Self-sampling for high-risk human papillomavirus as a follow-up alternative after treatment of high-grade cervical intraepithelial neoplasia

ELLINOR ÖSTENSSON1, KAREN BELKIC2-4, TORBJÖRN RAMQVIST2, MIRIAM MINTS1,5 and SONIA ANDERSSON1

1Department of Women's and Children's Health, Obstetrics-Gynecology Division; 2Department of Oncology-Pathology, Karolinska Institute, SE-17176 Stockholm, Sweden; 3School of Community/Global Health, Claremont Graduate University, Claremont, CA 91711; 4Institute for Health Promotion and Disease Prevention Research, Keck School of Medicine, University of Southern California, Los Angeles, CA 90032, USA; 5School of Medical Sciences, Faculty of Medicine-Health, Örebro University, SE-70182 Örebro, Sweden

Received November 1, 2020; Accepted January 11, 2021

DOI: 10.3892/ol.2021.12501

Abstract. Women treated for high-grade cervical-intraepithelial-neoplasia (CIN) require long-term follow-up with high-risk human-papillomavirus (HPV) testing. Self-sampling for HPV is well-accepted among these patients, but its role in follow-up for this group requires investigation. The present study examined how well HPV findings from self-sampled vaginal (VSS) and urine specimens correctly identified women from this cohort with recurrent CIN2+ compared with samples collected by clinicians. At 1st post-conization follow-up, 531 patients (99.8% participation) gave urine samples, performed VSS, underwent colposcopy with punch biopsy of visible lesions and clinician-collected cervical sampling for HPV analysis and liquid-based cytology. A total of 113 patients with positive HPV and/or abnormal cytology at 1st follow-up underwent 2nd follow-up. At 1st follow-up, all patients with recurrent CIN3 had positive HPV results by all methods. Clinician sampling and VSS revealed HPV16 positivity in 50% of recurrent cases and urine sampling revealed HPV16 positivity in 25% of recurrent cases. At 2nd follow-up, all 7 newly-detected CIN2/3 recurrences were associated with HPV positivity on VSS and clinician-samples. Only clinician-collected samples detected HPV positivity for two adenocarcinoma-in-situ recurrences, and both were HPV18 positive. A total of 77 patients had abnormal cytology at 1st follow-up, for which HPV positivity via VSS yielded highest sensitivity. The HPV findings were positive from VSS in 12 patients with high-grade squamous-intraepithelial-lesions (HSIL), and 11 patients with HSIL had positive HPV findings in clinician-collected and urine samples. All methods for assessing HPV presence yielded significant age-adjusted odds ratios for predicting abnormal lesions at 1st follow-up. For overall HPV results, Cohen's kappa revealed substantial agreement between VSS and clinician sampling, and moderate agreement between urine and clinician sampling. Clinician sampling and VSS were highly concordant for HPV16. Insofar as the pathology was squamous (not glandular), VSS appeared as sensitive as clinician sampling for HPV in predicting outcome among the present cohort. Since VSS can be performed at home, this option can maximize participation in the required long-term follow-up for these women at high-risk.

Introduction

Women in whom high-grade cervical intraepithelial neoplasia (CIN) has been identified and treated require long-term follow-up compared to the general population (1), because of their increased risk for disease recurrence (2). However, evidence-based guidelines to optimize post-therapeutic screening are still needed (3).

Because of the well-established role of high-risk human papilloma virus (HPV) in the etiology of cervical cancer, HPV testing is now accepted to be used to assess recurrence risk after high-grade CIN treatment. Indispensable insights are gleaned thereby (2,4,5).

Besides clinician-collected samples, women themselves can collect vaginal and/or urine samples for HPV testing. With
concerted efforts to maximize self-sampling reliability (6), using validated polymerase chain reaction (PCR)-based assays (7), accuracy is reportedly similar from self-collected compared to clinician-collected samples (8). With these developments, HPV testing from self-collected samples is becoming a viable, cost-effective cervical-screening option (9).

In Ref. (10) we recently examined the views on self-sampling for HPV among 479 women treated for high-grade CIN. The vast majority of these women considered self-sampling to be easily implementable, and could envision themselves performing self-sampling at home before their next gynecologic examination. We concluded that insofar as HPV self-sampling was as diagnostically accurate as clinician-collected samples for this high-risk cohort, the former could become an integral part of the post-therapeutic screening armamentarium.

This possibility becomes especially timely given the present COVID-19 pandemic. In other words, these women at elevated risk for cervical cancer could eventually perform at least a part of the needed screening outside the clinic setting. In a broader framework, given that long-term follow-up is essential for this cohort, whether or not HPV self-sampling is a viable option for these women becomes a critical issue to be examined.

The present study addresses this question, examining how well positive HPV findings from self-sampled vaginal and urine specimens, compared to clinician-collected cervical samples, correctly identify women from this cohort with recurrent high-grade CIN. We also compare how well HPV findings from self-collected vaginal and urine samples versus clinician-collected cervical samples identify women from this cohort with abnormal versus normal cytology at follow-up. The latter outcome variable currently impacts directly upon decision-making: Namely, whether the patient will be triaged for further intensive follow-up or whether she will be returned to the routine screening program.

Materials and methods

Study design, population and setting. This study includes patients first-time treated by conization for histologically-confirmed CIN2+ or adenocarcinoma-in-situ (AIS) at Stockholm Hospitals: Karolinska University, Danderyd or South General, from 10/2014-1/2017. The Research Coordinator, Ellinor Östensson, contacted these patients shortly after treatment, to arrange follow-up #1. The patient was sent for follow-up #2, which was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and cytology negative for intraepithelial lesions or malignancy (NILM) returned to routine triennial screening, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1.

