European Journal of Gynaecological Oncology

Original Research

Necessity for immediate referral to colposcopy according to human papillomavirus (HPV) genotypes in negative-cytology women

Taejong Song[1], Seok Ju Seong[2,*], Seon-Kyung Lee[3], Byoung-Ryun Kim[4], Woong Ju[5], Ki Hyung Kim[6], Kyehyun Nam[7], Jae Chul Sim[8], Tae Jin Kim[9]

[1] *Department of Obstetrics & Gynecology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 03181 Seoul, Republic of Korea*

[2] *Department of Obstetrics & Gynecology, CHA Gangnam Medical Center, CHA University, 06135 Seoul, Republic of Korea*

[3] *Department of Obstetrics & Gynecology, CHA Ilsan Medical Center, CHA University, 10414 Goyang, Republic of Korea*

[4] *Department of Obstetrics & Gynecology, School of Medicine, Wonkwang University, 54538 Iksan, Republic of Korea*

[5] *Department of Obstetrics & Gynecology, Ewha Womans University School of Medicine, 07985 Seoul, Republic of Korea*

[6] *Department of Obstetrics & Gynecology, Pusan National University School of Medicine, 49241 Busan, Republic of Korea*

[7] *Department of Obstetrics & Gynecology, Soonchunhyang University Bucheon Hospital, 14584 Bucheon, Republic of Korea*

[8] *Department of Obstetrics & Gynecology, Dongguk University Gyeongju Hospital, Graduate School of Medicine of Dongguk University, 38067 Gyeongju, Republic of Korea*

[9] *Department of Obstetrics and Gynecology, Konkuk University School of Medicine, 05030 Seoul, Republic of Korea*

*Correspondence: sjseongcheil@naver.com (Seok Ju Seong)

DOI:10.31083/j.ejgo4206170

Submitted: 9 February 2021 Revised: 24 March 2021 Accepted: 1 April 2021 Published: 15 December 2021

Objective: This study aimed to investigate the risk of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) according to high-risk (HR) human papilloma virus (HPV) genotypes in women with negative cytology. *Methods*: A total of 33,531 Korean women who received Pap cytology + HPV co-testing for cervical cancer screening were retrospectively collected. To evaluate the risk of CIN2+ according to HR-HPV genotypes, odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by a logistic regression model. *Results*: Of 1337 women with negative Pap result but HR-HPV positive included in the analysis, 160 (12.0%) women were infected by HPV16 or HPV18, while 1177 (88.0%) women were had other HR-HPVs infections. The prevalence of CIN2+ diseases was 3.7% (50 of 1337). In women with HPV16-negative, HPV18-negative, but other HR-HPV-positive (n = 1177), the risk for CIN2+ lesion was significantly increased in women with multiple HR-HPV infections (OR, 5.40; 95% CI, 2.37–12.73), those with HPV58 (OR, 4.83; 95% CI, 2.17–10.74), and those with HPV35 (OR, 4.77; 95% CI, 1.36–16.77). *Conclusion*: Colposcopy should also be referred to women with multiple HR-HPVs, HPV35, or HPV58 infections, as well as those with HPV16 and HPV18.

Keywords

Uterine cervical neoplasms; Human papillomavirus; Colposcopy; Cytology

1. Introduction

Human papilloma viruses (HPVs) are DNA viruses etiologically implicated in development of cervical, vaginal, and vulvar cancer and its precursors [1]. More than 200 types HPV ranging from HPV1 to HPV205 have been found and are classified as high-risk (HR) or low-risk types according to their oncogenicity [2]. HPV16 and HPV18 cause 70% of cervical cancers and cervical intraepithelial neoplasia (CIN) whereas HPV6 and HPV11 cause most of genital warts or condylomas [3, 4].

