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ORIGINAL RESEARCH

HPV Genotype Specific and Age Stratified Immediate Prevalence of Cervical Precancers and Cancers in Women with NILM/hrHPV+: A Single Center Retrospective Study of 26,228 Cases

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Purpose: To investigate the prevalence of precancers [high-grade squamous intraepithelial lesion (HSIL) and adenocarcinoma in situ (AIS)] and cancers [squamous cell carcinoma (SCC) and adenocarcinoma (ADC)] in various high-risk human papillomavirus (hrHPV) genotypes or age groups among women with negative for intraepithelial lesion or malignancy (NILM) and hrHPV-positive pap results.

Materials and Methods: In total, 26,228 women with NILM/hrHPV+ were included in the study. Among them, 5893 had immediate follow-up biopsy results available and were selected for further prevalence analysis.

Results: About 7.6% and 0.7% women with NILM/hrHPV+ had HSIL and AIS, respectively. The prevalence of HSIL+ squamous lesions is significantly higher in HPV-16+ group than that in other genotype groups ($p < 0.0001$). The prevalence of AIS+ glandular lesions is significantly higher in HPV-18/45+ groups than women in other genotype groups ($p < 0.0001$). In addition, the prevalence of HSIL+ lesions was significantly higher in age 25–39 years group than that in age 40–65 years group and >65 years group ($p < 0.0001$). Overall, the prevalence of HSIL+ in younger women was significantly higher than that in older women when using a cutoff age of 40 years (9.3% vs 5.9%, $p < 0.0001$) or 50 years (8.6% vs 4.9%, $p < 0.0001$). No significant difference in AIS+ prevalence was found among different age groups ($p = 0.611$). Interestingly, the prevalence of SCC and ADC in older women (≥40 years, 0.3% and 0.3%, respectively) was significantly higher than that in younger women (<40 years, 0% and 0.07%) ($p = 0.001$ for SCC; $p = 0.02$ for ADC).

Conclusion: The significant risk of cervical precancers and cancers still exists in women with NILM/hrHPV+, notably the older patient group had a lower risk of cervical precancer, but higher risk of cancer. Therefore, HPV genotyping can be an effective supplemental tool to cytology, and patient age also needs to be considered in the clinical management of patient.

Keywords: risk stratification, E6/E7 mRNA genotyping, NILM, hrHPV

Introduction

Despite advances in screening and treatment options, cervical cancer remains a significant public health problem, especially in developing countries.[1] In the vast majority of cases, it is caused by persistent high-risk human papillomavirus (hrHPV) infection.[2] Complex genetic and epigenetic processes occur during the integration of HPV genomes into host cell chromosomes, which eventually lead to the overexpression of HPV E6 and E7 oncoproteins, cervical cell immortalization, neoplastic

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transformation, and the development of invasive cancer.[3–5] There is evidence that the implementation of the cervical cancer screening program has significantly reduced the prevalence and mortality of cervical cancer worldwide in the past decades. However, ongoing debates have focused on what is the most cost-effective strategy for routine cervical cancer screening. Commonly used screening strategies include primary HPV testing, co-testing with HPV testing and cervical cytology, and cervical cytology alone.[6] The cytology alone approach has been proven to have low sensitivity and often poor inter-observer reproducibility.[7] The introduction of DNA-based HPV tests, such as the Hybrid Capture 2 assay (HC2) HPV and Cobas 4800 HPV, hrHPV test, has significantly improved the sensitivity of cervical screening.[8–11] DNA-based HPV tests cannot distinguish transit viral infection from integrated viral DNA.[12] In contrast, viral E6/E7 mRNA testing has demonstrated significantly higher clinical specificity, as E6/E7 mRNA directly reflects the active transcription of viral oncogenes.[13–17] Therefore, the E6/E7mRNA test has been used in cervical cancer primary screening due to its high sensitivity and even higher specificity.[18] In addition, HPV E6/E7 mRNA testing may be more useful as a screening test for early detection and prediction of subsequent progression to severe dysplasia.[19–21]

Patients with a result of negative for intraepithelial lesion or malignancy (NILM)/hrHPV+ have increasingly become a common cohort ever since cytology and HPV cotesting was approved by the FDA in 2003.[22] Meanwhile, it has raised a particular challenge regarding patient management of women with NILM/hrHPV+. Thus far, large-scale population studies have not been conducted in the Chinese population. Considering the size, socioeconomic, ethnic diversity of the Chinese population, a large-scale study is needed. Given the limited literature and data in this field, we report our experience of the prevalence of cervical precancer and cancer in women with NILM/hrHPV+ in a southern Chinese women population.

