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Screening capacity and cost-effectiveness of the human papillomavirus test versus cervicography as an adjunctive test to Pap cytology to detect high-grade cervical dysplasia

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ABSTRACT

Objective: This study compared the screening capacities and cost-effectiveness of the human papillomavirus (HPV) test versus cervicography as an adjunctive test to Papanicolaou (Pap) cytology to detect high-grade cervical neoplasia in Korea, a country with a high prevalence of cervical cancer.
Study design: Of 33,531 Korean women who underwent cervicography as a screening test for cervical cancer between January 2015 and December 2016, we retrospectively analyzed the records of 4117 women who simultaneously or subsequently underwent Pap cytology, an HPV test, cervicography, and colposcopically directed biopsy. At a threshold of cervical intraepithelial neoplasia grade 2 or worse (CIN2+), based on colposcopic biopsy, we compared the diagnostic capacities and cost-effectiveness of these screening tools.
Results: The CIN2+ prevalence was 10.8% (446 of 4117 women) and the positive rate of high-risk HPV was 61.0% (2511 of 4117 women). Cervicography as an adjunctive to Pap cytology was a more sensitive test (97.5% vs 93.7%) with a higher odds ratio (15.65 vs 5.86) than the HPV test for detection of CIN2+ (P-value = 0.003). Moreover, the cost of cervicography co-testing was 23% less than that of HPV co-testing, decreasing the cost per patient with CIN2+ lesions from $1474 to $1135.
Conclusion: Cervicography and Pap co-testing had superior screening capacity and cost-effectiveness for detection of preinvasive cervical lesions than HPV and Pap co-testing and may be an effective and cost-saving screening strategy in clinical practice in country with a high prevalence of cervical cancer.

Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide [1]. Screening using the Papanicolaou (Pap) cytology along with the introduction of the human papillomavirus (HPV) vaccination has very successfully decreased the incidence and prevalence of cervical cancer in developed countries [2–4]. A Pap cytology evaluation is usually regarded as a first-line test in cervical cancer screening. Nevertheless, false negative rates as high as 58% is a notable limitation of Pap cytology screening [3]. False negative results are mainly due to faulty sampling, improper fixation, or an issue of interpretation [5]. Therefore, adjunctive tests to Pap cytology, such as the HPV test, cervicography, visual inspection with acetic acid, and colposcopy have been introduced to overcome the shortcomings concerning false negative results in Pap cytology [4,6–8].

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Colposcopy is the most accurate test to identify high-grade cervical dysplasia (referred to as cervical intraepithelial neoplasia [CIN] grades 2 and 3) and is also very useful for locating precise sites for biopsy. However, equipping every clinic with this instrument is costly and this test requires an experienced colposcopist [9]. Adolph Stafl introduced cervicography to address the limitations of colposcopy, using a proprietary camera to take high-resolution colpophotographs that could be transmitted to expert colposcopists for interpretation [7]. Recently, a cervicography (also known as, tele-cervicography or digital cervicography) has gained attention as a means to reduce the both costs and performance time of conventional cervicography, and also to provide the opportunistic telemedicine-based screening [7,10]. In private Korean clinics, a cervicography is frequently used to examine women who require a check-up or for women with abnormal cytology findings [11]. However, there have been few studies comparing cervicography and the HPV test as complementary tests to Pap cytology to detect high-grade CIN or worse lesions [12–16]. The purpose of this study was to compare the screening capacities and the cost-effectiveness of cervicography and HPV testing as an adjunctive test to Pap cytology to detect high-grade cervical dysplasia in clinical practice in Korea, a country with a high prevalence of cervical cancer. Korean women have a high prevalence of cervical cancer, with an age-standardized incidence rate of cervical cancer averaging 10.6 per 100,000 in 2010 [17]. This rate is similar to the average for Uganda (10.04 per 100,000 in 2010) and higher than that of the United States (7.5 per 100,000 in 2010) [18,19].

Methods

Study population

This study was designed by the Korean Cervicography Research Group, established in 1997, and comprises 30 medical university hospital professors who are well trained colposcopists, and who have performed teaching and research activities for cervicography and cervical cancer prevention in Korea. Between January 2015 and December 2016, 33,531 women underwent a cervicography as a screening test for cervical cancer at private clinics and university hospitals in Korea. Colposcopic biopsy was conducted on patients with an initial diagnosis of abnormal screening test results. The inclusion criteria comprised healthy women aged between 18 and 80 years who attended for routine cervical cancer screening in Korea, and women who simultaneously or subsequently underwent Pap cytology, an HPV test, cervicography, and colposcopically directed biopsy. Exclusion criteria comprised a previous history of cytology or HPV abnormalities within the past 2 years, current pregnancy, or a history of hysterectomy. Institutional review board approval was obtained from the Kangbuk Samsung Hospital (Seoul, Republic of Korea). Given the retrospective nature of the study, the requirement for informed consent was waived.

