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High-risk HPV testing on self-sampled *versus* clinician-collected specimens: A review on the clinical accuracy and impact on population attendance in cervical cancer screening

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Mini Review

This review elaborates on the accuracy and feasibility of human papillomavirus (HPV) self-sampling, *i.e.*, offering self-sampling of (cervico-)vaginal cell material by women themselves in nonclinical settings for high-risk HPV (hrHPV) detection in the laboratory, for cervical screening. To that end a bibliographic database search (PubMed) was performed to identify studies (published between January 1992 and January 2012) that compared clinical accuracy of HPV testing on self-sampled material with that of cytology or HPV testing on clinician-taken samples, and studies comparing response to offering HPV self-sampling with a recall invitation. Overall, hrHPV testing on self-samples appeared to be at least as, if not more, sensitive for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) as cytology on clinician-obtained cervical samples, though often less specific. In most studies, hrHPV testing on self- and clinician-sampled specimens is similarly accurate with respect to CIN2+ detection. Variations in clinical performance likely reflect the use of different combinations of collection devices and HPV tests. Because it is known that underscreened women are at increased risk of cervical cancer, targeting non-attendees of the screening program could improve the effectiveness of cervical screening. In developed countries offering self-sampling has shown to be superior to a recall invitation for cytology in re-attracting original non-attendees into the screening program. Additionally, self-testing has shown to facilitate access to cervical screening for women in low resource areas. This updated review of the literature suggests that HPV self-sampling could be an additional strategy that can improve screening performance compared to current cytology-based call-recall programs.

For years, cervical scrapes taken by clinicians constituted the basis for cervical cancer screening *via* either conventional or liquid-based cytology (LBC).[1,2] However, several randomized controlled trials have shown that, given its higher sensitivity for cervical intraepithelial neoplasia grade 2 or worse (CIN2+), high-risk human papillomavirus (hrHPV) testing on clinician-taken cervical scrapes provides a better protection against cervical cancer than cytology.[3–5] Therefore, HPV testing is likely to become an important primary cervical screening tool in the near future.

Another item that got much attention in the last couple of years involves the use of self-collected (cervico-) vaginal material as an alternative for clinician-collected cervical scrapes for screening. Swabs, brushes, tampons or lavage devices have been used as self-collection devices. Surveys in which participants were asked for collection preference have shown that women prefer self-collection over clinician-collection, with time and place of sampling, privacy and ease of sampling being the mentioned advantages of self-sampling. Only a small number of women were reluctant because they either did not understand the provided instructions or were insecure if they had used the self-sampling test properly.[6–10] Self-sampling may have important implications for programs located in countries where cultural and program barriers may limit acceptance of and access to standard clinician-based cervical cancer screening. Indeed, self-sampling has shown to facilitate access to cervical screening in developing

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regions[11–13] and it may improve screening attendance in developed countries.[14–22]

However, adequate specimens for cytological assessment require clinicians to sample the cervical transformation zone. As such, self-collected (cervico-) vaginal samples are not suited for accurate cytological assessment, because of lower specimen quality (*i.e.*, deficiency of sufficient ectocervical and/or endocervical cells).[23,24] Indeed, Garcia *et al.* found a deficiency of endocervical cells in 66% of the self-sampled material compared to 14% in clinician-obtained material.[23] As a consequence, the concordance between cytology on self-sampled specimens *versus* cervical smears taken by a clinician is poor[23–27] and the sensitivity of cytology for high-grade cervical lesions is 23–77% lower when applied to self-samples compared to physician samples.[23,25–27] Thus, cytology is not an appropriate option for self-sampled specimens.

Many studies have instead addressed the use of self-collected samples for hrHPV analysis. Data have been summarized in previous meta-analyses and (systematic) reviews in which study parameters included concordance in hrHPV detection rates between self- *versus* clinician-collected samples through percent agreement and/or kappa values (*i.e.*, no reference standard was set).[6,7,28,29] The range of HPV test positivity rates varied considerably across the various studies, most likely reflecting differences in geographical areas, study populations (screening *versus* referral), age range, collection devices used and type of HPV tests used.

In most studies, a moderate to good agreement, reported as concordance rate and/or kappa value, between hrHPV test positivity in self- and clinician-collected samples was found. For example, Petignat *et al.* found a high level of concordance between self- and clinician-sampling for the detection of hrHPV DNA ((kappa = 0.66, 95% CI, 0.50–0.82). The pooled difference in the proportion of hrHPV DNA positivity rates between sampling methods (clinician *versus* self) was −0.4% (95% CI, −4.4 to 3.5%), indicating a similar hrHPV positivity rate in both types of samples. The authors concluded that self-sampling was as sensitive as clinician-obtained sampling to detect hrHPV DNA or overall HPV DNA.[7] Collectively, these data show that self-sampling is concordant with clinician-sampling in detecting hrHPV.

However, when considering self-sampling for screening or diagnostic purposes, it is most important to know how self-sampling performs with regard to relevant disease outcomes. Therefore, the objective of this literature review is to compare the accuracy and the impact on population attendance in cervical cancer screening on self-sampled *versus* clinician-collected specimens. More specifically, we assessed clinical accuracy of the HPV test on self-sampled material compared to cytology and HPV testing on clinician taken samples, and the effect of HPV self-sampling on screening coverage. The PICOS (P = patient, I = intervention, C = comparison, O = outcome, S = studies)[30] and the specific research questions are listed in Table 1.

