ARTICLE

Pooled Analysis of a Self-Sampling HPV DNA Test as a Cervical Cancer Primary Screening Method

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Background	Worldwide, one-seventh of cervical cancers occur in China, which lacks a national screening program. By evaluating the diagnostic accuracy of self-collected cervicovaginal specimens tested for human papillomavirus (HPV) DNA (Self-HPV testing) in China, we sought to determine whether Self-HPV testing may serve as a primary cervical cancer screening method in low-resource settings.
Methods	We compiled individual patient data from five population-based cervical cancer–screening studies in China. Participants (n = 13 140) received Self-HPV testing, physician-collected cervical specimens for HPV testing (Physician-HPV testing), liquid-based cytology (LBC), and visual inspection with acetic acid (VIA). Screen-positive women underwent colposcopy and confirmatory biopsy. We analyzed the accuracies of pooled Self-HPV testing, Physician-HPV testing, VIA, and LBC to detect biopsy-confirmed cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) and CIN3+. All statistical tests were two-sided.
Results	Of 13 004 women included in the analysis, 507 (3.9%) were diagnosed as CIN2+, 273 (2.1%) as CIN3+, and 37 (0.3%) with cervical cancer. Self-HPV testing had 86.2% sensitivity and 80.7% specificity for detecting CIN2+ and 86.1% sensitivity and 79.5% specificity for detecting CIN3+. VIA had statistically significantly lower sensitivity for detecting CIN2+ (50.3%) and CIN3+ (55.7%) and higher specificity for detecting CIN2+ (87.4%) and CIN3+ (86.9%) (all *P* values < .001) than Self-HPV testing, LBC had lower sensitivity for detecting CIN2+ (80.7%, *P* = .015), similar sensitivity for detecting CIN3+ (89.0%, *P* = .341), and higher specificity for detecting CIN2+ (94.0%, *P* < .001) and CIN3+ (92.8%, *P* < .001) than Self-HPV testing. Physician-HPV testing was more sensitive for detecting CIN2+ (97.0%) and CIN3+ (97.8%) but similarly specific for detecting CIN2+ (82.7%) and CIN3+ (81.3%) (all *P* values <.001) than Self-HPV testing.
Conclusions	The sensitivity of Self-HPV testing compared favorably with that of LBC and was superior to the sensitivity of VIA. Self-HPV testing may complement current screening programs by increasing population coverage in settings that do not have easy access to comprehensive cytology-based screening.
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Cervical cancer is the third most common cancer afflicting women, with an estimated 530 000 new cases and 275 000 deaths each year (1). Cervical cancer incidence and mortality rates in developed countries have declined via cervical cytology screening campaigns (2). However, more than 85% of the global cervical cancer resides in less-developed countries (2), which generally lack the infrastructure to obtain and store cytology specimens and train cytopathologists to interpret these specimens. Different methods for cervical cancer screening in less-developed countries have been explored, of which the one that is most often recommended is visual inspection with acetic acid (VIA) (2).

As the world's most populous country, with 70% of its population living in rural areas, China accounts for 14% of the world's annual incidence of cervical cancer (75 500 new cases) and 12% of the world's annual mortality from cervical cancer (34 000 deaths)

(1). Cervical cancer screening in China remains opportunistic and is based in cities, whereas rural areas in central China have the highest cervical cancer burden (3). In 2009, the Chinese government launched a cervical cancer prevention program that aims to screen 10 million rural Chinese women using a Pap smear or VIA over a 3-year period (4). However, with an estimated 500 million women in rural areas, China lacks a sufficient number of cytopathologists or trained health-care workers to screen all of these women by Pap smear or VIA, respectively.

Human papillomavirus (HPV) DNA testing has been proposed as an alternative to cytology for cervical cancer screening. Unlike VIA, HPV DNA testing provides highly sensitive, objective, and reliable results based on the presence of high-risk HPV DNA in cervicovaginal samples (5–9). A recent pooled analysis study in China (10) showed HPV DNA testing to be highly accurate

compared with cytology and VIA and concluded that HPV DNA testing could become a primary screening test for the secondary prevention of cervical cancer in developing countries. Historically, HPV DNA has been obtained from cervical specimens collected by a health-care professional during a pelvic speculum examination at a health-care clinic. However, a recent meta-analysis (11) concluded that there was good to very good concordance between self-collected cervicovaginal specimens and physician-directed cervical specimens for HPV DNA detection. Many women may also prefer self-collection compared with physician collection (11–13). Unlike physician-collected specimens, self-collection does not require a speculum examination, health-care professionals or a visit to a clinic because women can self-collect a specimen at home. It may be more practical as an initial screen in low-resource settings. To our knowledge, no large studies exist that analyze the diagnostic accuracy of self-collection with HPV DNA testing (Self-HPV testing) for histologically confirmed cervical precancer and cancer as a primary screening test in developing countries.

To address this gap in knowledge, we performed a pooled analysis of data from more than 13 000 women from five population-based cervical cancer screening studies conducted in rural China. By comparing the diagnostic accuracy of Self-HPV testing with that of physician-collected specimens tested for HPV DNA (Physician-HPV testing), VIA, and liquid-based cytology (LBC), we aim to define the role that Self-HPV testing may play in cervical cancer screening campaigns in China and other low-resource settings worldwide.

Subjects and Methods

The Cancer Institute and Hospital of the Chinese Academy of Medical Sciences (CICAMS, Beijing, China) and Cleveland Clinic (Cleveland, OH) screened women in population-based cross-sectional cervical cancer screening studies from 1999 to 2007. The Human Subjects Review Boards of CICAMS and Cleveland Clinic approved these studies. Eligible women were sexually active, not pregnant, with an intact uterus, and had no history of cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) disease or pelvic radiation. No women had been screened for cervical cancer for at least 5 years before enrollment, and all provided written informed consent. Women included in the pooled analysis all concurrently received HPV DNA testing (Hybrid Capture 2 [HC2] assay; Qiagen, Gaithersburg, MD) for self-collected and physician-obtained samples, LBC, and VIA. The study methods for each individual study have been outlined in detail elsewhere (3,14,15).

Study Populations

Our pooled analysis used individual patient data from five projects in the SPOCCS (Shanxi Province Cervical Cancer Screening Study). Individual study details are shown in Table 1. SPOCCS I and II were conducted in Shanxi province (3,14), whereas SPOCCS III (three projects) extended to also include Xinjiang and Henan provinces (15). In SPOCCS I, all women received colposcopy and biopsy (3). In SPOCCS II and III, women who tested positive for HPV DNA or VIA or had LBC results of atypical squamous cell of undetermined significance (ASC-US) or more severe (ASC-US or more) received colposcopy and biopsy (14,15).

