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Comparison of vaginal self-sampling and cervical sampling by medical professionals for the detection of HPV and CIN2+: A randomized study

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Abstract

Primary screening with human papillomavirus (HPV) test is more effective in reducing cervical cancer incidence than cytology and it also offers the opportunity to self-sample. We conducted a randomized study to compare vaginal self-sampling with cervical sampling by medical professionals for HPV testing concerning prevalence of HPV and detection of cervical intraepithelial neoplasia (CIN) of grade 2 or worse (CIN2+) or grade 3 or worse (CIN3+) in primary screening. In total, 11 951 women aged 30-60 years were randomized into two groups, 5961 for self-sampling (SS arm) and 5990 for sampling by medical professionals (SMP arm). Sampling was performed with a RoversViba-brush in the SS arm and a cytobrush in the SMP arm. All samples were applied to an indicating FTA elute card and analyzed for HPV using a clinically validated real-time PCR test (hpVIR). All HPV-positive women performed repeated sampling about 6 months later using the same procedure as used initially. All HPV-positive women in the second sampling were referred to colposcopy. The prevalence of HPV in the first test did not differ between the SS arm (6.8%, 167/2466) and the SMP arm (7.8%, 118/1519) (P = .255). The prevalence of CIN2+ per 1000 screened women was 17 (43/2466 × 1000) (95%CI 13-24) in the SS arm and 21 (32/1519 × 1000) (95%CI 15-30) in the SMP arm. For CIN3+, the prevalence per 1000 screened women was 14 (35/2466 × 1000) (95%CI 10-20) in the SS arm and 15 (23/1519 × 1000) (95%CI 10-23) in the SMP arm. In conclusion, self-sampling and sampling by medical professionals showed the same prevalence of HPV and detection rate of CIN2+ and CIN3+ in histology.

KEYWORDS
HPV test, primary cervical screening, self-sampling

1 | INTRODUCTION

A cervical screening program was introduced in the late 1960s in Sweden and has gradually become well-organized. In practice it offers

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; SMP, sampling by medical professionals; SS, self-sampling.

regular screening invitations to appointments at local midwife clinics with follow-up management after abnormal results according to current guidelines at gynecologic clinics. By way of this screening nearly half of the estimated cervical cancer cases are prevented,[1] but with no further decrease in incidence during the last few decades. Instead, there has been an increase in cervical cancer incidence in screened women in recent years.[2] Nonadherence to screening invitations has been identified as the most important risk factor as regards incident cervical cancer.[3,4] In Sweden, the population coverage for women aged 23-70 years has stagnated at a level of 75%,[5] with slight variations in different age groups and different parts of the country.

Evidence that human papilloma virus (HPV) testing is more effective in reducing cervical cancer incidence compared to cervical cytology[6] changed the screening recommendations in Sweden in 2015.[7] HPV testing is recommended as a primary screening method for women aged >30 years, and liquid-based cytology is used for triage following an HPV-positive sample. In contrast to cervical cytology, HPV testing offers an opportunity to vaginal self-sampling, which might increase the population coverage of a screening program. Among nonresponders to screening invitations, self-sampling for HPV testing has been successful, with a higher response rate compared to other options.[8-12] In a primary screening population, the majority of women prefer self-sampling to sampling by medical professionals, but some concerns remain with respect to test accuracy and ability to correctly perform the test.[13,14] Self-sampling also has health-economic advantages compared to sampling by medical professionals.[15,16]

However, it is essential to ensure that screening based on self-sampling has at least the same sensitivity to detect histological cervical intraepithelial neoplasia of grade 2 or worse (CIN2+), and grade 3 or worse (CIN3+), as sampling by medical professionals. Several factors might influence the accuracy of self-sampling. A self-sampling kit consists of a collection device and a storage medium and the sample is then processed and analyzed by means of an HPV test. Different collection devices and storage media have shown similar results,[17] but it is currently recommended that specific combinations of self-sampling devices and HPV tests are validated prior to being employed (VALHUDES).[18] In a large meta-analysis covering 56 studies, it was concluded that PCR-based HPV testing is as sensitive for detection of CIN2+ and CIN3+ in self-collected samples as in clinician-collected samples.[17] This opens the way for future implementation of self-sampling in primary screening, but its feasibility and effectiveness should be further evaluated.

