ORIGINAL ARTICLE

Comparison of Self- to Provider-Collected Cervical Screening with HPV DNA Test at Roi Et Province, Thailand during COVID-19 Pandemic

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Objective: The authors evaluated the concordance of positivity of self- and provider-sampling collection for high-risk human papillomavirus (hrHPV) DNA assay. Acceptance towards self-collection was also explored.

Materials and Methods: Five hundred thirty-five paired self- and provider-sampling cervical specimens were obtained from 30 to 59-year-old women enrolled at the gynecologic clinic at Phanomphrai Hospital, Roi Et Province, Thailand. Women performed self- and then received provider-sampling collection by trained nurse. Each sample was tested by COBAS® 4800 assay. Concordance in hrHPV detection between sample types was determined using Kappa (k) statistics. Sensitivity and specificity of hrHPV detection by self-collection were calculated. A hundred women were randomly invited to answer satisfaction survey afterward.

Results: Twenty-seven or 5.0% of the women were positive for hrHPV DNA, which 5, 4, and 18 were HPV-16, 18, and other pooled hrHPV genotypes, respectively. Self-collection showed good concordance to provider-collection (k=0.89; p<0.001). Self-collection of hrHPV detection had sensitivity of 81.5% (95% CI 61.9 to 93.7) and specificity of 100% (95% CI 99.3 to 100). Ninety-five percent of randomly selected 100 women were satisfied with self-collection.

Conclusion: Self-collected cervical sampling was comparable to provider-collected HPV DNA testing and was well-accepted. The present modality may help accelerate achieving the goal of elimination of cervical cancer campaign during the recovery phase of covid-19 pandemic.

Keywords: Cervical screening; HPV DNA Test; Self-collection; Covid-19

Received 13 March 2022 | Revised 14 November 2022 | Accepted 2 December 2022

J Med Assoc Thai 2023;106(1):8-13

Website: http://www.jmatonline.com

Cervical cancer continues to be one of the most common cancers among women[1]. In 2020 there were approximately 604,127 new cases with 341,831 deaths of cervical cancer worldwide[2]. In Thailand, there were nearly 6,000 new cases and 2,238 deaths of cervical cancer[3]. Though in a declining trend, recent incidence of 11.7 per 100,000 (2018) was nearly three times the target of the World Health Organization (WHO)'s Agenda to the Elimination of Cervical Cancer by 2030 campaign at 4.0 per 100,000[4,5], which would reduce cervical cancer mortality by almost 99% and save more than 62 million women's lives[6].

During the past 20 years, Roi Et Provincial Health Office (PHO) had collaborated with strategic partners to conduct a pilot project using visual inspection with acetic acid (VIA) and cryotherapy for cervical cancer[7]. Women received test results within a minute. For abnormal results, cryotherapy was provided immediately. This scheme also trained nurses to be the providers to solve staff shortages in rural and remote areas[8]. Phanomphrai Hospital was among the first four hospitals of Roi Et PHO to conduct this demonstration project[9], and Roi Et PHO had won a United Nations Public Service Award in 2018[10]. After a publication in "the Lancet" and was recommended by WHO as a component of comprehensive cervical cancer control, Thailand has extended VIA and cryotherapy services to around thirty out of seventy-seven provinces across the country[11]. For the first time, the Ministry of Public Health and the National Health Security Office (NHSO) of Thailand in 2019 has extended

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How to cite this article:

Eamratsameekool W, Phumiressunthon K, Sukprasert L, Pukdeesamai P. Comparison of Self- to Provider-Collected Cervical Screening with HPV DNA Test at Roi Et Province, Thailand during COVID-19 Pandemic. J Med Assoc Thai 2023;106:8-13.

DOI: 10.35755/jmedassocthai.2023.01.13727

the Universal Health Benefits Coverage (UHC) to include human papillomavirus (HPV) DNA testing as the primary cervical screening for target women aged 30 to 59 years, free of charge. In 2021 WHO strongly recommended HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches starting at the age of 30 with regular screening every 5 to 10 years[12]. WHO also suggests using either a sample taken by a healthcare provider or self-collected samples among the general population of women and women living with HIV[12]. In Thailand, provider-collection is a conventional method to obtain cervical specimens, and women had to visit health facilities to get the test done.