For this purpose, we searched the PubMed database for relevant papers published between January 1992 and January 2012. The Medical subject Headings (MesH) of disease-specific terms (Papillomaviridae, Uterine Cervical Diseases, Uterine Cervical Dysplasia, Cervical Intraepithelial Neoplasia) and the free-text word "HPV" were identified and combined with test-specific terms (self care, self sample*, self test*, self collect*, self exam*). The search was not limited by the English language or by any study-design.

We included studies if we could use the reported data to answer our main research questions ($n = 28$ in total) (Tables 2–5). Thereby, we added two studies which were not found in the electronic search strategy, but were considered relevant for our review by checking the references of the retrieved articles.[12,27]

Table 1. Research questions and PICOS

Research questions:
1. Is the clinical accuracy of hrHPV testing on self-collected samples comparable with cytology on clinician-taken samples to detect cervical intraepithelial neoplasia grade 2 or worse (CIN2+)?
2. Is the clinical accuracy of hrHPV testing on self-collected samples comparable with hrHPV testing on clinician-taken samples to detect CIN2+?
3. Does self-sampling increase the screening attendance compared to clinician-sampling?
PICOS[1]:
P: Women in general population or women referred to a gynecologist (because of abnormal test results or gynecological symptoms) or mixed population
I: HPV test on self-sampled (cervico-) vaginal cells
C: HPV test or cytology test on cervical cells obtained by a clinician
O: Detection of CIN2+ lesions:
HPV on self-sample *vs* cytology on clinician-sample
HPV on self-sample *vs* HPV on clinician-sample
Attendance rate: HPV on self-sample *vs* cytology on clinician-sample
S: Cross-sectional studies
Cohort studies
Concomitant testing (self-sample and clinician-sample taken from the same women)

[1]P = patient, I = intervention, C = comparison, O = outcome, S = studies.

Comparison of the Accuracy of hrHPV Testing on Self-Collected Samples With Cytology on Clinician-Collected Samples for Detection of CIN2+

Ten studies that have addressed the performance of hrHPV testing on self-samples in comparison with cytology on clinician-obtained cervical smears to detect CIN2+ have been performed in either screening or referral populations (see Table 2 for an overview of studies describing concomitant testing). Since both hrHPV and disease prevalence differ between screening and referral populations, the results from both populations are discussed separately below.

Table 2. Concomitant studies on diagnostic accuracy of hrHPV testing on self-samples *versus* cytology on clinician-collected samples to detect CIN2+

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV %	NPV %
Wright *et al.* (2000)[31]	1365 healthy subjects (community)	Colposcopy (all women with abnormal results of any screening tests)	HR HC2	Dacron swab *vs* Accellon Combispatula for conventional cytology:	Self: 66.1	Self: 81.4[2]	Self: 13.2[2]	Self: 98.2[2]
				1. ≥ASCUS	Clin 1: 67.9	Clin 1:86.4[2]	Clin 1: 17.8[2]	Clin 1: 98.4[2]
				2. ≥LSIL	Clin 2: 60.7	Clin 2: 95.9[2]	Clin 2: 39.1[2]	Clin 2: 98.3[2]
Sellors *et al.* (2000)[32]	200 women (colposcopy clinic)	Colposcopy (all women)	HR HC2	Vaginal Dacron swab *vs* Ayre spatula & endocervical brush for conventional cytology	Self: 86	Self: 54	Self: 43	Self:91
					Clin: 78	Clin: 81	Clin: 63	Clin: 90
Belinson *et al.* (2001)[33]	1,997 healthy subjects (community)	Colposcopy (all women)	HR HC2	Dacron swab *vs* cervical brush & plastic spatula for liquid-based cytology:	Self: 82.6	Self: 85.9	Self: 20.9	Self: 99.1
				1. ≥ASCUS	Clin 1: 94.2; $p < 0.025$	Clin 1: 77.8	Clin 1: 16.0	Clin 1: 99.7
				2. ≥LSIL	Clin 2: 87.2	Clin 2: 93.6	Clin 2: 37.9	Clin 2: 99.4
Nobbenhuis *et al.* (2002)[26]	71 women (colposcopy clinic)	Colposcopy (all women)	HR GP5+/ 6+ PCR	Lavage *vs* cervical brush	Self: 81	Self: 68	Self: 70	Self: 79
					Clin: 100	Clin: 39	Clin: 59	Clin: 100
Belinson *et al.* (2003)[34]	8,497 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Vaginal conical brush *vs* Rovex liquid based cytology:	Self: 87.5	Self: 77.2	Self: 15.1[2]	Self: 99.3[2]
				1. ≥ASCUS	Clin 1: 88.3; $p = 0.815$	Clin 1: 81.2; $p < 0.001$	Clin 1: 17.9[2]	Clin 1: 99.3[2]
				2. ≥LSIL	Clin 2: 78.4; $p = 0.001$	Clin 2: 93.2	Clin 2: 34.6[2]	Clin 2: 98.9[2]
Salmeron *et al.* (2003)[35]	7,732 healthy subjects (screening program)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Dacron swab *vs* Dentilab cytobrush + spatula for conventional cytology	Self: 71.3	Self: 89.2	Self: 9.1	Self: 99.6
					Clin: 59.4	Clin: 98.3	Clin: 36.1	Clin: 99.5

