The Korean Journal of Pathology
2004; 38: 258-64

Evaluation of Self-collected Pad Sampling for the Detection of HPV In Cervicovaginal Secretion

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Received : June 21, 2004
Accepted : August 3, 2004

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Background : Self-collection of secretion samples for HPV testing is a feasible alternative method for women who would decline to participate in population based cervical cancer programs. The purpose of this study was to determine the sensitivity and specificity of self-sampling for HPV in determining high grade squamous intraepithelial lesion (HSIL) using the pad, and we also wished to compare the results from samples collected by women themselves and those results from samples collected by physicians. **Methods :** Fifty patients voluntarily participated in the sensitivity and specificity study at the university hospitals and 290 volunteers participated in the agreement study at local clinics. DNA was extracted and amplified using HPV L1 consensus primers for the direct sequencing of the pad samples. **Results :** For the detection of HSIL, self-collected pad sampling showed good sensitivity (75.0%) and excellent specificity (100%). Two hundreds eighty-six samples from the pads and concurrent physicians' samples showed the agreement at 98.6% with the Kappa, 0.9622 (p=0.0000). **Conclusions :** A self-sampling method using the pad for the detection of HPV DNA is suggested to be an efficient method to access many women for screening easily, rapidly and conveniently. Testing the pad method's utility for a country- or large area-based mass screening study will be necessary in the future.

Key Words : Self-Collection-Cervical Cancer-DNA Probes, HPV

Cervical cancer is the second most common female cancer in the world with the incidence approximating 450,000 cases per year.[1] Several studies have shown that an infection with high risk HPV is the main cause for the cervical carcinogenesis.[2,3] Women with normal cervical cytology and a positive test for high risk HPV are more at risk of developing a high grade squamous intraepithelial lesion (HSIL) than women who are not positive for high risk HPV.[4,5] Therefore, testing for HPV as an adjunct to cervical cytology screening technique has been recommended as a screening procedure to identify individuals at high risk of developing cervical neoplasia.[6] However, one of the most important problems in screening programs for cervical cancer is that 50% of the patients with invasive cervical cancer are women who were not adequately screened.[7] In a attempt to overcome this limitation, several investigators have tried to use at-home obtained, self-collected samples of cervicovaginal secretions for clinical screening testing.[7-21] The sensitivity for HSIL in these studies, which have variously used urine, vaginal swab or tampon specimens, has ranged from 66% to 94%. Thus, self-collection of samples for HPV testing is a feasible alternative method for women who decline to participate in the population based cervical cancer programs.[7]

The purpose of our study was to determine the sensitivity and specificity of self-sampling for HPV in determining HSIL using

the collection pad. The secondary purpose was to compare the results from samples collected by women themselves who used the pad and those results obtained from samples collected by physicians using the conventional cytobrush.

MATERIALS AND METHODS

Patient selection and self-collection of cervicovaginal secretion using the pad

From August 2003 to October 2003, volunteer women who visited any of five local Obstetrics and Gynecology clinics for the routine health examination were included in the agreement study. All the volunteers were informed about the HPV DNA study and they were given instruction about the HPVpad™ (Medplan, Seongnam, Korea). The women put on the HPVpad™ before going to bed and they removed it after waking up. The women then followed the manufacturer's recommended protocol. All the procedures were performed in home the day before the women visited at the clinic.

From March 2004 to May 2004, another group of volunteer women who had been referred to two University hospitals for the evaluation of abnormal cytology were included in the sensitivity and specificity study. The study procedures were the same as in the agreement study.

Cytologic examination and histologic examination

Cervical cytology specimens were collected by gynecologists at each hospital using the Cytobrush Plus GT (Medscand, Malmoe, Sweden), and the samples were processed using the ThinPrep2™ (Monogen, Vernon Hills, IL, USA) kit according to the manufacturer's protocol. Slide preparation and staining were performed at the pathology laboratory center. The produced slides were then screened and diagnosed according to the Bethesda 2001 criteria.[22]

For the histologic examination, the removed cervical specimens were fixed in neutrally buffered formalin, embedded in paraffin and stained with hematoxylin and eosin. The pathologist was blinded to the previous reported clinical diagnosis to minimize any classification bias. CIN 1, 2, 3 and invasive carcinomas including squamous cell carcinoma and adenocarcinoma were distinguished. CIN 2 and 3 were converted to HSIL and CIN 1 was converted to LSIL for the diagnostic uniformity. Chronic cervicitis with or without squamous metaplasia and normal cervix specimens were included in the negative group.

