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Chapter 2

Brush-based self-sampling in combination with GP5+/6+-PCR-based hrHPV testing: high concordance with physician-taken cervical scrapes for HPV genotyping and detection of high-grade CIN

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ABSTRACT**Background:**

Studies have shown that self-sampling for hrHPV testing (HPV self-sampling) is highly acceptable to women, increases screening participation rate, and may therefore further reduce cervical cancer incidence. However, it is important to clinically validate HPV self-sampling procedures for screening purposes.

Objectives:

Clinical validation of combined brush-based self-sampling with GP5+/6+-PCR EIA for primary cervical screening. In addition, HPV type-specific agreement between sample types and acceptability of brush-based self-sampling were evaluated.

Study design:

135 women referred for colposcopy took a self-sample at home prior to vaginal- and cervical sampling by a gynaecologist. All women were biopsied for histology. HPV testing was done by GP5+/6+-PCR EIA, with genotyping by reverse line blotting (RLB). Acceptability of sampling methods was measured with a questionnaire.

Results:

In this outpatient population, hrHPV test results showed good concordance between self-samples and physician-taken cervical scrapes (86%, $k = 0.70$), with sensitivities and specificities for CIN2+ that did not differ significantly (93% and 51%, 91% and 51%, respectively ($P = 1.0$)). The clinical sensitivity of brush-based self-sampling combined with GP5+/6+-PCR EIA hrHPV testing for detection of CIN2+ was non-inferior to that of hrHPV testing on physician-taken cervical samples ($P = 0.018$). In addition, hrHPV genotyping results were highly concordant between sample types, with almost perfect agreement for HPV16 ($k = 0.81$) and HPV18 ($k = 0.92$). Finally, 91% of participants described brush-based self-sampling as easy-to-use.

Conclusions:

Brush-based self-sampling in combination with GP5+/6+-PCR EIA hrHPV testing is acceptable to women and valid for assessing the risk of CIN2+ in comparison to hrHPV testing on physician-taken scrapes. In addition, there was high concordance of HPV genotyping results. Therefore, this HPV self-sampling procedure may be considered for use in routine cervical screening.

1. BACKGROUND

In forthcoming years, self-sampling may become increasingly important in cervical screening since self-collection for HPV testing (HPV self-sampling) has shown to persuade a subset of non-attendees to participate¹⁻⁶. Targeting non-attendees is important, because they are at higher risk of developing cervical cancer⁷⁻⁹. Additionally, self-sampling may make cervical screening accessible to women in developing regions¹⁰⁻¹². Studies have shown that HPV testing on self-samples is non-inferior to that of physician-collected cervical samples for the detection of CIN2+, although reported data are rather inconsistent¹³⁻¹⁷. This most likely reflects the use of different self-collection devices in combination with different HPV tests^{17,18}. Therefore, it is important that a self-collection device is clinically validated in combination with an HPV test, prior to use as an HPV self-sampling procedure in cervical cancer screening. In addition, compatibility between self- and physician-collected samples at the level of HPV genotyping is of interest, since discerning individual types may be relevant for CIN2+ risk assessment as HPV16 is correlated with an increased risk of CIN2+ compared to all non-HPV16 genotypes¹⁹.

2. OBJECTIVES

The Viba-brush® (Rovers Medical Devices B.V.) has been used for self-sampling by non-attendees²⁴, and the GP5+/6+-PCR enzyme immunoassay (EIA) HPV test is clinically validated for cervical screening purposes²⁰. Here, we aimed firstly to determine whether the combination of this self-sampling device and GP5+/6+-PCR EIA-based hrHPV testing has an equal clinical performance to detect CIN2+ as GP5+/6+-PCR EIA-testing on physician-taken cervical scrapes, in a gynaecology outpatient population. In addition, the prevalence of HPV genotypes was compared between self-samples and physician-taken vaginal- and cervical samples. Finally, acceptability and user-friendliness of the brush-based self-collection device were assessed with a short questionnaire.