Routine follow-up tests, further patient management. The LBC was performed at the Cytology Department, Karolinska University Hospital, according to the Bethesda system (14). The HPV DNA testing was completed on-site with the hospital’s standard: Cobas 4800 HPV (Roche Diagnostics). Cobas HPV and LBC results from follow-up #1 informed subsequent management: Women with positive Cobas HPV and/or cytological abnormalities were referred for follow-up #2, which entailed the same standard protocol as follow-up #1, according to national guidelines and was most often scheduled at about one year after follow-up #1. Women with negative HPV Cobas findings and cytology negative for intraepithelial lesions or malignancy (NILM) returned to routine triennial screening, as per national guidelines. When a recurrent lesion was found, the patient was sent for follow-up treatment. Depending on the clinical evaluation and other considerations, treatment entailed re-excision or simple total hysterectomy.

Handling of triplet samples for comparative HPV testing. Within 1 h of collection, urine samples were vortexed for 15-20 sec prior to transferring a 2.5 ml aliquot to a Cervi-Collect transport tube (Abbott-Molecular), containing transport medium. The tubes were labeled with a unique identifier, mixed with transport medium by vortexing for 15-20 sec prior to storage at -10°C or colder up to 1 month before shipment. Urine samples packed in plastic bags were put in polyethylene boxes with dry ice for cold-chain maintenance (-78.5°C) during air-transport. The VSS were air dried for ~3-5 min before the Qvintip device brush-heads were placed into barcoded capped tubes. The VSS were stored at room temperature for maximum 1 month before shipment. For clinician-collected samples, LBC vials were vortexed for 15-20 sec
followed by immediate transfer of a 2 ml aliquot into a test tube labeled with a unique identifier. The aliquots were stored at room temperature for maximum 1 month before shipment. All matched triplet samples (urine, VSS, clinician-collected) were air-transported from Karolinska University Hospital to the testing laboratory: Fürst Medical Laboratory, Oslo.

**Comparative HPV testing.** At Fürst Laboratory, the triplet samples were analyzed for the presence of HPV-DNA with the RealTime High-Risk HPV PCR assay (hereafter termed ‘Abbott’), as per manufacturer instructions. These results were for comparative purposes only and not considered for patient management.

Abbott is a clinically-validated, qualitative, multiplex real-time PCR test which detects HPV16, HPV18, plus 12 other high-risk HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) reported as a pooled signal. The assay detects a sequence of endogenous human β-globin as sample validity control for cell adequacy, sample extraction, and amplification efficiency in each reaction. Signal strength for HPV types and for β-globin gene was expressed as cycle numbers (CN): The number of PCR cycles in which a positive signal is observed. High viral load corresponds to low CN values and vice-verse; 32 was the cut-off between positive results and noise (negative signal). CN were reported by the assay software and recorded by the testing lab. Tests with negative signal for HPV and β-globin were excluded.

**Statistical analysis.** Univariate data analysis was performed, with attention to HPV findings: Any HPV, HPV16, HPV18 or other HPV with side-by-side comparisons of the methods by which these were assessed. Pearson χ² tests (or Fisher's if any expected cell was ≤5) were used to assess the relation between biopsy or cytology vis-à-vis HPV results from each of the four methods. Biopsy results were dichotomized: (CIN2+ or AIS) vs. (normal findings or CIN1). Cytology results were dichotomized as abnormal versus NILM, negative for intraepithelial lesions or malignancy. Biopsy and cytology results at each follow-up were assessed in relation to the HPV test results taken at follow-up #1. Additionally, biopsy and cytology results at follow-up #2 were analyzed vis-à-vis HPV results from clinician-taken samples at follow-up #2. Fisher's and Pearson χ² tests were employed, respectively, to evaluate the relation between biopsy and cytology results at follow-up versus HPV16 and/or HPV18 positivity, as assessed from Abbott clinician-collected samples, VSS and urine samples. Sensitivity and specificity were computed with 95% confidence intervals (CI). Negative predictive values (NPV) and positive predictive values (PPV) were also computed. Using logistic regression, odds ratios (OR) and 95% CI were computed for dichotomized clinical outcomes. Each method for assessing HPV results was the independent variable, with age as a covariate. Concordance between methods for HPV sampling was assessed using Cohen's kappa statistic with 95% CI.

**Results**

**Univariate data and protocol by which the patients were triaged.** Altogether, 531 were patients included in the study. Tables I-III summarize the univariate data. At the time of treatment, the mean age was 34 years, with most patients between age 21-50; four were 20 or younger and twenty-seven were over age 50. The majority of the patients had completed university education and over 70% were gainfully employed. More detailed demographic information about the patients can be found in Ref. (11).

The histology in the excised cone was CIN2 in 133 patients (25%), CIN3 in 370 patients (69.7%), CIN3/AIDS in fifteen patients (2.8%) and AIS in thirteen patients (2.5%). Most patients came to follow-up #1 within eight months.

Table IIA shows that at follow-up #1, recurrent CIN2+ (CIN3 in all cases) was found in four of thirteen patients who underwent biopsy (30.8%). Thus, at 1st follow-up the diagnosed recurrence rate among the 531 patients was 0.8%. At follow-up #2, biopsy was performed in twenty patients, including the four who had recurrent CIN2+ at follow-up #1. Nine more patients were found to have recurrence on biopsy: Seven with CIN2+ and two with AIS among those sixteen patients (56.3%) who underwent biopsy at follow-up #2, excluding the four patients with CIN3 who underwent repeat biopsy at follow-up #2. The newly diagnosed recurrence rate among the remaining 109 patients who came to 2nd follow-up was thus 8.3%.

On Table IIB, for follow-up #1, seventy-seven patients had abnormal cytology, eighty-six patients had HPV positive findings according to the standard clinician-taken COBAS analysis and thirty-seven patients had both positive HPV via COBAS and abnormal cytology. Thus, altogether, 126 patients were referred to 2nd follow-up, 113 of whom attended. Most patients had NILM on cytology at follow-up #2. One patient had AIS and ~11% had high-grade squamous intraepithelial lesions (HSIL).

