RESEARCH ARTICLE

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Clinical Performance of Self-collected Specimen HPV-DNA vs Clinician- collected Specimen HPV-mRNA to Detect High-risk HPV and High-grade Cervical Lesions and Cancer

Thannaporn Kittisiam[1], Saranya Chanpanitkitchot[2]*, Siriwan Tangjitgamol[1,3], Sunamchok Srijaipracharoen[1], Sumonmal Manusirivithaya[1], Jatupol Srisomboon[4], Wichai Termrungruanglert[4], Thai Gynecologic Cancer Society Research Group

Abstract

Objective: Self- collected specimens to detect high-risk (hr) HPV and high-grade cervical lesions (CIN2+) has been introduced aiming to increase cervical cancer screening coverage. The performance of self- collected specimen compared to clinician collected specimen is one major concern. This study aimed to compare self-sampling HPV-DNA and clinician-sampling HPV-mRNA to detect hr-HPV and high-grade cervical lesions. **Methods:** Women with abnormal cervical cytology and/ or positive hr-HPV who attended the colposcopy clinics in 10 tertiary hospitals in Bangkok were enrolled. Self-collected specimens were evaluated for HPV DNA using Cobas® 4800 HPV test prior to the clinician-collected specimens which were tested for HPV mRNA with APTIMA® HPV Assay. Subsequent colposcopy with biopsy was performed. The detection rates of hr-HPV from both HPV tests and their performance to detect high-grade lesions pathology were compared. **Results:** Data from 497 women's specimens were analyzed. Both samplings had 86.8% concordance rate in detecting hr-HPV (Kappa 0.670; 95% confidence interval [CI] 0.599-0.746, P value < 0.001). The sensitivity (95% CI) of self-collected specimen HPV DNA and clinician- collected specimen HPV-mRNA to detect high-grade lesions were 91.8% (85.4%-96.0%) and 90.2% (83.6%-94.9%) respectively. The corresponding negative predictive values (95% CI) were 91.9% (85.6%-96.0%) and 91.7% (86.0%-95.7%) respectively. **Conclusion:** HPV DNA testing from self-collected specimen to detect HR-HPV demonstrates high concordance with HPV mRNA testing from clinician-collected specimen. The sensitivity and negative predictive value of both tests to detect high-grade lesions are comparable.

Keywords: Self-collected HPV DNA- clinician-collected HPV mRNA- cervical cancer screening

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Introduction

Cervical cancer is the fourth common cancer in women worldwide [1]. Up to 604000 new cases and 342000 deaths were reported in 2020 and most cases occurred in low- and middle- income countries [1, 2]. In Thailand, cervical cancer is the third most common women cancer with ASIR and mortality rate of 16.4 and 7.4 per 100,000 women-years respectively [1].

Primary prevention with HPV vaccine is the ideal method to reduce the incidence of cervical cancer. However, the vaccination coverages are still low in some countries [3]. Hence, secondary prevention with cervical cancer screening is still the main key to reduce its incidence [4]. Cytologic testing, which was the main method of cervical cancer screening for several decades had been recently replaced by primary HPV testing due to its higher sensitivity to detect cervical cancer.

Not only the high sensitivity of the screening tool, a high coverage of target population to have screening is also crucial for cervical cancer reduction. Despite a wide availability of the screening services by health care providers, one major problem is still encountered. The women, themselves, may not adhere to the screening recommendation. Previous studies in many countries [5, 6] as well as in Thailand [7-9] had revealed many reasons for the non-adherence. This included fear, embarrassment, no time, distance to the service, negligence, or cultural background.

With many reasons of women not to undergo screening

*[1]College of Medicine, Rangsit University,Rajavithi Hospital, Thailand. [2]Department of Obstetrics and Gynecology, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand. [3]Chiang Mai University, Thailand. [4]King Chulalongkorn Memorial Hospital, Chulalongkorn University, Thailand. *For Correspondence: saranya.jibi@gmail.com*

by the physician or in health service unit, self-collected HPV testing might be an alternative option to overcome these barriers and to increase the population to participate with the cancer screening program. In 2020 WHO announced that using self-sampling HPV testing can help to reach a global target of 70% coverage of screening by 2030 [10].