Materials and Methods

Patients and Samples

This study was approved by the ethics committee of the Zhejiang University School of Medicine Women's Hospital (IRB-20210162-R) and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective nature of the study, the requirement for informed consent was waived. As one of the largest women's hospitals in China, Zhejiang University Women's Hospital provides care for over 1,500,000 outpatients and 77,000 inpatients annually. Women's hospital is also a cervical cancer screening center of Zhejiang province, one of the most developed and populated provinces of China. A retrospective, computer-based search in the clinical information system database at the hospital was performed to identify cases that had undergone the Aptima human papillomavirus (AHPV) assay and Pap smear test between September 2016 and May 2020. Patients included in this study represent the female population of southern China undergoing routine clinical cervical cancer screening, with a mixture of urban and rural settings, as shown in Figure 1. Among them, 26,228 cases with NILM/hrHPV+ were identified, of which 5893 cases had undergone follow-up colposcopy examination with biopsy and/or curettage based on the ASCCP guidelines.[6] Generally, if the colposcopy examination was unsatisfactory (the squamocolumnar junction was not completely visible) or no viable lesion identified, ECC was performed. Colposcopists were made aware of the cytology and AHPV results before the colposcopy visit was performed. The lack of histologic follow-up results of the rest of the patients is due to the patients being lost to follow up or receiving care elsewhere.

Liquid-Based Cytology (LBC) and hrHPV mRNA Testing

ThinPrep Pap tests (Hologic, Inc., San Diego, CA) were prepared according to the manufacturer's specifications. Cytology slides were produced automatically by Thin Prep 2000 (Cytyc Corporation, Marlborough, MA). All the cytological diagnoses were made by cytopathologists and in accordance with the 2014 Bethesda system. Residual LBC samples were processed for the AHPV assay (Hologic, Inc., San Diego, CA), according to the manufacturer's specifications. The E6/E7 oncogenic mRNA, which is associated with 14 hrHPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), was detected. AHPV-positive samples were reflex-tested by HPV 16, 18/45 Genotype assay.

Follow-Up Histopathologic Diagnoses in Patients

Immediate histological correlation results including cervical biopsy and endocervical curettage performed within 6 months of the Pap and AHPV tests were included in the current study. The histopathologic results were categorized into 4 general groups: 1) normal (including no pathologic alteration and benign or reactive changes); 2) Low-grade squamous