After the WHO's declaration of the COVID-19 outbreak, a pandemic, on March 11, 2020[13], cervical screening uptakes declined and were deferred[14]. All health facilities operated with new normal measures such as social distancing and gathering at a facility, including gynecologic and screening clinics, which could put women at risk during COVID-19 pandemic[15]. Cervical self-collection improved the participation of women who did not routinely attend cervical screening programs[16] and may be complementary to the provider-collected method for HPV DNA testing, especially under new normal measures during the post-COVID-19 recovery phase.

The present study aimed to evaluate the concordance of high-risk human papillomavirus (hrHPV) positivity by self- compared to provider-collection. The authors also assessed the women's acceptance and preferences towards the present modality.

Materials and Methods

The present study was conducted at the gynecologic clinic at Phanomphrai Hospital, Phanomphrai District, Roi Et Province, Thailand. Eligible women aged 30 to 59 years that attended the clinic between June 1 and August 31, 2021 were enrolled. Informed consents were obtained from all participants. All women attending the clinic were informed and voluntarily decide to enroll. A 15-minute counselling session was provided. Content included HPV and cervical cancer, HPV DNA test screening methods, how self- and provider-sampling were performed, the meaning of test results, the management protocol, and questions and answers. Every woman also received a health information brochure for self-study details of performing self-sampling and a QR code to link to 3-minute footage (https://youtu.be/ya5iCb80CyU) to ensure effective self-sampling cervical collection technique, which participants could re-play if needed. The women first performed self-sampling in the washroom at the clinic and then received provider-sampling cervical specimen collection. A sterile swab stick was used for self-sampling and a cervical broom for the provider-collected method. PreservCyt Solution® was used as transport medium. The study hrHPV DNA testing system runs by Roche COBAS® 4800 assays, including COBAS x 480 Hamilton, COBAS z 480 analyzer, and laboratory information system (LIS) component. HPV DNA testing results was reported as invalid if no beta globin found, negative, positive for HPV 16, HPV 18, and pooled hrHPV, which include HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 genotypes. Phanomphrai Hospital Laboratory has been certified for Laboratory Accreditation (LA) by the Department of Medical Sciences, Ministry of Public Health for HPV DNA Testing (Certificate Registry No. SMP64/2029) and was approved by the NHSO for e-claim reimbursement system. HPV Detection was using the COBAS 4800 HPV Test System. Lysis Buffer, Wash Buffer, Elution Buffer, HPV Positive, and Negative Control Kits, and all other reagents were purchased from Roche Diagnostic Inc. Each sample had an internal control, beta-globin, to monitor cell adequacy, and each run included a set of HPV Positive and Negative Controls. DNA extraction and purification were done with the COBAS x 480 instruments according to the manufacturer's instructions. Briefly, the preservation of cytology solution samples was vortexed and placed on the sample carrier, and the reagents such as lysis buffer, wash buffer, and elution buffer were loaded in respective reagent reservoir carriers. After sample and reagent loading, DNA preparation was completed automatically, and final DNA products were collected into a microwell plate. Subsequently, the microwell plate containing DNA was manually sealed and loaded on the COBAS x 480 analyzer, and the amplification and hybridization were completed automatically.

Descriptive data frequency, percent, 95% confidence interval, Cohen's coefficient power, sensitivity, specificity, positive and negative predictive value were calculated. For continuous data, medians, means, and interquartile range (IQR) were calculated. Using provider-collection as a reference, sensitivity, specificity, positive and negative predictive values of self-collection were calculated. Agreement of self- results to provider-collection was

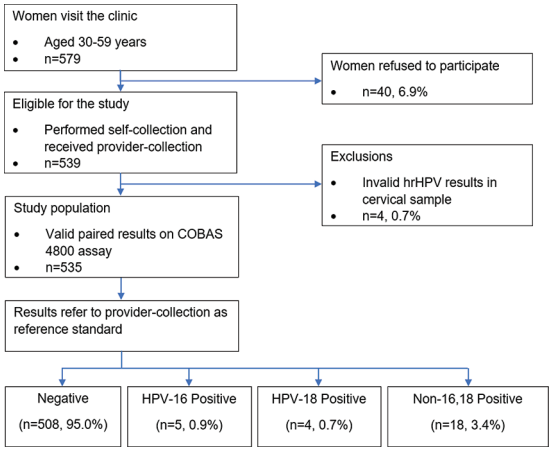

Figure 1. Study diagram for comparison of self- and provider-collected cervical screening with HPV DNA testing.