Table III further reveals that testing for any high-risk HPV at follow-up #1 yielded all valid results for clinician-collected samples and VSS; 44 urine samples were ‘invalid’ due to absent HPV and β-globin. For HPV16 or HPV18, there were more omitted results due to CN ≥32 for VSS than for clinician-collected samples. For HPV16 VSS showed the highest positivity rate (4.6%), whereas for HPV18, clinician-samples had the highest positivity rate (1.7%). Overall, VSS yielded the largest number of positive results for HPV16 and for other high-risk HPV.

Fig. 1 summarizes the protocol according to which the patients were triaged. Numerical information is provided therein concerning the various outcomes.

**HPV findings in relation to the biopsy results.** Table IV presents the predictive value of HPV findings vis-à-vis biopsy results. All 4 methods revealed positive HPV findings in the four patients with recurrent CIN2+ at follow-up #1. Two patients showed positive HPV16 and/or HPV18 results with clinician-sampling and VSS. For all the patients who underwent biopsy, the HPV16 and 18 results were complete for clinician-sampling and VSS. However, for the urine self-samples, at follow-up #1 the results for HPV16 and/or HPV18 were missing due to CN >32 for one patient with recurrent CIN2+ and at follow-up #2 for two patients: One with recurrent CIN2+ and one with AIS.

Both clinician-sampling methods and VSS, all taken at follow-up #1, revealed HPV positive findings in the seven patients with newly-detected CIN2+ at follow-up #2. From urine self-samples, HPV positivity was seen in five of those
patients. Only Abbott clinician-taken samples were HPV positive for both patients with AIS at follow-up #2; in both cases HPV18 was also positive.

As noted at the end of Table IV, eight of the nine patients with high-grade cervical dysplasia on biopsy at follow-up #2 showed HPV positivity via the standard assessment with Cobas clinician sampling taken at follow-up #2. The HPV data were missing for the ninth patient with recurrent high-grade CIN detected on biopsy at follow-up #2. With clinician sampling using the Abbott assay, all nine cases with high-grade cervical dysplasia on biopsy showed HPV positivity at follow-up #1. Thus, it appears that these biopsy-diagnosed recurrent cases at follow-up #2 had persistent HPV positivity.

**HPV findings in relation to the cytology results.** Table V shows the HPV findings in relation to abnormal cytology versus NILM. At follow-up #1, overall HPV positivity from VSS was most sensitive in predicting abnormal cytology. Further analysis revealed positive HPV findings from VSS in twelve patients with HSIL, whereas eleven patients with HSIL had positive HPV findings on clinician-taken and urine samples. Positivity for HPV16 and/or HPV18 showed low sensitivity for predicting abnormal cytology at follow-up #1, but very high NPV and specificity with all three methods. At follow-up #2, twenty-eight patients with abnormal cytology had HPV positive findings with VSS and both clinician-samples from follow-up #1. With missing data for urine samples, there were fewer cases of positive HPV associated with abnormal cytology at both follow-ups.

**Concordance between the methods for assessing HPV.** The highest Cohen’s kappa was for the two clinician-sampling

---

Table I. Univariate findings for semi-continuous data.

| Variable                              | No.  | Mean | Minimum | Maximum | SD  |
|---------------------------------------|------|------|---------|---------|-----|
| Age at time of treatment, years       | 531  | 86   | 16      | 66      | 9   |
| Days from treatment to 1st follow-up  | 531  | 184  | 37      | 447     | 40  |
| Days from 1st to 2nd follow-up        | 113  | 389  | 9       | 1,291   | 229 |

Table II. Univariate findings for biopsy and cytology results.

A, Biopsy results

| Variable | Follow-up 1, n | Follow-up 1, % | Follow-up 2, n | Follow-up 2, % |
|----------|----------------|----------------|----------------|----------------|
| Within normal limits          | 6              | 46             | 2              | 13             |
| CIN1      | 3              | 23             | 5              | 31             |
| CIN2+     | 4              | 31             | 7*             | 44             |
| AIS       | 0              | 0              | 2              | 13             |

B, Cytology results (via LBC)

| Variable | Follow-up 1, n | Follow-up 1, % | Follow-up 2, n | Follow-up 2, % |
|----------|----------------|----------------|----------------|----------------|
| NILM     | 454            | 86             | 75             | 68             |
| ASC-US   | 28             | 5              | 6              | 6              |
| AGC      | 5              | 1              | 2              | 2              |
| LSIL     | 27             | 5              | 14             | 13             |
| ASC-H    | 1              | 0              | 0              | 0              |
| HSIL     | 16             | 3              | 12             | 11             |
| AIS      | 0              | 0              | 1              | 1              |

*Only recurrent cases with newly-diagnosed CIN2+ at follow-up 2 are included in the presented biopsy data for follow-up 2. *Cytology data are missing for three patients at follow-up 2. AGC, atypical glandular cells; AIS, adenocarcinoma-in-situ; ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesions; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesions; NILM, negative for intraepithelial lesions or malignancy.
Agreement was substantial between VSS and clinician-sampling methods, and moderate for urine sampling versus clinician-sampling or VSS. For valid HPV16 there was close agreement for each pair. Agreement was substantial between clinician and VSS for HPV18. Concordance between clinician and urine sampling was fair for HPV18; VSS versus urine sampling agreement was moderate. Concordance was substantial for the three methods assessing other HPV.

Discussion

The present results indicate that VSS is as sensitive as clinician-collected samples for predicting recurrent high-grade pathohistologic results on biopsy and cytologic abnormalities among women treated for high-grade CIN, unless the pathology is glandular. Urine self-sampling yielded slightly poorer sensitivity compared to VSS.