CONTEXTS AND CAVEATS

Prior knowledge
Liquid-based cytology (LBC), visual inspection with acetic acid (VIA), and human papillomavirus (HPV) DNA testing of cervical specimens (physician-collected cervical specimens for HPV testing [Physician-HPV testing]) can be effective to screen for women at high risk for cervical cancer, but all of these methods require medical resources. The authors sought to determine whether HPV testing of self-collection of cervical specimens (Self-HPV testing) could be an accurate screening method for women in low-resource settings.

Study design
More than 13 000 rural Chinese women received Self-HPV testing, Physician-HPV testing, LBC, and VIA. Screen-positive women received colposcopy and cervical biopsies. The accuracy of each screening method to detect biopsy-confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+) was compared.

Contribution
There were 507 (3.9%) women diagnosed with CIN2+, 273 (2.1%) with CIN3+, and 37 (0.3%) with cervical cancer. Patient compliance with Self-HPV testing was high. Self-HPV testing had 86.2% sensitivity and 80.7% specificity for detecting CIN2+ and 86.1% sensitivity and 79.5% specificity for detecting CIN3+. Self-HPV testing was more sensitive and less specific than VIA and LBC but less sensitive and similarly specific compared with Physician-HPV testing.

Implication
Self-HPV testing may be a more effective means than VIA or cytology to provide cervical cancer screening in low-resource settings.

Limitations
In this study, women were instructed by medical professionals on self-sampling procedures, and it remains to be seen whether unsupervised self-sampling would give comparable outcomes. The cost and laboratory requirements of the HPV DNA assay might also be prohibitive in some settings.

From the Editors

Screening Tests

HPV Testing. HPV DNA testing was performed using the high-risk probe of the HC2 test, which detects a pool of 13 high-risk HPV types (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, and HPV68). All women performed self-collection followed by physician-directed sampling according to previously described protocols (3,14,15). The majority (85.2%) of sample processing and laboratory testing was performed at CICAMS in Beijing, China. For primary analyses, HPV DNA positivity was defined according to the manufacturer's recommended positive cut point of 1.0 relative light units per cutoff (1.0 RLU/CO; approximately equal to 1.0 pg DNA per mL), as was used in clinical studies for colposcopy referral (3,5).

Cytology and Visual Inspection. All patients underwent LBC, and the results were graded according to the Bethesda system (16). Almost all studies had cytology read by cytopathologists at CICAMS in Beijing; the exception was SPOCCS III-Xinjiang,

Table 1. Characteristics of pooled studies*

No	Study name	Study year and location	Number screened	Age (y)	Screening tests	Follow-up procedure	Histology or cytology location and review
1	SPOCCS I	1999; Xiangyuan County, Shanxi Province	1997	35–45	HC2 (self, physician), fluorescence test, LBC, VIA, colposcopy	All women received four-quadrant biopsies and ECC under colposcopy.	CICAMS; Blinded International Review
2	SPOCCS II	2001–2002; Xiangyuan and Yangcheng Counties, Shanxi Province	8497	35–50	HC2 (self, physician), LBC, VIA, AFB	Positive VIA, self-test or physician-test for high-risk HPV, or an abnormal AFB, or a positive Pap test (ASC–US or worse): four-quadrant biopsies and ECC.	CICAMS
3	SPOCCS III-(1)	2006; Xiangyuan County, Shanxi Province	884	16–54	HC2 (self, physician), LBC, VIA	(1) Positive VIA or positive self-collected HC2: colposcopy and directed biopsy, ECC if necessary; (2) positive physician-collected HC2 or ASC-H and LSIL+ on LBC: colposcopy and four-quadrant biopsies, ECC if necessary.	CICAMS; Blinded International Review (only histology)
4	SPOCCS III-(2)	2006; Xinmi, Henan Province	879	16–54	HC2 (self, physician), LBC, VIA	Same as SPOCCS III-(1)	CICAMS; Blinded International Review (only histology)
5	SPOCCS III-(3)	2006; Yutian County, Xinjiang Uygur Autonomous Region	883	16–54	HC2 (self, physician), LBC, VIA	Same as SPOCCS III-(1)	CICAMS; Blinded International Review (Histology); People's Hospital of Xinjiang Uygur Autonomous Region; Blinded CICAMS Review (Cytology)
	Total		13 140				

* AFB = Ampersand's fluorescent bio-molecular markers; ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cell of undetermined significance; CICAMS = Cancer Institute of the Chinese Academy of Medical Sciences; ECC = endocervical curettage; HC2 = Hybrid Capture 2; HPV = human papillomavirus; LBC = liquid-based cytology; LSIL+ = low-grade squamous intraepithelial lesion or more severe; SPOCCS = Shanxi Province Cervical Cancer Screening Study; VIA = visual inspection with acetic acid.

where cytology was read on-site by local pathologists and reviewed by senior cytopathologists at CICAMS. Unpublished internal analyses showed the sensitivity and specificity of SPOCCS III-Xinjiang cytology to be comparable to those of other sites (data not shown). Trained Chinese gynecologists conducted VIA on all women.

Biopsy. Women who were positive for any screening test in SPOCCS II and III and all women in SPOCCS I underwent colposcopy. Directed biopsy using a 2-mm brochoscopy biopsy instrument was taken from all visible cervical lesions. When the four-quadrant punch biopsy method was indicated (see Table 1), biopsies were taken at positions of 2, 4, 8, and 10 o'clock.

Verification of Disease Status. This study combined individual data from five studies to estimate pooled sensitivity and specificity for the detection of histological CIN2+ and CIN3+. In most studies, cytology and biopsy slides were read at CICAMS. International pathology experts reviewed 14.8% of cytology and 35.0% of biopsy results and independently assessed them for quality control.

To pool the data, we unified the criteria to verify disease status. The gold standard was histologically confirmed biopsy results. In our study population, the 7449 (56%) of 13 140 women who had no biopsy results, negative Physician-HPV tests, and negative or ASC-US results from LBC were considered to be disease free. This standard was based on findings from the SPOCCS I project that only one women with CIN2+ (1 [0.07%] of 1511 women, 95% confidence interval [CI] = 0.003% to 0.4%) and no women with CIN3+ (0 [0.0%] of 1511 women, 95% CI = 0.0% to 0.2%) were diagnosed among the group of women who had negative Physician-HPV tests and negative or ASC-US results from LBC and had received colposcopy and biopsy (3). One woman who had no biopsy, negative cytology, a positive Physician-HPV test, and negative colposcopy was also categorized as disease negative. Women without biopsy results were considered to have incomplete results if they had the following test results and were therefore excluded from analysis: 1) 17 (0.1%) of 13 140 women with positive Pap tests that indicated presence of low-grade squamous intraepithelial lesion or more severe cytology; 2) seven (0.05%) of 13 140 women with ASC-US Pap tests and positive Physician-HPV tests, and 3)

27 (0.2%) of 13 140 women with positive Physician-HPV tests and negative cytology and missing or positive colposcopy.