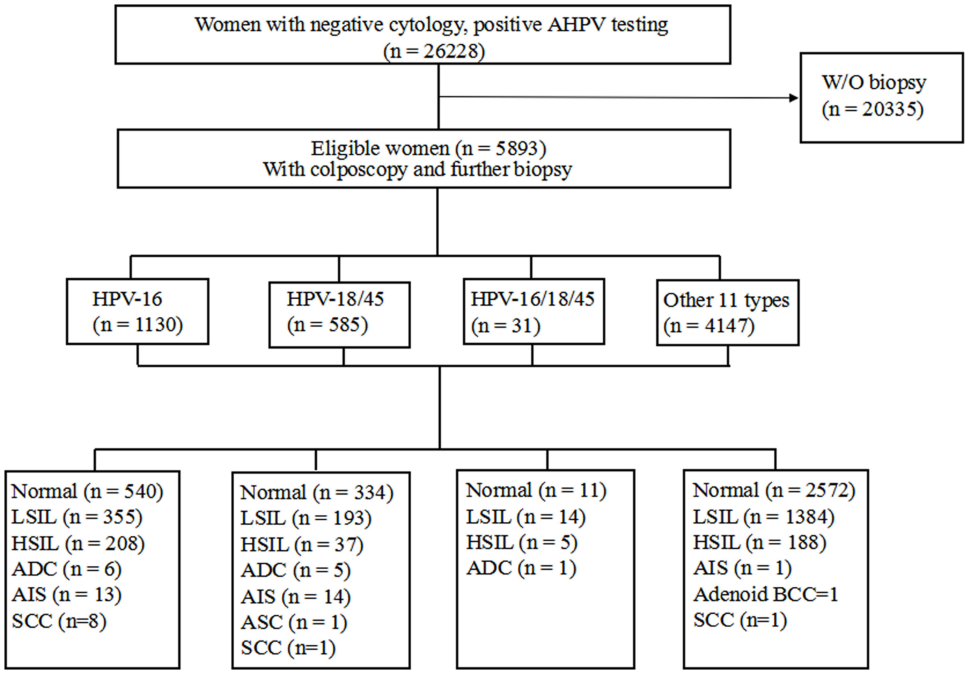

Figure 1 Flow chart of selection criteria of participants.
Abbreviations: W/O, Without; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; ABC, adenoid basal carcinoma; ASC, adenosquamous carcinoma; hrHPV, high-risk human papillomavirus.

intraepithelial lesion (LSIL); 3) High grade cervical squamous lesion (HSIL+), defined as high-grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma (SCC), and 4) high grade cervical glandular lesion (AIS+), defined as adenocarcinoma in situ (AIS) or adenocarcinoma (ADC). HSILs were confirmed by immunohistochemical staining for p16 and Ki-67. In patients with more than one tissue sample, the most abnormal diagnosis was recorded. HSIL and AIS lesions were considered as cervical precancers.

Statistical Analysis

Statistical analyses were performed using the Pearson chi-square or Fisher exact test using SPSS software (IBM, Armonk, NY, USA) to compare distribution of HSIL+ and AIS+ in different age groups; Kruskal–Wallis test were performed for comparisons of the distribution of histologic results among the NILM population in different hrHPV genotypes. $p<0.05$ was considered statistically significant.

Results

Specific HPV Genotype Prevalence per Histologic Diagnosis Among Women with NILM/hrHPV+

Detailed analysis is included in Table 1. A total of 26,228 cases with negative cytology and positive hrHPV testing were retrieved. The mean age of all patients was 41.3 years (range 17 from to 88). Among them, 12.9% were HPV-16 positive, 6.1% were HPV-18/45 positive, 0.4% were HPV 16 and 18/45 dual, and 80.7% were positive for other 11 HPV types. Totally, 5893 cases had available immediate follow-up biopsy or ECC (within three months) and the biopsy rate for HPV-16, HPV-18/45, HPV-16 and 18/45 dual, and other 11 HPV types positive women were 33.5%, 36.9%, 32.3%, 19.6%, respectively. 3457 (58.7%) were regarded as benign, 1946 (33.0%) had LSIL, 438 (7.4%) had HSIL, 28 (0.5%) had AIS, and 24 (0.4%) had cervical carcinoma including 10 SCC, 12 ADC, 1 adenoid basal carcinoma, and 1 adenosquamous carcinoma.

The Prevalence of Cervical Precancers and Cancers Among Women with NILM/hrHPV+

Among 5893 women with NILM/hrHPV+, 448 (7.6%) were diagnosed with HSIL+ squamous lesion, and 40 (0.7%) were diagnosed with AIS+ glandular lesion. When further analyzed along the genotypes, genotype-specific risk stratification of HSIL+ and AIS+ lesions were observed. The prevalence of HSIL+ squamous lesions in the HPV-16+ group was 19.1%, while in the HPV-18/45 and other 11 HPV types positive group, the