3. STUDY DESIGN

3.1. Study population

Between October 2009 and November 2010, 135 women were recruited at the Department of Obstetrics and Gynaecology of the VU University Medical Center and Albert Schweitzer Ziekenhuis, the Netherlands. 105 women were referred for colposcopy-directed biopsy because of a cervical smear with moderate dyskaryosis or worse, or repeated equivocal Pap smear results and 30 women referred for post-coital bleeding had normal cytology. The median age of the participants was 34 years (range 20–68). All women were given an illustrated instruction leaflet and were asked to self-collect a vaginal sample in a 20 ml Thinprep® vial (PreservCyt®, Hologic Inc.), one week prior to their visit to the gynaecologist. In addition, participants received a short questionnaire with questions using a 3-point ordinal scale on the acceptability of self-sampling,

preferences for self- or clinician sampling and physical (dis)comfort and perceived (dis)advantages of the procedure. During the subsequent visit to the outpatient clinic, first a vaginal sample was taken by the gynaecologist with a Viba-brush, and then a vaginal speculum was inserted to take a regular cervical scrape using a Rovers® Cervex-brush. Both clinician samples were collected in 20 ml Thinprep® preservation medium. Self-collected-and physician-obtained vials were blinded for the procedure, prior to delivery to the laboratory. The time between sample collection and hrHPV testing was at maximum two weeks. During colposcopy, a biopsy specimen was taken of any cervical lesion observed. In case no lesions were visualised, at least one random biopsy was taken. The most severe histological finding per woman was used for comparison calculations. Participants were treated according to the Dutch guidelines ²¹.

3.2. HPV detection

Testing for HPV DNA was performed by GP5+/6+-PCR EIA and subsequent reverse line blot (RLB) assay for genotyping. DNA was extracted from 1/10th of the samples by using the Hamilton MICROLAB STARlet robot, and subjected to GP5+/6+-PCR EIA as described previously ²². EIA-positive GP5+/6+-PCR products were genotyped by RLB according to a previously described protocol ²³. As a quality control for the presence of amplifiable DNA and absence of PCR inhibitors in the isolated material, we performed a PCR for B-globin.

3.3. Data and statistical analysis

Cohen's kappa statistics were used to assess concordance between type-specific HPV test results of corresponding self-collected- and physician-taken samples. Strength of agreement was judged according to Landis and Koch ²⁴: kappa < 0: poor; 0–0.20: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1.00: almost perfect. For assessing overall genotype concordance, results were scored as either concordant (methods yielded completely identical genotyping results), compatible (one or more of the same genotypes were detected), or discordant (no similarities between genotypes detected). Type-specific agreement was calculated only for those types that had at least six positive results. Differences in sensitivity and specificity between sampling methods were assessed using Chi-square tests (McNemar). In addition, clinical sensitivity was compared by using a non-inferiority score test (software R), using a sensitivity threshold for CIN2+ of at least 90% relative to that of GP5+/6+-PCR EIA hrHPV testing on physician-taken cervical samples.²⁵ Confidence intervals were calculated, and the significant level was set at 0.05. All statistical analyses were performed using SPSS11.5-software

4. RESULTS

4.1. hrHPV DNA detection and histological diagnosis

Eighty-five of the one hundred and thirty-five participants (63%) had a self-collected vaginal specimen that tested positive for hrHPV DNA, compared to 84 (62%) in physician-taken cervical samples. This high prevalence of hrHPV is in line with the expectations for women attending a colposcopy clinic. hrHPV test results in self-collected samples and corresponding physician-obtained cervical samples show a substantial agreement, i.e., 86% resulting in a kappa of 0.70 (95% CI: 0.60–0.78; Table 1). Prevalence of CIN2+ lesions was 32% (43/135). The sensitivities and specificities for CIN2+ did not differ significantly between sampling methods (i.e., sensitivity: 93% vs. 91%, and specificity both 51%, for GP5+/6+-PCR EIA hrHPV testing on self-collected samples and physician-taken cervical samples, respectively ($P = 1.0$)). Using a sensitivity threshold for CIN2+ of at least 90% relative to that of GP5+/6+-PCR EIA hrHPV testing on physician-taken cervical samples²⁵, the clinical sensitivity for CIN2+ of GP5+/6+-PCR EIA hrHPV testing on self-collected samples was non-inferior to that of GP5+/6+-PCR EIA hrHPV testing on physician-taken cervical specimen ($P = 0.018$). Two CIN2 lesions were hrHPV negative in both sample types, whereas one CIN2 lesion was hrHPV negative in the self-sample while positive in the clinician sample, and vice versa for a CIN2 and one CIN3 lesion (Table 1).