Statistical Analysis

This pooled analysis presents the accuracy of Self-HPV testing, Physician-HPV testing, VIA, and LBC to detect CIN2+ and CIN3+. To assess heterogeneity between studies, Q tests and I^2 tests were used. If inter-study heterogeneity was not statistically significant, sensitivities and specificities were pooled by the fixed-effect model using the F distribution method. When inter-study heterogeneity was statistically significant, a random-effect model with normal approximation was used to correct overdispersion. Sensitivities and specificities of these four screening methods were also calculated after stratifying the population by age (15–34, 35–44, and ≥45 years).

Women without biopsy results—including 7450 screen-negative women and 51 screen-positive women—were stratified into subgroups according to Physician-HPV, LBC, colposcopy, Self-HPV, and VIA results to assess whether the established criteria for women without biopsy results affect the accuracy of screening tests. The estimated number of women with CIN2+ and CIN3+ who might have been missed in each subgroup was calculated using the probabilities of CIN2+ and CIN3+ generated from SPOCCS I data as the weights (in SPOCCS I, all women had biopsies). The corrected accuracy was computed with the estimated number of women with CIN2+ and CIN3+.

Forest plots were used to display the variations of sensitivities and specificities in Self-HPV testing among the individual studies and pooled analysis measures. Receiver operating characteristic (ROC) curve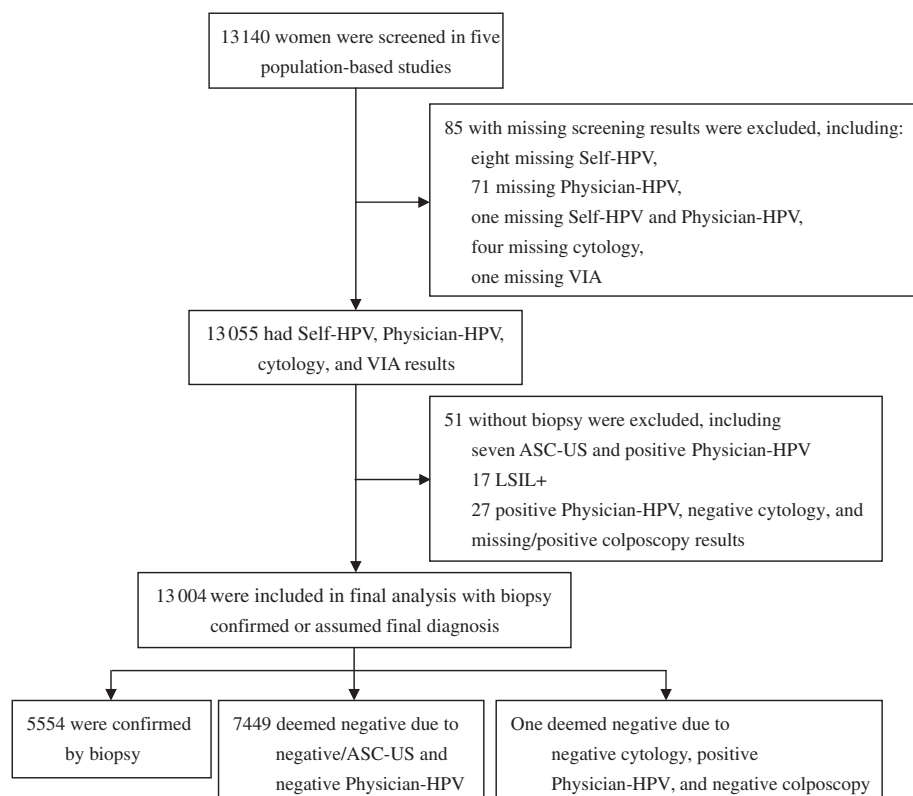s were created to compare the trade-offs in sensitivity and specificity with cutoff values of 1.0 and 2.0 pg/mL. The above pooled analyses on the accuracy of screening methods were performed using Meta-Disc 1.4 (Meta-analysis of Diagnostic and Screening Tests, Version 1.4) (17). The pooled positivity of screening methods was calculated with random-effect models.

Trends in screening method accuracy with age groups were calculated using the Cochran–Armitage trend test. McNemar tests were used to compare paired matching data like the sensitivities, specificities, and fraction of positive results between different tests or positive results between the 1.0 and 2.0 pg/mL cutoff values of the Self-HPV testing. Continuous variables were estimated by calculating the means, medians, and standard deviations. These two statistical analyses were performed using SAS 9.1 (SAS Institute Inc, Cary, NC). All statistical tests were two-sided, with P values less than or equal to .05 considered to be statistically significant.

Results

In total, 13 140 rural Chinese women aged 17–56 years were screened using Self-HPV testing, VIA, Physician-HPV testing, and LBC. None of these women refused to perform self-collection. Of the 13 140 women, eight (0.1%) had Self-HPV testing data missing, 71 (0.5%) had Physician-HPV testing data missing, one (0.01%) had Self-HPV and Physician-HPV testing data missing, four (0.03%) had LBC data missing, and one (0.01%) had VIA data missing; all 85 women with missing data were excluded (Figure 1). Exclusion of an additional 51 women with positive Pap or physician-HPV results, but no biopsy resulted in inclusion of 13 004 women in the final analysis. Of these, 5554 (42.7%) had diagnoses that were

Figure 1. Flow chart of inclusion and exclusion criteria of the study sample. ASC-US = atypical squamous cell of undetermined significance; LBC = liquid-based cytology; LSIL+ = low-grade squamous intraepithelial lesion or more severe; HPV = human papillomavirus; Physician-HPV, physician-collected cervical specimens for HPV testing; Self-HPV = self-collected cervicovaginal specimens tested by HPV DNA testing; VIA = visual inspection with acetic acid.