One major concern of self-collected specimen HPV testing is the efficacy to detect high-risk HPV (hr-HPV) and pre-invasive cervical lesions comparing to health-care worker collection. Some previous studies had shown a good correlation of self- and clinician-collected specimen to detect hr-HPV [11, 12]. However, those studies focused on the HPV DNA testing.

From the evidence that detection of high-risk HPV E6 and E7 mRNA might be specific than detection of HPV DNA. Some authors reported similar sensitivity and slightly higher specificity of HPV messenger RNA (HPV mRNA) and HPV DNA testing to detect high-grade cervical intraepithelial neoplasia or more severe lesions [13]. In 2021, WHO has suggested HPV mRNA detection using samples taken by the health-care provider as a primary screening test [14].

However, data comparing the performance between self- collected specimen HPV-DNA vs clinician- collected specimen HPV-mRNA are still limited. This study aimed to compare the performance of self-collected specimen HPV-DNA vs clinician-collected specimen HPV-mRNA to detect hr-HPV and high-grade cervical lesions and cancer (High-grade squamous intraepithelial lesion or worse: CIN 2+).

Materials and Methods

Study population and study design

This study was approved by the Central Research Ethics Committee of Thailand (COA-CREC082/2021). A multicenter prospective trial collaboration of 10 institutes in Thailand which was conducted under the support of the Thai Gynecologic Cancer Society (TGCS). This study was one among the large project along with a few other studies with other objectives.

The study population included women aged ≥ 18 years who attended colposcopy clinic due to abnormal cervical cytology and/or abnormal HPV testing during October 2021- May 2022. The exclusion criteria were women who were pregnant, diagnosed with cervical cancer, previous treatment with hysterectomy, radiation therapy or chemotherapy, had active bleeding or used vaginal douching within 48 hours before collecting the specimen. The process of study conduct is shown in Figure 1

Specimen collection

Self-collected specimen and HPV DNA testing

The purpose of the study was explained to each woman who met inclusion criteria. After obtaining written informed consent, the process of self-collected specimen was described to the participants by a research assistant along with manufacturer's illustrated instructions and a video demonstration. The self-collected specimen procedure was performed in a separate room using self-collected specimen tools from the Aptima multitest swab specimen collection Kit (Hologic, Inc., San Diego, CA, USA).

HPV-DNA testing was analyzed using Cobas 4800 HPV. The Cobas 4800 HPV test (Roche Diagnostic Inc., Thailand) is an automated, real time PCR to detect 14 high risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). The result demonstrates positive high-risk HPV (genotype 16, 18 and other high-risk HPV) and negative HPV.

Clinician-collected specimen and HPV mRNA testing

The clinician who performed colposcopy collected the cervical sampling using ThinPrep specimen collection kit for mRNA testing (Aptima® HPV assay ®, Hologic, Inc., USA).

Clinician-collected specimen collection was analyzed using Aptima mRNA assay (Aptima® HPV assay ®, Hologic, Inc., USA). The APTIMA is a diagnostic kit using transcription mediated amplification to detect E6/E7 mRNA from HPV. The result demonstrates positive high-risk HPV (genotype 16, 18, 45 and other high-risk HPV) and negative HPV.

Colposcopy and cervical tissue collection

After the clinician specimen collection, colposcopy, and cervical biopsy with or without endocervical sampling were performed. Tissue obtained were sent to pathologic laboratory of each institution for histopathological analysis.

Data collection and Statistical analysis

Data collected were: baseline characteristics, history of cervical cancer screening, the results of HPV tests, and subsequent histopathology. Statistical analyses using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corporation, Armonk, NY, USA) were carried out. A p-value of < 0.05 was considered as statistically significant. Cohen's Kappa coefficients was calculated to evaluate the agreement between two sampling collection method. The scale to express the strength of the agreement were as follow: 0.00-0.20 (low), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial) and ≥ 0.81 (almost perfect).

Results

Overall, 500 participants were accessed for eligibility. Except one whose age was under 18 years old, a total of 499 participants were enrolled in the study. Five of them were further excluded: 2 had missing of socio-economic characteristic feature, 1 had hysterectomy and 2 had history of cervical cancer. A total of 494 participants had vaginal self-collected specimen and were included for the analysis.