While self-sampling is regarded inadequate for cytological analysis,[19] different triage is needed following an HPV-positive self-sample. Triage on the initial screening sample would be optimal, with no loss of follow-up at this stage. Molecular reflex tests (eg, hypermethylation) have shown promising results but are still under evaluation.[20] We have previously described a triage strategy with a repeated self-sampling for HPV testing a couple of months after the initial positive HPV test to define persistent HPV infections.[21] Primary screening by way of this strategy led to the detection of more than twice as many women with CIN2+ compared to conventional screening by Pap smear, and was associated with high follow-up compliance of screening-positive women.[22]

What's new?

Primary screening with human papillomavirus (HPV) test is more effective in reducing cervical cancer incidence than cytology and offers the opportunity for self-sampling. However, the feasibility and effectiveness of self-sampling in primary screening should be further evaluated. Our study shows that, in women aged 30-60 years, self-sampling yields similar rates of HPV prevalence and CIN2+ and CIN3+ detection compared to sampling by medical professionals when using an FTA card as storage medium and PCR-based HPV test. Considering health-economics aspects, resources should be directed toward self-sampling as a first choice for primary cervical screening, with careful follow-up of this strategy.

When it comes to clinical performance it is important that the combination of a self-sampling kit and an HPV test performs well with regard to detection of CIN2+ and CIN3+. In a recent randomized study on women aged >50 years, where vaginal self-sampling was compared to cervical sampling by medical professionals we found similar HPV prevalence rate and detection of CIN2+ in the study arms.[23] The aim of the present study was to compare self-sampling and sampling by medical professionals concerning prevalence of HPV and detection of CIN2+ and CIN3+ in women aged 30-60 years.

2 | MATERIALS AND METHODS

2.1 | Study population

Women scheduled for a regular screening invitation in Uppsala County during March and April in 2016 were randomized into two groups: an intervention group of women who performed vaginal self-sampling for HPV testing (SS arm), and a control group of women who received an invitation to undergo cervical sampling by medical professionals for HPV testing (SMP arm). A computer-based allocation process was used for the randomization. The protocols in the two arms are described below. The women and the gynecologists performing colposcopy were not blinded to the study group, but the pathologists were. To be eligible for the study the woman had to be 30-60 years of age at entry (date of invitation), with no clinical test results (cytology, HPV test, or histology) related to cervical cancer registered within 1 year prior to the start of the study period (first study invitation). The women whose first HPV samples arrived at the HPV laboratory in 2016 were included in the analysis. The follow-up period was 18 months from the starting point. During the study period the regular screening program in Uppsala County was 3-yearly Pap smears for women aged 23-49 years and

5-yearly HPV tests for women aged 50-60 years. Women not attending screening were recalled the following year.

2.2 | Self-sampling (SS arm)

Women in the SS arm were sent an invitation together with a kit including a RoversViba-brush (Rover Medical Devices B.V., Oss, the Netherlands), an indicating FTA elute micro card (art. no WB129308, GE Healthcare, Longwood Dr., Cardiff CF14 7YT, UK), a postage-paid return envelope and information on how to perform the sampling. Briefly, the women were asked to place the brush approximately 5-10 cm into the vagina and gently rotate it once, then remove the brush and apply the vaginal sample to the FTA card by placing the brush in the middle of the application area and rolling it one full circle across that area and letting it air-dry for a few minutes. They were then required to close the lid, place the card in the envelope and send it by regular mail to the Department of Immunology, Genetics and Pathology at Uppsala University (HPV laboratory) for HPV testing. A reminder was sent to women who did not return their self-sample within 1-2 months. The women were informed of the test result within 2-3 weeks after their sample was returned for HPV testing. Women that were HPV-positive in their first self-sample were also informed that they would be sent an additional kit to repeat the self-sampling about 6 months after the first sample was collected, but that they could contact a midwife or a gynecologist if they had questions or symptoms.

2.3 | Sampling by medical professionals (SMP arm)

Women in the SMP arm were sent an FTA card together with an invitation to book an appointment at a local midwife clinic for cervical sampling with a cytobrush. After sampling, the FTA card was sent to the HPV laboratory for HPV testing. A reminder was sent to women whose samples did not arrive at the laboratory within 3-4 months. The women were informed of the test result within 2-3 weeks after their sample was returned for HPV testing. Women that were HPV-positive in their first sample were also informed that they would be sent an additional FTA card with an invitation to book an appointment at the midwife clinic to repeat the sampling about 6 months after the first sample was collected, but that they could contact a midwife or a gynecologist earlier if they had questions or symptoms.

