vaccines prevent precancerous lesions related to HR-HPV 16 and 18 [24,25]. Recently, a nonavalent vaccine became available to protect against HR-HPV 31, 33, 45, 52, and 58, in addition to HPV 16 and 18 [26]. Our data will be useful in the assessment of effectiveness of HPV vaccination and will provide additional information on the risk of developing cervical cancer in HPV infected women.

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