Pap cytology, HPV test, cervicography, and colposcopy

Pap cytology was performed using a conventional smear or liquid-based method and reported according to the revised Bethesda guidelines (2001) by pathologists in a routine clinical practice setting. Pap cytology was considered to be positive at three cutoff levels: the presence of atypical squamous cells of undetermined significance or worse (ASCUS+); low-grade squamous intraepithelial cells or worse (LSIL+); and high-grade squamous intraepithelial cells or worse (HSIL+).

An HPV test was performed on cervicovaginal swab samples, using commercial nucleic acids amplification assays available in Korea to detect the high-risk (HR) HPV group (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, or 82). The results of the HPV tests were interpreted according to the manufacturer's instructions. A sample was considered to be positive if the HPV test detected an HR-HPV type.

Cervicography was undertaken using TeleCervico system (Dr.Cervicam; NTL Medical Institute, Yongin, Korea). The apparatus was composed of a camera body, a ring flash, and an examination light. After inserting a vaginal speculum, the cervix was smeared with 5% acetic acid for 15 s, again with 5% acetic acid for 15–20 seconds, and for a third time with 5% acetic acid. Under a cervicoscope, images were captured twice through focusing on the cervix and moving the camera back and forth. The images were transmitted to a server via the internet for immediate evaluation. Transmitted images were evaluated on a video monitor. The cervicography image was interpreted, as noted in Supplementary Table 1, by expert colposcopists, all of whom were professors at hospitals associated with medical universities in Korea and who had considerable experience in colposcopy. The cervicography results were considered to be positive at three cutoff thresholds: positive 0 or worse (P0+), positive 1 or worse (P1+), or positive 2 or worse (P2+).

Cervical punch biopsies were obtained using a full colposcopic assessment of the anogenital area using 5% acetic acid with or without Lugol's solution from all patients for histological examination. Tissue samples were fixed in 4%-buffered formalin, embedded in paraffin, cut as 4-μm-thick sections, and stained for hematoxylin–eosin. Tissues were classified according to the CIN classification system as either within normal limits (including cases of chronic inflammation), mild dysplasia (CIN1), moderate dysplasia (CIN2), severe dysplasia or carcinoma in situ (CIN3), or invasive carcinoma.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data were presented as mean ± standard deviation or median (interquartile range) for quantitative variables and frequency (%) for qualitative variables. Sensitivity, specificity, positive predictive value, and negative predictive value of each screening tool were calculated at the CIN2 or worse (CIN2+) threshold, based on the colposcopic biopsy result as the 'gold standard'. We then compared the accuracy measures of two double-combined tests (Pap cytology with an HPV test versus a Pap smear with cervicography) using McNemar's test at the CIN2 or worse (CIN2+) threshold. The 95% confidence intervals (95% CIs) were computed based on the binomial distribution. A two-tailed Fisher's exact test was applied in order to assess the screening efficacy of each tool alone, as well as their combinations. The Mantel-Haenszel method was applied for the calculation of odds ratios (ORs) and their 95% CI. A P-value < 0.05 was considered to indicate statistical significance.

Results

A total of 33,531 women underwent cervicography for a cervical cancer screening during the study period, of whom 29,414 were excluded because of duplicated data (n = 334) or no available data concerning the HPV test or the cervical biopsy (n = 29,180). Therefore, 4117 women evaluable valid results for Pap cytology, HPV test, cervicography, and colposcopically directed biopsy were included in this study. The average age of the 4117 women was 36.9 ± 11.4 years and their characteristics are summarized in Table 1. Pap cytology results revealed 2472 women (60.0%) with normal cytology, 1001 women (24.3%) with ASCUS, 360 women (8.7%) with LSIL, 249 women (6.0%) with HSIL, and 35 women (0.9%) with cancer. DNA sequences of HR-HPV were identified in

Table 1
Patients characteristics (n = 4117) [a].