2.4 | Sample processing and HPV analysis

At the HPV laboratory, the FTA cards were processed using an automated laboratory system (easyPunch STARlet, Hamilton Robotics, Via Crusch 8 CH-7402 Bonaduz, GR, Switzerland). A robot arm picks up each card, takes a photograph of the sampling area, and using machine-learning software for calculation of which parts of the card contain the highest concentrations of cells, and thereafter punches four circular pieces of 3 mm diameter. All four pieces are collected into a single well in a 96-well microtiter plate and DNA extracted as described earlier.[24]

HPV testing was performed using a clinically validated real-time PCR-based test (hpVIR).[25-27] This test detects and quantifies a human single-copy gene (housekeeping gene), HMBS (*Homo sapiens* hydroxymethylbilane synthase; GenBank accession no. M95623.1) as a control to ensure that the sample contains enough cellular material for the test to be informative. The test detects and quantifies the following HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. The results are presented as individual types, except for HPV18/45 which are detected as a group and HPV33/52/58 which are also detected as a group. The limit of detection of HPV is 10 HPV copies per PCR. In order for a sample to contain enough material for the HPV test to be informative, a threshold of 10 copies of the nuclear single-copy gene per PCR is used.[25]

2.5 | Colposcopy, cytology, and histology

Women that were HPV-negative in their first or second sample were referred back to regular screening. Women that were HPV-positive in two consecutive samples were referred to colposcopy. At the colposcopy visit a conventional Pap smear on a glass slide was collected for cytological analysis. The colposcopic evaluation included identification of the squamocolumnar junction and transformation zone (TZ) with application of 5% acetic acid and iodine solution. Directed biopsy samples were obtained from all the identified abnormal areas and a random biopsy sample was obtained in women with normal colposcopy. In TZ type 3 with an invisible squamocolumnar junction, an additional sample for endocervical cytology was collected. All colposcopies were performed at the Clinic of Obstetrics and Gynecology, Uppsala University Hospital. All cytological and histological analyses were performed at the Clinic of Pathology and Cytology, Uppsala University Hospital, Uppsala. Classification was carried out according to the Swedish modification of SNOMED (Systematized Nomenclature of Medicine; College of American Pathologists, Skokie, Illinois), describing the findings concerning cervical intraepithelial neoplasia (CIN), and the highest histological grade found in each patient was used for interpretation of the results.

2.6 | Statistical analysis

Power analysis was based on a noninferiority design. The HPV prevalence was estimated to be 4.5% and we decided on a noninferiority limit of 2.5% and a significance level of 5%. This gives a power of 95% to exclude a difference in favor of SMP. Sample size was calculated to 1489 women required per group, that is, 2978 totally. The data was analyzed by using both a per-protocol approach, that is, including only women assigned to the two arms who complied with the protocol, and an intention-to-treat approach, that is, also including women who were HPV-positive in their initial self-sample but who requested clinical follow-up before receiving their second kit/invitation. The primary outcome was the prevalence of detected CIN2+ and CIN3+ per 1000 screened women. Statistical calculations were performed by using R (version 3.5.3) and IBM SPSS (version 26) software. Fisher's exact test was used to compare proportions between the two independent

study groups with respect to nominal variables (sampling method, participation and diagnostic outcomes). *P*-values <.05 were considered to indicate statistical significance.

3 | RESULTS

3.1 | Patient characteristics and participation rate

The numbers of women included at each stage of the study and the numbers of CIN2+, CIN3+ and cancer cases detected are shown in Figure 1. In total, 11 951 women scheduled for invitation to screening during March and April in 2016 were defined as the study group. In the SS arm 5767 women received the invitation (no returning mail) and in the SMP arm 5844 women received the invitation. The participation rate was significantly higher in the SS arm (44.3%, 2556/5767) than in the SMP arm (26.5%, 1548/5844) (*P* < .001). In total, 3985 women were eligible for the study, 2466 in the SS arm and 1519 in the SMP arm. The mean age of participating and eligible women was 42.4 years in the SS arm and 41.5 years in the SMP arm, with a significant difference between the arms (*P* = .001) (Table 1).