Overall HPV infection prevalence worldwide was estimated to be 10% [5]. However, the HR-HPVs prevalence in women with cervical cancer was as high as approximately 95% (range, 91%–99.7%) [6, 7]. Therefore, detection of HR-HPV is becoming increasingly attractive as a primary screening tool for cervical cancer because of its sensitivity and cost-effectiveness [8, 9]. In 2014, the United States Food and Drug Administration (FDA) approved the first assay to be used as a first-line cervical cancer screening to detect HR-HPV in women 25 years of age or older. Approval was based on results from the Addressing THE Need for Advanced HPV Diagnosis (ATHENA) observational clinical trial that assessed HPV-alone screening in 42,209 women [10].

The 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) guideline for cervical cancer screening recommends that women with negative Pap cytology but HPV16 or HPV18 positive should undergo colposcopy [11, 12]. In women with cytology negative but other HR-HPVs positive except HPV16 and HPV18 types, the 2019 ASCCP guidelines recommend co-testing of Pap cytology and HPV test again in one year without the immediate referral to colposcopy [11, 12]. However, this can be lead to a significant problem in the diagnosis and treatment for cervical cancer women with a false-negative error of Pap cytology. Because

understanding the natural history of HPV infection is important to identify high risk population of cervical cancer and guide the prevention of cervical cancer, this study aimed to evaluate the risk of CIN grade 2 or worse (CIN2+) according to specific HR-HPV type infection in women with negative cytology.

2. Materials and methods

This cross-sectional study retrospectively analyzed data of the private clinics/hospitals and health examination centers of university hospital for 29,282 women who had undergone Pap + HPV co-testing for the cervical cancer screening in Korea from January 2015 to December 2016. Colposcopic examination was carried out if co-testing revealed any abnormal results. Inclusion criteria were as follows: age between 18 and 80 years, HPV genotyping data available, and the presence of data of colposcopic cervical biopsy as the gold standard diagnostic test. Exclusion criteria were: history of operative hysterectomy, current or prior history of CIN or worse within the recent two years, or pregnant status. This retrospective study was approved by the local ethics committee of Kangbuk Samsung Hospital (Approval No.: KBSMC 2018-05-023; Approval date: 15 May 2018), and the need for written informed consent was waived.

HPV DNA test was carried out for cervical swab samples with nucleic acid amplification assays (DNA chip array, Ahngookbio, Chuncheon, Korea; PCR-RFMP assay, EONE Laboratories, Incheon, Korea; RT-PCR assay, Seegene, Seoul, Korea) to detect the HR-HPV (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82). In this study, HPV DNA tests were considered to be positive for other HR-HPV if type 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, or 82 was detected on swab sample. Colposcopic punch biopsy was carried out when any HR-HPV positive was found on cervical swab sample.

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Qualitative data were presented as frequencies (percentages) whereas quantitative variables were presented as means ± standard deviations (SDs) or medians (interquartile ranges) after checking for normality of data distribution. To evaluate the risk of CIN2 or worse (CIN2+) according to specific HR-HPV types, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by a logistic regression model. Statistical significance was set at p-values < 0.05.

3. Results

Of 33,531 women who received Pap + HPV co-testing for cervical cancer screening during the study period, 32,123 women were excluded because of follow-up screening data of identical person (n = 334), co-testing not conducted simultaneously (n = 4249), no available data of colposcopic punch biopsy (n = 24,760), or Pap cytology results of ASCUS or worse (n = 2780). A total of 1408 women with negative Pap result but HR-HPV positive were identified. However, 71 women were further excluded due to no available data about other HR-HPV genotyping. Therefore, 1337 women were finally included in this study (Fig. 1).

The mean age of these 1337 women was 34.5 ± 9.8 years and the baseline characteristics are displayed in Table 1. Pap cytology was carried out using liquid-based method in 851 (63.6%) cases and conventional smear in 485 (36.3%) cases. All cytology results were negative for intraepithelial lesions or malignancy (NILM). HPV16 or HPV18 infection was found in 160 (12.0%) cases whereas other HR-HPV infections were found in 1177 (88.0%) cases. Colposcopic cervical biopsy revealed no CIN abnormalities in 878 (78.7%) cases, CIN1 in 409 (30.6%) cases, CIN2 in 32 (2.4%) cases, CIN3 in 16 (1.2%) cases, and cancer in 2 (0.1%) cases. Therefore, disease prevalence at CIN2 or worse (CIN2+) threshold was 3.7% (50 of 1337 cases).