Table 1 Distribution of hrHPV Infection Patterns Among the Women with NILM/hrHPV+

hrHPV Genotype	Normal	LSIL	HSIL	SCC	ADC	AIS	ASC	ABC	With F/U	W/O Biopsy	Total
HPV16	540 (47.8%)	355 (31.4%)	208 (18.4%)	8 (0.7%)	6 (0.5%)	13 (1.2%)	0 (0)	0 (0%)	1130 (33.5%)	2242 (66.5%)	3372 (12.9%)
HPV18/45	334 (57.1%)	193 (33.0%)	37 (6.3%)	1 (0.2%)	5 (0.9%)	14 (2.4%)	1 (0.2%)	0 (0%)	585 (36.9%)	1002 (63.1%)	1587 (6.1%)
Other 11 types	2572 (62.0%)	1384 (33.4%)	188 (4.5%)	1 (0.02%)	0 (0%)	1 (0.0%)	0 (0%)	1 (0.0%)	4147 (19.6%)	17,026 (80.4%)	21,173 (80.7%)
HPV16, 18/45	11 (35.5%)	14 (45.2%)	5 (16.1%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	0 (0%)	31 (32.3%)	65 (67.7%)	96 (0.4%)
Total	3457 (58.7%)	1946 (33.0%)	438 (7.4%)	10 (0.2%)	12 (0.2%)	28 (0.5%)	1 (0.0%)	1 (0.0%)	5893 (22.5%)	20,335 (77.5%)	26,228

Abbreviations: F/U, follow-up; W/O, Without; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; ABC, adenoid basal carcinoma; ASC, adenosquamous carcinoma; hrHPV, high-risk human papillomavirus.

prevalence of HSIL+ was 6.5% and 4.6%, respectively ($p<0.0001$). Similarly, the prevalence of AIS+ lesions in HPV-18/45 positive group was 3.2% while in HPV-16 and other 11 HPV types positive group the risk was 1.7% ($p=0.036$) and 0.02% ($p<0.0001$), respectively. The prevalence of HSIL+ and AIS+ in HPV-16 and 18/45 dual positive women was 16.1% and 3.2%, respectively. No statistical analysis was performed in HPV-16 and 18/45 dual positive women due to limited case numbers (n=31).

Among patients with HSIL+ lesions, HPV-16 accounted for 48.2% of HSIL+. HPV-18/45 accounted for 8.5% of HSIL+ and other 11 genotypes accounted for 42.2% HSIL+. Among patients with AIS+ lesions, HPV-16 accounted for 47.5%, HPV-18/45 accounted for 47.5%, and other 11 genotypes accounted for 2.5%. The overall prevalence of SCC and ADC among women with HILM/hrHPV+ was low (0.2% and 0.2%, respectively). Although the prevalence of SCC is low in the HPV-16 or 18/45+ group (0.5%), it is still significantly higher than that of other genotype group (0.02%) ($p=0.000024$). Similarly, the prevalence of ADC in HPV-16 or 18/45+ group (0.6%) is significantly higher that of other genotype group (0%) ($p<0.00001$). Detailed analysis is included in Table 2.

Age-Stratified Immediate Histologic Correlation Results Among Women with NILM/hrHPV+

We analyzed the distribution of hrHPV genotypes in different age groups. For the total of 26,228 cases with NILM/hrHPV+, 1481 (5.6%) were younger than 25 years, 11,533 (44.0%) were 25–39 years, 12,552 (47.9%) were 40–65 years, and 662 (2.5%) were over 65 years. Among the available follow-up biopsies in 5893 cases, 265 patients were younger than 25 years, 86 (32.5%) were HPV-16 positive, 35 (13.2%) were HPV-18/45 positive, 5 (1.9%) were HPV-16 and 18/45 dual positive, and 139 (52.5%) were positive for other 11 types of HPV. Of the 2687 patients in group aged 25 to 39 years, 550 (20.5%) were HPV-16 positive, 287 (10.7%) were HPV-18/45 positive, 15 (0.6%) were HPV-16 and 18/45 dual positive, and 1835 (68.3%) were positive for other 11 HPV types. Of the 2839 patients in the age group of 40 to 65 years, 467 (16.4%) were HPV-16 positive, 253 (8.9%) were HPV-18/45 positive, 10 (0.4%) were HPV-16 and 18/45 dual positive, 2109 (74.3%) were positive for other 11 HPV types. Of the 102 patients in the age group of over 65 years, 27 (26.5%) were HPV-16 positive, 10 (9.8%)