3.2 | HPV prevalence and type distribution

One sample in the SMP arm and 3 samples in the SS arm contained insufficient material for HPV analysis. All these women performed a new self-sampling that was sufficient for HPV analysis in all cases. Prevalence rates of HPV among the study population in the first and second HPV tests, sorted by study arm and divided into age groups, are shown in Table 2. The prevalence of HPV in the first test was 6.8% (167/2466) in the SS arm and 7.8% (118/1519) in the SMP arm (*P* = .26). Compliance of HPV-positive women for second sampling was 88.6% (148/167) in the SS arm and 89.8% (106/118) in the SMP arm (*P* = .85). The second sample was collected on average 7.2 months after the first in the SS arm and 7.7 months after the first in the SMP arm. Of those positive in the first test the second HPV test was positive in 67.6% (100/148) in the SS arm and in 61.3% (65/106) in the SMP arm (*P* = .37). The screening positive rate needing clinical follow-up was 4.1% (100/2466) in the SS arm and 4.3% (65/1519) in the SMP arm (*P* = .74). No significant difference was noted in overall prevalence between the study arms. When the study population was divided into age groups, there was no significant difference in prevalence but there was a trend in the youngest

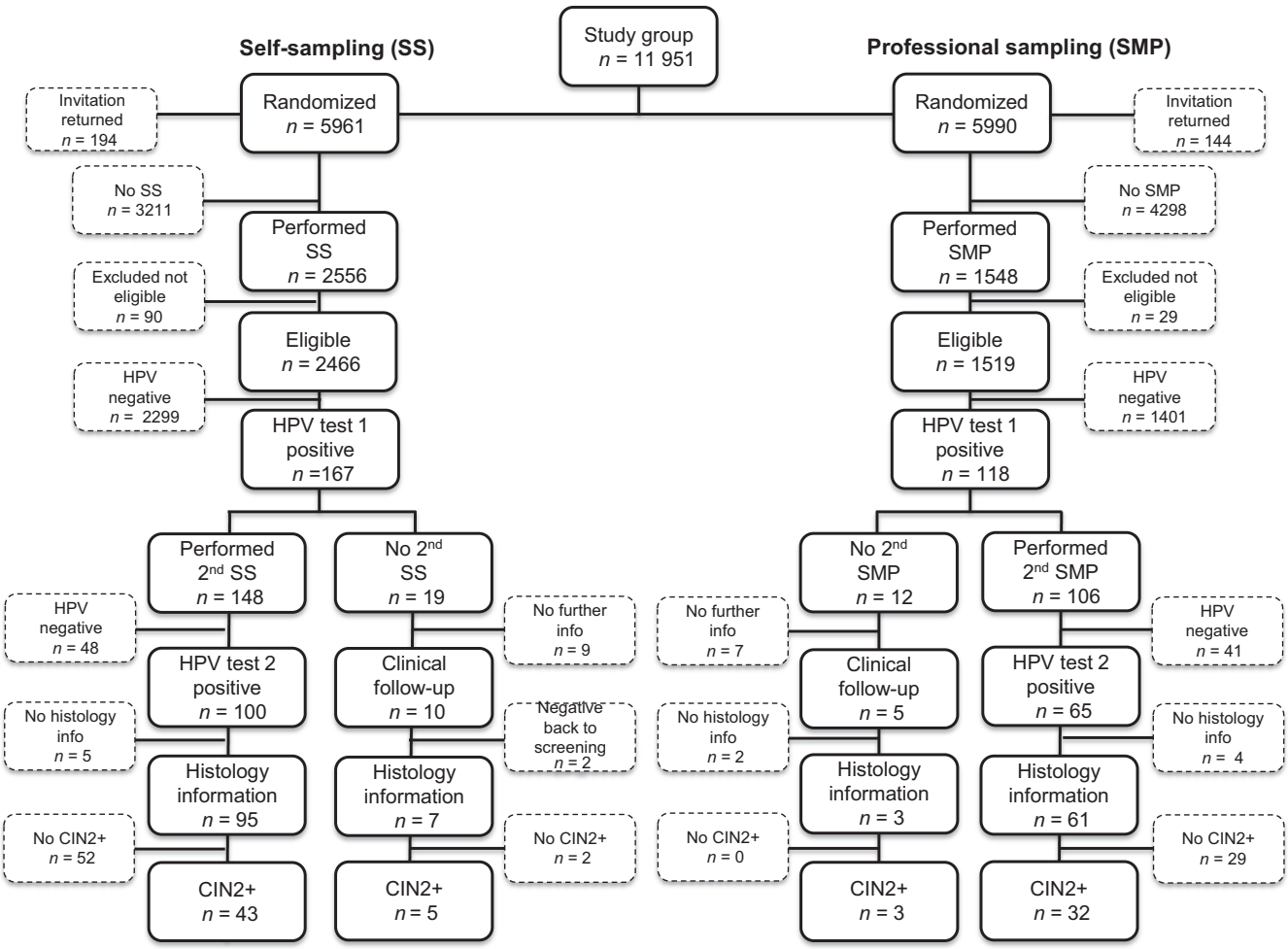

FIGURE 1 Study design with number of women included and excluded at different steps in the self-sampling arm and the sampling by medical professionals arm

TABLE 1 Baseline information and compliance in follow-up

	Study arms		
	Self-sampling	Professional sampling	*P* values
Randomized women, n	5961	5990	–
Invitation received, n	5767	5846	–
Nonparticipating women, n	3211	4298	–
Participating women, n (%)	2556 (44.3)	1548 (26.5)	<.001
Eligible women, n	2466	1519	–
Age of participating eligible women, mean (SD)	42.4 (8.1)	41.5 (7.6)	.001
30-39 years (SD)	34.3 (3.0)	34.5 (3.1)	.09
40-49 years (SD)	44.5 (2.9)	44.6 (2.9)	.52
50-60 years (SD)	54.8 (2.9)	55.3 (3.0)	.08
Follow-up compliance; second HPV test, n (%)	148 (88.6)	106 (89.8)	.85
Follow-up compliance; histology, n (%)	95 (95.0)	61 (93.8)	.74

TABLE 2 HPV-positive women in the study arms and different age groups

Per-protocol approach			
	Self-sampling n (%)	Professional sampling n (%)	*P* values
First HPV test, all ages	167 (6.8)	118 (7.8)	.26
30-39 years	74 (7.6)	68 (10.3)	.06