The mean age of 497 women was 39.28 + 11.36 years. 335 of them (67.4%) were married. 353 (71.0%) have education bachelor's degree or higher and 326 women (65.6%) have family income over 24,000 THB per month (672 USD) (Table 1). 424 women (85.8%) are in pre-menopause status. Only 6 (1.2%) of them never

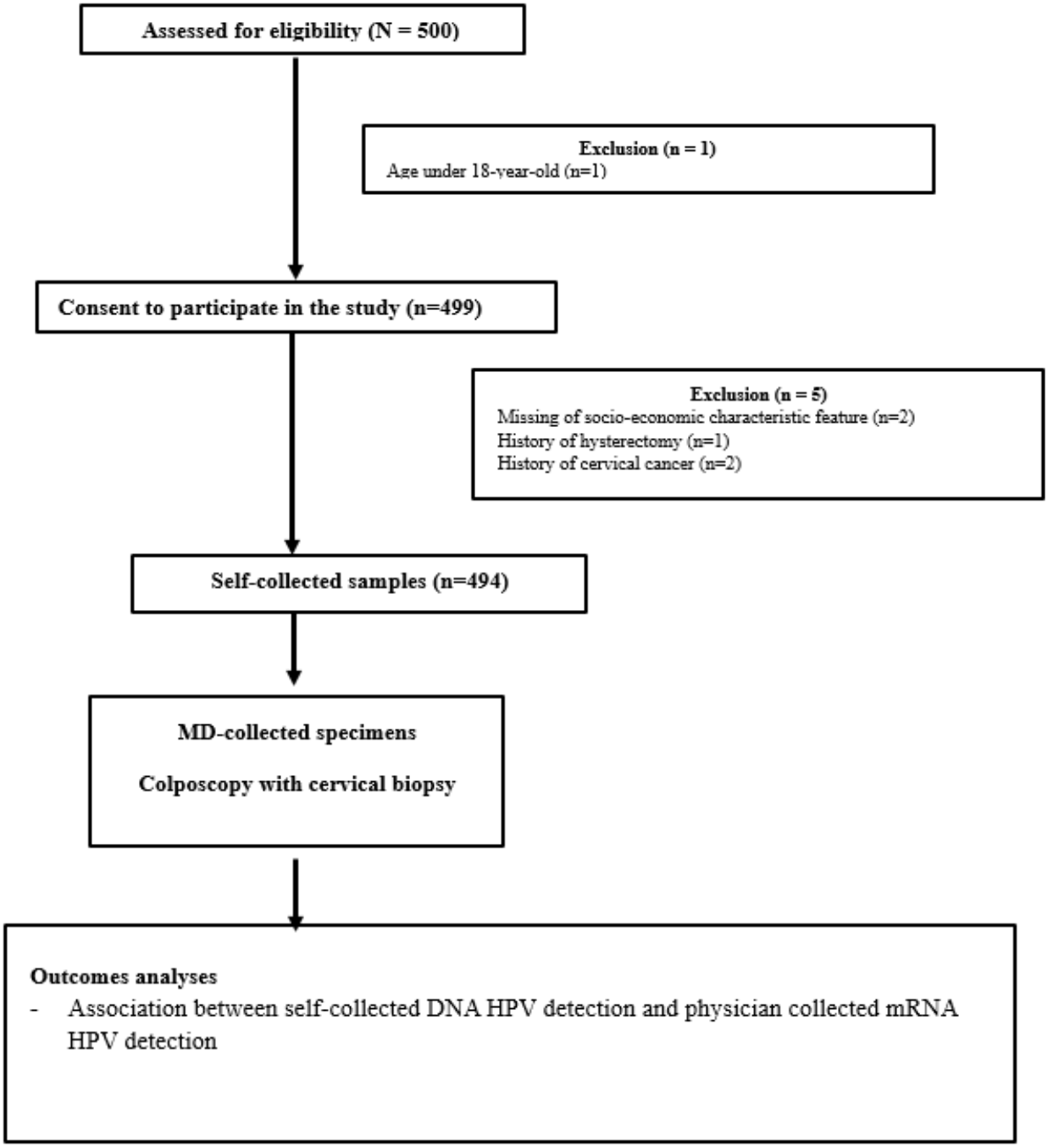

Figure1. Enrollment of 500 Women who had Abnormal Cervical Cancer Screening Test and were Scheduled to Undergo Colposcopy

had sexual activity. The most used method was oral contraceptive pills (162 women or 32.8%) among 330 women (66.4%) ever use any methods of contraception. Of note, 436 women (87.7%) had never received HPV vaccination, whereas 72% were still sexually active (Table 2) Among 70.0% who had ever had cervical cytology testing, 22.7% had history of abnormal cervical cytology. On the other hand, out of 21.7% who ever had HPV testing 15.3% had HR-HPV detected. We found 149 (30.0%) and 389 women (78.3%) had never had cervical cancer screening or particularly HPV assays respectively. Among 91 (18.3%) women who reported history of abnormal cervical lesions, 61 women (12.3%) were diagnosed CIN1/LSIL/HPV effect (Table 3).