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13 140 women were screened in five
population-based studies
        │
        │──────► 85 with missing screening results were excluded, including:
        │             eight missing Self-HPV,
        │             71 missing Physician-HPV,
        │             one missing Self-HPV and Physician-HPV,
        │             four missing cytology,
        │             one missing VIA
        ▼
13 055 had Self-HPV, Physician-HPV,
cytology, and VIA results
        │
        │──────► 51 without biopsy were excluded, including
        │             seven ASC-US and positive Physician-HPV
        │             17 LSIL+
        │             27 positive Physician-HPV, negative cytology, and
        │             missing/positive colposcopy results
        ▼
13 004 were included in final analysis with biopsy
confirmed or assumed final diagnosis
   │              │                │
   ▼              ▼                ▼
5554 were    7449 deemed       One deemed negative due to
confirmed    negative due to   negative cytology, positive
by biopsy    negative/ASC-US   Physician-HPV, and negative colposcopy
             and negative
             Physician-HPV
```

confirmed by biopsy. Most women were 35–49 years old (11 140 [85.7%] of 13 004) and had one lifetime sexual partner (9008 [69.5%] of 12 967; 37 with missing data). Nearly all of the women were nonsmokers (12 556 [96.6%] of 12 997; seven with missing data) and married (12 772 [98.3%] of 12 999; five with missing data). Of 13 004 women included in the study, there were 234 (1.8%) diagnosed as CIN2+, 236 (1.8%) as CIN3+, and 37 (0.3%) with cervical cancer.

Test Positivity

We examined the pooled data to determine the percentages of the 13 004 women who tested positive for CIN1, CIN2, and CIN3+ diagnoses with Self-HPV testing, Physician-HPV testing, LBC, and VIA (Table 2). The overall test positivity of LBC (6.0%) was statistically significantly lower than that of the other testing modalities, which ranged from 14.7% for Physician-HPV testing to 16.4% for VIA ($P < .001$). Physician-HPV and Self-HPV testing showed good agreement for HPV testing results ($\kappa = 0.67$ [95% CI = 0.52 to 0.79]; agreement rate = 91.8% [95% CI = 84.9% to 95.7%]) with Self-HPV testing demonstrating greater overall test positivity than Physician-HPV testing (15.6% vs 14.7%; $P < .001$).

Test positivity increased in all screening methods with increasing severity of histopathologic diagnosis. Physician-HPV testing was the most accurate screening method for high-grade lesions ($P < .001$), detecting 95.4% of CIN2 and 97.8% of CIN3+. For CIN2 diagnoses, Self-HPV testing was more likely to test positive than LBC (82.8% vs 72.1%; $P < .001$) but was similarly positive for those with CIN3+ diagnoses (86.1% vs 89.0%; $P = .341$). In comparison, VIA was the least sensitive screening method for identifying women with CIN2 and CIN3+ diagnoses (49.3% and 55.7% positivity, respectively; both $P < .001$).

Sensitivity and Specificity of Screening Tests

We then compared the overall and age-stratified sensitivities and specificities of each testing method for CIN2+ and CIN3+ (Table 3). For Self-HPV testing, the pooled sensitivity was 86.2% for CIN2+ and 86.1% for CIN3+ (Figure 2). The pooled sensitivity for Physician-HPV testing was much higher for CIN2+ (97.0%) and CIN3+ (97.8%) (P values < .001), whereas that of LBC was lower for CIN2+ (80.7%; $P = .015$) and non-significantly higher for CIN3+ (89.0%; $P = .341$). There was no statistically significant variation between age groups in the sensitivities of Self-HPV testing, Physician-HPV testing, and LBC for detecting CIN2+ or CIN3+ lesions. Conversely, the pooled sensitivity of VIA was not

only statistically significantly lower than that of Self-HPV testing for detecting CIN2+ (50.3% vs 86.2%) and CIN3+ (55.7% vs 86.1%) (P values were <.001), but it also decreased statistically significantly in older age groups. For example, the sensitivity of VIA to detect CIN3+ lesions deceased from 75.0% in women aged younger than 35 years to 48.4% in women aged 45 years or older ($P_{trend} = .054$).

Pooled specificity of Self-HPV was the lowest of all testing methods for both less than CIN2 (80.7%) and less than CIN3 (79.5%) (P values were <.001) (Figure 2); furthermore, Self-HPV specificity varied statistically significantly with age, with the highest specificity in women aged younger than 35 years and the lowest in women aged 35–44 years for less than CIN2 ($P_{trend} < .001$) and less than CIN3 ($P_{trend} < .001$). Pooled specificities of Physician-HPV testing had a similar trend. Comparatively, the pooled specificity of VIA for less than CIN2 (87.4%) and for less than CIN3 (86.9%) increased with age ($P_{trend} < .001$) and peaked in women aged 45 years or older. The pooled specificity of LBC was the highest of all testing methods for less than CIN2 (94.0%) and less than CIN3 (92.8%) (P values < .001) and varied with age for less than CIN2 ($P_{trend} = .028$) and less than CIN3 ($P_{trend} = .011$).

We calculated the corrected accuracy of each screening test for CIN2+ and CIN3+ using results from SPOCCS I as weighted controls because women without biopsies in SPOCCS II and III were assumed to be negative or incomplete in uncorrected specificity and sensitivity (Table 4). This statistical analysis detected an additional seven CIN2+ and one CIN3+ lesions, of which five instances of CIN2+ and no instances of CIN3+ were diagnosed in women who were previously categorized as negative. The remainders were from women with incomplete results. Because no screening test had any statistically significant variation between uncorrected and corrected sensitivities and specificities, we focused our data analysis on the uncorrected values. A further sensitivity analysis including the 51 women in the negative biopsy group found no impact on sensitivities and specificities of all tests (data not shown).