4.2. HPV genotyping

Overall, thirty different HPV genotypes were detected in self-samples compared to 31, and 30 in physician-obtained vaginal- and cervical samples, respectively. Of all participants, 82 women tested HPV DNA-positive by each of the three collection methods, with perfect type agreement in 54 (66%) cases, and compatible results in 26 (32%) specimens. Two women showed discordant types in their physician-taken cervical samples compared to corresponding self- and physician-collected vaginal specimens (i.e., HPV16 vs. HPV42 and HPV52 vs. HPV42, respectively). Low-risk HPV types (LrHPV) were slightly more prevalent in vaginal specimens (self- (39%) and physician-obtained (40%)) than in cervical samples (37%; $P = 1.0$). Further, the prevalence of multiple (i.e., two or more) HPV genotypes was significantly lower in cervical samples (21%) than in self-collected- (28%) and physician-taken vaginal samples (33%) ($P = 0.029$). The “extra” genotypes detected in these multiple infections were predominately LrHPV types (mainly HPV6, HPV11 and HPV42). Regardless of the collection method, HPV16 was the most prevalent hrHPV type followed by types HPV31 and HPV51 (Table 2). The type-specific agreement between self-collected samples and physician-taken cervical samples ranged from substantial to almost perfect ($k = 0.79$ – 1.00). The latter included types HPV16 ($k = 0.81$ (95% CI: 0.72–0.87)) and HPV18 ($k = 0.92$ (95% CI: 0.88–0.95)). Comparable results were seen for concordance between both vaginal samples (self- and physician-obtained) with kappa values ranging from 0.79 to 0.87.

Table 1. hrHPV DNA test results and sensitivity for underlying CIN lesions of self-collected vaginal samples and corresponding physician-taken cervical samples.

Histology	hrHPV DNA		physician cervical sample		Total
	vaginal self-sample		pos	neg	
≤ CIN1	pos		37	8	45
	neg		8	39	47
≥ CIN2 *	pos		38	2	40
	neg		1	2	3
	Total		84	51	135

* Discrepancies in detection CIN2+ lesions: double neg = 2x CIN2; self-sample neg = 1x CIN2; physician-taken sample neg = 1x CIN2 and 1x CIN3

Table 2. Prevalence of hrHPV genotypes in different sample types.

Genotype	Number of samples found positive by ^a :			Concordance (kappa (95% CI))	
	self-collected VS	physician-taken VS	physician-taken CS	self-collected VS - physician-taken VS	self-collected VS - physician-taken CS
HPV 16	26	22	27	0.79 (0.71-0.85)	0.81 (0.72-0.87)
HPV 18	6	8	7	0.85 (0.79-0.89)	0.92 (0.88-0.95)
HPV 31	11	11	11	0.86 (0.80-0.90)	0.79 (0.67-0.86)
HPV 39	6	6	6	1,00	1,00
HPV 51	10	11	12	0.85 (0.79-0.89)	0.88 (0.82-0.93)
HPV 56	7	8	7	0.87 (0.82-0.91)	0.92 (0.87-0.95)

VS, vaginal sample; CS, cervical sample; a = frequencies indicated here include presence of types both in single and multiple infections

4.3. Acceptability of self-sampling

The far majority of participants (91%) described the brush as easy-to-use (Fig. 1), and many of these women mentioned the aspect of self-sampling being less time-consuming as the greatest benefit. Approximately one third of participants was concerned about performing the test properly, and said to prefer an “expert” taking the sample. Nevertheless, the majority of interviewed women (70%) favoured self-sampling over physician sampling when given a choice (Fig. 1), for reasons of comfort and convenience.

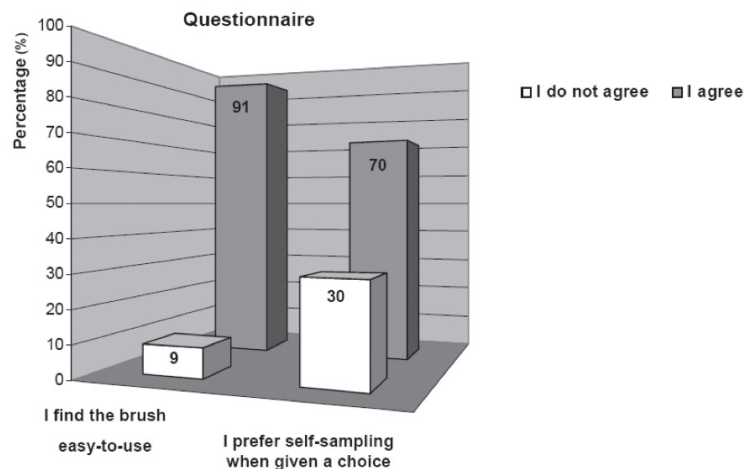


Fig. 1. Results of a short questionnaire on the acceptability of brush-based self-sampling