The indication for colposcopy included abnormal cytology and/or positive HVP test. Abnormal cervical cytology in 142 women were: ASC-US/ASC-H/AGC. 60 women (12.1%) were presented with hr-HPV test without cervical cytology.

The diagnostic analysis of 494 matched specimen were analyzed. The results of self-sampling HPV-DNA (Cobas® 4800 HPV) and clinician-collected specimen HPV-mRNA (APTIMA® HPV) were shown in Table 4. The prevalence of positive hr-HPV from self-collected specimen HPV-DNA and clinician-collected specimen HPV-mRNA were 369 (74.7%) and 348 (70.4%)

Table 1. Socio-economic Characteristic Features of Women in the Study (N = 497)

Characteristics	N	Percent
Age group, mean age ± SD (years)	39.28 ± 11.36	
≤40	280	56.4
41-60	191	38.4
>60	26	5.2
Marital status		
Single	128	25.8
Married	335	67.4
Separate/divorces	34	6.8
Education level		
Up to primary level	42	8.5
High school/ Diploma	102	20.5
Bachelor's degree	286	57.5
Master's degree and higher	67	13.5
Family monthly income (USD)		
≤ 672 (<24,000 THB)	171	34.4
>673-1570 (>24,000-50,000 THB)	202	40.6
> 1570 (>50,000 THB)	124	25.0
Occupation		
Unemployed/ Student/ Housewife	94	18.9
Employee	166	33.4
Personal business	86	17.3
Government officer	141	28.4
Others	10	2.0

Table 2. General and Gynecologic Health History (N = 497)

Characteristics	N	Percent
Menstrual status		
Pre-menopause	424	85.3
Post-menopause	73	14.7
Sexual activity		
Never	6	1.2
Ever, not active for 1 year	133	26.8
Still active within the past year	358	72.0
Parity, median (range)	1	(0-2)
Contraception		
Never	167	33.6
Ever use*	330	66.4
OCPs	162	32.6
Condom	90	18.1
DMPA/ implant	49	9.9
TR	34	6.8
Coitus interruptus	15	3.0
IUD	4	0.8
Vasectomy	4	0.8
HPV vaccination		
No	436	87.7
Yes	61	12.3

respectively. The overall agreement between self-collected specimen HPV-DNA and clinician-collected specimen HPV-mRNA was 86.8%, k=0.670, 95% CI, 0.599-0.746: P value < 0.001 for hr-HPV detection (Table 5).

The histologic outcomes according to HPV results are shown in Table 6. Almost all clinician-collected specimen HPV negative mRNA, 91.8% revealed less than CIN2 lesion from histology and 32.2% of HPV positive mRNA revealed histological high grade cervical lesion (CIN2+). Furthermore, 92% of HPV negative self-collected specimen HPV-DNA reveal low grade cervical lesion (normal, inflammation or CIN1) and 30.8% of HPV-positive individuals showed high-grade pathology from colposcopic biopsy. The clinical performance for HPV assays to detect high grade cervical pathology are shown in Table 7. The sensitivity (95% CI) of self-collected specimen HPV DNA and clinician-collected specimen HPV-mRNA to detect CIN2+ were 91.8% (85.4%-96.0%) and 90.2% (83.6%-94.9%) respectively. The corresponding negative predictive value (95% CI) to exclude CIN2+ was 91.9% (85.6%-96.0%) and 91.7% (86.0%-95.7%) respectively.