Our results for VSS cohere with the literature concerning the value of post-therapeutic HPV testing from clinician-collected samples for predicting subsequent outcome among patients treated for high-grade CIN (2,5,15-19). Higher positivity rates of VSS compared to clinician-taken samples for overall HPV and HPV16 found herein, were also reported in Reference (20).

Positive HPV findings have been shown to powerfully predict high-grade cervical lesions among patients with glandular pathology (21,22). Positive HPV18 is strongly associated with cervical adenocarcinoma risk, especially in its more aggressive form (23,24). In our cohort, it was only HPV18 which was less frequently detected with VSS compared to clinician-collected samples.

To our knowledge, there is only one other study evaluating self-sampling versus clinician-collected samples as follow-up among patients treated for high-grade CIN (25). In Reference (25) fifty-two of 103 treated patients (50.4%) participated in tri-monthly urine self-collection and cervical scrapings. All three cases of CIN2+ detected during one-year follow-up showed repeated positive HPV findings on self-sampled urine and cervical scrapings. All pre-treatment and recurrent findings were squamous in Reference (25). A recent investigation (26) comparing histologic findings and triple HPV results in women undergoing colposcopy revealed that urine-based HPV testing was somewhat less sensitive in identifying women with high-grade CIN, compared to VSS and provider-sampled HPV results, similarly to our study. Our samples were from the initial urine stream, thought to contain highest concentrations of diagnostically relevant components (27) and to be more accurate for detecting cervical HPV than mid-stream or end-stream samples (28). Timing of collection may also impact the amount of viral DNA in the sample, since more HPV DNA could be present with an increased interval between two urinations because more excreted mucus and debris from the genital organs can accumulate (4). Thus, there should be sufficient time between urine collection and previous urination (29). We specifically instructed the participants to collect urine samples before

### Table III. HPV results.

| HPV results                          | Clinician sampled: Cobas-4800, n | Clinician sampled: Abbott, n | Self-sampled: Vaginal, n | Self-sampled: Urine, n |
|-------------------------------------|----------------------------------|-----------------------------|--------------------------|------------------------|
| Positive for any high-risk type     | 86                               | 100                         | 139                      | 85                     |
| Negative for any high-risk type     | 445                              | 431                         | 392                      | 402                    |
| HPV16 positive                      | 18                               | 24                          | 16                       |
| HPV16 negative                      | 502                              | 494                         | 462                      |
| CN ≥32                              | 11                               | 13                          | 9                        |
| HPV18 positive                      | 9                                | 7                           | 5                        |
| HPV18 negative                      | 517                              | 517                         | 476                      |
| CN ≥32                              | 5                                | 7                           | 6                        |
| HPV Other positive                  | 77                               | 117                         | 71                       |
| HPV Other negative                  | 423                              | 355                         | 358                      |
| CN ≥32                              | 31                               | 59                          | 58                       |

*Altogether, 44 results were invalid for HPV analysis for any high-risk type from urine. These 44 are excluded from HPV-subtype analyses for urine self-samples. *HPV data at follow-up 2 were missing for 14 patients. CN, cycle numbers; HPV, high-risk human papillomavirus.
ÖSTENSSON et al: SELF-SAMPLING POST-CIN TREATMENT FOLLOW-UP

VSS to avoid interfering with the material from the cervicovaginal tract. However, the urine samples were not collected first-void in the morning, but randomly during the day. We paid careful attention to storage conditions and preparation of urine samples, in light of their importance for HPV DNA detection (30). Nevertheless, 44 of the 531 urine samples were invalid due to absence of high-risk HPV and β-globin, whereas all VSS and clinician-collected samples were valid.

Assessment of HPV16 and/or HPV18 was nearly always associated with higher specificity than overall HPV findings. This is particularly notable for VSS for which there was the largest number, 100, of overall HPV positive findings associated with normal cytology at follow-up #1, whereas only twenty-two patients with normal cytology showed positive HPV16 and/or HPV18 findings on VSS. The importance of assessing HPV16 and 18 was underscored in the review of patterns of HPV infection after treatment of high-grade CIN (3).

The present findings indicate that VSS could be a viable option for follow-up of women treated for high-grade CIN, if the pathology is squamous. In considering the self-sampling option, the advantages and disadvantages need to be presented to the patient. Namely, the chances of false positive findings are a bit higher with VSS than with clinician-sampling, such that repeated self-sampling might be needed. This is reflected in a much higher percentage of positive ‘other HPV’ with VSS, compared to clinician-sampling. Notably, among women below age 30, positive findings only for other HPV may not impact substantially upon risk of future high-grade CIN (31). 

Based on these results, our recommendation would be against self-sampling for patients with glandular pathology. This recommendation is based on the two patients with recurrence in whom VSS did not yield a positive result, both of whom had glandular pathology. In both these patients, clinician-sampling revealed HPV18 positivity, which, as noted, appears to be a particularly important risk indicator (23,24). To more completely address this cautious clinical recommendation, further research is needed vis-à-vis self-sampling for follow-up among treated patients with glandular pathology, with special attention to HPV18. Longer follow-up and repeated HPV assessments are also needed in future studies comparing self-sampling and clinician-sampling among patients treated for high-grade CIN.

Practically complete data were available for this cohort of patients followed-up post-conization treatment for CIN2+.
Table IV. Predictive value of HPV findings vis-à-vis biopsy results.