Table 2. (Continued)

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV %	NPV %
Brink *et al.* (2006)[27]	64 symptomatic women and 32 healthy volunteers (gynecological clinic)	Colposcopy (all referred women and the volunteers)	HRGP 5+/ 6+ PCR	Cervico-vaginal lavage *vs* cervical brush for liquid based cytology	Self: 91.9	Self: 45.6[2]	Self: 52.3[2]	Self: 89.7[2]
					Clin: 83.8; $p = 0.5$	Clin: 50.0[2]	Clin: 51.7[2]	Clin: 82.9[2]
Szarewski *et al.* (2007)[36]	920 healthy subjects (screening program or family planning clinic)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Cotton swab *vs* pointed spatula & endocervical brush for conventional cytology	Self: 81.0	Self: 82.2	Self: 9.6	Self: 99.5
					Clin: 81.0	Clin: 96.2	Clin: 33.3	Clin: 99.5
Bhatla *et al.* (2009)[37]	546 symptomatic women (gynecological clinic)	Colposcopy (all women)	HR HC2 and PGMY09/ 11 PCR	Vaginal brush *vs* endocervical brush & spatula for conventional cytology:,	HC2	HC2	HC2	HC2
					Self: 80.0	Self: 88.1	Self: 36.4	Self: 98.1
					PCR	PCR	PCR	PCR
					Self: 82.5	Self: 93.6	Self: 52.4	Self: 98.4
				1. ≥ASCUS	Clin 1: 77.5	Clin 1: 87.3	Clin 1: 34.1	Clin 1: 97.9
				2. ≥LSIL	Clin 2: 70.0	Clin 2: 94.7	Clin 2: 52.8	Clin 2: 97.4
Dijkstra *et al.* (2012)[38]; unpublished data)	135 symptomatic women	Colposcopy (all women)	HR GP 5+/ 6+ PCR	Vaginal brush *vs* Cervex-Brush for liquid based cytology	Self: 93.0	Self: 51.1	Self: 37.1[2]	Self: 86.7[2]
					Clin: 90.7	Clin: 28.3	Clin: 47.1[2]	Clin: 94.0[2]

[1]When reported P values are given. [2]Authors calculation
Abbreviations: Self = self-collected specimen tested on hrHPV; Clin = clinician-collected specimen tested by cytology.

Table 3. Concomitant studies on diagnostic accuracy of hrHPV testing on self- *versus* clinician-samples to predict CIN2+ in healthy subjects (screening population)

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV (%)	NPV (%)
Wright *et al.*[2] (2000)[31]	1,365 healthy subjects (community)	Colposcopy (all women with abnormal results on any tests)	HR HC2	Dacron swab *vs* conical brush	Self: 66	Self: 81	Self: 13	Self: 98
					Clin: 84	Clin: 83	Clin: 17	Clin: 99
					$p = 0.01$			
Belinson *et al.*[2] (2001)[33]	1,997 healthy subjects (community)	Colposcopy (all women)	HR HC2	Dacron swab *vs* cervical brush & plastic spatula	Self: 83	Self: 86	Self: 21	Self: 99
					Clin: 95	Clin: 85	Clin: 23	Clin: 100
Lorenzato *et al.* (2002)[39]	253 high-risk population (screening program)	Colposcopy (all women)	MY09/11 PCR	Vaginal swab *vs* cervical brush	Self: 47	Self: 86	Self: 53	Self: 82
					Clin: 76	Clin: 88	Clin: 69	Clin: 91
					p value < 0.03			
Belinson *et al.*[2] (2003)[34]	8,497 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Vaginal *vs* cervical conical brush	Self: 88	Self: 77	Self: 15	Self: 99
					Clin: 97	Clin: 80	Clin: 18	Clin: 100
					$p < 0.001$	$p = 0.001$		
Salmeron *et al.*[2] (2003)[35]	7732 healthy subjects (screening program)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Dacron swab *vs* cervical conical brush	Self: 71	Self: 89	Self: 9	Self: 100
					Clin: 93	Clin: 92	Clin: 15	Clin:100
Holanda *et al.* (2006)[11]	878 healthy subjects community	Colposcopy and histology (all women)	HR HC2	Vaginal *vs* cervical brush	Self: 88.9	Self: 66.7	NR	NR
					Clin: 88.9	Clin: 72.0		
					p value: 1	p value: 0.056		
Szarewski *et al.* (2007)[36]	920 healthy subjects screening program family planning clinic	Colposcopy (all women with abnormal HPV and/or cytology results and at random (5%) with HPV negative and normal cytology results)	HR HC2	Cotton swab *vs* cervical conical brush	Self: 81	Self: 82	Self: 10	Self: 99
					Clin: 100 (not significant)	Clin: 85 (marginally significant)	Clin: 13	Clin: 100

Table 3. (Continued)