DNA extraction and PCR amplification

Six hundreds forty-four cervical samples were centrifuged at 13,000 rpm for 10 min and the supernatant was removed. The sample pellet was washed with 1.0 mL of PBS. DNA extraction was then performed using the QIAamp DNA mini kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. The HPV L1 region were amplified using general consensus primers.[23] PCR amplifications were performed consisting of 4.5 μL of template DNA, 0.5 μM primer set, 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl (pH 8.4), 0.1 mM dNTPs, and 1 Unit of Super-therm *Taq* polymerase (JMR Holdings, London, England) in a final volume of 20 μL. DNAs from cervical samples were amplified following as initial denaturation at 94℃ for 3 min followed by 40 cycles of 94℃ for 45 sec, 55℃ for 45 sec, 72℃ for 45 sec, and a final cycle of 72℃ for 10 min. PCR amplifications were confirmed following electrophoresis in a 2.0% agarose gel. The PCR products were purified using the QIAquick PCR Purification kit (Qiagen).

Direct sequencing of PCR products and analyses

Subsequently, sequencing reactions were performed with the BigDye Terminator v3.1 sequencing kit (Applied Biosystem, Foster City, CA, USA) by using of the PCR primers as a sequencing primer. Sequencing reactions were purified and run on an automated Genetic Analyzer, ABI 3730XL or ABI 3100 DNA sequencer (Applied Biosystem). All data were analyzed using BLAST in GenBank.

Tissue microdissection and hybrid capture II HPV DNA assay

Twenty-seven biopsy specimens were routinely microdissected under a light microscope for accurate tumor sampling. A Hybrid capture II assay was run according to the manufacture's protocol (Digene Corp., Beltsville, MD, USA) using the microtiter plate based format and probes for high carcinogenic risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68).

Statistical analyses

The sensitivity, specificity and Kappa analysis were performed using dBSTAT for windows (version 4.0, www.dbstat.com) com-

puter software program. For the sensitivity and specificity studies, HSIL (CIN 2 and 3), and invasive carcinomas were included in the positive "disease" group and the detection of high risk HPV was included in the positive "diagnosis" group.

RESULTS

General profiles of volunteers and patients

Fifty patients voluntarily participated in the sensitivity and specificity study at the university hospitals and 297 volunteers participated in the agreement study at the local clinics. Seven volunteers at the local clinics were excluded during this study due to inadequate cytologic examination.

The university hospital volunteers were 50 patients, ranging from 24 to 65 years old, with the average age of 43.2 year. The age groups were: 20-29, 6 people (12.0%); 30-39, 12 people (24.0%); 40-49, 21 people (42.0%); and 50 or older, 11 people (22.0%) (Table 1). The histologic diagnoses were: chronic cervicitis with or without squamous metaplasia, 14 people (28.0%); LSIL (CIN 1), 0 people (0%); HSIL (CIN 2 and 3), 33 people (66.0%); invasive squamous cell carcinoma 2 people (4.0%) and adenocarcinoma, 1 people (2.0%). The local clinic volunteers were 290 patients, ranging from 24 to 74 years old, with the average age being 42.4 year. The age groups are: 20-29, 24 people (8.3%); 30-39, 109 people (37.6%); 40-49, 78 people (26.9%); and 50 or older, 79 people (27.2%) (Table 1).

HPV detection profiles

Among the 50 university hospital volunteers, 27 women (54.0 %) were positive for HPV DNA by use of the self-collected pad sampling. Thirty-one subtypes of HPV were detected in the pad samples of 27 women, including 4 multiple infections (Table 2). The prevalence rates of HPV subtypes were: 58 (29.0%); 16 (19.4%); 18 (6.5%); 33 (6.5%); and 53 (6.5%). The remaining subtypes were 6, 17, 31, 51, 52, 56, 61, 69, 70 and 82. HPV detection according to the age groups were: 20s, 4 people (66.7%); 30s, 6 people (50.0%); 40s, 12 people (57.1%); and 50s or older, 5 people (45.4%) (Table 1). Although HPV type 58 and 16 were the most frequently found subtypes for the women in their 20s and 40s, respectively, the type distribution was varied.