Table 2 The Prevalence of Precancer and Cancer Among Women with NILM/hrHPV+

hrHPV Genotype	Total	With F/U	Squamous Lesions				Glandular Lesions			
			HSIL+	p-value	SCC	p-value	AIS+	p-value	ADC	p-value
HPV16	3372	1130 (33.5%)	216 (19.1%)	<0.0001*	8 (0.7%)	<0.0001*	19 (1.7%)	<0.0001*	6 (0.5%)	<0.0001*
HPV18/45	1587	585 (36.9%)	38 (6.5%)		1 (0.2%)		19 (3.2%)		5 (0.9%)	
Other 11 types	21,173	4147 (19.6%)	189 (4.6%)		1 (0.02%)		1 (0.02%)		0	
HPV16, 18/45	96	31 (32.3%)	5 (16.1%)		0		1 (3.2%)		1 (3.2%)	
Total	26,228	5891 (22.5%)	448 (7.6%)		10 (0.2%)		40 (0.7%)		12 (0.2%)	

Note: *p<0.05 was considered statistically significant.

Abbreviations: F/U, follow-up; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; HSIL+, HSIL or SCC; AIS+, AIS or ADC.

were HPV-18/45 positive, 1 (0.1%) were HPV 16 and 18/45 dual positive, and 64 (62.7%) were positive for high-risk genotypes other than 16 and/or 18/45.

Among women with HSIL+ lesions: 23 (5.1%) were younger than 25 years, 252 (56.3%) were aged 25 to 39 years, 166 (37.1%) were aged 40 to 65 years, 7 (1.6%) were patients aged over 65 years old. The prevalence of HSIL+ lesions was significantly higher in the age group of 25–39 years (9.4%) than in the younger than 25 years (8.7%) age group, in the 40–65 years (5.8%) group, and the >65 years group (6.9%) ($p<0.0001$). We further analyzed the prevalence of HSIL+/AIS+ lesions along different single age cutoffs. A significant difference in prevalence of HSIL+ lesions is noted when 40 or 50 years was chosen as the cutoff. The prevalence of HSIL+ lesion is significantly different in patients aged <40 years and ≥40 years (9.3% vs 5.9%) ($p<0.0001$) compared to those aged <50 and ≥50 years (8.6% vs 4.9%) ($p<0.0001$). The prevalence for HSIL+ lesions in women in patients aged <25 and ≥25 years was similar ($p=0.52$). There were no significant differences for AIS+ lesions among the different age group. In contrast to that of HSIL+ squamous lesions, the prevalence of SCC and ADC in patients aged ≥40 years (0.3% and 0.3%, respectively) was significantly higher than that in patients aged <40 years (0% and 0.07%) ($p=0.004$ for SCC; $p=0.02$ for ADC). Detailed analysis is included in Tables 3 and 4.

Discussion

Multiple studies have consistently reported that HPV combined with cytology testing is a more effective cervical cancer screening method compared with cytology alone, as such co-testing carries a high sensitivity to detect cervical cancer precursors.[23–26] In comparison with DNA-based HPV tests, the mRNA-based AHPV test has been found to be more specific in detecting high-grade cervical lesions.[12,27] Further, a number of comparison studies have demonstrated that the clinical performance of the AHPV assay is equivalent to that of the Cobas HPV assay and shows a similar sensitivity for detection of CIN3+ and a significantly higher specificity than the HC2 assay.[28–32] Therefore, the AHPV assay has been considered suitable for primary screening of cervical cancer.