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV (%)	NPV (%)
Qiao *et al.* (2008)[12]	2,388 healthy subjects (community)	Colposcopy (all women)	careHPV	Vaginal *vs* cervical brush	Self: 72.9	Self: 87.7	Self: 15.1	Self: 99.1
					Clin: 84.3	Clin: 87.5	Clin: 16.9	Clin: 99.5
					p value: 0.06 (AUC ROC curve)	*p* value: 0.06 (AUC ROC curve)		
Belinson *et al.* (2010)[40]	2,625 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	HC2	Vaginal *vs* cervical brush	Self: 80.9	Self: 88.6	Self: 11.4[3]	Self: 99.6[3]
					Clin: 97.9	Clin: 90.2	Clin: 15.4[3]	Clin: 100.0[3]
					$p = 0.008$	$p = 0.001$		
Belinson *et al.*[4] (2011)[41]	8,556 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	Cervista and MALDI-TOF assay	Vaginal sample (POI/NIH or brush) *vs* cervical brush	Cervista	Cervista	Cervista	Cervista
					Self: 70.9	Self: 86.1	Self: 7.93	Self: 99.43
					Clin: 95.0	Clin: 90.3	Clin: 14.13	Clin: 99.93
					$p = 0.0001$	$p < 0.001$		
					MALDI-TOF	MALDI-TOF	MALDI-TOF	MALDI-TOF
					Self: 94.3	Self: 87.63	Self: 11.33	Self: 99.93
					Clin: 94.3	Clin: 89.4	Clin: 13.03	Clin: 99.93
					$p = 1.0$	$p < 0.001$		

[1]When reported P values are given. [2]Calculations drafted from the systematic review of Stewart *et al* (2007). [3]Authors calculations. [4]Data on diagnostic accuracy to detect CIN 3+ lesion were reported.
Abbreviations: NR = not reported, Self = self-collected specimen, Clin= clinician-collected specimen.

Table 4. Concomitant studies on diagnostic accuracy of hrHPV testing on self- *versus* clinician-samples to predict CIN2+ in referral population

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV (%)	NPV (%)
Morrison *et al.*[2] (1992)[42]	17 evaluated for abnormal cytology (colposcopy clinic)	Colposcopy (all women)	PCR (11 types)	Lavage *vs* lavage	Self: 100	Self: 14	Self: 54	Self: 100
					Clin: 100	Clin: 29	Clin: 58	Clin: 100
Hillemanns *et al.* (1999)[43]	247 high-risk population (colposcopy clinic)	Colposcopy (all women)	HR HC2	Vaginal *vs* cervical brush	Self: 92	Self: 62[3]	Self: NR	Self: NR
					Clin: 92 (NS)	Clin: 72[3]	Clin: NR	Clin: NR
Sellors *et al.*[2] (2000)[32]	200 women (colposcopy clinic)	Colposcopy (all women)	HR HC2	Vaginal (1), vulvar (2) swab, urine specimen (3) *vs* cervical brush	Self (1): 86	Self (1): 54	Self (1): 43	Self (1):91
					Self (2): 62	Self (2): 63	Self (2): 40	Self (2): 80
					Self (3): 45	Self (3): 70	Self (3): 38	Self (3): 76
					Clin: 98	Clin: 52	Clin: 46	Clin: 99
Nobbenhuis *et al.*[2] (2002)[26]	71 women (colposcopy clinic)	Colposcopy (all women)	HR GP5+/6+ PCR	Lavage *vs* cervical brush	Self: 81	Self: 68	Self: 70	Self: 79
					Clin: 91	Clin: 42	Clin: 58	Clin: 84
Garcia *et al.*[2] (2003)[23]	334 women[4] (colposcopy clinic)	Colposcopy (all women)	PGMY09/11 PCR	Vaginal brush *vs*. cervical brush	Self: 49	Self: 73	Self: 44	Self: 77
Seo *et al.*[5] (2006)[44]	118 women evaluated for abnormal cytology (hospital)	Colposcopy (all women)	HPVDNAChip	Vaginal swab *vs*. cervical brush	Self: 90.5	Self: 29.0	Self: 41.3	Self: 84.6
					Clin: 88.1	Clin: 32.9	Clin: 42.1	Clin: 83.3
Daponte *et al.* (2006)[45]	137 women evaluated for abnormal cytology (colposcopy clinic)	Colposcopy (all women)	HPV 16 PCR	Vaginal cytobrush *vs* cervical cytobrush (device not reported)	Self: 67.4[6]	Self: 84.6[6]	Self: 82.9[6]	Self: 70.2[6]
					Clin: 72.1[6]	Clin: 87.2[6]	Clin: 86.1[6]	Clin: 73.9[6]
Brink *et al.* (2006)[27]	64 women evaluated for abnormal cytology and 32 healthy volunteers (gynecologic clinic)	Colposcopy (all referral women plus cytology + volunteers)	HR GP5+/6+-PCR	Cervico-vaginal lavage *vs* cervical brush	Self: 92	Self: 46	Self: 52[3]	Self: 90[3]
					Clin. 95	Clin: 46	Clin: 55[3]	Clin:93[3]
					p value: 1.0	$p = 1.0$		

Table 4. (Continued)