Discussion

There are five HPV assays which have been approved by US-FDA as HPV screening: Hybrid CaptureII, Cervista, Cobas, Aptima and BD Onclarity [15]. Technology to detect high-risk HPV includes DNA-RNA hybridization, signal amplification and PCR based which detected hr-HPV DNA. To date, Aptima is only HPV assays to detected viral mRNA (E6/E7) which is transcriptional active virus which seems more specific to high grade cervical lesion [15]. The systematic review and meta-analysis demonstrated slightly higher specificity (1.03 [95%CI: 1.02-1.04]) of mRNA HPV testing over HPV DNA testing for detection of CIN2+ with similar sensitivity (0.98 [95%CI: 0.95-1.01]) [16]. Cumulative detection rates of high-grade cervical lesion after negative mRNA or negative DNA screening were also comparable [16]. Currently, the mRNA HPV test for cervical cancer screening was approved and recommended by WHO in 2021.

Previous studies reported that vaginal self-collected specimen technique could increase participation of women in cervical cancer screening [17, 10, 18]. Regarding the clinical performance of self-collected specimen, the results comparing to the clinician-collected specimen were still controversial. The accuracy of self-collected specimen HPV testing was validated against clinician-collected specimens across different settings [19- 25]. The difference might lie on multiple factors such as attitude of the women, collection technique, performance of the test, and laboratory logistics of the specimen. The meta-analysis from 36 studies enrolled 154,556 women to identified accuracy of HPV test on self-collected versus clinician-collected sampling for cervical cancer prevention revealed pooled sensitivity of HPV testing on self-collected specimen was lower than clinical-collected specimen for high grade cervical lesion (CIN2+) [19]. Interestingly, some PCR-based assays showed similar sensitivity on both techniques of sample collection [19].

Table 3. History of Cervical Screening and Abnormal Findings (n=497)

History of previous cervical cancer screening	N	Percent
Previous cervical cancer cytology		
Never had screening	149	30.0
Normal	235	47.3
Abnormal	113	22.7
ACA	1	0.2
AGC-NOS	2	0.4
ASC-H	16	3.2
ASC-US	20	4.0
HSIL	22	4.4
LSIL	44	8.9
Abnormal unknown type	8	1.6
Abnormal HPV testing (n = 499)		
Negative	32	6.4
HPV 16,18	36	7.3
Other HR-HPV	40	8.0
Not done/ not available	389	78.3
Previous histology		
Normal	61	12.3
CIN1/LSIL/HPV effect	61	12.3
CIN2	4	0.8
CIN3	13	2.6
CIN2-3/HSIL	10	2
CA Adeno	1	0.2
CA SCC	2	0.4
No histology/ not available	345	69.4
Definite treatment of previous abnormality (n=195)		
Follow-up	139	71.3
Ablation	5	2.6
LEEP	25	12.8
CKC	1	0.5
Others	22	11.3
Loss to follow-up	3	1.5

Table 4. Result of Self-Collected Specimen and Clinician-Collected Specimen (N=494)

	N	Percent
Self-collected specimen HPV-DNA		
Negative	125	25.3
Positive high-risk HPV	369	74.7
Positive 16, 18	155	31.4
Other high risk	214	43.3
Clinician-collected specimen HPV-mRNA		
Negative	146	29.6
Positive high-risk HPV	348	70.4
Positive 16, 18	124	25.1
Other high risk	224	45.3

This study which was a multicenter prospective clinical trial demonstrated comparable clinical performance of self-collected specimen HPV-DNA and clinician-collected specimen HPV-mRNA to detect high grade cervical lesion in abnormal cervical cytology and/or HPV testing patients who attended colposcopy clinic in Bangkok, Thailand.

We demonstrated similarly high prevalence of hr-HPV detection in self-collected specimen HPV-DNA and clinician-collected specimen HPV-mRNA (74.7% and 70.4% respectively). These rates were comparable with the results from one systematic review on the performance of HPV mRNA [16] However, our prevalence of hr-HPV in self-collected specimen and clinician- collected specimen were higher than 46.6% and 48.0% respectively from Tiiti's study [26]. The difference may partly lie on the characteristic features of women included in the study. Our population were women who attended colposcopy clinic with abnormal cervical cytology and/or positive HPV test whereas their study included general women who sought for service in their gynecology department [26].