Table 1. Frequency of HPV detection in self-collected cervicovaginal secretions according to the level of hospital and age

Age (years)	University hospital (%)		Local clinic (%)	
	HR HPV +	HSIL	HR HPV +	Abnormal cytology
-29	4/6 (66.7)	4/6 (66.7)	3/24 (12.5)	1/24 (4.2)
30-39	6/12 (50.0)	9/12 (75.0)	15/109 (13.8)	3/109 (2.8)
40-49	12/21 (57.1)	18/21 (85.7)	13/78 (16.7)	4/78 (5.1)
50-	5/11 (45.5)	5/11 (45.5)	18/79 (22.8)	3/79 (3.8)
Total	27/50 (54.0)	36/50 (72.0)	49/290 (16.9)	11/290 (3.8)

HR, high risk; HSIL, high grade squamous intraepithelial lesion.

Among 290 local clinic volunteers, 49 women (16.9%) were positive for HPV DNA by use of the self-collected pad sampling. Fifty-four subtypes of HPV were detected in the pad samples of 49 women, including 5 multiple infections (Table 2). The prevalence rates of HPV subtypes were: 16 (33.3%); 53 (7.4%); 58 (7.4%); 61 (7.4%); and 56 (5.6%). The remaining subtypes were 18, 22, 31, 33, 39, 45, 52, 54, 59, 62, 66, 68, 70, 71 and 84. The results for HPV detection according to age groups were: 20-29, 3 people (12.5%); 30-39, 15 people (13.8%); 40-49, 13 people (16.7%); and 50 or older, 18 people (22.8%) (Table 1). Although HPV type 16 was the most frequently found type in all age groups, the type distribution varied among the different age groups.

Sensitivity and specificity of self-collected pad sampling method

Among the 36 cases of histologically proven HSIL (CIN 2 and 3), high risk HPV was detected in 27 cases by the self-collected pad method. None of 14 cases without HSIL had high risk HPV by the self-collected pad method. For the detection of HSIL, the self-collected pad sampling had good sensitivity (75.0%) and excellent specificity (100%) (Table 3). Among the 19 cases of histologically proven HSIL, HPV was detected in 17 cases by hybrid capture II assay. Among the 8 cases without HSIL, HPV was detected in 3 cases by hybrid capture II assay. Detection of high-risk HPV using hybrid capture II assay showed excellent sensitivity (89.5%) and good specificity (62.5%).

Self-collected pad sampling compared with physician-directed sampling

Agreement was defined as the detection of the same HPV DNA sequences from both the self-collected pads and the physician-directed cervical brush samples, with either perfect or near perfect agreement with regard to multiple infections. Perfect agreement meant that there was absolute concordance of all HPV types between the pads and their concurrent brush samples. Near per-

Table 2. Frequency of HPV genotypes detected in self-collected cervicovaginal secretions according to results of cervical biopsy and cytology

HPV type	Biopsy results*			Total (%)	Cytology result†			Total (%)
	IC	HSIL	Negative		LSIL	ASC	Negative	
6	0	1	0	1 (3.2)	0	0	0	0
16	1	5	0	6 (19.4)	0	1	17	18 (33.3)
17	0	1	0	1 (3.2)	0	0	0	0
18	1	1	0	2 (6.5)	0	0	2	2 (3.7)
22	0	0	0	0	0	0	1	1 (1.9)
31	0	1	0	1 (3.2)	1	0	1	2 (3.7)
33	0	2	0	2 (6.5)	0	0	2	2 (3.7)
39	0	0	0	0	0	0	1	1 (1.9)
45	0	0	0	0	0	0	2	2 (3.7)
51	1	0	0	1 (3.2)	0	0	0	0
52	0	1	0	1 (3.2)	0	0	1	1 (1.9)
53	0	2	0	2 (6.5)	0	0	4	4 (7.4)
54	0	0	0	0	0	0	1	1 (1.9)
56	0	1	0	1 (3.2)	0	0	3	3 (5.6)
58	1	8	0	9 (29.0)	0	0	4	4 (7.4)
59	0	0	0	0	0	0	1	1 (1.9)
61	0	1	0	1 (3.2)	0	0	4	4 (7.4)
62	0	0	0	0	0	0	1	1 (1.9)
66	0	0	0	0	0	0	2	2 (3.7)
68	0	0	0	0	0	0	1	1 (1.9)
69	0	1	0	1 (3.2)	0	0	0	0
70	0	1	0	1 (3.2)	0	0	2	2 (3.7)
71	0	0	0	0	0	0	1	1 (1.9)
82	0	1	0	1 (3.2)	0	0	0	0
84	0	0	0	0	0	0	1	1 (1.9)
Total	4	27	0	31	1	1	52	54

ASC, atypical squamous cells; HSIL, high grade squamous intraepithelial lesion; IC, invasive carcinoma; LSIL, low grade squamous intraepithelial lesion.
*Biopsy results were from 50 university hospital volunteers. Thirty-one subtypes of HPV were detected in the pad samples of 27 women, including 4 multiple infections.
†Cytology results were from 290 local clinic volunteers. Fifty four subtypes of HPV were detected in the pad samples of 49 women, including 5 multiple infections.