	Characteristic	Value
Age (years)		36.9 ± 11.4
Pap cytology results	Negative	2472 (60.0%)
	ASCUS	1001 (24.3%)
	LSIL	360 (8.7%)
	HSIL	249 (6.0%)
	Cancer	35 (0.9%)
HPV results	Negative	1011 (24.5%)
	Low-risk	595 (14.5%)
	High-risk [b]	2511 (61.0%)
Cervicography results	Negative	692 (16.8%)
	Atypical	1137 (27.7%)
	Positive 0	190 (4.6%)
	Positive 1	1890 (45.9%)
	Positive 2	183 (4.4%)
	Positive 3	25 (0.6%)
Biopsy result	Within normal limits	2547 (62.3%)
	CIN1	1124 (27.3%)
	CIN2	224 (5.4%)
	CIN3	161 (3.9%)
	Cancer	61 (1.5%)
Prevalence	Threshold: CIN2 or worse lesions	446 (10.8%)

Abbreviation: Pap, Papanicolaou; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial neoplasia; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia.

[a] A total of 33,531 women underwent cervicography for a cervical cancer screening during the study period, of whom 29,414 were excluded because of duplicated data (n = 334) or no available data concerning the HPV test or the cervical biopsy (n = 29,180). Therefore, 4117 women evaluable valid results for Pap cytology, HPV test, cervicography, and colposcopically directed biopsy were included in this study.

[b] High-risk HPV was defined as HPV type 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, or 82.

2511 women (61.0%), while low-risk HPV was identified in 595 women (14.5%). The most prevalent interpretation of cervicography was positive 1 (n = 1890, 45.9%), followed by atypical (n = 1137, 27.7%), negative (n = 692, 16.8%), positive 0 (n = 190, 4.6%), positive 2 (n = 183, 4.4%), and positive 3 (n = 25, 0.6%). Colposcopic cervical biopsy, considered as the gold standard for the diagnosis of high-grade cervical dysplasia in this study, revealed that cancer was present in 61 (1.5%) women, CIN3 in 161 (1.5%) women, CIN2 in 224 (5.4%) women, and CIN1 in 1124 (27.3%) women, whereas no CIN abnormalities were present in 2547 (76.7%) women. Therefore, the disease prevalence at the CIN2+ threshold was 10.8% (446 of 4117 women).

Table 2 shows the diagnostic capacities of each single screening test at different thresholds in detecting CIN2+ lesions. Estimates of the sensitivity of Pap cytology (threshold: ASCUS+), the HPV test (threshold: HR-HPV) and cervicography (threshold: P0+) were 81.2% (95% CI, 77.5–83.8%), 84.3% (95% CI, 80.9–87.7%) and 89.2% (95% CI, 86.4–92.1%), respectively. Specificity estimates for Pap cytology (threshold: ASCUS+), the HPV test (threshold: HR-HPV) and cervicography (threshold: P0+) were 65.1% (95% CI, 63.5–66.6%), 41.8% (95% CI, 40.2–43.4%), and 48.5% (95% CI, 46.9–50.1%), respectively.

Comparison of the HPV test and cervicography as an adjunctive test to Pap cytology to detect CIN2+ is shown in Table 3. With a co-testing threshold set as any positive test, cervicography as a complementary test to Pap cytology was a more sensitive test for detection of CIN2+, compared with the HPV test (97.5% vs 93.7%; *P*-value, 0.003). With a co-testing threshold for both tests set as positive, cervicography was also a more efficient test, compared with the HPV test (sensitivity, 73.1% vs 71.7%; specificity, 85.3% vs 78.7%). The screening efficacy of each test for cervical cancer screening as well as their combinations for histological detection of CIN2+ are shown in Table 4. Among several scenarios for cervical cancer screening, co-testing with Pap cytology and cervicography was the best test for detecting high-grade CIN (OR, 15.65; 95% CI, 8.56–28.60).

Based on the Korean health care system and a per patient cost of $40 for Pap cytology, $60 for an HPV test, $30 for cervicography, and $67 for colposcopic cervical biopsy and a histologic exam (Table 4), cost estimates were calculated per patient with CIN2+ lesions. Similarly to a study reported by Schneider at al. [12], a combination of Pap cytology with an HPV test identified 418 of 446 CIN2+ results correctly and identified 2636 of 3671 false-positive results, whereas Pap cytology with combined cervicography yielded 2630 of 3671 false-positives and a higher number of correct positives (435/446). In Korea, the cost per patient with CIN2+ is $1474 with the HPV test, and $1135 when cervicography is combined with Pap cytology. Therefore, cervicography co-testing

Table 2
Diagnostic capacities of each single screening test at different thresholds (n = 4117).