calculated. Cohen's Kappa results were interpreted as follows, values ≤0 as indicating no agreement and 0.01 to 0.20 as none to slight, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1.00 as almost perfect agreement[17]. The sample size was calculated to estimate a 95% confidence interval (CI) with a ±5% width. With an expected 80% sensitivity and 85% specificity of HPV DNA detection using sterile swab stick and a PCR-based HPV DNA assay. With the prevalence of HPV in women around 6.9%[18], a minimum of 502 women had to be included. Data were collected and analyzed by Stata, version xx (StataCorp LP, College Station, TX, USA) for Windows. The present project was approved by the local Ethical Committee of Roi Et Provincial Health Office on June 1, 2021 (COE 0172564).

Results

Five hundred seventy-nine women aged 30 to 59 years visited to the GYN clinic, and 539 were enrolled and participated in the present study (Figure 1). Four women or 0.7% had invalid results from self-collection (Table 1) and were excluded from the eligible 535 paired results for analyses.

The median age was 50 years (IQR 43 to 54 years) (Table 2). Most women were farmers at 86.4% and were married at 97.1%. Most women had parity 1 to 2 and 3 or more parity at 73.1% and 20.4%, respectively and 6.7% were nulliparous. Most women at 62.2% said they did not use contraceptive pills. Almost all women reported having previous cervical screening during the last five years at 98.7%.

HPV DNA testing results showed 508 (95.0%) were negative (Table 3). Twenty-seven or 5.0% had positive results with 5 (0.9%), 4 (0.7%), and 18 (3.4%) that were HPV 16, 18, and other pooled hrHPV, respectively. Compared to provider-sampling, self-collection had a sensitivity of 81.5% and a specificity of 100% (Table 4). According to Cohen's

Table 1. Demographic data of eligible participants (n=535)

Characteristics	n (%)
Age (years)	
30 to 39	90 (16.8)
40 to 49	193 (36.1)
50 to 59	252 (47.1)
Occupation	
Farmer	462 (86.4)
Governance servant	33 (6.1)
Employee	40 (7.5)
Marital status	
Single	12 (2.2)
Married	519 (97.1)
Divorced	4 (0.7)
Parity	
0	36 (6.7)
1 to 2	391 (73.1)
≥3	108 (20.2)
Contraceptive pill usage	
No	333 (62.2)
Yes	202 (37.8)
Previous cervical screening	
No	7 (1.3)
Yes	528 (98.7)

Table 2. Reports of HPV DNA testing (n=535)

Testing report	Self-collected; n (%)	Provider-collected; n (%)
Eligible tests	535 (100)	535 (100)
Negative	513 (95.9)	508 (95.0)
Positive	22 (4.1)	27 (5.0)
HPV-16	3 (0.6)	5 (0.9)
HPV-18	4 (0.7)	4 (0.7)
Non-16, 18 HPV	15 (2.8)	18 (3.4)

Table 3. Results of self-compared to provider-collection for HPV DNA test

	Provider-collection		Total
	Positive	Negative	
Self-collection			
Positive	22	0	22
Negative	5	508	513
Total	27	508	535

Table 4. Diagnostic values statistics analysis

Statistical analysis	Results; percent (95% CI)
Sensitivity	81.5 (61.9 to 93.7)
Specificity	100 (99.3 to 100)
Positive predictive value	100 (84.6 to 100)
Negative predictive value	99.0 (97.7 to 99.7)
Kappa coefficient	0.89, p<0.001

CI=confidence interval

criteria, concordance between self- and provider-collected samples was in an almost perfect agreement (Kappa=0.89, p<0.001).

Discussion

Self-collected cervical samplings along with hrHPV DNA testing has provided more option to increase cervical screening uptakes. The present modality should allow the shift in service settings from in-clinic to more people-centered. Nevertheless, this comes to the authors' area at the same time as the COVID-19 pandemic, making it more challenging to deliver cervical screening to target women. The self-sampling cervical collection has been introduced at Phanomphrai Hospital, along with the new normal standards and universal prevention. The authors expect that self-sampling may help reduce the number of in-clinic visits while maintaining the good diagnostic values.