We also calculated the sensitivity and specificity for combined screening strategies that used Self-HPV testing as a primary screen. The first combination was for Self-HPV testing–positive women who were referred for follow-up cytology screening. Compared with that of Self-HPV testing or cytology as stand-alone tests, the sensitivity of Self-HPV testing with cytology triage was lower for CIN2+ (71.2% [95% CI = 67.0% to 75.1%]; $P < .001$) and CIN3+ (77.7% [95% CI = 72.2% to 82.5%]; $P < .001$). Conversely, the

Table 2. Pooled data on percentage of women testing positive with Self-HPV, Physician-HPV, LBC, and VIA by the grade of histopathology (HPV DNA positivity: RLU/CO ≥ 1 pg/mL)*

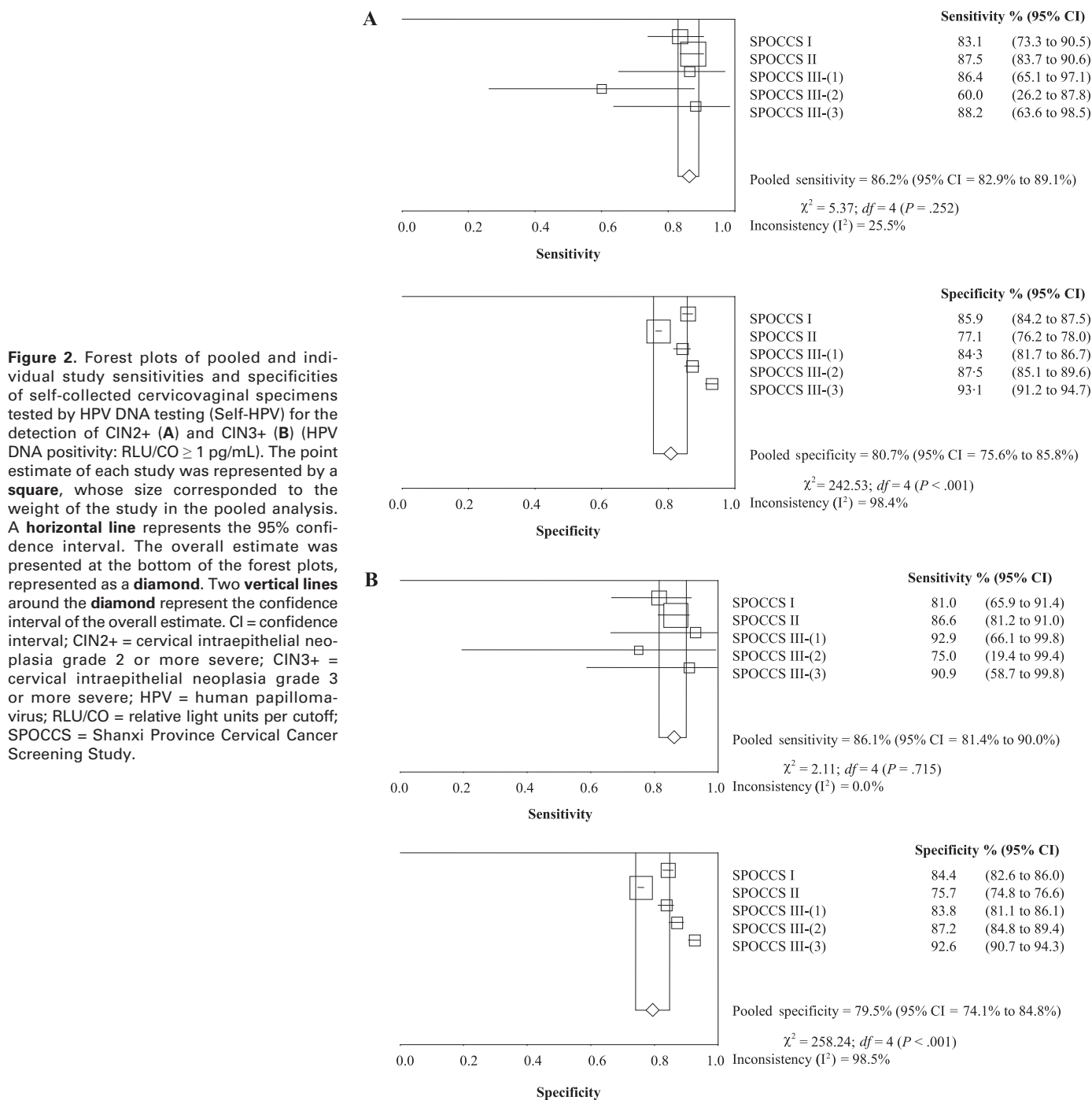| Grade of histopathology	No. of women	Self-HPV, % (95% CI)	Physician-HPV, % (95% CI)	LBC, % (95% CI)	VIA, % (95% CI)
Normal	11 935	10.8 (6.7 to 17.0)	9.3 (6.0 to 14.1)	2.5 (1.6 to 3.9)	13.9 (6.8 to 26.2)
CIN1	562	80.1 (61.0 to 91.1)	80.4 (62.9 to 90.8)	40.3 (28.9 to 52.9)	33.3 (21.7 to 47.3)
CIN2	234	82.8 (72.0 to 90.0)	95.4 (91.7 to 97.5)	72.1 (60.8 to 81.2)	49.3 (35.8 to 63.0)
CIN3+	273	86.1 (81.4 to 90.0)	97.8 (95.3 to 99.2)	89.0 (84.7 to 92.5)	55.7 (45.1 to 66.3)
Total	13 004	15.6 (10.7 to 22.3)	14.7 (10.4 to 20.3)	6.0 (4.1 to 8.8)	16.4 (8.8 to 28.3)

* CI = confidence interval; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe; HPV = human papillomavirus; LBC = liquid-based cytology; RLU/CO = relative light units per cutoff; VIA = visual inspection with acetic acid.

Table 3. Pooled sensitivities and specificities of Self-HPV, Physician-HPV, LBC, and VIA for CIN2+ and CIN3+ by age groups*

Accuracy index and outcome	Age < 35 y		Age 35–44 y		Age ≥ 45 y		All ages		Z_{trend}	P_{trend}†
	Proportion of true positives or negatives detected, No. (%)	95% CI	Proportion of true positives or negatives detected, No. (%)	95% CI	Proportion of true positives or negatives detected, No. (%)	95% CI	Proportion of true positives or negatives detected, No. (%)	95% CI		
Self-HPV (positivity cutoff: RLU/CO ≥ 1 pg/mL)										
Sensitivity										
CIN2+	22/24 (91.7)	(73.0 to 99.0)	285/336 (84.8)	(80.5 to 88.5)	130/147 (88.4)	(78.6 to 98.3)	437/507 (86.2)	(82.9 to 89.1)	0.48	.629
CIN3+	8/8 (100.0)	(63.1 to 100.0)	147/174 (84.5)	(78.2 to 89.5)	80/91 (87.9)	(79.4 to 93.8)	235/273 (86.1)	(81.4 to 90.0)	0.19	.852
Specificity										
<CIN2	1211/1390 (87.1)	(83.1 to 99.1)	6719/8439 (79.6)	(74.8 to 84.4)	2156/2668 (80.8)	(79.3 to 82.3)	10 086/12 497 (80.7)	(75.6 to 85.8)	3.50	<.001
<CIN3	1213/1406 (86.3)	(84.4 to 88.0)	6743/8601 (78.4)	(73.6 to 83.2)	2162/2724 (79.4)	(77.8 to 80.9)	10 118/12 731 (79.5)	(74.1 to 84.8)	3.86	<.001
Physician-HPV (positivity cutoff: RLU/CO ≥ 1 pg/mL)										
Sensitivity										
CIN2+	24/24 (100.0)	(85.8 to 100.0)	324/336 (96.4)	(93.8 to 98.1)	144/147 (98.0)	(94.2 to 99.6)	492/507 (97.0)	(95.2 to 98.3)	0.32	.751
CIN3+	8/8 (100.0)	(63.1 to 100.0)	169/174 (97.1)	(93.4 to 99.1)	90/91 (98.9)	(94.0 to 100.0)	267/273 (97.8)	(95.3 to 99.2)	0.65	.513
Specificity										
<CIN2	1240/1390 (89.2)	(85.0 to 93.5)	6870/8439 (81.4)	(78.2 to 84.6)	2226/2668 (83.4)	(82.0 to 84.8)	10 336/12 497 (82.7)	(78.4 to 87.0)	3.00	.003
<CIN3	1240/1406 (88.2)	(86.4 to 89.8)	6877/8601 (80.0)	(76.6 to 83.3)	2228/2724 (81.8)	(76.1 to 87.3)	10 345/12 731 (81.3)	(76.7 to 85.8)	3.37	<.001
LBC (positivity cutoff: ASC-H and LSIL+)										
Sensitivity										
CIN2+	19/24 (79.2)	(52.6 to 100.0)	268/336 (79.8)	(75.1 to 83.9)	122/147 (83.0)	(75.9 to 88.7)	409/507 (80.7)	(77.0 to 84.0)	0.80	.421
CIN3+	7/8 (87.5)	(47.3 to 99.7)	153/174 (87.9)	(82.1 to 92.4)	83/91 (91.2)	(83.4 to 96.1)	243/273 (89.0)	(84.7 to 92.5)	0.79	.430
Specificity										
<CIN2	1351/1390 (97.2)	(96.2 to 98.0)	7973/8439 (93.3)	(91.9 to 94.7)	2519/2668 (94.4)	(93.5 to 95.3)	11 743/12 497 (94.0)	(92.2 to 95.8)	2.20	.028
<CIN3	1355/1406 (96.4)	(95.3 to 97.3)	7920/8601 (92.1)	(90.5 to 93.6)	2536/2724 (93.1)	(92.1 to 94.0)	11 811/12 731 (92.8)	(90.6 to 94.9)	2.55	.011
VIA (positivity cutoff: AW lesions or growth)										
Sensitivity										
CIN2+	14/24 (58.3)	(42.6 to 74.1)	177/336 (52.7)	(42.2 to 63.1)	64/147 (43.5)	(35.4 to 52.0)	255/507 (50.3)	(40.9 to 59.7)	−2.00	.046
CIN3+	6/8 (75.0)	(34.9 to 96.8)	102/174 (58.6)	(46.2 to 71.0)	44/91 (48.4)	(37.7 to 59.1)	152/273 (55.7)	(45.1 to 66.3)	−1.92	.054
Specificity										
<CIN2	1155/1390 (83.1)	(74.2 to 92.0)	7321/8439 (86.8)	(79.2 to 94.3)	2452/2668 (91.9)	(90.8 to 92.9)	10 928/12 497 (87.4)	(79.5 to 95.4)	−8.64	<.001
<CIN3	1163/1406 (82.7)	(80.6 to 84.7)	7408/8601 (86.1)	(78.6 to 93.7)	2488/2724 (91.3)	(90.2 to 92.4)	11 059/12 731 (86.9)	(78.9 to 94.8)	−8.44	<.001

* ASC-H = atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; AW = acetowhite; CI = confidence interval; <CIN2 = cervical intraepithelial neoplasia grade 2 or less severe; CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe; <CIN3 = cervical intraepithelial neoplasia grade 3 or less severe; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe; HPV = human papillomavirus; LBC = liquid-based cytology; LSIL+ = low-grade squamous intraepithelial lesion or more severe; RLU/CO = relative light units per cutoff; VIA = visual inspection with acetic acid.

