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Can human papillomavirus DNA testing of self-collected vaginal samples compare with physician-collected cervical samples and cytology for cervical cancer screening in developing countries?

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Abstract

Background—To determine human papillomavirus (HPV) types by polymerase chain reaction (PCR)-reverse line blot assay and examine the concordance between HPV by Hybrid Capture 2 (HC2) and PCR on self-collected vaginal and physician-collected cervical samples and cytology.

Methods—This was a cross-sectional study of 546 sexually active women aged ≥30 years with persistent vaginal discharge, intermenstrual or postcoital bleeding or an unhealthy cervix. Participants self-collected vaginal samples (HPV-S) and physicians collected cervical samples for conventional Pap smear and HPV DNA (HPV-P) testing and performed colposcopy, with directed biopsy, if indicated. HPV testing and genotyping was done by HC2 and PCR reverse line blot assay. Concordance between HC2 and PCR results of self- and physician-collected samples was determined using a Kappa statistic (κ) and Chi-square test.

Results—Complete data were available for 512 sets with 98% of women providing a satisfactory self-sample. PCR detected oncogenic HPV in 12.3% of self- and 13.0% of physician-collected samples. Overall, there was 93.8% agreement between physician-collected and self-samples (κ = 76.31%, 95% confidence interval [CI]: 64.97–82.29%, $p = 0.04$)—complete concordance in 473 cases (57 positive, 416 negative), partial concordance in seven pairs and discordance in 32 pairs. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of self-sampling for detection of cervical intraepithelial neoplasia (CIN)2+ disease were 82.5%, 93.6%, 52.4% and 98.4%, respectively; for physician-sampling they were 87.5%, 93.2%, 52.2% and 98.9%, respectively; and for cytology they were 77.5%, 87.3%, 34.1% and 97.9%,

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Conflict of interest
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respectively. Concordance between HC2 and PCR was 90.9% for self-samples (κ = 63.7%, 95% CI: 55.2–72.2%) and 95.3% for physician-collected samples (κ = 80.4%, 95% CI: 71.8–89.0%).

Conclusions—Self-HPV sampling compares favourably with physician-sampling and cytology. A rapid, affordable, HPV self-test kit can be used as the primary method of cervical cancer screening in low-resource situations.

Keywords

HPV types; Self-sampling; Screening; Hybrid Capture 2; PCR; CIN; Genotyping

1. Introduction

Cervical cancer is the second most common cancer among women worldwide and the most common cause of cancer among women in India [1]. There are facilities for opportunistic screening but no regular screening programmes are in place. It is known that persistent infection with high-risk types of human papillomavirus (HR-HPV) is a major cause of cervical cancer [2] and that HPV DNA testing of cervical samples has higher sensitivity for detection of high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer than the Pap smear test [3,4]. HPV testing has been recommended for primary cervical screening and with the introduction of a rapid, affordable test may be possible, even in low-resource situations [5,6]. Physician-obtained HPV samples also require gynaecological examination, which self-collected vaginal sampling can obviate in remote areas. The majority of studies have reported equivalent or less than equivalent sensitivity of self-sampling as compared to physician-sampling in the detection of high-grade lesions [7–11]. The present study aimed to compare the HPV types, test characteristics and concordance between self- and physician-collected samples as well as conventional cytology, to understand how a rapid test may perform in this setting.

2. Materials and methods

This cross-sectional study was carried out in the Gynaecology Outpatient Department (OPD) from January 2003 through to June 2005. Women presenting with complaints of persistent vaginal discharge, irregular menstrual bleeding, postcoital bleeding, or those found on examination to have an unhealthy cervix were invited to participate in a cancer-screening programme. Exclusion criteria were: age <30 years; unmarried; hysterectomised; prior surgical procedures on cervix; gross tumour on the cervix; and pregnancy. Informed written consent was taken from the women. Ethical clearance was obtained from the Institutional Review Board. A total of 625 potential participants were recruited, of which 74 were found ineligible and 5 refused to participate; thus 546 eligible women were enrolled and an enrolment questionnaire completed.

2.1. Clinical examination and investigation

Patients underwent the following tests in sequence: (1) self-collection of vaginal sample for HPV testing, (2) conventional Pap smear, (3) physician-collected cervical sample for HPV testing, and (4) colposcopy.

2.1.1. Procedure of self-sampling—The procedure of self-sampling was first explained to the patient with the help of a chart. A pre-labelled Digene HPV collection tube containing Specimen Transport Medium (STM, Qiagen Gaithersburg, Inc., USA) and a cervical sampler were then provided to the patient. She was instructed to introduce the cervical sampling brush into the vagina till she met with resistance, rotate the brush 3–5 times, remove it and place it in the tube containing the collection medium. The extra length of the

brush was snapped off, the bottle re-capped and deposited with the doctor. The collection procedure was supervised.