Table 3. Results of testing for high risk (HR) HPV detection by direct sequencing using self-collected pad samples and by hybrid capture II (HCII) assay using microdissected tissue specimens

HR HPV	Presence of HSIL and IC by histology			Test indices	
	Yes	No	Total	Sensitivity	Specificity
+ by pad	27	0	27	75.0%	100%
- by pad	9	14	23		
+ by HC II	17	3	20	89.5%	62.5%
- by HC II	2	5	7		

HSIL, high grade squamous intraepithelial lesion; IC, invasive carcinoma.

Table 4. Comparison of physician-directed brush sampling of cervical cells with self-collected pad sampling of cervicovaginal secretion for the detection of HPV using direct sequencing method

Self-collected pad sampling	Physician-directed brush sampling		Total
	HPV +	HPV -	
HPV+by pad	46	2	48
HPV-by pad	1	240	241
Total	47	242	289
Kappa	Standard error	z value	p value
0.9622	0.0588	16.3589	0.0000

fect agreement meant that there were additional HPV types either in the pads or in their concurrent brush samples.

Two hundreds eighty-six samples from the pads and concurrent physicians' samples showed the agreement at 98.6%. Only four cases exhibited a difference of agreement between the pads and concurrent physicians' samples. Two cases of disagreement were the result of detection failure in physicians' samples; one case was the result of detection failure in the pad sample, and the other case was the result of a type difference between them. Among the 286 agreement cases, 281 cases (98.3%) showed perfect agreement including 5 multiple infections. Only 5 multiple infection cases exhibited near perfect agreement consisting of 3 multiple HPV types in physicians' samples and 2 multiple HPV

Table 5. Comparison of physician-directed brush sampling of cervical cells with self-collected pad sampling of cervicovaginal secretion for the results of cytological diagnosis by MonoPrep2 method

MonoPrep2 cytology	HR HPV+by physician (%)	HR HPV+ by pad (%)
Negative (n=279)	46 (16.5)	47 (16.9)
ASC-US (n=6)	1 (16.7)	1 (16.7)
ASC-H (n=2)	0	0
LSIL (n=3)	1 (33.3)	1 (33.3)
Total (n=290)	48 (16.6)	49 (16.9)

ASC-H, atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HR, high risk; LSIL, low grade squamous intraepithelial lesion.

types in the pad samples. Kappa analysis showed the excellent agreement at 0.9622 (p=0.0000) (Table 4). The one case with the different HPV type was deleted in the Kappa analysis.

For the pathologic analysis, we reviewed the liquid-based cytology smears. Among the 290 cases, 11 cases showed abnormal cytology results, such as 3 LSIL, 2 ASC-H and 6 ASCUS (Table 5). HPV DNA detection rates were 16.5-16.9% in normal and ASCUS, and 33.3% in LSIL.

DISCUSSION

The benefits of cervical cancer screening are relative to the proportion of the population that is covered and the efficacy of the method that is used.[9] The use of an economic and accurate method for the detection of cervical HPV infection is important for improvements in cervical cancer screening programs based on cytologic examination. Both the screening cost and cultural prohibitions in many countries decrease the effectiveness of public health measures to control and reduce the incidence of cervical cancer. Self-collection of cervicovaginal cells, if this method is effective for the detection of cervical cells or HPV DNA, would be convenient for many women and could increase cervical cancer screening coverage for women in cultures where prohibitions prevent exposure of the genitals to a male physician.[9] It has long been a matter of controversy whether self-sampling for HPV detection and typing provides enough cells from a representative proportion of the cervical ectocervix and canal to produce results that are matched in efficacy and safety to the cells that are collected by the current routine practice of cervical scrapes taken by physicians.

Some of the initial self-sampling studies for HPV detection did not get the satisfactory result. The relatively low concordance of positive and negative results of 44% and 38%, respectively, were reported in a study with 48 women using self-collected samples by a wooden spatula and a cotton-tipped swab and Southern blot hybridization.[24] However, the results of self-sampling studies for HPV detection have been gotten better with technical improvements. Morrison *et al*.[20] have shown concordance of positive and negative results of 75% and 83%, respectively. Fairley *et al*.[21] reported that there were correlations of 90% (Kappa 0.64) and 88% (Kappa 0.70) of the positive results, respectively.