The present study found four or 0.74% invalid hrHPV DNA testing results among self-collection and was lower than other studies[19]. All testing were valid among provider-collection. The 5% prevalence was close to the prevalence seen elsewhere in Thailand[20]. The invalid results happened although participants attended a 15-minute counselling session and performed self-sampling at the clinic. It is important to be cautious while scaling up a self-sampling program that health education and information must be emphasized, especially in a rural and remote area like Phanomphrai District, to minimize invalid results.

The present study results revealed that self-collected cervical screening had a sensitivity of 81.5% (95% CI 61.9 to 93.7) and a specificity of 100.0% (95%CI 99.3 to 100.0), compared to the provider-collected method (Table 4). The present study found that the Kappa coefficient between self- and provider-collected cervical methods was 0.89 (p<0.001), classified as 'almost perfect agreement' by Cohen's criteria.

One hundred women answered the questionnaire and 95.0% had overall satisfaction with this method (Table 5).

Results of the present study indicated that most women accepted (95.0%) and preferred (97.0%) self-collection, which was consistent with a previous review[21]. The introduction of self-sampling provides opportunities to significantly increase the uptake of cervical screening[22] and offer opportunities to reach those reluctant to undergo gynecological examinations[23], especially during the recovery phase of COVID-19 under new normal measures such as social distancing.

The limitation of the present study was that self-collected cervical specimens used transport medium (PreservCyte® Solution), which is the same as provider-sampling. It may be difficult for the patient to use or manage the logistic processes. A study found that vaginal self-sampling without preservatives was adequate for HPV testing[24]. This should be an excellent choice to ease the specimen collection at a community level.

Method limitations must be kept in mind and realize that cancer screening is a complex multistep process that includes identification and characterization of the screening target population, recruitment for screening by direct or invitational and indirect or public health education and promotion to raise awareness and encourage participation, as well as primary healthcare counselling methods, pre-screening counselling, and assessment of individual cancer risk, conducting screening tests, processing screening tests, using screening test results together with an individual's personal history and clinical profile to plan subsequent care and assessment of

Table 5. Client satisfaction survey for self-collection (n=100)

Client's perspective on self-collection	Disagree	Uncertain	Agree
Convenient accessibility	0	3	97
Adequate information and counselling medias	0	16	84
Accept that self-collection is easy to perform	1	4	95
Preference that this mode help avoiding embarrassment and shyness	0	3	97
Overall satisfaction with self-collection	0	5	95

follow-up results, planning subsequent care, and monitoring patient compliance until the person is eventually returned to routine screening recall or is discharged from the screening program[25]. Missed opportunities to detect other gynecological conditions by the clinician may be a significant disadvantage. However, there is a firm basis for HPV self-sampling for cervical screening, especially in under-resourced areas lacking medical services and for women reluctant to participate in screening programs to improve screening coverage and acceptability[26].

HPV self-sampling should be a potential complementary tool to speed up efforts to achieve the target of the WHO's Agenda 2030 to eliminate cervical cancer as a public health problem. Thailand is extending the Universal Health Benefits Coverage Scheme (UHC) to include free HPV DNA testing. This free access shall accelerate its pace to the goals of the United Nations' Sustainable Development Goals.

Conclusion

Self-collected cervical sampling was comparable to provider-obtained screening with HPV DNA testing at a clinic and was well-accepted. The present modality may help to achieve the goal of eliminating cervical cancer during the recovery phase of the COVID-19 pandemic under the new normal measures.

What is already known on this topic?

The COVID-19 pandemic has put Thailand into health-threatened issues including cervical screening. HPV DNA test has very high sensitivity and both provider- and self-collection were suggested by the WHO. Thailand's NHSO included this method to health benefit packages since 2020.

What this study adds?

This study found self-collected was comparable to provider-performed cervical sampling for HPV DNA testing. With this modality cervical screenings can be maintained and expanded during the post-COVID-19 phase in accordance with the new normal measures. If shared, the authors hope colleagues in settings like Thailand can accelerate the achievement of campaign for the elimination of cervical cancer as a public health problem by 2030.

Acknowledgement

The authors would like to thank Professor Emeritus Khunying Kobchitt Limphapayom, Professor Pisake Lumbhiganon, Associate Professors Bandit Chumworathayi and Wichai Termroongreunglert for their kind support.

Authors' contributions

WE was responsible for overall activities. KP had done in part of participant invitation, counselling for self-collection and performed provider-collection. LS covered laboratory works and quality assurance. PP did all data and statistic processes from sample size calculation to statistical analysis.

Conflicts of interest

The authors declare no competing interests.

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