40-49 years	65 (6.3)	37 (5.5)	.53
50-60 years	28 (6.1)	13 (6.9)	.72
Second HPV test, all ages	100 (4.1)	65 (4.3)	.74
30-39 years	42 (4.3)	39 (5.9)	.16
40-49 years	40 (3.9)	20 (3.0)	.35
50-60 years	18 (3.9)	6 (3.2)	.82
Intention-to-treat approach			
	Self-sampling n (%)	Professional sampling n (%)	*P* values
Second HPV test, all ages	101 (4.1)	65 (4.3)	.81
30-39 years	43 (4.4)	39 (5.9)	.20
40-49 years	40 (3.9)	20 (3.0)	.35
50-60 years	18 (3.9)	6 (3.2)	.82

group (30-39 years), where the HPV prevalence tended to be lower in the SS arm (7.6%) than in the SMP arm (10.3%) (*P* = .06) in the first HPV test.

The prevalence of different HPV types in the first HPV test was similar in the two study arms (Table 3). HPV16 was the most common type, followed by HPV33/52/58 in both study arms. HPV51 was the only type clearly more common in the SMP arm than in the SS arm, but in the second HPV test this difference had disappeared and most HPV51 infections turned out to be transient (only two infections persisted in both arms).

3.3 | Detection of CIN2+ and CIN3+

The compliance of women with a positive second HPV test result to attend colposcopy was high and similar in the two study arms: 95.0% (95/100) (95%CI 88.2-98.1) in the SS arm and 93.8% (61/65) (95%CI 84.2-98.0) in the SMP arm (*P* = .74). In the SS arm, 43 of women with a positive second HPV test result received a CIN2+ diagnosis in histology and 35 received a CIN3+ diagnosis (per-protocol approach). Among the women that were HPV-positive in their first self-sample test result, 19 did not obtain a second self-sample, but instead, 10 of

them requested earlier clinical follow-up. Among these women, seven had biopsy sample taken, and five of them received a CIN3+ diagnosis and these women were included in the intention-to-treat calculation of CIN2+ and CIN3+ detection (Table 4). In the SMP arm, 32 of women with positive second HPV test result received a CIN2+ diagnosis in histology and 23 received a CIN3+ diagnosis (per-protocol approach). Among the women that were HPV-positive in their first self-sample, 12 did not obtain a second sample by a midwife, but instead, five of them requested earlier clinical follow-up. Among the clinical follow-ups, three women received a CIN3 diagnosis and one a CIN2 diagnosis and were included in the intention-to-treat calculation of CIN2+ and CIN3+ detection (Table 4).