Our study demonstrated high agreement (86.8%) of self-collected specimen HPV-DNA versus clinician-collected specimen HPV-mRNA with kappa of 0.670 (95%CI: 0.599-0.746). The concordance rate between self-collected specimen HPV-DNA and clinician-collected specimen HPV-mRNA in this study is substantial agreement which is higher than the studies of Phoolcharoen et al. which reported 74.5% (k=0.46) concordance rate between vaginal self- and clinician-collected HPV-DNA [21] and to the study of Aranda Flores et al. which found 78.2% concordance rate (k=0.34) for HPV-DNA and 92.5% (k=0.40) for HPV-mRNA [19, 24]. Moreover, the clinical performance of clinician-collected specimen HPV-mRNA to detect CIN2+ in our study which showed high sensitivity (90.2[95%CI: 83.6-94.9] and high negative predictive value (91.7[95%CI: 86.0-95.7] were consistent with a prior systematic review demonstrated high relative sensitivity for CIN2+ for clinician-collected specimen HPV mRNA (98[95%CI: 0.95-1.01]) [16]. Our study revealed slightly high sensitivity for self-collected specimen-HPV DNA (91.8[95%CI: 85.4-96.0]) compared with prior systematic review which relative sensitivity of self-collected specimen-HPV DNA (0.88[95%CI: 0.85-0.91]) for CIN2+ [19].

Table 5. Agreement of Self-Collected Specimen HPV DNA and clinician-collected specimen HPV mRNA (N=494)

	Clinician-collected specimen HPV mRNA		Agreement	Keppa (k)	p-value
	Negative n (%)	Positive n (%)	(%)	(95%CI)	
Self-collected specimen-HPV DNA					
Negative	103 (20.8)	22 (4.5)	86.8	0.67	<0.001
Positive	43 (8.7)	326 (66.0)		(0.599 - 0.746)	

Table 6. Histological Analysis according to HPV Results

	Histology			p-value
	Normal/ inflammation	<CIN2	≥ CIN2	
	n (%)	n (%)	n (%)	
Clinician-collected specimen HPV mRNA (n = 494)				
Negative	61 (41.8)	73 (50.0)	12 (8.2)	<0.001
Positive	97 (27.9)	139 (39.9)	112 (32.2)	
Self-collected specimen-HPV DNA (n = 492*)				
Negative	56 (44.8)	59 (47.2)	10 (8.0)	<0.001
Positive	102 (27.8)	152 (41.4)	113 (30.8)	

*2 missing data for histopathology

Table 7. The Clinical Performance of HPV Assays to Detected High Grade Cervical Lesion

Test	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	LR+ (95%CI)	LR- (95%CI)	AuROC (95%CI)
Clinician-collected specimen HPV mRNA	90.2 (83.6 - 94.9)	36.1 (31.2 - 41.3)	32.1 (27.2 - 37.3)	91.7 (86.0 - 95.7)	1.41 (1.28 - 1.56)	0.27 (0.16 - 0.47)	0.63 (0.60 - 0.67)
Self-collected specimen-HPV DNA	91.8 (85.4 – 96.0)	30.8 (26.1 - 35.8)	30.6 (25.9 - 35.6)	91.9 (85.6 – 96.0)	1.33 (1.22 - 1.45)	0.27 (0.14 - 0.49)	0.613 (0.60 - 0.65)

Since our study focused on only the women with abnormal cervical screening as the indications for colposcopy, the rates of hr-HPV may be higher than normal women. Nevertheless, findings from this group of women highlight the difference or similarity of HPV detection rates between the 2 tests.

The strength of our study which could be noted is that it is a prospective multicenter study, the number of participants was large enough to assess a clinical association between different techniques of cervical specimens' collection (self- vs clinician-) and HPV assays (HPV-DNA vs HPV-mRNA). Our findings support that self-sampling can serve as an alternative screening test to a physician sampling. Furthermore, either HPV-DNA test or -mRNA test could be used in clinical practice for cervical screening.

In conclusion, HPV-DNA testing from self-collected specimen demonstrates high concordance with HPV-mRNA testing from clinician-collected specimen to detect high-risk HPV. The sensitivity and negative predictive value of both tests to detect high grade lesions are also comparable. To increase coverage of cervical cancer screening in Thailand, the self-collected specimen might be another assay for women who are inconvenience to seek the healthcare providers.

Author Contribution Statement

All authors contributed equally in this study.

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Conflict of Interest

All authors had no conflict of interest. The Winnergy Medical Public Company Limited did not involve in the research conduct including data collection and analyses.

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