In this cohort, HPV-16 accounts for 12.9%, HPV-18/45 accounts for 6.1%, HPV 16 and 18/45 dual accounts for 0.4%, and the other 11 genotypes account for 80.7% of NILM/hrHPV+ cases. A study by Han et al[22] reported the

Table 3 Age-Stratified Immediate Histopathologic Correlation Among Women with NILM/hrHPV+

Age	Total	With F/U	Squamous Lesions				Glandular Lesions					*p*-value
			HSIL+	*p*-value	SCC	*p*-value	AIS+	*p*-value	ADC	*p*-value	Total	
<25	1481	265 (17.9%)	23 (8.7%)	<0.0001*	0	0.017*	0	0.611	0	0.0392 (25–39 vs 40–65)	0	0.585
25–39	11,533	2687 (23.3%)	252 (9.4%)		0		16 (0.6%)		2 (0.07%)		18 (0.7%)	
40–65	12,552	2839 (22.6%)	166 (5.8%)		9 (0.3%)		12 (0.4%)		10 (0.4%)		22 (0.8%)	
>65	662	102 (15.4%)	7 (6.9%)		1 (1.0%)		0		0		0	
Total	26,228	5893					28		12		40	

Note: *p<0.05 was considered statistically significant.

Abbreviations: F/U, follow-up; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; HSIL+, HSIL or SCC; AIS+, AIS or ADC.

Table 4 Immediate Risk of Precancer and Cancer Between Older and Younger Group with NILM/AHPV+

Age	Total	With F/U	Squamous Lesions				Glandular Lesions			
			HSIL+	*p*-value	SCC	*p*-value	AIS+	*p*-value	ADC	*p*-value
25-y cutoff										
<25 y	1481	265 (17.9%)	23 (8.7%)	0.52	0	1.0	0	0.320	0	0.956
≥25 y	24,747	5628 (22.7%)	425 (7.6%)		10 (0.2%)		40 (0.7%)		12 (0.2%)	
40-y cutoff										
<40 y	13,014	2952 (22.7%)	275 (9.3%)	<0.0001*	0	0.004*	18 (0.6%)	0.518	2 (0.07%)	0.02*
≥40 y	13,214	2941 (22.3%)	173 (5.9%)		10 (0.3%)		22 (0.7%)		10 (0.3%)	
50-y cutoff										
<50 y	18,951	4340 (22.9%)	372 (8.6%)	<0.0001*	3 (0.07%)	0.006*	31 (0.7%)	0.58	7 (0.2%)	0.380
≥50 y	7277	1553 (21.3%)	76 (4.9%)		7 (0.5%)		9 (0.6%)		5 (0.3%)	

Note: *p<0.05 was considered statistically significant.

Abbreviations: F/U, follow-up; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; HSIL+, HSIL or SCC; AIS+, AIS or ADC.

rate for HPV-16 and HPV-18/45 positivity based on the AHPV assay in NILM/hrHPV+ women was 10.0% and 8.4%, and for other 11 HPV types was 81.6%. In Korea, it is reported that the prevalence of HPV-16 and HPV-18 was 19.6% and 7.5% in 265 NILM/hrHPV+ women, respectively.[33] In another retrospective study, the results from the Cobas assay demonstrated a slightly lower HPV-16 and/or HPV-18 prevalence in Chinese women with NILM/hrHPV+ (17.6% for HPV-16, 6.2% for HPV-18, and 0.6% for HPV-16 and HPV-18) than in Korean women.[34] The distribution of HPV genotypes in women with NILM/hrHPV+ differs among countries; this may be attributed to different subtypes of HPV infection in different races and regions, and the different detection platforms.[35]

As mentioned earlier, the mRNA-based AHPV assay has been found to be more specific in detecting high-grade cervical lesions.[13–17] The results showed that women with NILM/hrHPV+ still have significant risk of cervical cancer, and the AHPV assay can be an effective screening test for early detection and prediction of subsequent progression to severe dysplasia. A recent study found that the colposcopy referral rate could be reduced by more than 30% with combined cytology-Aptima triage compared with co-testing of cytology and HPV DNA assays.[36] Compared with HPV DNA-based tests, the AHPV test reduced false-positive results by 24% in a negative for NILM group.[28,37] In our study, the immediate histologic results demonstrated that approximately 7.6% were HSIL+ and 0.7% were AIS+ among women with NILM/hrHPV+. HPV-16 or 18/45+ women have significantly higher prevalence of HSIL+ and AIS+ lesions than women infected with other high-risk genotypes. HPV-16+ and HPV-18/45+ women showing the highest prevalence for HSIL+ lesions (19.1%) and AIS+ lesions (3.3%) in follow-up biopsies, respectively. In contrast, only 4.6% and 0.02% of women positive for other 11 HPV genotypes were diagnosed with HSIL+ lesion and AIS+ lesions in follow-up cervical biopsies, respectively. Our data is similar to that of a previous study by Han et al,[22] in which 11.5% of HPV-16 or 18/45+ women and 3.6% of women positive for other 11 HPV genotypes were diagnosed with HSIL+ lesions in follow-up biopsies. Since routine cytologic cervical screening has been significantly less effective in preventing rare cervical cancers in young women, surveillance alone is likely to be too risky for HPV-16 or 18/45+ women with NILM cytology.