The detection of both CIN2+ and CIN3+ per 1000 screened women are shown in Table 4. In the per-protocol approach, the prevalence of CIN2+ per 1000 screened women was 17 (43/2466 × 1000) (95%CI 13-24) in the SS arm and 21 (32/1519 × 1000) (95%CI 15-30) in the SMP arm. The prevalence of CIN3+ per 1000 screened women was 14 (35/2466 × 1000) (95%CI 10-20) in the SS arm and 15 (23/1519 × 1000) (95%CI 10-23) in the SMP arm. Including women from the intention-to-treat approach did not influence the prevalence markedly (Table 4).

The study arms did not differ significantly in the prevalence of CIN2+ or CIN3+ when dividing the women into age groups, but in the youngest age group (30-39 years; per-protocol approach), a tendency toward lower detection of CIN2+ and CIN3+ was observed. In the SS arm, the prevalence of CIN2+ per 1000 screened women was 17 (95%CI 11-28) compared to 30 (95%CI 19-47) in the SMP arm (P = .09), and the prevalence of CIN3+ per 1000 screened woman was 14 (95%CI 8-25) in the SS arm and 27 (95%CI 17-44) in the SMP arm (P = .07) (Table 4).

TABLE 3 Prevalence of different HPV types

Total number of infections[a] and percentage (%) in the study arms		
HPV type	Self-sampling (n = 2466)	Professional sampling (n = 1519)
16	60 (2.4)	40 (2.6)
33/52/58[b]	40 (1.6)	28 (1.8)
31	25 (1.0)	17 (1.1)
51	8 (0.3)	16 (1.1)
18/45[b]	24 (1.0)	13 (0.9)
39	12 (0.5)	10 (0.7)
56	14 (0.6)	7 (0.5)
35	8 (0.3)	5 (0.3)
59	6 (0.2)	5 (0.3)

[a]The number of infections includes multiple types and therefore the total sum is higher than the number of HPV-positive women in each arm.
[b]Detected together as a group.

TABLE 4 Detection of CIN2+ and CIN3+

Prevalence per 1000 women screened (95% CI)			
	Per-protocol approach		
	Self-sampling (n = 2466)	Professional sampling (n = 1519)	*P* values
CIN2+, all ages	17 [13–24] (n = 43)	21 [15–30] (n = 32)	.47
30-39 years (n = 976)	17 [11-28] (n = 17)	30 [19-47] (n = 20)	.09
40-49 years (n = 1030)	19 [12-30] (n = 20)	15 [8-28] (n = 10)	.57
50-60 years (n = 460)	13 [5-30] (n = 6)	11 [2-42] (n = 2)	1.00
CIN3+, all ages	14 [10-20] (n = 35)	15 [10-23] (n = 23)	.79
30-39 years (n = 976)	14 [8-25] (n = 14)	27 [17-44] (n = 18)	.07
40-49 years (n = 1030)	15 [8-24] (n = 15)	6 [2-16] (n = 4)	.16
50-60 years (n = 460)	13 [5-30] (n = 6)	5 [0-34] (n = 1)	.68
Intention-to-treat approach			
	Self-sampling (n = 2466)	**Professional sampling (n = 1519)**	***P* values**
CIN2+, all ages	19 [15-26] (n = 48)	23 [16-32] (n = 35)	.49
30-39 years (n = 976)	22 [14-33] (n = 21)	35 [23-53] (n = 23)	.12
40-49 years (n = 1030)	20 [13-32] (n = 21)	15 [8-28] (n = 10)	.46
50-60 years (n = 460)	13 [5-30] (n = 6)	11 [2-42] (n = 2)	1.00
CIN3+, all ages	16 [12-22] (n = 40)	16 [11-25] (n = 25)	1.00
30-39 years (n = 976)	18 [11-30] (n = 18)	30 [19-47] (n = 20)	.13
40-49 years (n = 1030)	16 [9-26] (n = 16)	6 [2-16] (n = 4)	.11
50-60 years (n = 460)	13 [5-30] (n = 6)	5 [0-34] (n = 1)	.68

Notes: n = eligible women in different age groups.