Table 1. Baseline characteristics of study subjects (n = 1337).

	Characteristic	Value
Age (years)	Mean ± SD	34.5 ± 9.8
Age group	age <30 years	545 (40.8%)
	30≤ age <40 years	401 (30.0%)
	40≤ age <50 years	277 (20.7%)
	age ≥50 years	114 (8.5%)
Institution	Private clinics	1256 (93.9%)
	University hospitals	81 (6.1%)
Pap cytology method	Liquid-based	851 (63.6%)
	Conventional	485 (36.3%)
	Not reported	1 (0.1%)
Pap cytology result	NILM	1337 (100.0%)
HPV method	DNA chip array	204 (15.3%)
	PCR-RFMP assay	816 (61.0%)
	RT-PCR assay	317 (23.7%)
HPV infection type	HPV16 or HPV18 positive	160 (12.0%)
	Others HR-HPV positive [a]	1177 (88.0%)
Biopsy result	Within normal limits	878 (78.7%)
	CIN1	409 (30.6%)
	CIN2	32 (2.4%)
	CIN3	16 (1.2%)
	Cancer	2 (0.1%)
Disease prevalence	Threshold: CIN2 or worse	50 (3.7%)

Abbreviation: SD, standard deviation; Pap, Papanicolaou; NILM, negative for intraepithelial lesion or malignancy; HPV, human papillomavirus; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; RFMP, restriction fragment mass polymorphism; RT, real-time; HR, high risk; CIN, cervical intraepithelial neoplasia.

[a] Other HR-HPVs were defined as HPV types 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, or 82.

Distribution of HR-HPV genotype infection is shown in Table 2. The most common HR-HPV genotype was HPV58 (15.4%) infection, followed by, HPV39 (11.6%), HPV52 (11.6%), HPV16 (9.9%), HPV56 (9.4%), and HPV51 (9.2%).