2.1.2. Physician-collected sampling—Patients were asked to lie in the dorsal position and a Cusco bivalve vaginal speculum was introduced. A Pap smear was taken with an Ayre spatula and endocervical brush. The cervical brush sampler was then introduced inside the endocervix with the lowermost bristles touching the ectocervix, rotated 3–5 times in a counter-clockwise direction and then placed in the Digene specimen collection tube as described for self-sampling.

2.1.3. Colposcopy—All women underwent a colposcopic examination by an experienced gynaecologist. Biopsies were taken from all lesions with a Reid score ≥ 0. Women were considered to be free of disease if CIN or invasive cancer were ruled out after biopsy or if colposcopy was normal, thereby obviating the need for taking a biopsy.

2.1.4. Sample storage and processing and HPV testing—Both the samples collected in Digene STM were divided into two aliquots and stored at −70 °C till further processing. One aliquot was tested for 13 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) by HC2 as per the manufacturer's recommendation (Qiagen Gaithersburg, Inc., USA). The second aliquot underwent testing by polymerase chain reaction (PCR) amplification with the use of the PGMY09/11 L1 consensus primer system and a reverse line blot detection strip that individually identifies 22 high-risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82 and its sub-type ISO39) and 15 low-risk HPV types (6, 11, 40, 42, 54, 55, 57, 61, 62, 64, 71, 72, 83, 84 and 89) [12]. The sample was processed as previously described [13,14]. In brief, 150 µl of the sample were digested with 15 µl of 10× digestion buffer (containing 700 µl of 20 mM Tris–HCl—1 mM EDTA (TE) buffer, 100 µl 10% Tween-20 and 200 µl of 20 mg/ml proteinase K) at 65 °C for 1 h followed by heat inactivation at 95 °C for 10 min. The DNA was precipitated with ethanol and ammonium acetate at −20 °C overnight. After centrifugation at 21,000 × *g* for 30 min at 4 °C for pelleting the DNA, the pellet was dried, resuspended in 75 µl of TE and stored at −20 °C until amplification for HPV testing.

The specimen DNA was amplified using PGMY 09/11 HPV-specific primers that amplify the 450 bp fragment of L1 ORF of genital HPV. Human β-globin target was co-amplified with HPV consensus primers to determine adequacy of the specimen. The PCR products were denatured and hybridised to an immobilised HPV probe array on strips (*kind gift of Roche Molecular Systems, Alameda, CA, USA*). Positive hybridisation was detected by colour precipitation at the probe site and the type determined by reading from a reference overlay. Each amplification run included HPV DNA positive controls (SiHa cell line/HeLa cell line) as well as no HPV DNA negative controls.

For analysis purposes, samples were considered sufficient for HPV determination if the β-globin probe was detected. All β-globin negative samples were excluded from further analysis.

2.1.5. Statistical analysis—Overall agreement with a 95% confidence interval was computed. The discordance between the two methods and between self- and physician-collected specimens was tested by Mc-Nemar Chi-square test. Chance corrected agreement was assessed by Kappa statistic along with a 95% confidence interval. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the self- and physician-collected samples and cytology were calculated taking lesions ≥CIN2 on biopsy as the reference standard for disease positivity. All analyses were performed using Stata 9.1.

3. Results

The median age of women enrolled in the study was 36 years, with 62.3% in the age group of 30–40 years; 39.2% of the women had no formal education, 26.0% had received some primary education and 23.7% of women had received high school or higher education. The majority of women belonged to lower (47.1%) and middle (49.2%) socio-economic class; 187 (36.4%) reported having had four or more births. The mean age at first coitus was 19.0 ± 3.3 years.

Out of 546 women enrolled and questionnaires completed, six absconded after being handed the specimen collection tube for self-sampling. The remaining 540 women were asked to provide a self-collected vaginal sample and physician-collected cervical sampling was also performed. In five women, the self-collection tubes were found to contain no fluid so HPV DNA could not be tested. In six samples, the β-globin gene could not be amplified (two physician-collected samples, three self-collected samples, and, in one case, in both physician and self-collected samples) so it was not possible to comment on presence and type of HPV. Therefore, 96.9% (529/546) of women enrolled were able to provide a satisfactory sample for testing. However, four women refused colposcopy, PCR results were missing in nine women and HC2 results were missing in four women. Thus, complete results were available for 512 pairs of HPV DNA samples (self- and physician-collected). Colposcopy was performed in all these cases and a biopsy taken in 315 cases. Biopsy-positive CIN or invasive cancer was present in 66 women (CIN1—26; CIN2—13; CIN3—19; invasive cancer—8).