The positive predictive value (PPV) for detection of CIN2+ (per-protocol approach) was 0.43 (95% CI 0.33-0.53, n = 43 of 100) for the SS arm and 0.49 (95% CI 0.37-0.62, n = 32 of 65) for the SMP arm; with no statistical significance (P = .52, two-sided Binomial test).

3.4 | Cytology testing

In all women with histological CIN2+, the Pap smears collected at the study visit were abnormal (≥ASCUS) in 38/48 (79.2%) in the SS arm and in 18/35 (51.4%) in the SMP arm. In all women with histological CIN3+, the Pap smears were abnormal (≥ASCUS) in 31/40 (77.5%) in the SS arm and in 16/25 (64.0%) in the SMP arm. In the overall study population, the sensitivity of Pap smear was 67.5% in the detection of histological CIN2+ and 72.3% in the detection of histological CIN3+.

4 | DISCUSSION

Vaginal self-sampling and cervical sampling by medical professionals results in similar estimates of HPV prevalence and detection of CIN2+ and CIN3+ when using a combination of an indicating FTA elute card as storage medium and the PCR-based hpVIR assay as a primary screening method in women aged 30-60 years. This, together with a higher participation rate in the SS arm compared to the SMP arm makes a screening strategy based on self-sampling attractive. The prevalence of HPV did not differ between the study arms in the first and second HPV tests (Table 2). There was a tendency toward a slightly lower HPV prevalence in the first sample in the SS arm among the youngest age group (30-39 years), compared to the SMP arm, but when comparing all ages there was no such difference. Such a tendency for women aged 30-39 years has not been seen in any previous study and the observed difference is therefore not easily explained. Women included in the study were invited since they were scheduled for regular invitation to screening and thus belong to the screening population. Even if the number of women was rather small it is less likely that this is the only explanation. It must be remembered that the power analysis was done on the total number of women and not for the age groups. It is thus possible that a larger number of participants might have revealed a significant difference in HPV detection rate between the study arms for women aged 30-39 years.

The distribution of different HPV types was similar in the two study arms, with HPV16 being the dominant type in both arms (Table 3). HPV51 was the only type that differed more prominently between the study arms, with a higher prevalence in the SMP arm (Table 3), which is in contrast to results of previous studies where HPV51 has been found to be the more common type in the SS arm[23] and the second-most common type in vaginal self-samples from nonattenders.[28] However, as in the present study, the clearance of an HPV51 infection was high and HPV51 was also categorized to a lower-risk group with a weak association with progression to CIN3+,[29] thus reducing the significance of this difference.

In a large meta-analysis, it was shown that PCR-based HPV testing was as sensitive for detection of CIN2+ and CIN3+ on self-samples compared to clinician samples, and self-sampling therefore could be considered in primary screening.[17] Two randomized studies performed with different sampling devices combined with dry-transport media and PCR-based HPV tests showed no difference between self-samples and samples obtained by medical professionals as regards the detection of CIN2+.[23,30] The IMPROVE study[30] was carried out to evaluate the clinical accuracy of HPV self-sampling vs clinician-based HPV testing in primary screening. The study involved a high-powered randomized noninferiority design with cross testing of all the HPV-positive women (paired screen-positive design). Similar accuracy was shown between self-collected and clinician-collected samples in terms of the detection of CIN2+ or CIN3+ using a combination of a dry self-sampling device and a clinically validated PCR-based HPV test. The detection of CIN2+ was equal in both the self-sampling and clinician-collected arms (15 per 1000 women screened) which is similar to the results in the present study (17 per 1000 women screened). Follow-up for HPV-positive women was cytology in the IMPROVE study and repeated self-sampling for HPV testing in the present study.