Study	Participants and setting	Reference standard	HPV test	Method (self *vs* clinician)	Sensitivity[1] (%)	Specificity[1] (%)	PPV (%)	NPV (%)
Bhatla *et al.* (2009)[37]	546 symptomatic women (gynecological clinic)	Colposcopy (all women)	HR HC2 and PGMY09/11 PCR	Vaginal *vs* cervical brush (PCR or HC2)	*PCR*	*PCR*	*PCR*	*PCR*
					Self: 82.5	Self: 93.6	Self: 52.4	Self: 98.4
					Clin: 87.5	Clin: 93.2	Clin: 52.2	Clin: 98.9
					HC2	*HC2*	*HC2*	*HC2*
					Self: 80.0	Self: 88.1	Self: 36.4	Self: 98.1
					Clin: 90.0	Clin: 91.7	Clin: 48.0	Clin: 99.1
Twu *et al.*[5] (2011)[46]	252 women evaluated for abnormal cytology or abnormal colposcopy (colposcopy clinic)	Colposcopy (all women)	MY11/MY09 nested GP5+/ 6+ PCR	Vaginal *vs* cervical brush	Self: 75.0	Self: 75.8[3]	Self: 17.4[3]	Self: 97.8[3]
					Clin: 87.5	Clin: 73.7[3]	Clin: 18.4[3]	Clin: 98.9[3]
					$p = 0.48$			
Dijkstra *et al.* (2012)[38]	135 symptomatic women (gynecologic clinic)	Colposcopy (all women)	HR GP5+/ 6+-PCR	Vaginal *vs* cervical brush	Self: 93.0	Self: 51.1	Self: 47.1[3]	Self: 94.0[3]
					Clin: 90.7	Clin: 51.2	Clin: 46.4[3]	Clin: 92.2[3]

[1]When reported *p* values are given. [2]Calculations drafted from the systematic review of Stewart *et al.* (2007). [3]Authors calculations. [4]population not clear. [5]Data on diagnostic accuracy to detect CIN 3+ lesion were reported. [6]Reported for CIN 2 and CIN 3 lesions, not carcinomas.
Abbreviations: Self = self-collected specimen, Clin = clinician-collected specimen, NR = not reported, NS = not significant.

Table 5. Attendance rate by offering hrHPV self-sampling to non-attendees of cervical screening programs

Study	Participants and setting	Age	Study design	Method (self *vs* clinician)	Attendance rate[1]
Bais *et al.* (2007)[14]	Developed country (NL)	30–50 years	Self-sampling *vs* recall letter: 9:1	Self-sampling (VibaBrush) at home *vs* ecall letter for cervical smear	Self: 34.2%
	2,830 non-responders of the regular screening program				Recall letter: 17.6%
					$p < 0.001$
Sanner *et al.* (2009)[15]	Developed country (SE)	30–58 years	Self-sampling (no control group)	Self-sampling (Qvintip) on demand	Self: 39.1%
	2,829 non-responders of the regular screening program				
Gök *et al.* (2010)[16]	Developed country (NL)	30–60 years	RCT	Self-sampling (Delphi Screener) at home *vs* recall letter for cervical smear	Self: 27.5%
	28,073 non-responders of the regular screening program		Self-sampling *vs* recall letter: 99:1		Recall letter: 16.6%
					$p < 0.001$
Gök et al. (2012)[17]	Developed country (NL)	30–60 years	RCT	Self-sampling (VibaBrush) at home *vs* recall letter for cervical smear	Self: 30.8%
	26,409 non-responders of the regular screening program		Self-sampling *vs* recall letter: 99:1		Recall letter: 6.5%
					$p < 0.001$
Virtanen *et al.* (2011)[18]	Developed country (FI)	30–60 years	RCT	Self-sampling (Delphi Screener) at home *vs* recall letter for cervical smear	Self: 29.8%
	4,160 non-responders of the regular screening program		Self-sampling *vs* recall letter: 1:2.7		Recall letter: 26.2%
					$p = 0.02$[2]
Virtanen *et al.* (2011)[19]	Developed country (FI)	30–60 years	RCT	Self-sampling (Delphi Screener) at home *vs* recall letter for cervical smear[3]	Self: 31.5%
	8,699 non-responders of the regular screening program		Self-sampling *vs* recall letter: 1:2.7		Recall letter: 25.9%
					$p < 0.001$[2]
Szarewski *et al.* (2011)[20]	Developed country (GB)	25–64 years	RCT	Self-sampling (cotton swab, Qiagen) at home *vs* recall letter for cervical smear	Self: 10.2%

Table 5. (Continued)