Single screening tool	Pathologic diagnosis [threshold: CIN2+]		Total, n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Positive, n	Negative, n					
Pap cytology [threshold: ASCUS+]				81.2% (77.5-83.8)	65.1% (63.5-66.6)	22.2%	96.6%
Positive	362	1283	1645				
Negative	84	2388	2472				
Pap cytology [threshold: LSIL+]				60.8% (56.2-65.3)	89.8% (88.9-90.8)	42.1%	95.0%
Positive	271	373	644				
Negative	175	3298	3473				
Pap cytology [threshold: HSIL+]				46.0% (41.3-50.6)	97.8% (97.4-98.3)	72.2%	93.7%
Positive	205	79	284				
Negative	241	3592	3833				
HPV test [threshold: HR-HPV]				84.3% (80.9-87.7)	41.8% (40.2-43.4)	15%	95.6%
Positive	376	2135	2511				
Negative	70	1536	1606				
Cervicography [threshold: P0+]				89.2% (86.4-92.1)	48.5% (46.9-50.1)	17.4%	97.4%
Positive	398	1890	2288				
Negative	48	1781	1829				
Cervicography [threshold: P1+]				83.6% (80.2-87.1)	53.0 (51.4-54.6)	17.8%	96.4%
Positive	373	1725	2098				
Negative	73	1946	2019				
Cervicography [threshold: P2+]				35.2% (30.8-39.6)	98.6 (98.2-99.0)	75.5%	92.6%
Positive	157	51	208				
Negative	289	3620	3909				

Abbreviation: CIN2+, CIN2 or worse; PPV, positive predictive value; NPV, negative predictive value: ASCUS+, ASCUS or worse; LSIL+, LSIL or worse; HSIL+, HSIL or worse; HR-HPV, high-risk HPV; P0+, positive 0 or worse; P1+, positive 1 or worse; P2+, positive 2 or worse.

Table 3
Diagnostic capacities of double-combined testing as screening methods for detection of CIN2+ (n = 4117).

Combination screening tool [a]	Pathologic diagnosis [threshold: CIN2+]		Total, n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Positive, n	Negative, n						
Combination of Pap cytology and HPV test [any test positive]				93.7% (91.1-95.8)	28.2% (26.7-29.7)	13.7%	97.4%	35.3%
Positive	418	2636	3054					
Negative	28	1035	1063					
Combination of Pap cytology and HPV test [both tests positive]				71.7% (67.6-75.9)	78.7% (77.4-80.0)	29.0%	95.8%	77.9%
Positive	320	782	1102					
Negative	126	2889	3015					
Combination of Pap cytology and Cervicography [any test positive]				97.5% (95.6-98.8)	28.4% (26.2-29.2)	14.2%	98.9%	35.9%
Positive	435	2655	3090					
Negative	11	1016	1027					
Combination of Pap cytology and Cervicography [both tests positive]				73.1% (69.0-77.2)	85.3% (84.2-86.5)	37.7%	96.3%	84.0%
Positive	326	539	865					
Negative	120	3132	3252					

[a] Thresholds of Pap cytology, HPV test, and cervicography were ASCUS+, high-risk HPV, and P0+, respectively.

Table 4
Screening efficacy and cost estimate of several scenarios for cervical cancer screening for detecting CIN2+ lesions (n = 4117).

Screening scenarios	Threshold	Histological detection of CIN2+			Test cost	Cost for case of CIN2+
		OR	95% CI	*P*-value [a]		
Pap cytology	ASCUS+	8.02	6.23-10.27	<0.001	$40 [a]	–
HPV test	HR-HPV	3.86	2.97-5.03	<0.001	$60	–
Cervicography	P0+	7.81	5.75-10.61	<0.001	$30	–
Pap cytology + HPV test	Any ASCUS + or HR-HPV	5.86	3.97-8.65	<0.001	$100 [a]	$1474
Pap cytology + Cervicography	Any ASCUS + or P0+	15.65	8.56-28.60	<0.001	$70 [a]	$1135

Abbreviation: OR, odds ratio; CI, confidence interval.
[a] Cost for Pap cytology was calculated based on liquid-based method.

would decrease the cost per patient with CIN2+ lesions by approximately 23% compared to the cost of HPV co-testing.