† Two-sided, Cochran–Armitage trend test was used to test the age trend.

A

	Sensitivity % (95% CI)	
SPOCCS I	83.1	(73.3 to 90.5)
SPOCCS II	87.5	(83.7 to 90.6)
SPOCCS III-(1)	86.4	(65.1 to 97.1)
SPOCCS III-(2)	60.0	(26.2 to 87.8)
SPOCCS III-(3)	88.2	(63.6 to 98.5)

Pooled sensitivity = 86.2% (95% CI = 82.9% to 89.1%)

$\chi^2 = 5.37$; $df = 4$ ($P = .252$)

Inconsistency (I^2) = 25.5%

0.0   0.2   0.4   0.6   0.8   1.0
Sensitivity

	Specificity % (95% CI)	
SPOCCS I	85.9	(84.2 to 87.5)
SPOCCS II	77.1	(76.2 to 78.0)
SPOCCS III-(1)	84·3	(81.7 to 86.7)
SPOCCS III-(2)	87·5	(85.1 to 89.6)
SPOCCS III-(3)	93·1	(91.2 to 94.7)

Pooled specificity = 80.7% (95% CI = 75.6% to 85.8%)

$\chi^2 = 242.53$; $df = 4$ ($P < .001$)

Inconsistency (I^2) = 98.4%

0.0   0.2   0.4   0.6   0.8   1.0
Specificity

B

	Sensitivity % (95% CI)	
SPOCCS I	81.0	(65.9 to 91.4)
SPOCCS II	86.6	(81.2 to 91.0)
SPOCCS III-(1)	92.9	(66.1 to 99.8)
SPOCCS III-(2)	75.0	(19.4 to 99.4)
SPOCCS III-(3)	90.9	(58.7 to 99.8)

Pooled sensitivity = 86.1% (95% CI = 81.4% to 90.0%)

$\chi^2 = 2.11$; $df = 4$ ($P = .715$)

Inconsistency (I^2) = 0.0%

0.0   0.2   0.4   0.6   0.8   1.0
Sensitivity

	Specificity % (95% CI)	
SPOCCS I	84.4	(82.6 to 86.0)
SPOCCS II	75.7	(74.8 to 76.6)
SPOCCS III-(1)	83.8	(81.1 to 86.1)
SPOCCS III-(2)	87.2	(84.8 to 89.4)
SPOCCS III-(3)	92.6	(90.7 to 94.3)

Pooled specificity = 79.5% (95% CI = 74.1% to 84.8%)

$\chi^2 = 258.24$; $df = 4$ ($P < .001$)

Inconsistency (I^2) = 98.5%

0.0   0.2   0.4   0.6   0.8   1.0
Specificity

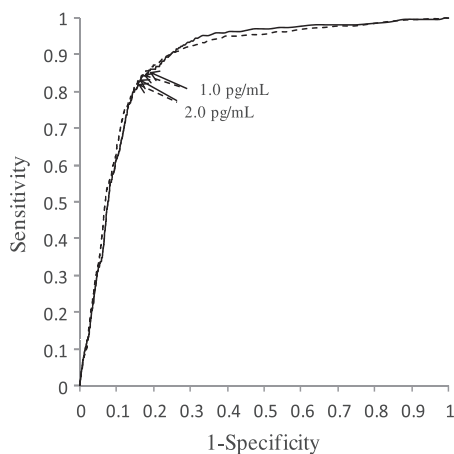**Figure 2.** Forest plots of pooled and individual study sensitivities and specificities of self-collected cervicovaginal specimens tested by HPV DNA testing (Self-HPV) for the detection of CIN2+ (**A**) and CIN3+ (**B**) (HPV DNA positivity: RLU/CO ≥ 1 pg/mL). The point estimate of each study was represented by a **square**, whose size corresponded to the weight of the study in the pooled analysis. A **horizontal line** represents the 95% confidence interval. The overall estimate was presented at the bottom of the forest plots, represented as a **diamond**. Two **vertical lines** around the **diamond** represent the confidence interval of the overall estimate. CI = confidence interval; CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe; HPV = human papillomavirus; RLU/CO = relative light units per cutoff; SPOCCS = Shanxi Province Cervical Cancer Screening Study.

specificity of the combined screening strategy was increased for CIN2+ (95.9% [95% CI = 94.9% to 96.9%]; $P < .001$) and CIN3+ (94.8% [95% CI = 93.5% to 96.1%]; $P < .001$). The colposcopy referral rate for Self-HPV testing with cytology would be 4.8% (95% CI = 3.3% to 6.7%). If Self-HPV testing–positive women were referred for VIA, the sensitivity decreased statistically significantly to 46.2% (95% CI = 37.7% to 54.6%; $P < .001$) for CIN2+ and to 51.3% (95% CI = 41.8% to 60.8%; $P < .001$) for CIN3+. Specificity increased to 97.1% (95% CI = 96.2% to 98.0%; $P < .001$) for CIN2+ and 96.4% (95% CI = 95.4% to 97.5%) for CIN3+. The colposcopy referral rate for this combined strategy would be 4.5% (95% CI = 3.3% to 6.1%).

RLU/CO for Positivity

Increasing cutoffs for Self-HPV test positivity from the standard 1.0 to 2.0 pg/mL decreased the overall test positivity from 15.6% (95% CI = 10.7% to 22.3%) to 13.0% (95% CI = 8.9% to 18.7%) ($P < .001$). Increasing to 2.0 pg/mL only slightly decreased pooled sensitivity from 86.2% (95% CI = 82.9% to 89.1%) to 83.2% (95% CI = 79.7% to 86.4%) ($P < .001$) and increased specificity from 80.7% (95% CI = 75.6% to 85.8%) to 84.0% (95% CI = 79.7% to 88.3%) ($P < .001$) for CIN2+ (Figure 3). Similar patterns were observed for CIN3+ sensitivity (from 86.1% [95% CI = 81.4% to 90.0%] to 84.2% [95% CI = 79.4% to 88.4%]; $P = .06$) and specificity (from 79.5% [95% CI = 74.1 to 84.8%] to 82.8%

Table 4. Uncorrected and corrected HC2 accuracy of Self-HPV, Physician-HPV, LBC and VIA for CIN2+ and CIN3+ (HPV DNA positivity: RLU/CO $\geq$ 1 pg/mL)*

Screening methods	CIN2+		CIN3+	
	Sensitivity, %, (95% CI)	Specificity, %, (95% CI)	Sensitivity, %, (95% CI)	Specificity, %, (95% CI)
Self-HPV				
Uncorrected	86.2 (82.9 to 89.1)	80.7 (75.6 to 85.8)	86.1 (81.4 to 90.0)	79.5 (74.1 to 84.8)
Corrected	85.0 (81.6 to 88.0)	80.8 (80.1 to 81.4)	85.8 (81.1 to 89.7)	79.5 (78.8 to 80.2)
Difference	1.2	−0.1	0.3	0.0
Physician-HPV				
Uncorrected	97.0 (95.2 to 98.3)	82.7 (78.4 to 87.0)	97.8 (95.3 to 99.2)	81.3 (76.7 to 85.8)
Corrected	96.1 (94.1 to 97.6)	82.5 (81.8 to 83.2)	97.8 (95.3 to 99.2)	81.1 (80.4 to 81.7)
Difference	0.9	0.2	0.0	0.2
LBC				
Uncorrected	80.7 (77.0 to 84.0)	94.0 (92.2 to 95.8)	89.0 (84.7 to 92.5)	92.8 (90.6 to 94.9)
Corrected	80.0 (75.8 to 83.0)	93.9 (93.4 to 94.3)	88.8 (84.3 to 92.2)	92.7 (92.2 to 93.1)
Difference	0.7	0.1	0.2	0.1
VIA				
Uncorrected	50.3 (40.9 to 59.7)	87.4 (79.5 to 95.4)	55.7 (45.1 to 66.3)	86.9 (78.9 to 94.8)
Corrected	49.6 (45.2 to 54.0)	87.5 (86.9 to 88.0)	55.6 (49.6 to 61.7)	86.9 (86.3 to 87.5)
Difference	0.7	−0.1	0.1	0.0

* CI = confidence interval; CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe; LBC = liquid-based cytology; HC2 = Hybrid Capture 2; HPV = human papillomavirus; RLU/CO = relative light units per cutoff; VIA = visual inspection with acetic acid.