3.1. Prevalence of HPV infection

96 (18.75%) women were found positive for any HPV type while 73 (14.3%) were found positive for HR-HPV by PCR on self- or physician-collected samples. HR-HPV infection was detected in 67 (13.1%) of the physician-collected cervical samples and in 63 (12.3%) of the self-collected vaginal samples.

Table 1 shows the prevalence of HPV DNA positivity with respect to histopathology in physician-collected samples. Seventeen high-risk and six low-risk HPV types were identified by the line blot assay (Table 2). HPV-16 was the most prevalent type, seen in 47.5% of HPV positive cervical samples (55.9% of HR types). HPV-18 was seen in five cases and HPV-33 in four cases. There was no case of HPV-45. Infection with multiple high-risk types was seen in 13 cases in either self- or physician samples, together with low-risk types in five cases.

Table 2 shows the concordance between HPV types detected on self-collected vaginal samples and physician-collected cervical samples. Complete concordance was seen in 473 pairs (57 positive for same HPV type(s), 416 negative). Partial concordance (both positive, different types) was seen in seven pairs. In six of them, the difference was additional low-risk type(s) in the vaginal sample and, in one case, there was an additional low-risk type in the cervical sample. Complete discordance was found in 32 pairs (physician positive, self-negative—15; physician negative, self-positive—17). One case each of CIN3 and invasive cancer, both of which were positive for HPV-18, would have been missed by self-sampling alone. Overall, there was 93.8% agreement (480/512 pairs) between the results obtained with HPV DNA testing of self-collected vaginal samples and physician-collected cervical samples ($\kappa = 0.76$, 95% CI: 71.8–89.0%, $p = 0.045$).

Table 3 shows that there was 90.9% concordance between HC2 and PCR in self-samples ($\kappa = 63.7\%$, 95% CI: 55.2–72.2%) and 95.3% in physician-collected samples ($\kappa = 80.4\%$, 95% CI: 71.8–89.0%). HC2-physician showed the best performance for detection of CIN2+

disease, notwithstanding the fact that the line blot assay detects 22 high-risk types while HC2 detects only 13 high-risk types. This was because in three subjects single infection with these types (HPV-53, -70 and -73) was found in both self- and physician samples and in one subject in the self-sample alone (HPV-53), but none of these were associated with disease. In six subjects, multiple infections were detected where the additional types (HPV-53, -66, -72 and -83) occurred in association with types detected by HC2 (HPV-16, -18, -31, -51, -56 and -59). Four of these were associated with CIN.

HPV testing of self- and physician samples compared well with the Pap smear at the LSIL threshold and was better than the Pap smear at the ASCUS threshold in terms of diagnostic accuracy (Table 4). PCR of both physician and self-samples had the highest diagnostic accuracy (92.8%); HC2 of physician samples was very comparable (91.6%) although HC2 of self-samples showed a somewhat lower accuracy (87%).

4. Discussion

Even as the spotlight focuses on primary prevention by HPV vaccination, secondary prevention by effective screening is still going to be the mainstay of cancer control programmes in the foreseeable future. For the developing world, none of the established screening techniques offer a viable option, mainly due to logistical problems. At this time, the magnitude of the problem, coupled with a lack of services, has led to a policy where a once-in-a-lifetime screen at age 35–40 years is being recommended. It is hoped that with the rapid HPV test, a screen-and-treat policy can be adopted, but some of the barriers to screening do impact follow-up. Increased awareness of cervical cancer following the introduction of HPV vaccination is making some difference in this regard.

The possibility of a rapid, affordable HPV test [5,6] has come as a new ray of hope but some of the problems of cytology will remain with this as well, mainly availability of appropriate facilities for pelvic examination. Self-collection of HPV samples is an attractive option as it obviates the need for a speculum examination and also the need to visit a physician or hospital for this purpose. It is especially suitable for remote geographical areas where these facilities may not even exist.

Digene® brush samplers were used for both self- and physician-sampling in this study to avoid bias from different collection devices. The brush was well accepted by the women. Vaginal sampling was always done first, followed by collection of a sample for cervical cytology prior to cervical sampling for HPV DNA. 98.1% of women were able to provide a satisfactory self-sample, thus negating fears that this technique may not be suitable in India.