The participation rate in the present study was significantly higher in the SS arm compared to the SMP arm (44.3% vs 26.5%) (Table 1), which is in line with the results of our earlier studies, with a similar routine for invitation. The routine in these two studies was to send a self-sampling kit directly or an invitation to book an appointment for sampling. The present study differed from these two earlier studies in that a reminder was sent to women in the SMP arm during the study period. However, there was no obvious positive effect on participation by these reminders in comparison with the two earlier studies. It is known that offering invitations with timed appointments results in significantly higher compliance.[31] This strategy was not feasible in our study, since it was not the regular invitation routine in Uppsala County. A British study on nonattenders at a first screening visit showed that sending self-sampling kits or providing timed appointments resulted in a similar 10% increase in participation.[32] A Finnish study on nonattenders showed higher compliance by self-sampling (31%) than reminder letter (26%) while combining a reminder with self-sampling resulted in the highest compliance (40%).[33] A recent Swedish study showed markedly higher compliance to direct sent self-sampling kit (19%) in comparison with reminder letter (2%) on long-term nonattenders (10 years).[34] In the current study there was a higher number of noneligible women in the SS arm (n = 90, 3.5%) compared to the SMP arm (n = 29, 1.9%). The reason for this difference is not known. A computer-based allocation process was used for the randomization of one group of women to the two the SS and SMP arms. After randomization women that were not 30-60 years of age at entry or had a clinical test results related to cervical cancer screening registered within 1 year prior to the start of the study period were considered as noneligible for the study and they were excluded. The most reasonable reason for the difference is that more noneligible women by chance were randomized to the SS-arm.

High-level compliance to follow-up is crucial in the self-sampling strategy, since cytological triage is not applicable on self-samples.

Compliance to a follow-up test after a positive first HPV test was high in both arms (88.6% in the SS arm vs 89.8% in the SMP arm) (Table 1) and is in line with earlier studies.[22,35-37] In the SMP arm this approach needs an additional appointment for a second test, but compliance was actually the same as in the SS arm, which offers a more user-friendly and beneficial economic alternative. Compliance in attending colposcopy was high in both study arms with those undergoing biopsy being 95.0% in the SS arm and 93.8% in the SMP arm (Table 1).

Jentschke and coworkers[38] compared two different dry self-sampling devices (Evalyn brush and Qvintip) with a physician-collected reference sample, using the PCR-based Abbott Real-Time High-Risk HPV test and showed no difference in accuracy. There was, however, a demanding laboratory workload, which was not suitable in a primary screening setting. FTA cards, on the other hand, are easy to apply in a screening setting since the extraction of DNA is fast and automated, and requires only a simple wash with warm water[24] before the PCR-based hpVIR HPV test.[27]

A strength of the present study is that we used similar protocols in both study arms, including a reminder during the study period, the dry storage medium (FTA card), the HPV test (hpVIR) and the same follow-up with colposcopy and histology. Concerning sampling, there was a limitation, since different sampling brushes and sampling locations were used in the arms; a RoversViba-brush was used in the SS arm for vaginal-fluid sampling and a cytobrush in the SMP arm for cervical sampling. The RoversViba-brush is CE-marked and widely used in self-sampling studies, while the cytobrush is widely used in clinical sampling. Another limitation is the size of the study, which may have limited our ability to discover a difference in HPV prevalence or the detection rate of CIN2+ and CIN3+ between the study arms. A possible bias is that we have no screening history available. In the screening population there is always a proportion of women that do not take part in the screening, nonresponders. It is known from previous studies that some of the nonresponders accept invitations to perform self-sampling. It is also known from previous studies that the proportion of women with HPV and dysplasia is higher in this group. There is thus a risk that women in the SS arm consist of a larger proportion of nonresponders with a higher risk for HPV and CIN2+ than in the SMP arm.

The fact that a PCR-based HPV test showed similar accuracy in self-samples compared to clinician samples[17] offers not only a promising new primary cervical screening strategy but also opens up other opportunities to use self-sampling. As a positive HPV result after treatment of CIN2+ predicts treatment failure accurately,[39] self-samples might even be used in "test of cure",[40] and as an HPV test has a high negative predictive value for CIN3+[41] and invasive cervical cancer[42] in screening, self-sampling might be used in follow-up of low-grade squamous abnormalities, diminishing the need for repeated colposcopies.

5 | CONCLUSIONS

Using the combination of an FTA card as storage medium and a PCR-based HPV test (hpVIR) in self-sampling leads to similar rates of HPV prevalence and detection of CIN2+ and CIN3+ compared to sampling by medical professionals. As self-sampling also is cost-saving compared to sampling by medical professionals, resources should be directed to offer self-sampling as a first choice in primary cervical screening, with careful follow-up of this strategy.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee in Uppsala (Dnr 2016/008 and Dnr 2019/929). All participants received written information and implied consent was given.

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