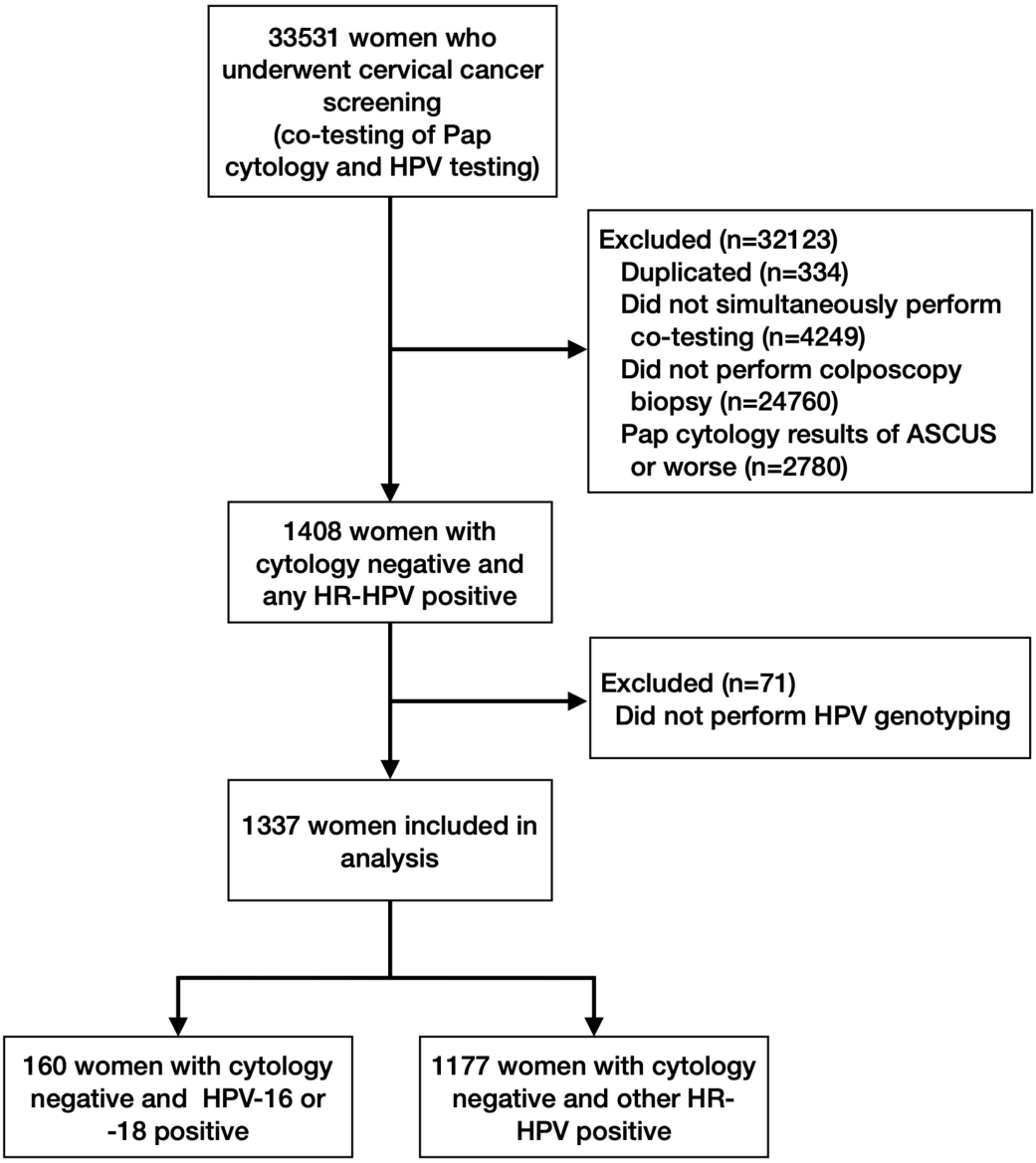

Fig. 1. CONSORT diagram for case selection.

Multiple and single HR-HPV infection rates were 12.4% and 86.6%, respectively. Four or more different HR-HPV infections were found in 14 (1.0%) cases.

HPV16 or HPV18 was significantly associated with a diagnosis of CIN2+ lesion compared to other HR-HPV genotypes (risk for CIN2+, 15.6%; OR, 8.53; 95% CI, 4.77–15.28; p-value < 0.001) (Table 3). In women with HPV16-negative, HPV18-negative, but other HR-HPV-positive genotypes (n = 1177), the risk for CIN2+ was significantly increased in women with multiple HR-HPV genotypes infections (risk for CIN2+ lesion, 7.8%; OR, 5.40; 95% CI, 2.37–12.73, p-value < 0.001), those with HPV58 (risk for CIN2+ lesion, 6.1%; OR, 4.83; 95% CI, 2.17–10.74, p-value < 0.001), and those with HPV35 (risk for CIN2+ lesion, 8.6%; OR, 4.77; 95% CI, 1.36–16.77, p-value = 0.015) (Table 4).

4. Discussion

Our data confirmed the 2012 and 2019 ASCCP guideline for HR-HPV genotyping. It recommends immediate referral to colposcopy of HPV16 or HPV18 positive women with negative Pap result. Our data suggest that colposcopy should also be referred to women with multiple HR-HPVs, HPV35, or HPV58 infections. We believe that this study is very valuable because understanding the natural history of specific HR-HPV genotype infections is important to build cervical cancer screening guideline.

In this study, HPV16 or 18 (risk for CIN2+, 15.6%; p-value < 0.001), HPV35 (risk for CIN2+, 8.6%; p-value = 0.015), and HPV58 (risk for CIN2+, 6.1%; p-value < 0.001) infections were closely associated with a diagnosis of CIN2+ compared to other HR-HPVs. This finding was a little differ-

Table 2. Distribution of high-risk HPV infections (n = 1337).