Study	Participants and setting	Age	Study design	Method (self *vs* clinician)	Attendance rate[1]
	3,000 non-responders of the regular screening program		Self-sampling *vs* recall letter: 1:1		Recall letter: 4.5%
					$p < 0.001$
Giorgi Rossi *et al.* (2011)[22]	Developed country (IT)	35–64 years	RCT Randomly assigned:	Self-sample (Delphi Screener):	Self:
	2,480 non-responders of the regular screening program		Self-sample:	1. sent at home	1. sent to home address: 19.6%
			1. HPV-test sent to home address	2. on demand	2. on demand: 8.7%
			2. HPV-test on demand	*vs*	Recall letter:
			Recall-letter:	Recall-letter	3. Cytology clinic: 13.9%
			3. Cytology clinic	3. Cytology at clinic	4. HPV-test clinic: 14.9%
			4. HPV-test clinic	4. HPV-test at clinic	*p*-value *vs* cytology clinic:
					p (1 *vs* 3) = 0.007[2]
					p (2 *vs* 3) = 0.004[2]
					p (4 *vs* 3) = 0.6[2]
					p-value *vs* HPV-test clinic:
					p (1 *vs* 4) = 0.03[2]
					p (2 *vs* 4) = 0.0006[2]
Wikström *et al.* (2011)[21]	Developed country (SE)	39–60 years	RCT	Self-sampling (Qvintip) at home *vs* recall letter for cervical smear	Self: 39.0%
	4,060 non-responders of the regular screening program		Self-sampling (n = 2,000) *vs* recall letter (n = 2,060)		Recall letter: 9.0%
					$p < 0.001$

[1]When reported *p* values are given. [2]Authors calculations (X^2-test). [3]Data of self-sampling *vs* recall letter for cervical smear are given in this table (=second intervention), third intervention not described in this table.
Abbreviations: Self = self-collected specimen, NL = the Netherlands, SE = Sweden, FI = Finland, GB = United Kingdom, IT = Italy, RCT = randomized-controlled trial.

Comparison in a screening setting

Amongst the studies performed with hrHPV Hybrid capture 2 (HC2) in which at least women with abnormal hrHPV and/or cytology results were referred for colposcopy, Wright *et al.*[31] measured CIN2+ yields in 1,365 women (with complete tests) of whom a vaginal sample with a Dacron swab and a clinician-collected cervical smear sample were tested by hrHPV HC2 and cytology, respectively. Sensitivity for CIN2+ of the hrHPV self-test (*i.e.*, 66.1%) was equivalent to that of cytology at ASCUS (*i.e.*, 67.9%) threshold, but higher when compared to cytology at low-grade squamous intraepithelial lesion (LSIL) as threshold (*i.e.*, 60.7%). Specificity of the hrHPV self-test (81.4%) was lower than that of cytology at both ASCUS (86.4%) and LSIL threshold (95.9%). Salmeron *et al.*[35] compared sensitivity for CIN2+ of hrHPV HC2 on vaginal swabs with clinician-obtained cytology at ASCUS threshold and showed a higher sensitivity (71.3% *versus* 59.4%) but lower specificity (89.2% *versus* 98.3%) of the hrHPV self-test compared to cytology. Belinson *et al.*[34] compared in 8,497 women CIN2+ yield by hrHPV HC2 on a self-collected vaginal brush with cytology performed on LBC material derived from a cervical brush sample taken by a clinician 3–16 months later. Sensitivity of the hrHPV self-test exceeded that of LBC at LSIL threshold (87.5% *versus* 78.4%; $p = 0.001$) and was similar to cytology at ASCUS threshold (*i.e.*, 88.3%; $p = 0.815$). The specificity of the hrHPV self-test for CIN2+ was lower than that of LBC at both ASCUS (77.2% *versus* 81.2%; $p < 0.001$) and LSIL threshold (93.2%). Particularly, the sensitivity of the hrHPV self-test for CIN2+ relative to that of LBC differed from that found in a previous large study performed by these investigators[33] in which vaginal Dacron swabs instead of brush samples were collected. In the swab sample study, the hrHPV self-test had a significantly lower sensitivity for CIN2+ than LBC at the ASCUS threshold (82.6% *versus* 94.2%; $p < 0.025$). Most likely, this difference reflects a worse performance of hrHPV HC2 on swab compared to brush samples, probably because of lower cell yields in swab samples. Recently, a pooled analysis was performed using individual patient data from five cervical screening studies in China.[47] In total 13,140 participants were screened using LBC, visual inspection with acetic acid (VIA), physician-collected HPV testing and self-sampled HPV-testing.[33,34,40] Self-sampled HPV testing had a significantly higher sensitivity (86.2% *vs.* 80.7%), but lower specificity (80.7% *vs.* 94.0%) than LBC at the ASCUS threshold for the detection of CIN2+ lesions. Szarewski *et al.*[36] described the application of self-sampling with a cotton swab followed by hrHPV HC2 testing on 920 women attending routine cervical screening by conventional cytology. In this study, the sensitivity of the hrHPV self-test was similar to that of conventional cytology at a mild dyskaryosis (LSIL) threshold (both 81.0%), whereas the specificity was lower (82.0% *versus* 96.2%).