A, HPV vs. biopsy results at follow-up #1

| HPV results                  | Normal,  | CIN1,  | P-value | CIN2+,  | AIS,  | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-----------------------------|----------|--------|---------|---------|-------|-------------------------|-------------------------|--------|--------|
| Clinician-Sampled: Cobas-4800 |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 1        | 4      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 57     |
| Negative for any high-risk type | 5        | 1      | ≤0.09   | 0       | 0     |                         |                         |        |        |
| Clinician-Sampled: Abbott    |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 1        | 2      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 57     |
| Negative for any high-risk type | 5        | 1      | ≤0.09   | 0       | 0     |                         |                         |        |        |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 1        | 2      | 2       | 2       | 2     | 50 (7-93)               | 67 (30-93)              | 75     | 40     |
| HPV16 and HPV18 negative      | 5        | 1      | NS      | 2       | 2     |                         |                         |        |        |
| Self-sampled: Vaginal         |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 2        | 1      | ≤0.09   | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 57     |
| Negative for any high-risk type | 4        | 2      | ≤0.09   | 0       | 0     |                         |                         |        |        |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 1        | 1      | 2       | 2       | 2     | 100 (66-100)            | 43 (10-82)              | 100    | 69     |
| HPV16 and HPV18 negative      | 5        | 2      | NS      | 2       | 2     |                         |                         |        |        |
| Self-sampled: Urine           |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 2        | 1      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 69     |
| Negative for any high-risk type | 4        | 2      | ≤0.09   | 0       | 0     | 100 (40-100)            | 67 (30-93)              | 100    | 69     |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 0        | 0      | <0.05   | 3       | 3     | 56 (21-86)             | 100 (59-100)           | 64     | 100    |
| HPV 16 and 18 negative        | 2        | 5      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 69     |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 0        | 0      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 69     |

B, HPV results at follow-up #1 vs. biopsy results at follow-up #2

| HPV results                  | Normal,  | CIN1,  | P-value | CIN2+,  | AIS,  | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-----------------------------|----------|--------|---------|---------|-------|-------------------------|-------------------------|--------|--------|
| Clinician-Sampled: Cobas-4800 |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 0        | 4      | 7       | 7       | 7     | 89 (52-100)            | 43 (10-82)              | 75     | 67     |
| Negative for any high-risk type | 2        | 1      | NS      | 0       | 0     |                         |                         |        |        |
| Clinician-Sampled: Abbott    |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 0        | 4      | ≤0.09   | 7       | 7     | 100 (66-100)            | 43 (10-82)              | 100    | 69     |
| Negative for any high-risk type | 2        | 1      | ≤0.09   | 0       | 0     | 100 (66-100)            | 43 (10-82)              | 100    | 69     |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 0        | 0      | <0.05   | 3       | 3     | 56 (21-86)             | 100 (59-100)           | 64     | 100    |
| HPV 16 and 18 negative        | 2        | 5      | 4       | 4       | 4     | 100 (40-100)            | 67 (30-93)              | 100    | 69     |
| Self-sampled: Vaginal         |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 0        | 4      | NS      | 7       | 7     | 78 (40-97)             | 43 (10-82)              | 60     | 64     |
| Negative for any high-risk type | 2        | 1      | NS      | 0       | 0     | 78 (40-97)             | 43 (10-82)              | 60     | 64     |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 0        | 0      | 4       | 4       | 4     | 44 (14-79)             | 100 (59-100)           | 58     | 100    |
| HPV 16 and 18 negative        | 2        | 5      | ≤0.09   | 3       | 3     | 44 (14-79)             | 100 (59-100)           | 58     | 100    |
| Self-sampled: Urine           |          |        |         |         |       |                         |                         |        |        |
| Positive for any high-risk type | 0        | 2      | 5       | 5       | 5     | 56 (21-86)             | 71 (29-96)              | 56     | 71     |
| Negative for any high-risk type | 2        | 3      | NS      | 2       | 2     | 56 (21-86)             | 71 (29-96)              | 56     | 71     |
| HPV16 and/or 18               |          |        |         |         |       |                         |                         |        |        |
| HPV16 and/or 18 positive      | 0        | 0      | 3       | 3       | 3     | 43 (10-82)             | 100 (59-100)           | 64     | 100    |
| HPV 16 and 18 negative        | 2        | 5      | NS      | 3       | 3     | 43 (10-82)             | 100 (59-100)           | 64     | 100    |
### Table IV. Continued.

| HPV results | Normal, n | CIN1, n | P-value | CIN2+, n | AIS, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-------------|-----------|---------|---------|----------|--------|------------------------|------------------------|-------|-------|
| Clinician-Sampled: Cobas-4800 | | | | | | 100 (63-100) | 33 (4-78) | 100 | 67 |
| Positive for any high-risk type | 0 | 4 | 6 | 2 |
| Negative for any high-risk type | 1 | 1 | NS | 0 | 0 |

aMissing HPV16/18 data for 1 patient with CIN2+. bOnly the 7 recurrent cases newly diagnosed with CIN2+ at follow-up #2 are included in the data for biopsy #2. cMissing HPV 16/18 data for 1 patient with CIN2+ and 1 patient with AIS. dNo HPV data at follow-up #2 for 1 patient with normal findings and for 1 patient with CIN2+. Statistical analysis via 2-tailed Fisher's exact test comparing the biopsy categories: (Normal or CIN1) vs. (CIN2+ and AIS). CI, confidence interval; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma-in-situ; NPV, negative predictive value; NS, not statistically significant (P>0.09); PPV, positive predictive value.