[95% CI = 78.2% to 87.3%]; $P < .001$). In other words, changing the cut point from 1.0 to 2.0 would decrease the sensitivity of CIN2+ and CIN3+ by 3% and 1.9%, respectively, while increasing the specificity of both CIN2+ and CIN3+ by 3.3%. Thus, if the elevated cut point were applied to the age-standardized female population in China, there would be 72 fewer CIN2+ diagnoses per 100000 women or 25 fewer CIN3+ diagnoses per 100000 women, but false-positive tests would decrease by 3221 per 100000 women with less than CIN2 or by 3257 per 100000 women with less than CIN3.

Discussion

This pooled analysis from China is the largest study worldwide, to our knowledge, to examine the diagnostic accuracy of Self-HPV

Figure 3. ROC curves of self-collected cervicovaginal specimens tested by HPV DNA testing (Self-HPV) for the detection of CIN2+ and CIN3+. **Solid lines** represent detection of CIN2+; **dotted lines** represent detection of CIN3+. CIN2+ = cervical intraepithelial neoplasia grade 2 or more severe; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe; HPV = human papillomavirus; ROC = receiver operating characteristic.

testing as a primary screening tool for CIN2+ and CIN3+ detection. Data were generated in rural women from a less-developed country, where comprehensive cervical cytology screening campaigns are difficult to establish and maintain. Our findings indicate that Self-HPV testing is more sensitive, though less specific, than LBC or VIA and that the sensitivity and specificity of Self-HPV testing moderately agrees with those of Physician-HPV testing.

The pooled Self-HPV sensitivity for CIN2+ in this study (86.2%) was higher than the sensitivities reported for population-based studies of Self-HPV testing in South Africa (66%) [18] and the Americas (49%) [19], but similar to those from the United Kingdom (81%) [20], in a referral population from India (83%) [21], and in young women from the United States (85%) [22]. Discrepancies in observed test sensitivity between studies may be because of differences in sampling methods, population characteristics, diagnostic ascertainment or criteria, or disease burden. Our results were consistent with some previous reports that Self-HPV testing has a lower sensitivity than Physician-HPV testing [11,21,22], but not others [19,23]. The sensitivity of Self-HPV testing may be lower than that of Physician-HPV testing because self-collected samples are less likely to sample cervical lesions [15]. The lower specificity of Self-HPV testing is likely because of the common presence of vaginal HPV [24–26] that is not necessarily associated with CIN2+ [15].

Our finding that Self-HPV testing is more sensitive but less specific than cytology is consistent with previous studies [5,14,21,22]. The specificity of HPV DNA testing decreases with age in our study population, similar to previous reports in China [10], but unlike prior studies in the United States, which show increasing HPV DNA specificity with age [5]. This disparity likely relates to varying patterns of HPV prevalence in these two countries: HPV prevalence peaks in young- and middle-aged women in China [10] but peaks only in young women in the United States [5]. Of note, our cytology results are more sensitive than those previously reported [for CIN2+, 80.7% vs 57% [5] and 53% [27]] because

most of slides were reviewed by expert cytopathologists from CICAMS instead of local pathologists. The costs of LBC and the requirement of qualified cytopathologists may prohibit its use as a screening test without a concomitant increase in CIN2+ detection (28).

One strength of this pooled analysis was that nearly half of the women, any with a positive screening testing, received colposcopy and diagnostic biopsy, including four-quadrant punch biopsies when no suspicious lesion was observed in colposcopy (29). Thus, disease misclassification was minimized (30). Another strength was that the population-based study design determined the feasibility of conducting Self-HPV testing in rural China. Approximately 70% of invited women agreed to participate, and no participants refused to perform self-collection. Almost all women (99.9%) provided a sufficient self-collected sample, consistent with previous studies that found Self-HPV testing to be a satisfactory initial screening method for screened women (12,31,32) as well as for nonattendees of European Pap smear programs (13).

One limitation in our study is that medical professionals instructed participants on self-sampling procedures in clinics. To include women without health-care access, Self-HPV screening campaigns should also offer to deliver self-sampling kits with straightforward instructions to women's homes for unsupervised specimen collection and should then refer HPV-positive women for further management. One study of women living in India concluded that unsupervised collection was impractical because many participants provided inadequate samples (21). However, studies from Western Europe mailed self-collection kits with instructional pamphlets to participants' homes and reported near-perfect specimen collection (33) with 90% adherence to follow-up for women with positive HPV results from self-collection (13). More research is needed to determine an educational intervention that can be sent with self-collection kits to ensure that unsupervised women from low-resource settings will provide adequate samples for HPV DNA testing.