In a community-based, randomized equivalence trial in a low resource area in Mexico, 25,061 women were randomly allocated to one of the two interventions: HPV testing on self-collected vaginal samples taken with a conical shaped brush at home or cytology on cervical samples taken by cytobrush and wooden spatula in a local clinic. HPV self-testing was 3.4 times more sensitive than cytology for CIN2+ lesions. However, self-sampled HPV testing revealed a much higher number of false-positive results compared to cytology at the threshold "any suspected dysplasia or cancer" (positive predictive value (PPV): 12.2% *versus* 90.5%).[13]

Comparison in a referral population

In a study on 546 women attending a gynecologic outpatient clinic, hrHPV HC2 self-test on vaginal brush samples displayed a sensitivity for CIN2+ of 80.0%; for cytology on the corresponding clinician samples these figures were 77.5% and 70.0% at ASCUS and LSIL threshold, respectively. The specificity for CIN2+ of self-sampled hrHPV was similar to that of cytology at ASCUS threshold (88.1% *versus* 87.3%).[37]

A good performance of hrHPV self-testing compared to cytology was also demonstrated in studies conducted with consensus hrHPV GP5+/6+-PCR. In a recent study performed on a referral population of women visiting a gynecologic outpatient clinic ($n = 135$), hrHPV GP5+/6+-PCR testing on vaginal brush samples resulted in a sensitivity for CIN2+ of 93.0% (specificity: 51.1%), against a sensitivity of cytology (ASCUS threshold) of 90.7% (at a specificity of 28.3%)[38] (unpublished results). A similar good performance of hrHPV GP5+/6+-PCR testing was earlier found in a study using cervico-vaginal self-samples collected by the Delphi screener.[27]

Collectively, these data indicate that hrHPV testing on self-sampled specimens is at least as, if not more, sensitive for CIN2+ as cytology on clinician-obtained cervical smears, though often less specific. Most likely, this specificity reduction of hrHPV tests largely reflects the detection of transient hrHPV infections and hrHPV infections which have not yet progressed to CIN2+. Moreover, in a number of studies the lower specificity of HPV self-sampling can partly also be attributed to the detection of vaginal infections (typically with low-risk HPV types that to some degree are detected by hrHPV HC2 due to cross-reactivity).[48,49]

Furthermore, the impression exists that the studies performed with brush-based and lavage-based self-collection devices show an increased sensitivity for CIN2+ compared to those performed with swab- or tampon-based self-collection. This argues for the use of collection methods that ensure sufficient cell yield to allow reliable HPV detection, particularly when using a non-target amplification method like HC2. The use of a clinically proven combination of self-collection device and hrHPV test should be considered to ensure sufficient clinical performance. Further research and a meta-analytic pooling may provide further evidence.

Comparison of the Accuracy of HPV Testing on Self-*Versus* Clinician-Collected Samples for Detecting CIN2+

Twenty-one studies have addressed the clinical performance to detect CIN2+ of hrHPV testing on self-samples *versus*

clinician-taken smears. These comprise 10 studies on screening and 11 studies on referral populations, as summarized in Tables 3 and 4, respectively. Almost all studies were cross-sectional, and no randomized trials have been performed thus far.

The detection of CIN2+ by hrHPV testing on self- *versus* clinician sampling displayed substantial variations between studies. Most studies reported the hrHPV self-test being equally or less sensitive for CIN2+ compared to HPV testing on clinician samples, whereas only a few studies reported a higher sensitivity for hrHPV self-sampling.[38,44] However, in most studies no statistical difference in clinical sensitivity of hrHPV self-test *versus* hrHPV testing on clinician-collected samples was found, due to the low number of CIN2+ cases. Only a few studies reported statistically different CIN2+ sensitivities between hrHPV self-sampling and hrHPV testing on clinician-collected samples, *i.e.*, a significantly higher sensitivity obtained with clinician-collected samples (Table 3[47]). Accordingly, a meta-analytical pooling could provide more insight in the true clinical sensitivity for CIN2+ of hrHPV self-sampling relative to that of hrHPV testing on clinician-taken cervical samples.

With respect to clinical specificity, the large majority of studies reported that the CIN2+ specificity of HPV testing on self-samples was equivalent to that of clinician-samples (Tables 3 and 4). However, one must recognize the relatively low sample size of the studies in relation to specificity assessment. A slight specificity reduction in self-collected specimens could be expected given either some cross-reactivity with low-risk HPV types with hrHPV tests such as HC2, or detection of hrHPV present solely in the vagina and not associated with CIN2.[40]

Altogether, the data indicate that HPV testing on self- and clinician-sampled specimens is similarly sensitive with respect to CIN2+ detection. Variations in reported study results likely reflect the use of different collection devices, HPV tests and protocols. For example, in studies that reached equality in sensitivity between self- and clinician-collected samples, the same sampling device was used for self- and clinician-sampling (Table 3: Hillemanns *et al.*[43]: brushes; Holanda *et al.*[11]: brushes; Table 4: Morrison *et al.*[42]: lavages). Amongst the devices that were used in combination with HPV tests that are clinically validated for screening (*i.e.*, HC2 or GP5+/6+ PCR[50]), brushes and lavage-based Delphi screener tend to perform well (Table 4: Hillemanns *et al.*[43]; Brink *et al.*[27] and Dijkstra *et al.*[38]) whereas swabs may be more problematic. On average, a four-fold higher cell yield is obtained from Delphi lavage-based compared to brush-based collection (Verhoef *et al.*, unpublished data). A self-sampling study performed with a cotton tip swab revealed that a substantial number of cervical cancers were missed compared to clinician sampling.[39] One could imagine that such swab samples collect too few cells for reliable HPV analysis.