Variable	n (%)
HPV type specific prevalence	
HPV16	132 (9.9%)
HPV18	33 (2.5%)
HPV26	41 (3.1%)
HPV31	28 (2.1%)
HPV33	68 (5.1%)
HPV35	41 (3.1%)
HPV39	155 (11.6%)
HPV45	76 (5.7%)
HPV51	123 (9.2%)
HPV52	155 (11.6%)
HPV53	90 (6.7%)
HPV56	126 (9.4%)
HPV58	206 (15.4%)
HPV59	41 (3.1%)
HPV66	81 (6.1%)
HPV68	53 (4.0%)
HPV69	30 (2.2%)
HPV70	45 (3.4%)
HPV73	22 (1.6%)
HPV83	24 (1.8%)
Number of HR-HPV infections	
Single infection	1171 (87.6%)
Multiple infections	166 (12.4%)
2 types	118 (8.8%)
3 types	34 (2.5%)
4 types	10 (0.7%)
5 types	3 (0.2%)
6 types	1 (0.1%)

ent from data of western countries. Monsonego *et al.* [8] have studied the prevalence of HR-HPVs and its risk for cervical precancerous lesions based on data from the ATHENA trial. In 3444 USA women with negative Pap result but HR-HPV positive, HPV16 was the most prevalent genotype for HR infection in 497 (1.3%) women. The next most prevalent genotype was HPV52 in 333 (0.9%) women, followed by HPV31 in 255 (0.7%), HPV39 in 249 (0.7%), HPV58 in 226 women (0.6%), HPV45 in 226 (0.6%), and HPV18 in 220 (0.6%) women. HPV16 conferred the greatest risk for CIN2 or worse lesion in women cytology negative but HR-HPV-positive (11.8%), followed by HPV31 (10.5%), HPV52 (6.7%), HPV18 (5.3%), HPV33 (4.8%), HPV35 (4.0%), HPV58 (3.9%), HPV39 (3.7%), and HPV45 (3.7%). The distribution and prevalence of HPV types differ between countries. The importance of HPV genotypes also varies by region. In the Europe and United States, five types are most often found in women with cervical cancer, with HPV16 accounting for most (approximately 50%) cases, followed by HPV18, HPV31, HPV45, and HPV52 [6]. In Asia, HPV52 is the most common, followed by HPV58, HPV16, HPV56, HPV68, and HPV33 [13, 14]. The prevalence of HPV16 infection was the highest (17.6%) in women with CIN and HPV16 was significantly associated with a diagnosis of CIN2+ (OR, 20.5; 95% CI, 3.0–107.1; p-value < 0.001) [15].

Cervical cancer screening strategies vary from country to country [12, 16–18]. Some countries have population-based screening programs for cervical cancer, which this program can be implemented nationwide or only in specific province. The most common method used for cervical cancer screening is Pap cytology, followed by HPV DNA test, visual inspection with acetic acid (VIA), and cervicography. VIA is an alternate screening program to Pap cytology in low-resource settings (so-called 'see and treat' method). Cervicography is a photographic diagnostic test which a non-gynecologic oncologist takes pictures of the cervix and submits them to a gynecologic oncologist for interpretation. HPV test is being introduced into some middle- or high-resource countries as the primary screening program or as an adjunct test to Pap cytology screening [12, 16–18].

Recently, ASCCP guidelines for management of cervical cancer screening abnormality have been updated to the 2019 version [12]. Four new guiding principles were added to the 2019 version. First, HPV DNA test is based on the risk estimation. The HPV test can be performed either primary HPV testing alone or co-testing in conjunction with Pap cytology. Second, personalized management is recommendable with understanding of current results and individual history. Third, guidelines should allow updates to unify new screening methods because of risk reduction from HPV vaccination. Finally, colposcopy practice should be performed with guidance detailed in the ASCCP Colposcopy Standards [19].