### Table V. Predictive value of HPV findings vis-à-vis cytology results.

#### A. HPV vs. cytology results (both at follow-up #1)

| HPV results | NILM, n | P-value | Abnormal, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-------------|---------|---------|------------|------------------------|------------------------|-------|-------|
| Clinician-Sampled: Cobas-4800 | | | | | | | |
| Positive for any high-risk type | 49 | <0.001 | 37 | 48 (37-60) | 89 (86-92) | 91 | 43 |
| Negative for any high-risk type | 405 | | 40 | |
| Clinician-Sampled: Abbott | | | | | | | |
| Positive for any high-risk type | 62 | <0.001 | 38 | 49 (38-61) | 86 (83-89) | 91 | 38 |
| Negative for any high-risk type | 392 | | 39 | |
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 16 | <0.001 | 11 | 14 (7-24) | 96 (94-98) | 87 | 41 |
| HPV16 and 18 negative | 423 | | 66 | |
| Self-Sampled: Vaginal | | | | | | | |
| Positive for any high-risk type | 100 | | 39 | |
| Negative for any high-risk type | 354 | <0.001 | 38 | |
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 22 | <0.05 | 9 | 12 (6-21) | 95 (92-97) | 86 | 41 |
| HPV16 and 18 negative | 413 | | 67 | |
| Self-Sampled: Urine | | | | | | | |
| Positive for any high-risk type | 54 | <0.001 | 31 | 43 (31-55) | 87 (83-90) | 90 | 37 |
| Negative for any high-risk type | 360 | | 42 | |
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 12 | <0.001 | 9 | 13 (6-23) | 97 (95-99) | 87 | 43 |
| HPV16 and 18 negative | 392 | | 60 | |

#### B. HPV at follow-up #1 vs. cytology results at follow-up #2

| HPV results | NILM, n | P-value | Abnormal, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-------------|---------|---------|------------|------------------------|------------------------|-------|-------|
| Clinician-Sampled: Cobas-4800 | | | | | | | |
| Positive for any high-risk type | 48 | NS | 28 | 80 (63-92) | 36 (25-48) | 79 | 37 |
| Negative for any high-risk type | 27 | | 7 | |
| Clinician-Sampled: Abbott | | | | | | | |
| Positive for any high-risk type | 45 | <0.05 | 28 | 80 (63-92) | 40 (29-52) | 81 | 38 |
| Negative for any high-risk type | 30 | | 7 | |
or AIS. To our knowledge, this is the largest, most complete follow-up study in which HPV results were compared for two different clinician-sampling methods and two different self-sampling methods. Besides biopsy data, complete cytology data were available for all 531 patients. Inclusion of this latter outcome-variable provides further insight into the post-therapeutic clinical status of these patients. However, follow-up thereafter is limited; only 21% attended follow-up #2. Of 127 patients referred to follow-up #2 for abnormal cytology and/or HPV positive findings from standard COBAS clinician samples, 113 patients attended. The 404 patients with normal cytology and negative HPV findings from standard-COBAS clinician-samples returned to routine screening, without follow-up within this study. The latter includes fifty-nine patients with positive HPV findings on VSS and/or Abbott clinician-sampling. Another limitation of the study may have been reliance upon colposcopically-visible lesions for biopsy. This could have underestimated the actual number of recurrences, since biopsies taken from colposcopically-negative sites may also identify patients with high-grade cervical dysplasia (32).

All participants performed self-sampling in the clinic restroom. Questionnaire data were available from 479 of 531 patients concerning their readiness to perform self-sampling at home and whether self-sampling was easy to carry-out. These statements were endorsed, respectively, by 74 and 86% of the 479 women. In a study using the same questionnaire (33), forty-one long-term screening non-attenders performed VSS at home with positive HPV results, for which they subsequently underwent gynecologic examination. All forty-one patients endorsed both statements regarding self-sampling; 95% cited comfort as a reason for

Table V. Continued.

B, HPV at follow-up #1 vs. cytology results at follow-up #2

| HPV results | NILM, n | P-value | Abnormal, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-------------|---------|---------|-------------|-------------------------|--------------------------|--------|--------|
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 11 | NS | 8 | 23 (10-40) | 85 (75-92) | 70 | 42 |
| HPV16 and 18 negative | 63 | | | 27 |
| Self-Sampled: Vaginal | | | | | | | |
| Positive for any high-risk type | 48 | NS | 28 | 80 (63-92) | 36 (25-48) | 79 | 37 |
| Negative for any high-risk type | 27 | | 7 |
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 11 | NS | 7 | 20 (8-37) | 85 (75-92) | 69 | 39 |
| HPV16 and 18 negative | 63 | | 28 |
| Self-Sampled: Urine | | | | | | | |
| Positive for any high-risk type | 30 | <0.05 | 23 | 68 (50-83) | 58 (45-69) | 79 | 43 |
| Negative for any high-risk type | 41 | | 11 |
| HPV 16 and/or 18 | | | | | | | |
| HPV16 and/or 18 positive | 8 | NS | 5 | 16 (6-34) | 88 (78-95) | 69 | 39 |
| HPV16 and 18 negative | 59 | | 26 |

C, HPV results at follow-up #2 vs. cytology results at follow-up #2

| HPV results | NILM, n | P-value | Abnormal, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | NPV, % | PPV, % |
|-------------|---------|---------|-------------|-------------------------|--------------------------|--------|--------|
| Clinician-sampled:Cobas-4800 | | | | | | | |
| Positive for any high-risk type | 20 | <0.001 | 26 | 84 (66-95) | 68 (55-79) | 90 | 57 |
| Negative for any high-risk type | 43 | | 5 |

*Missing Abbott-Clinician HPV16 and/or 18 for 15 patients with NILM at follow-up #1. *Missing vaginal HPV16 and/or 18 for 19 patients with NILM and one patient with abnormal cytology at follow-up #1. *No HPV data from urine for 40 patients with NILM and 4 patients with abnormal cytology at follow-up #1. *Missing urine HPV16 and/or 18 for 50 patients with NILM and 8 patients with abnormal cytology at follow-up #1. *Missing Abbott-Clinician and vaginal HPV16 and/or 18 for 1 patient with NILM at follow-up #2. *No HPV data from urine for 4 patients with NILM and 1 patient with abnormal cytology at follow-up #2. *Missing urine HPV16 and/or 18 for 8 patients with NILM and 4 patients with abnormal cytology at follow-up #2. *No HPV data at follow-up #2 for 10 patients with NILM and 2 patients with abnormal cytology at follow-up #2. Statistical analysis via two-tailed Pearson's χ² test. CI, confidence interval; NILM, negative for intraepithelial lesions or malignancy; NS, not statistically significant (P≥0.05); NPV, negative predictive value; PPV, positive predictive value.
performing self-sampling. In contrast, only 14% of the women in the present study cited comfort as a reason for performing self-sampling. Indeed, the home-setting is more comfortable for carrying-out VSS. Home self-sampling is also practical and cost-effective for repeated assessment. On the other hand, the quality of home self-sampling might not be as high as self-sampling performed in the clinic immediately after specific instructions are directly given. This underscores the need to provide very clear written instructions, and that health professionals are easily accessible to answer any queries that arise when performing self-sampling at home.