Moscicki[18] has investigated the usefulness of self-sampling for HPV detection by employing the HPV profile method, which is basically an improvement of the ViraPap (Digene Diagnostic, Inc, MA, USA) test. The author analyzed samples from 104 women and reported no significant difference in the results of HPV positivity in self-collected samples with a standard Dacron polyester swab compared with samples also collected with a Dacron polyester swab, but done by nurse practitioners under direct observation of the cervix. The agreement was 91%. Harper *et al*.[25] reported a concordance of positive and negative results of 17.3% and 62.4%, respectively, which is a fair agreement (Kappa 0.49. In addition to this study, Harper *et al*. have continuously improved their results for detecting HPV DNA by self-sampling.[8,10] Hillemanns *et al*.[15] showed a significant difference between the overall HPV positivity of the results from self-sampling (53%) and physician sampling (42%). They used hybrid capture II for HPV detection. Wright *et al*.[14] reported an 82% overall concordance of self-sampling and nurse-sampling results, and they stated that there was a moderate agreement between the HPV results from self-collected vaginal cotton-tipped swabs and health personnel-collected Dacron-tipped vaginal swabs (Kappa 0.45). Besides these results, there were many studies suggesting the self-sampling method as a valid future tool for cervical cancer and HPV screening.[8-12]

In spite of technical improvements, a couple of recent self-sampling studies for HPV detection did not get the satisfactory result. One study used self-sampling with a Dacron swab from the vagina, vulva, and urine and this method was compared to physician sampling with a cone-shaped cervical brush from the transformation zone using hybrid capture II assay. This study showed the following agreements: for urine (Kappa 0.41), vulva (Kappa 0.55), and vaginal samples (Kappa 0.76).[13] They reported that the sensitivity of testing was progressively lower with the increasing distance from the cervix and that the specificity rates for physician sampling from the cervix and self-sampling from the vagina were 52.1% and 53.5%, respectively. Lorenzato *et al*.[9] studied 253 women randomly selected from a high-risk population for cervical neoplasia. The difference among HPV results in sam-

ples that were self-collected versus physician collected was significant. The agreements were poor among patients with CIN 3 (Kappa <0.29) and cervical cancer (Kappa <0.10), and self-sampling missed 50% more cancers than did the physician sampling procedures.

To the best of our knowledge, the pad sampling method has not yet been reported in this field. Our first goal was to confirm the usefulness of detecting HPV DNA by the self-collected pad method. The result was promising for using the pad as a screening tool, especially for women who do not want to visit a male doctor or for those women who live in areas with poor medical services. The sensitivity (75.0%) in this study was good and the specificity (100%) was excellent. However, the sample number must increase in future studies because 50 cases are insufficient for studies of this kind. This result of a relatively low sensitivity and high specificity seems to be related to the direct sequencing method. Although accurate, the result of the direct sequencing method is generally lower than for other methods. However, in spite of some minor problems, our results demonstrated the utility of the pad as a method for detecting HPV DNA.

Our next goal was to confirm agreement between self-collected samples by the pad and conventional physician sampling methods. Here in this study, we got the excellent result (Kappa 0.9622) that was the best Kappa score among all the related studies.

The tampon is one of the best alternative tools to detect HPV DNA for women with poor accessibility to the medical services. Furthermore, the tampon has been proven to collect a sizable cellular pellet that the swab cannot do, which could increase the possible variability in the cell concentration aliquotted from each sample for the PCR.[10] The pad may have the same advantage like the tampon. In addition to this, many Korean women favors the pad rather than the tampon as a menstrual aid (personal data).

The Dacron swab is also an excellent alternative tool to detect HPV DNA in women with low accessibility to hospital services. However, its breakage during the self-sampling has been reported, and this would require its removal by a clinician. Furthermore, its introduction into the female genital tract would be a mental burden to those women who do not want to visit a physician's clinic.

Based on our results, a self-sampling method using the pad for the detection of HPV DNA is clinically and socially important for the success of primary screening for cervical cancer. We proved that using the pad is an efficient self-sampling method for many women due to its ease, convenience and quickness of use. Clinic practices using the pad can reduce their clinical setup and cleanup time. The utility of the method for mass screenings in rural areas should be analyzed in a future study.

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