This study also showed that the risk for CIN2+ lesion was significantly increased in patients with multiple HR-HPV infections (risk for CIN2+, 7.8%; OR, 5.40; 95% CI, 2.37–12.73, p-value < 0.001). In previous studies, multiple HR-HPV infections have been observed more frequently in patients with abnormal Pap cytology or with impaired immune system [20–22]. Women with multiple HR-HPVs have increased risk for persistent CIN [23]. In addition, multiple HR-HPV infections seem to promote cervical oncogenesis, increasing the risk for high-grade cervical dysplasia and invasive carcinoma through a synergistic effect of HR-HPV genotypes [24, 25]. Therefore, the relatively high rate (12.4%) of multiple HR-HPV infection in this study has implications for cervical cancer screening and predicting outcome of HR-HPV infections.

This study had some limitations. First, colposcopic biopsy samples were not centralized because of the following two reasons: (1) approximately 60% of CIN1 lesions could spontaneously regress without any treatment [26], and (2) the intraobserver and interobserver agreements for pathologic diagnosis of CIN1 were poor, while agreements for CIN2+ lesions were good [27]. However, according to data from histology reviews from population-based studies, diagnosis of CIN2 was a less reproducible and less confirmative than those of CIN3 [28–30]. Second, our findings could not be simply extended to Western women because HPV infection is

Table 3. HPV type-specific risk for CIN2 or worse lesion in HR-HPV infected women with negative cytology (n = 1337).

HR-HPV genotyping	Pathologic diagnosis [threshold: CIN2+]		OR	95% CI	*p*-value
	Positive, n (%)	Negative, n (%)			
HPV16 or 18 (n = 160)	25 (15.6%)	135 (84.4%)	8.53	4.77–15.28	<0.001
Other HR-HPVs (n = 1177)	25 (2.1%)	1152 (89.5%)	1		
Separate risk of HPV16 or 18					
HPV16 positive (n = 132)	20 (17.9%)	112 (82.1%)	7.79	4.23–14.34	<0.001
HPV16 negative (n = 1205)	27 (2.3%)	1178 (97.7%)	1		
HPV18 positive (n = 33)	6 (22.2%)	27 (77.9%)	5.81	2.29–14.74	0.002
HPV18 negative (n =1304)	48 (3.8%)	1256 (96.2%)	1		

Abbreviation: OR, odds ratio; CI, confidence interval; CIN2+, CIN2 or worse.

Table 4. HPV type-specific risk for CIN2 or worse lesion in type 16-negative, type 18-negative, but other HR-positive HPV infected women with cytology negative (n = 1177).

HPV type	Pathologic diagnosis [threshold: CIN2+]		OR	95% CI	*p*-value
	Positive, n (%)	Negative, n (%)			
No. of infection					
Single infection	16 (1.5%)	1045 (98.5%)	1		
Multiple infections	9 (7.8%)	107 (92.2%)	5.49	2.37–12.73	<0.001
Individual infection					
HPV26	1 (2.5%)	39 (97.5%)	1.19	0.15–9.02	0.867
HPV31	1 (3.6%)	27 (96.4%)	1.74	0.23–12.31	0.595
HPV33	3 (4.5%)	63 (95.5%)	2.36	0.69–8.09	0.173
HPV35	3 (8.6%)	32 (93.4%)	4.77	1.36–16.77	0.015
HPV39	0	145 (100%)	-	-	0.996
HPV45	1 (1.4%)	72 (98.6%)	0.63	0.08–4.69	0.647
HPV51	3 (2.6%)	111 (97.4%)	1.28	0.38–4.34	0.693
HPV52	6 (4.1%)	140 (95.9%)	2.28	0.90–5.81	0.084
HPV53	0	97 (100%)	-	-	0.997
HPV56	2 (1.7%)	118 (98.3%)	0.76	0.18–3.28	0.715
HPV58	12 (6.1%)	185 (93.9%)	4.83	2.17–10.74	<0.001
HPV59	0	40 (100%)	-	-	0.998
HPV66	2 (2.6%)	74 (97.4%)	1.27	0.29–5.48	0.752
HPV68	1 (2.0%)	49 (98.0%)	0.94	0.12–7.08	0.950
HPV69	0	29 (100%)	-	-	0.998
HPV70	0	43 (100%)	-	-	0.998
HPV73	0	18 (100%)	-	-	0.999
HPV83	0	19 (100%)	-	-	0.998