The present findings concerning urine self-sampling cohere substantially with the literature. In home-based settings for collecting first-void urine (27), urine self-sampling may also hold promise for follow-up after treatment for high-grade CIN. These considerations reflect more personalized approaches for women at elevated risk of recurrent high-grade CIN. Embodied therein is empowerment, whereby women would be well-informed about available options, actively participating in decision-making regarding cervical screening. Such a strategy has been successful in other cervical screening contexts (43,44) and is likely to enhance fuller participation in the needed long-term follow-up for these women at increased cervical cancer risk.

In conclusion, for patients with squamous cell pathology, post-therapeutic follow-up based on HPV analysis from self-collected vaginal samples appears to be as sensitive as HPV analysis from clinician-collected cervical samples for...
predicting outcome. Based on a very small number of patients with the far less common glandular pathology, the present study suggests that vaginal self-sampling is not adequately sensitive, such that HPV analysis should be based on clinician-collected cervical samples when assessing risk of recurrence. The vast majority of patients treated for high-grade cervical intraepithelial neoplasia have squamous pathology. For these patients, vaginal self-sampling for HPV analysis may well be a viable option that can maximize participation in the needed long-term follow-up for these women at increased cervical cancer risk.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Swedish Cancer Foundation (grant no. 110544, CAN2011/471), Karolinska Institute (Cancer Strategic Grants; grant no. 5888/05-722), Swedish Research Council (grant no. 521-2008-2899), Stockholm County Council (grant nos. 20130097 and 20160155) and Gustaf V Jubilee Fund (grant nos. 154022 and 151202).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EÖ participated in the design and conception of the study, was responsible for identifying and recruiting all the participants, met with all the participants, gave the instructions for self-sampling, prepared the self-samples for transport, assessed the authenticity of the raw data, prepared the data set for analysis, collected the related literature, participated in drafting the manuscript and revised the manuscript. KB performed the statistical analysis, collected the related literature, and wrote and revised the manuscript. MM participated in the design and conception of the study, performed colposcopy, cervical sampling and punch biopsies of visible lesions, and revised the manuscript. SA conceived and designed the study, performed colposcopy, cervical sampling and punch biopsies of visible lesions, assessed the authenticity of the raw data, reviewed the data, collected the related literature, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Karolinska Ethics Committee approved the study protocol (2006/1273-31, 2014/2034-3). Informed consent by each patient was signed with options: Agreement or decline to participate.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ebisch RMF, Rutten DWF, IntHout J, Melchers WJG, Massuger LFAG, Bulten J, Bekkers RLM and Siebers AG: Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: A population-based cohort study. J Clin Oncol 35: 2542-2550, 2017.
2. Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nolbenhuis MA, Buis AG, Hogewoning CJ, Zaal A, Verheijen RH, Snijders PJ and Meijer CJ: Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: A long-term multi-cohort study. Lancet Oncol 12: 441-450, 2011.
3. Hoffman SR, Le T, Lockhart A, Sanusi A, Dal Santo L, Davis M, McKinney DA, Brown M, Poole C, Willame C and Smith JS: Patterns of persistent HPV infection after treatment for cervical intraepithelial neoplasia (CIN): A systematic review. Int J Cancer 141: 8-23, 2017.
4. Arbyn M, Ronco G, Anttila A, Meijer C, Poljak M, Ogilvie G, Koliopoulos G, Nacler P, Sankaranarayanan R and Peto J: Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 30 (Suppl 5): F88-F99, 2012.
5. Bruhn LV, Anderssen SJ and Hariri J: HPV-testing versus HPV-cytology co-testing to predict the outcome after conization. Acta Obstet Gynecol Scand 97: 758-765, 2018.
6. Arbyn M, Verdoordt F, Snijders PJ, Verhoeft VM, Suonio E, Dillner L, Moinozi S, Bellisario C, Banzi R, Zhao F, et al: Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: A meta-analysis. Lancet Oncol 15: 172-183, 2014.
7. Arbyn M, Snijders PJ, Meijer CJ, Berkhof J, Cuschieri K, Kocjan BJ and Poljak M: Which high-risk HPV assays fulfill criteria for use in primary cervical cancer screening? Clin Microbiol Infect 21: 817-826, 2015.
8. Jentschke M, Chen K, Arbyn M, Hertel B, Noskowicz M, Soergel P and Hillemans P: Direct comparison of two vaginal self-sampling devices for the detection of human papillomavirus infections. J Clin Virol 82: 46-50, 2016.
9. Östensson E, Hellström AC, Hellman K, Gustavsson J, Gyllensten U, Wilander E, Zethraeus N and Andersson S: Projected cost-effectiveness of repeat HPV testing using self-collected vaginal samples in the Swedish cervical cancer screening program. Acta Obstet Gynecol Scand 92: 830-840, 2013.
10. Andersson S, Belkic K, Mints M and Östensson E: Is self-sampling to test for high-risk papillomavirus an acceptable option among women who have been treated for high-grade cervical intraepithelial neoplasia? PLoS One 13: e0199038, 2018.
11. Andersson S, Belkic K, Saer Demirbiker SK, Mints M and Östensson E: Perceived cervical cancer risk among women treated for high-grade cervical intraepithelial neoplasia: The importance of specific knowledge. PLoS One 12: e190156, 2017.
12. Kocken RM: Cervical intraepithelial neoplasia. Pathol Annu 8: 301-328, 1973.
13. Jordan J, Martin-Hirsch P, Arbyn M, Schenk U, Baldauf JJ, Da Silva D, Anttila A, Nieminen P and Prendiville W: European guidelines for clinical management of abnormal cervical cytology, part-2. Cytopathology 20: 5-16, 2009.
14. Solomon D, Daves D, Kurman R, Moriarty A, O’Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T Jr, et al: The 2001 Bethesda system: Terminology for reporting results of cervical cytology. JAMA 287: 2114-2119, 2002.
15. Brander S, Johannsson R, Berglund M, Arbyn M and Andersson S: Follow-up after treatment of cervical intraepithelial neoplasia by human papillomavirus genotyping. Am J Obstet Gynecol 201: 17.e1-8, 2009.
16. Kocken M, Uijterwaal MH, de Vries AL, Berkhof J, Ket JC, Helmerhorst TJ and Meijer CJ: High-risk human papillomavirus testing versus cytology in predicting post-treatment disease in women treated for high-grade cervical disease: A systematic review and meta-analysis. Gynecol Oncol 125: 500-507, 2012.
17. Persson M, Brismar Wendel S, Ljungblad L, Johansson B, Weiderpass E and Andersson S: High-risk human papillomavirus E6/E7 mRNA and L1 DNA as markers of residual/recurrent cervical intraepithelial neoplasia. Oncol Rep 28: 346-352, 2012.