There was good concordance between self- and physician-collected samples. Physician-collected sampling had better results but the difference was not significant. Overall, a 93.6% agreement was present between the two tests for combined high- and low-risk types. Chang et al. found that the concordance between the two tests was 93% [15]. However, Garcia et al. found the patient-collected samples had a significantly lower sensitivity than physician-collected ones [16]. Higher false positivity of self-collected samples compared to physician-collected samples has been reported by Hillemanns et al. [17], which could be due to the presence of low-risk types in the vagina. In the present study, LR-HPV i.e., HPV-61 and -89, were found in self-collected vaginal samples in three women but their physician-collected cervical samples were negative on PCR. On the contrary, in three women, HR-HPV types, i.e., HPV-31, -33 and -39, were isolated from cervical samples, but not from self-collected vaginal ones. HPV-16 was the most common type seen in healthy women as well as women with CIN. There was also good type-concordance in women with multiple

infections. The results compared very favourably with those of cytology. Self-sampling performed better than cytology and was nearly equivalent to physician–self-sampling.

Petignat et al., in a meta-analysis of 18 studies (5441 participants), reported a high level of concordance of 0.87 (95% CI, 0.82–0.91) between self- and physician-sampling for detection of HPV DNA (kappa 0.66, 95% CI, 0.56–0.76) [18]. They found that the results were similar when restricting the analysis to HR-HPV but the prevalence of LR-HPV types was higher in self-collected samples. They concluded that self-sampling was as sensitive as physician-obtained sampling to detect HR-HPV or HPV DNA and that self-sampling may be a suitable alternative method for studies on HPV transmission and vaccine trials. Similar results have also been reported from other community trials [19].

This study was carried out in women coming to hospital with symptoms, and we found that self-sampling was feasible and well accepted by them. More studies are needed in the community to establish acceptability among asymptomatic healthy women, but our preliminary experience suggests that it should work. The problem in remote areas is lack of infrastructure, electricity, facilities for sterilisation of speculum, etc. However, field workers can supervise collection of samples in women's homes or at field clinics. We feel that this will be the best way to implement self-sampling because our pilot testing showed that many women did not understand how to provide the sample when unsupervised—some went away while others returned empty tubes after spilling out the medium.

In this study we used the method of reverse line blot assay in order to be able to assess the concordance of HPV types. The concordance between PCR and HC2, a simpler method of testing, shows the merits of testing for HPV DNA as a screening test. Recently, it has been shown that HPV DNA testing is the best screening strategy for low-resource situations [20]. The rapid, affordable test will allow consideration of inclusion of HPV testing as a method of primary screening in developing countries. Further, self-sampling will be a powerful tool for populations with limited access to health care or limited access to cervical screening.

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Table 1

Comparison of PCR for high-risk types only between self-collected vaginal and physician-collected cervical samples relative to histology.

Diagnosis	Both −	Physician+, Self −	Physician −, Self +	Both +	*p*
Normal (*n* = 446)	417	7	6	16	0.98
Low-grade lesion (*n*=26)	17	1	0	8	0.99
High-grade lesion (*n* = 40)	5	2	0	33	0.50
Total (*n* = 512)	439	10	6	57	0.45

Observed agreement 96.9% (κ = 85.9%, SE 0.0442, $p < 0.001$) (95% CI: 77.24–94.56%).

Table 2

HPV type concordance in self- and physician-collected samples in relation to histopathology

HPV type doctor	HPV type self	Number	Histopathology grade and no. of cases
A. Completely concordant			
16	16	27	CIN1—3; CIN2—8; CIN3—8; Ca—3
18	18	1	CIN2—1
33	33	3	CIN2—1; CIN3—1; Ca—1
35	35	1	CIN1—1
39	39	2	CIN2—1
51	51	1	
52	52	1	CIN1—1
53	53	1	
58	58	2	
70	70	1	
73	73	1	
42 *	42 *	1	
62 *	62 *	1	
84 *	84 *	1	
89 *	89 *	1	CIN1—1
16,35	16,35	1	CIN3—1
16,55 *	16,55 *	1	CIN2—1
16,56	16,56	1	CIN2—1
16,62 *	16,62 *	1	CIN3—1
16,66	16,66	1	
16,68	16,68	1	CIN3—1
16,73	16,73	1	CIN2—1
18,66,62 *	18,66,62 *	1	CIN1—1
51,52,82	51,52,82	1	CIN1—1
51,82,84 *	51,82,84 *	1	CIN2—1