The World Health Organization recommends VIA as a primary screening method in developing countries (2), and a cluster randomized controlled trial in India found VIA to be a technically undemanding, inexpensive screen-and-treat intervention for cervical cancer (34). However, our results have shown that Self-HPV testing is statistically significantly more effective than VIA at detecting CIN2+ and CIN3+ lesions, supporting previous research (35). We also have demonstrated that Self-HPV testing, unlike VIA, provides age-independent sensitivity. A recent study of women living in Tanzania showed that VIA positivity peaks immediately after training and retraining (36), suggesting that the sensitivity of VIA may be practitioner and training dependent. Self-HPV testing provides objective results independent of physician training and women's ages and therefore may prove to be more sustainable than VIA in countries with limited resources for cervical cancer screening.

The HC2 assay's expense, duration of testing, and laboratory requirements may potentially impede the large-scale incorporation of Self-HPV testing in the screening campaigns of low-resource countries (5,37,38). However, a new portable HPV DNA test, *care* HPV, provides results within 2.5 hours and costs one-tenth as much as HC2. Results from *care* HPV testing were found to be comparable to HC2 in sensitivity, specificity, and positive vs negative predictive values, even though *care*HPV testing was conducted in suboptimal laboratory conditions (39). Self-collection with *care*HPV testing may provide the most viable primary screening option in low-resource settings.

Although developed countries use cytology-based cervical cancer screening programs, most developing countries lack a sufficient number of cytopathologists, gynecologists, and medical facilities to support comprehensive cytology screening (2). In these settings, Self-HPV testing could serve as a primary screening test and use of the more specific tests, cytology or HPV genotyping, could be reserved for women who have tested positive by Self-HPV testing and require further management. As shown in this study, cytology could be reserved for the 15% of Chinese women whose Self-HPV testing was positive, allowing the limited number of cytopathologists to focus on high-risk women. Although this study did not directly evaluate a strategy of screening women with Self-HPV testing and triage of positives by cytology, our statistical simulation of this algorithm projected a substantially lower colposcopy referral rate and a moderate loss of sensitivity compared with Self-HPV testing alone, in accordance with previous research (22). We also simulated the performance of VIA on Self-HPV testing–positive women, which substantially improves specificity but worsens sensitivity. This strategy may be beneficial to one-visit screen-and-treat programs in low-resource settings that wish to minimize overtreatment. More research is needed not only to determine how to implement effective Self-HPV testing screening programs but also to determine how to optimize the management of women with positive HPV test results, particularly in low-resource settings (40).

There are important programmatic implications of our study regarding the accuracy of HPV DNA testing on self-collected cervical specimens. A computer-based modeling study (38) showed that it was cost-effective in resource-poor settings, compared with conventional three-visit cytology-based screening, to screen women once in their lifetime between the ages of 35 and 45 years with one or two clinical visits strategies involving VIA or DNA testing for HPV in cervical cell samples. The most cost-effective strategies were those that required the fewest visits. Visual inspection of the cervix requires a pelvic examination with a sterile speculum, and cytology and Physician-HPV testing also require medical professionals to be present to obtain the cervical samples. Although China historically has used minimally trained "barefoot doctors" to provide basic medical care in rural areas, health-care reforms in the 1980s drastically decreased federal funding for barefoot doctors, causing a severe reduction of medical providers and public health efforts in rural China (41). Primary health care is a key and central component of China's health-care reform program, which was announced in 2009 (42). However, many critical challenges, including the lack of qualified personnel, need to be overcome to rebuild a comprehensive health-care system in China. Furthermore, the most medically underserved Chinese women live in remote or mountainous areas with limited access to health care. Thus, even though we found that Physician-HPV testing is more sensitive than Self-HPV testing and others have shown that Self-HPV testing followed by cytology is more cost-effective than Self-HPV testing alone (22), the current shortage of adequately trained medical professionals in China renders the establishment of a

comprehensive physician-dependent cervical cancer screening program infeasible. Although it is not specific enough to be a stand-alone test, Self-HPV testing provides sensitive results without pelvic exams, medical professionals, or health-care facilities and thus has the potential to serve as a primary cervical cancer screening method for women, regardless of their geographic location or access to health care. Limited resources can then be focused on the clinical follow-up of the smaller percentage of women who tested positive. The incorporation of Self-HPV testing in the Chinese government's ongoing cervical cancer screening program would complement the current program by increasing its coverage of unscreened populations, particularly the large number of geographically isolated Chinese women.

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