population-specific. Third, HPV genotyping was evaluated in various laboratories under real clinical practice. Therefore, there were three different assays used for HPV-detection in this study. Because of the limitation of the retrospective study, we could not assess the distribution of genotypes between the different HPV tests. Meanwhile, this study has several strengths of this study. First, it included a large number of women who were evaluated. In addition, all women enrolled had Pap cytology, HPV genotyping, and colposcopic punch biopsy performed. Moreover, real-world data in clinical practice were used.

In conclusion, our findings suggest that colposcopy should also be referred to women with multiple HR-HPVs, HPV35, or HPV58 infections, as well as those with HPV16 and HPV18, although the current 2019 ASCCP guideline recommends that HPV16+ or HPV18+ women with Pap cytology result referred for immediate colposcopy whereas those who are positive for the other HR-HPV genotypes are recommended to undergo repeated co-testing with both Pap cytology and HPV test at 12 months. This is the first study that documents referral to colposcopy of multiple HR-HPVs, HPV35, or HPV58 positive women with negative cytology. However, further large and randomized controlled trials are needed to change current guideline based on our findings.

Author contributions

TS and SJS designed the study and wrote the paper. SKL, BRK, WJ, KHK, KN, JCS, and TJK participated in the design of the study and performed the static analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee (Approval No.: KBSMC 2018-05-023; Approval date: 15 May 2018), and the need for written informed consent was waived.

Acknowledgment

Thanks to all the patients.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Jin J. HPV Infection and Cancer. Journal of the American Medical Association. 2018; 319: 1058.

[2] Burd EM. Human papillomavirus and cervical cancer. Clinical Microbiology Reviews. 2003; 16: 1–17.

[3] Lagheden C, Eklund C, Lamin H, Kleppe SN, Lei J, Elfström KM, *et al.* Nationwide comprehensive human papillomavirus (HPV) genotyping of invasive cervical cancer. British Journal of Cancer. 2018; 118: 1377–1381.

[4] Suligoi B, Vittori G, Salfa MC, Timelli L, Corsini D, Fattorini G, *et al.* Prevalence and incidence of external genital warts in a sample of Italian general female population. BMC Infectious Diseases. 2017; 17: 126.

[5] Clifford G, Gallus S, Herrero R, Muñoz N, Snijders P, Vaccarella S, *et al.* Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet. 2005; 366: 991–998.

[6] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, *et al.* Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncology. 2010; 11: 1048–1056.

[7] Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. Journal of Pathology. 1999; 189: 12–19.

[8] Monsonego J, Cox JT, Behrens C, Sandri M, Franco EL, Yap P, *et al.* Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. Gynecologic Oncology. 2015; 137: 47–54.

[9] Wright TC, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. American Journal of Obstetrics and Gynecology. 2012; 206: 46.e1–46.e11.

[10] Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecologic Oncology. 2015; 136: 189–197.

[11] Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, *et al.* 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstetrics and Gynecology. 2013; 121: 829–846.

[12] Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, *et al.* 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. Journal of Lower Genital Tract Disease. 2020; 24: 102–131.

[13] Lee G, Kim S, Rim S, Choi H, Park C, Nam J. Human papillomavirus (HPV) genotyping by HPV DNA chip in cervical cancer and precancerous lesions. International Journal of Gynecological Cancer. 2005; 15: 81–87.

[14] Li J, Huang R, Schmidt JE, Qiao Y. Epidemiological features of Human Papillomavirus (HPV) infection among women living in Mainland China. Asian Pacific Journal of Cancer Prevention. 2013; 14: 4015–4023.