HPV genotypes 16 or 18/45 are more likely to be integrated into the human genome than other HPV genotypes,[3] accounting for approximately 80% of all invasive cervical cancers worldwide.[38] In this study, 24 cases of cervical carcinoma were identified in women with NILM/hrHPV+, among which HPV-16 and 18/45 accounted for most of cervical carcinoma cases. In addition, 28 AIS were identified in the current study. Glandular cells on cervical smears have garnered more attention in the last decade because of the increase in the incidence of cervical ADC, especially in young women.[39] Some reports showed higher rates of detection of glandular abnormalities in LBC smears,[40] because of better endocervical sampling with improved cell transfer in liquid medium and improved morphology.[40,41] However, other studies did not demonstrate such findings.[42–44] These findings support a co-testing strategy, which may help with the detection of cervical carcinoma, especially for ADC and its precursor lesions.

In this study, we also showed that the prevalence of cervical precancer in younger women was significantly higher than those in older women when using cutoffs of 40 and 50 years. The highest risk of HSIL+ in patients with NILM/hrHPV+ aged 25–39 years was found among the different age group. In younger women, especially aged <25 years, the HPV usually regresses spontaneously and there is usually low risk of cervical precancer or cancer in the follow-up biopsy. Moscicki et al[45] showed that women aged 20–24 years with a diagnosis of HSIL had a 50% likelihood of regressing without intervention. While the prevalence of HSIL+ in younger women (<40 years) was significantly higher than that in older women (≥40 years), the prevalence of SCC and ADC in older patients (≥40 years) was significantly higher than that in younger patients (<40 years). This phenomenon may be interpreted that although hrHPV infections are less frequent in elder women compared with younger ones, the risk of persistent infections increases with age.[46,47] These findings are supportive of time (age) as a risk factor for transition from cervical precancers to cancer, and thus perimenopausal and postmenopausal women with NILM/hrHPV+ had a lower risk of cervical precancer, but high risk of cancer.

There were several limitations to our study: 1) Our data derived from a clinic-based population rather than a general population may represent a biased sample; 2) Due to the limitation of the test (Aptima assay), we were unable to analyze HPV-18 and HPV-45 separately.

However, both of them belong to clade alpha-7; 3) Our study only provided a "snapshot" of the prevalence of hrHPV genotypes and the immediate risk assessment of cervical lesions in this southern Chinese women population. A future large-scale study that includes hrHPV+ women with long-term regular follow-up biopsy history may provide more detailed and dynamic assessment of the accumulative risk of cervical precancer and cancer within this population.

Conclusion

This is one of the largest studies to investigate the immediate follow-up results for Chinese population with NILM/hrHPV+ based on Aptima assay. This study showed the highest prevalence of cervical precancers and cancers in HPV-16 positive cases and demonstrated that HPV-16 or 18/45 confer the greatest risk for cervical precancers and cancers. This large-scale study may be helpful to improve patient management of women with NILM/hrHPV+.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the Zhejiang University School of Medicine Women's Hospital (IRB-20210162-R) and was conducted in accordance with the Declaration of Helsinki. The ethics committee waived the requirement for informed written consent, as the study was a retrospective study and there was no additional risk to patients. All data were anonymized to maintain patient privacy.

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Disclosure

The authors report no conflicts of interest in this work.

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