A recent study that used two different HPV assays has revealed that also the type of HPV test can influence the clinical performance of HPV testing on self-samples.[41] One assay achieved equivalent CIN2+ sensitivity for self- *versus* physician-samples, whereas the other showed a significantly lower sensitivity with self-samples.[41] Therefore, for reaching clinical equivalence in terms of detecting CIN2+ the right combination of self-sampler and validated hrHPV test may be important. A multivariate meta-analytical assessment would be highly beneficial in this area to provide more clear explanations for the variation in the accuracy of HPV testing in self-collected specimens.

Comparison of Screening Attendance by Offering Self-Sampling Versus Clinician Sampling

Because it is known that women who have not been adequately screened are at increased risk of cervical cancer,[51,52] non-attendees of the regular screening program represent an important target population for improving the effectiveness of cervical screening. Self-sampling is regarded as a good alternative to facilitate the screening of women who are reluctant to participate in current screening programs. Data from recent studies indicate that compliance to screening may be improved when offering self-sampling methods for HPV testing to non-attendees.[14–22] An overview of nine studies reporting response rates to self-sampling amongst non-attendees is given in Table 5. Up to 39.1% (range 8.7%–39.1%) of non-attendees of the cervical screening program participated by sending a self-collected sample to the laboratory for HPV testing. In most studies response rate was significantly increased by offering self-sampling for hrHPV testing compared to a recall for regular cytology.[14,16–21]

However, in one Italian study a substantial decrease in participation to self-sampling was found when self-sampling was offered on demand (*i.e.*, opt-in) compared to sending self-sampling devices directly to all non-attendees at their home address (8.7% *versus* 19.6% response; Table 5[22]). Whereas direct sending of self-samplers yielded a participation that exceeded that of a recall invitation for clinician sampling, the participation rate achieved by self-sampling on demand was clearly inferior to that of a recall clinician invitation.[22] Hence, an opt-in approach for self-sampling is not recommended for screening non-attendees. On the other hand, in a study in Sweden in which 2,829 screening non-attendees were offered self-sampling on demand, 56.9% of the women did order a self-sampling device. Although not all these women submitted a self-sample, the response rate was still 39.1%.(Table 5[15]) These differences in response rates, with or without opt-in, likely reflect differences between populations, for example at cultural, religious and education level.[20,22] Indeed, a pooled analysis of two large studies on Dutch non-responders has revealed that the response rate was related to ethnicity.[53] Native Dutch women showed the highest response (32.4%), and amongst immigrant women, those from developed countries responded better than those from developing countries (24.0% *versus* 21.1%). However, of interest was that amongst under- and never screened women who had

been invited in two or more previous screening rounds, never screened women responded better (24.8% *versus* 22.6%). This may have contributed to the fact that CIN2+ yield of self-sampling responders was higher than those of screening participants.[53] Together with the fact that the majority of women included in the abovementioned self-sampling studies were ≥30 years of age, the high rates of acceptance are promising for self-sampling as a public health option.

Further Research

Topics of further research include ways to improve triage testing following a hrHPV-positive self-sample. Since cytomorphology on self-sampled specimens is not an option, women who tested hrHPV-positive on their self-sample are in most current protocols advised to visit a physician for a cervical smear. Although adherence at baseline to cytology triage of hrHPV-positive self-sampling women is generally high (about 90%[16,17]), this approach is unfeasible in under-resourced settings lacking medical services. Application of molecular triage testing (*i.e.*, testing for the presence of CIN2+ disease-related markers by molecular analysis) directly on the self-sampled specimens would be an ideal alternative to select women that need colposcopy. Pilot studies have shown that the detection of promoter hypermethylation of genes involved in cervical carcinogenesis is practicable in self-collected lavage specimens and allows the detection of cervical neoplasia[54] (unpublished data). Therefore, efficacy of molecular triage on self-samples is currently being evaluated against that of triage *via* the general practitioner (*i.e.*, cytology on a physician-taken cervical smear) in a trial approved by the Dutch Health Council.[55] Molecular triage on self-samples opens the possibility for complete women-friendly cervical screening using more objective, molecular methods that are all applicable to the same self-sample.

Conclusions

In conclusion, there is a firm basis for HPV self-sampling in cervical screening, especially in under-resourced areas lacking medical services and for women who are reluctant to participate in screening programs to improve screening coverage and acceptability. This updated comprehensive review of the literature also shows that HPV self-sampling is a promising alternative for screening on clinician samples and improves screening participation rates among non-responders.

HrHPV testing on self-samples appeared at least as sensitive for CIN2+ as cytology or hrHPV detection on clinician-obtained cervical samples, though often less specific. This specificity reduction can be tackled by application of proper triage methods, ideally applicable to the self-sampled specimens. The impression exists that the studies performed with brush- and lavage-based self-collection devices show an increased sensitivity for CIN2+ compared to those performed with swab samples, arguing for the use of collection methods that ensure sufficient cell yield for reliable hrHPV detection. For reaching clinical equivalence in terms of detecting CIN2+ between clinician-collection and self-collection, a certified combination of self-sampler and validated hrHPV test is important. Further data from a meta-analytic pooling will be helpful here. In conclusion, HPV self-sampling appears to be an attractive alternative to screening by clinicians.

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