18. Asciutto KC, Henic E, Darlin L, Forslund O and Borgfeldt C: Follow up with HPV test and cytology as test of cure, 6 months after conization, is reliable. Acta Obstet Gynecol Scand 95: 1251-1257, 2016.

19. Garuti P, Borghi C, Bedoni C, Bonacorsì G, Greco P, Tognon M and Martiní F: HPV-based strategy in follow-up of patients treated for high-grade cervical intra-epithelial neoplasia: 5-year results in a public health surveillance setting. Eur J Obstet Gynecol Reprod Biol 210: 236-241, 2017.

20. Saville M, Hawkes D, Keung M, Ip E, Silvers J, Sultana F, Malloy MJ, Veltens LS, Canfeli LK, Wrede CD and Brotherton J: Analytical performance of HPV assays on vaginal self-collected vs. practitioner-collected cervical samples. J Clin Virol 127: 104375, 2020.

21. Norman J, Hjerpe A and Dillner J: Risk of high-grade lesions after atypical glandular cells in cervical screening: A population-based cohort study. BMJ Open 7: e017070, 2017.

22. Patadji S, Li Z, Pradhan D and Zhao C: Significance of high-risk HPV detection in women with atypical glandular cells on pap testing: Analysis of 1857 cases from an academic institution. Cancer Cytopathol 125: 205-211, 2017.

23. Andersson S, Larson B, Hjerpe A, Silfverswärd C, Sällström J, Kouli G, Hjalmarsson D, Persson M, Brismar Wendel S, Ljungblad L, Johansson B, Weiderpass E and Andersson S: Acceptance of self-sampling among long-term cervical screening non-attenders with HPV positive results: Promising opportunity for specific cancer education. J Cancer Educ 36: 126-133, 2021.

24. Galbraith KV, Gilkey MB, Smith JS, Richman AR, Barclay L and Brewer NT: Perceptions of mailed HPV self-testing among women at higher risk for cervical cancer. J Community Health 39: 849-856, 2014.

25. Crofts V, Flahault E, Tebeu P, Umtiet S, Bosso G, Boulvain M, Vassilakos P and Petignat P: Education efforts may contribute to wider acceptance of human papillomavirus self-sampling. Int J Womens Health 7: 149-154, 2015.

26. Arrossi S, Ramos S, Straw C, Thouyaret L and Orellana L: HPV testing: A mixed-method approach to understand why women prefer self-collection in a middle-income country. BMC Public Health 16: 832, 2016.

27. Måsom M, Bhoo-Pathy N, Nasiri NH, Bellinson J, Subramaniam S, Ma Y, Yap SH, Goh PP, Gravitt P and Woo YL: Attitudes and factors affecting acceptability of self-administered cervicovaginal sampling for human papillomavirus (HPV) genotyping as an alternative to Pap testing among multietnic Malaysian women. BMJ Open 6: e011022, 2016.

28. Vahabi M and Lofters A: Muslim immigrant women's views on cervical cancer screening and HPV self-sampling in Ontario, Canada. BMC Public Health 16: 868, 2016.

29. Racey CS and Gessink DC: Barriers and facilitators to cervical cancer screening among women in rural Ontario, Canada: The role of self-collected HPV testing. J Rural Health 32: 136-145, 2016.

30. de Melo Kuil L, Lorenzi AT, Stein MD, Resende JCP, Antoniazzi M, Longatto-Filho A, Scapulatempo-Neto C and Fregnani HTG: The role of self-collection by vaginal lavage for the detection of HPV and high-grade intraepithelial neoplasia. Acta Cytol 61: 425-433, 2017.

31. Yao B, Cai J, Wu L, Zhong H, Jin M, Li H, Li C, Yang T, Gao L and Liu X: Self-sampling for HPV-based cervical cancer screening among Chinese women: A randomized controlled trial. BMJ Open 7: e017070, 2017.

32. Baasland I, Hagen B, Vogt C, Valla M and Romundstad PR: Colposcopy and additive diagnostic value of biopsies from colposcopy-negative areas to detect cervical dysplasia. Acta Obstet Gynecol Scand 95: 1258-1263, 2016.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.