HPV type doctor	HPV type self	Number	Histopathology grade and no. of cases
52,55*	52,55*	1	
62*,72*	62*,72*	1	
HPV type doctor	HPV type self	Number	Histopathology
B. Partial concordance			
16	16,42*	1	CIN1—1
16	16,62*	1	Ca—1
16	16,62*,72*	1	
31,53,59	31,53,59,62*,89*	1	CIN1—1
52,89*	52	1	
84*	84*,89*	1	
89*	84*,89*	1	
C. Discordant			
16	Neg	3	
18	Neg	3	CIN3—1, Ca—1
31	Neg	1	
33	Neg	1	CIN1—1
39	Neg	1	
39,62*	Neg	1	
53,56	Neg	1	
89*	Neg	4	CIN1—1
Neg	16	1	
Neg	52	1	
Neg	61*	1	
Neg	16,59	1	
Neg	42*	1	
Neg	51,70,61*,62*	1	
Neg	53,54*	1	

HPV type doctor	HPV type self	Number	Histopathology grade and no. of cases
Neg	54*	1	CIN1—1
Neg	59,61*	1	
Neg	61*	1	
Neg	62*	2	
Neg	84*	1	
Neg	89*	4	

CIN = cervical intraepithelial neoplasia; Ca = invasive cancer.

*Low-risk types.

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Table 3

Comparison of Hybrid Capture 2 (HC2) and PCR for high-risk HPV in physician-collected cervical samples and self-collected vaginal samples, relative to histological diagnosis.

Diagnosis	Physician-collected cervical samples					Self-collected vaginal samples				
	Both –	PCR–, HC2+	PCR+, HC2–	Both +	*p*	Both –	PCR–, HC2 +	PCR+, HC2–	Both +	*p*
Normal (*n* = 446)	408	15	7	16	0.13	391	33	6	16	<0.001
Low-grade lesion (CIN1) (*n* = 26)	17	0	1	8	0.98	17	1	2	6	0.98
High-grade lesion (CIN2+) (*n* = 40)	4	1	0	35	0.98	5	2	3	30	0.98
Total (*n* = 512)	429	16	8	59	0.15	413	36	11	52	<0.001

Cervical samples: Observed agreement 95.3% (κ = 80.4%, 95% CI: 71.8–89.0%, $p < 0.001$); *Vaginal samples*: Observed agreement 90.9% (κ = 63.7%; 95% CI: 55.2–72.2%; $p < 0.001$).

Table 4

Results of testing for human papillomavirus (HPV) by PCR, Hybrid Capture 2 (HC2) and Pap smear relative to histology (40 women with high-grade lesion[a], 26 with low-grade lesion[b] and 446 women with no lesion[c]).

Specimen	Type of lesion				Test index % (95% CI) for HSIL				
	High-grade	Low-grade	Other[c]	Total	Sensitivity	Specificity	PPV	NPV	DA
PCR-P	35	9	23	67	87.5 (77.2, 97.8)	93.2 (91.0, 95.5)	52.2 (40.3, 64.2)	98.9 (97.9, 99.9)	92.8 (90.6, 95.0)
PCR-S	33	8	22	63	82.5 (70.7, 94.3)	93.6 (91.5, 95.9)	52.4 (40.0, 64.7)	98.4 (97.3, 99.6)	92.8 (90.6, 95.0)
HC2-P	36	8	31	75	90.0 (80.7, 99.3)	91.7 (89.3, 94.2)	48.0 (36.7, 59.3)	99.1 (98.2, 100.0)	91.6 (89.2, 94.0)
HC2-S	32	7	49	88	80.0 (67.6, 92.4)	88.1 (85.3, 91.1)	36.4 (26.3, 46.4)	98.1 (96.8, 99.4)	87.5 (84.7, 90.4)
Pap≥ASCUS	31	8	52	91	77.5 (61.1, 88.6)	87.3 (83.9, 90.1)	34.1 (24.7, 44.8)	97.9 (95.8, 99.0)	86.5 (83.5, 89.5)
Pap≥LSIL	28	4	21	53	70.0 (53.3, 82.9)	94.7 (92.2, 96.5)	52.8 (32.8, 66.5)	97.4 (95.4, 98.6)	92.8 (90.6, 95.0)

PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy (true positive + true negative/total no. of cases); PCR-P: physician-collected sample tested by PCR; PCR-S: self-collected sample tested by PCR.

[a]Women with high-grade lesion equivalent to CIN2, 3 or Ca was diagnosed by cervical biopsy.

[b]Women with low-grade lesion equivalent to CIN1 was diagnosed by cervical biopsy.

[c]Women with cervical biopsy indicated no SIL and women with normal cervix on colposcopy.