[15] So KA, Hong JH, Lee JK. Human papillomavirus prevalence and type distribution among 968 women in South Korea. Journal of Cancer Prevention. 2016; 21: 104–109.

[16] Hamashima C, Aoki D, Miyagi E, Saito E, Nakayama T, Sagawa M, *et al.* The Japanese guideline for cervical cancer screening. Japanese Journal of Clinical Oncology. 2010; 40: 485–502.

[17] Min KJ, Lee YJ, Suh M, Yoo CW, Lim MC, Choi J, *et al.* The Korean guideline for cervical cancer screening. Journal of Gynecologic Oncology. 2015; 26: 232–239.

[18] Wang S, Qiao Y. Implementation of cervical cancer screening and prevention in China—challenges and reality. Japanese Journal of Clinical Oncology. 2015; 45: 7–11.

[19] Wentzensen N, Massad LS, Mayeaux EJ, Khan MJ, Waxman AG, Einstein MH, *et al.* Evidence-based consensus recommendations for colposcopy practice for cervical cancer prevention in the United States. Journal of Lower Genital Tract Disease. 2017; 21: 216–222.

[20] Ho GY, Palan PR, Basu J, Romney SL, Kadish AS, Mikhail M, *et al.* Viral characteristics of human papillomavirus infection and antioxidant levels as risk factors for cervical dysplasia. International Journal of Cancer. 1998; 78: 594–599.

[21] Levi JE, Kleter B, Quint WGV, Fink MCS, Canto CLM, Matsubara R, *et al.* High prevalence of human papillomavirus (HPV) infections and high frequency of multiple HPV genotypes in human immunodeficiency virus-infected women in Brazil. Journal of Clinical Microbiology. 2002; 40: 3341–3345.

[22] Rousseau M, Abrahamowicz M, Villa LL, Costa MC, Rohan TE, Franco EL. Predictors of cervical coinfection with multiple human papillomavirus types. Cancer Epidemiology, Biomarkers & Prevention. 2003; 12: 1029–1037.

[23] Ho GYF, Einstein MH, Romney SL, Kadish AS, Abadi M, Mikhail M, *et al.* Risk factors for persistent cervical intraepithelial neoplasia grades 1 and 2: managed by watchful waiting. Journal of Lower Genital Tract Disease. 2011; 15: 268–275.

[24] Trottier H, Mahmud S, Costa MC, Sobrinho JP, Duarte-Franco E, Rohan TE, *et al.* Human papillomavirus infections with multiple types and risk of cervical neoplasia. Cancer Epidemiology, Biomarkers & Prevention. 2006; 15: 1274–1280.

[25] van der Graaf Y, Molijn A, Doornewaard H, Quint W, van Doorn LJ, van den Tweel J. Human papillomavirus and the long-term risk of cervical neoplasia. American Journal of Epidemiology. 2002; 156: 158–164.

[26] Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. Obstetrics and Gynecology. 1986; 67: 665–669.

[27] Robertson AJ, Anderson JM, Beck JS, Burnett RA, Howatson SR, Lee FD, *et al.* Observer variability in histopathological reporting of cervical biopsy specimens. Journal of Clinical Pathology. 1989; 42: 231–238.

[28] Carreon JD, Sherman ME, Guillén D, Solomon D, Herrero R, Jerónimo J, *et al.* CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. International Journal of Gynecological Pathology. 2007; 26: 441–446.

[29] Dalla Palma P, Giorgi Rossi P, Collina G, Buccoliero AM, Ghiringhello B, Gilioli E, *et al.* The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. American Journal of Clinical Pathology. 2009; 132: 125–132.

[30] Mittal S, Ghosh I, Banerjee D, Singh P, Biswas J, Nijhawan R, *et al.* Reproducibility of cervical intraepithelial neoplasia diagnosis on histological review of cervical punch biopsies from a visual inspection with acetic acid and HPV detection-based screening program. International Journal of Gynaecology and Obstetrics. 2014; 126: 227–231.