Discussion

We performed this nationwide retrospective study to compare the screening capacity and cost-effectiveness of the HPV test versus cervicography as an adjunctive test to Pap cytology to detect high-grade cervical dysplasia in Korea, a country with a high prevalence of cervical cancer. We found that Pap and cervicography co-testing detected 97.5% (435 of 446 specimens) of all CIN2+ cervical biopsy results compared with 93.7% (418 of 446 specimens) of Pap and HPV co-testing. Moreover, cervicography co-testing would decrease the cost per patient with CIN2+ lesions to $1135, which is approximately 23% less than the cost of Pap and HPV co-testing. This study suggests that Pap and cervicography co-testing had a superior screening capacity and cost-effectiveness for detection of preinvasive cervical lesions, compared with co-testing using Pap cytology and an HPV test.

Our results show that Pap cytology and cervicography co-testing markedly improved the sensitivity of Pap cytology alone for cervical cancer screening (97.5% versus 81.2%). The false negative rate was 2.5% (11 of 446 CIN2+) in Pap and cervicography co-testing and 6.3% (28 of 446 CIN2+) in Pap and HPV co-testing. In clinical practice, the most important aspects of cervical cancer screening are the detection of high-grade lesions (especially invasive cervical cancer) and the reassurance provided from a negative test. Although early detection and the ability to extend the screening interval following a negative screening test are important benefits of Pap and HPV co-testing [20–22], they are secondary to the detection of high-grade lesions and invasive cervical cancers. As such, the combination of Pap cytology and cervicography provides the greatest reassurance following a negative test (false negative rate of 2.5%), and the greatest sensitivity (97.5%) in detecting high-grade cervical lesions.

Previous studies have identified additional tests for an adjunctive method to Pap cytology to detect high-grade cervical dysplasia [12–16]. Our findings were consistent with those of previous studies. Kim et al. reported that Pap and cervicography co-testing, with a sensitivity of 98.1%, was more sensitive than Pap and HPV co-testing (92.4%) in 261 Korean women who underwent routine screening for cervical cancer [13]. However, those studies were conducted among selected populations in developed countries and the findings were inconsistent with our study. Schneider et al. analyzed 967 German women with a mean age of 37.1 years who underwent routine Pap cytology, cervicography, and the HPV test using the hybrid capture assay method to detect CIN2+ lesions [12]. They reported that the sensitivity of Pap and cervicography co-testing was comparable to that of Pap and HPV co-testing (both 58%), while the specificity of Pap and cervicography co-testing was lower than Pap and HPV co-testing (88% versus 92%).

Tjalma et al. studied the impact on women's health the cervical cancer screening budget of primary HPV screening with dual-stain cytology triage through the cost-effectiveness model set-up in Belgium [23]. Dual-stain cytology triage reduced both the number and frequency of follow-up visits required. After two cycles (6 years), the prevalence of CIN and cervical cancer was decreased significantly in the screened population. At a population level, these shifts could reduce the screening budget by 21%, resulting in savings of 5.3 million euro a year in Belgium. They concluded that diagnostic cytology benefits all stakeholders involved in cervical cancer screening. Future studies should evaluate and compare the cost-effectiveness of nationwide budget of several primary cervical screening scenarios.

This study had some limitations. First, the generalizability of this study is limited because it was conducted among a Korean population with an age standardized incidence rate of cervical cancer averaging 10.6 per 100,000 in 2010 [17]. This rate is similar to the average for Uganda (10.04 per 100,000 in 2010) and higher than that for the United States (7.5 per 100,000 in 2010) [18,19]. The

performance of any screening test may differ according to a population with a different prevalence of disease. Second, cervical biopsy samples were not reviewed by a single pathologist. However, we restricted analysis to a threshold of disease prevalence of CIN2+ for two reasons: 1) CIN1 may regress spontaneously in up to 60% [24] and; 2) the interobserver and intraobserver agreement for histologic diagnosis of CIN1 is poor, while agreement for CIN2+ is good [25]. The final limitation is its retrospective design. Nevertheless, a major strength of this study is that it was conducted using a large, real-world population-based sample.

In conclusion, this study suggests that cervicography as an adjunctive test increases detection of cervical cancer and its precursor lesions through reducing false negative errors (2.5% versus 6.3%), compared to the HPV test. Moreover, Pap and cervicography co-testing would be more cost-effective than Pap and HPV testing in terms of the cost per patient with CIN2+ lesions (23% off the cost). Therefore, co-testing of Pap cytology and cervicography may be an effective and cost-saving screening strategy in Korea, a country with a high prevalence of cervical cancer. However, further large, randomized controlled trials comparing the screening capacities of HPV test versus cervicography as an adjunctive test to Pap cytology to detect high-grade cervical neoplasia in general population are needed to obtain more conclusive data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.01.008.

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