5. DISCUSSION

In this study we show that the clinical performance of HPV self-sampling, consisting of Viba-brush-based self-collection combined with GP5+/6+-PCR-EIA-based hrHPV testing, to detect CIN2+ shows high agreement with that of hrHPV testing on physician-obtained cervical samples. hrHPV testing on self-collected material was equally effective in detecting high-grade CIN (40/43 vs. 39/43), while at the same time the specificity did not differ significantly between both sampling methods (both 51%). One CIN3 case was even detected by hrHPV testing on the self-collected sample only. Our data support the concept that the right combination of self-collection device and clinically validated HPV test is clinically equivalent to HPV testing on physician-taken cervical smears. Previous studies have reported similar data on the clinical performance of hrHPV testing on self-collected specimen^{11-13;17;26-28}. Some other studies reported a lower sensitivity and specificity of hrHPV testing on self-samples²⁹⁻³². This difference may relate to the use of different devices for self-collection (swab, brush, tampon or lavage) and clinician sampling (cone shaped brush, cytobrush, Dacron swab or Cervex brush), or to the use of different hrHPV detection methods. The lower specificity in some studies may be due to cross-reactivity of the hrHPV test with IrHPV types³³. Belinson et al. showed that this can be

lowered when HPV detection assays are used that do not show cross-reactivity with IrPV types¹⁷. It should be noticed, that our study was done in a gynaecology out-patient clinic population with higher rates of HPV infection and CIN2+ lesions than average detected in women attending screening. This might have led to an overcalling of the specificity of the HPV test.

Our evaluation of HPV genotypes showed a slightly higher prevalence of low-risk types in vaginal samples compared to physician-taken cervical scrapes, though not statistically significant ($P = 1.0$), in line with previous reports^{15;34}. Also, the prevalence of multiple HPV types was higher by vaginal sampling ($P = 0.029$). Mainly, additional IrHPV types were detected in these multiple infections, which supports the idea that vaginal samples represent a mixture of infected vaginal cells and exfoliated cervical cells. The high-risk type-specific agreement between sampling methods, however, ranged from substantial to almost perfect ($k = 0.79-1.00$), indicating that self-samples are representative of the hrHPV types that infect the cervix. These results are in line with data from a recent study by Deleré et al.³⁵ This is important for CIN2+ risk assessment and monitoring of HPV genotype persistence^{36;37;38}. The good representation of types HPV16 and HPV18 in self-samples, in our study, is especially interesting as these genotypes confer an increased risk of CIN2+ compared to other hrHPV types^{19;39-42}. Earlier we have validated a lavage-based self-sampling device (Delphi screener) in combination with the GP5+/6+-PCR EIA,¹³ and here we show that the Viba-brush self-sampling device in combination with the GP5+/6+-PCR EIA is equally suitable for primary hrHPV-based cervical screening. Future research needs to address triage strategies for self-collected specimens, as currently women tested HPV-positive on their self-samples are referred to the general practitioner for cytology, because self-collected specimens generally yield insufficient amounts of cervical cells for reliable cytology⁴³⁻⁴⁶. Molecular markers such as promoter methylation analysis of tumour suppressor genes are interesting alternatives and directly applicable to self-sampled specimens^{47;48}. This potentially leads to more compliance and less loss to follow-up. Suitability of Viba-brush-based self-collected specimens for molecular triage needs further investigation. In conclusion, this study shows that in combination with GP5+/6+-PCR EIA-based hrHPV testing, self-samples taken by the Viba-brush are highly representative to determine the risk for underlying CIN2+, and that its use is well acceptable to women. In addition, the data show that self-collected specimens are reliable for type-specific hrHPV detection, which is useful for CIN2+ risk assessment and monitoring of HPV genotype persistence. Therefore, this HPV self-sampling procedure might be used to re-attract non-attendees in population-based screening, or even for primary hrHPV-based cervical screening.

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