RESEARCH ARTICLE

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Agreement between Self- and Physician-Sampling for Detection of High-Risk Human Papillomavirus Infections in Women Attending Cervical Screening at National Cancer Institute, Thailand

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Abstract

Background: We determined testing of self-sampling vagina swabs for Human Papilloma Virus (HPV) can be used to screen for cervical disease in outpatient clinics. **Methods:** In this study, women attending cervical cancer screening clinic and gynecology clinic of the National Cancer Institute were invited to take a vaginal self-sampling and physician-collected cervical sampling. **Results:** Of 268 participants, 20 (7.5%) were HPV-positive on the physician-collected samples. Among these screen-positive women, only two (0.7%) had HPV 18 and/or 45 and none had HPV 16 infections. For the self-collected samples, 4 participants had invalid HPV test results. Of the remaining 264 women with valid test results on self-collected samples, 29 (11.0 %) were HPV-positive, of whom, two (0.8%) were infected with HPV 16 and one (0.4%) with HPV 18 and/or 45 infections. The agreement between self-sampling and physician-sampling HPV test results (when two HPV results categories were considered) was 92. 8% with a moderate Kappa value of 0.57. **Conclusion:** Overall, self-sampling seems to be a reliable alternative to health-provider collection. However, instructions on proper procedures for sample collection to the women are important step before general roll out.

Keywords: Self-sampling- HPV DNA test- cervical cancer screening- National Cancer Institute- Thailand

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Introduction

Cervical cancer is a major public health problem in Thailand, as it has been the most common cancer in Thai women since 1990. Our country has cervical cancer screening program however, it was promoted as opportunistic program. In 2005, the Ministry of Public Health in cooperation with the National Health Security Office, launched the National Cervical Cancer Screening Program to provide free cervical screening tests for Thai women aged 30-60 years once every five years. Through this program, eligible women are able to access screening facilities at the nearby Sub-District Health Promotion Centers. There are nearly 10,000 such centers nationwide. In coordination with various stakeholders, 15,882,672 women have been screened mainly with cytology since 2005. As such, the age-standardized rate (ASR) of cervical cancer has declined from 17.7 per 100,000 women in 2005 to 11.1 per 100,000 women in 2017 (Rojanamatin et al., 2021).

The latest guidelines from the World Health Organization (WHO) suggests that use of hr-HPV testing for primary screening linked with appropriate treatment of those screen-positive and/or diagnosed with precancerous lesions, is more effective and efficient for the prevention of invasive cervical cancer than screening with cytology (WHO, 2021). Therefore, hr-HPV testing is replacing cytology as the primary screening test in many countries. In Thailand, hr-HPV detection test was introduced for primary screening in 2020 and replaced pap smear cytology across the country in 2022.

Several surveys from Thailand have shown that embarrassment to undergo a gynecological examination is often the key underlying reason for women not attending screening appointments and the current practice of HPV sample collection by a physician may aggravate this cultural barrier (Oranratanaphan et al., 2014; Thurston et al., 2005). Previous studies have suggested that HPV self-sampling offers an option to improve cervical cancer screening coverage without any significant compromise

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on test accuracy (Arbyn et al., 2018). An assessment of efficacy of self-collected HPV test in detection of cervical intraepithelial neoplasia (CIN) and its agreement with physician-collected samples in detection of high-risk HPV are warranted in Thailand to convince the policy-makers in the country. The present study aimed to evaluate the agreement between hr-HPV detection tests from self-collected upper vaginal specimen and physician-collected cervical samples. In addition, we compared detection of cervical intraepithelial neoplasia (CIN) based on the two sampling modalities.

Materials and Methods

Enrollment and Data Collection

Women aged 30–60 years who visited cervical cancer screening clinic and gynecology clinic at National Cancer Institute, Bangkok, Thailand were invited to participate in the project during March 1, 2021 and September 30, 2021. This study was approved by the National Cancer Institute Research Ethics Committee

After providing informed consent, eligible women underwent interviews to provide information on sociodemographic characteristics.

Sample collection

This study evaluated the detection of HPV infection using two sampling methods of cervical exfoliated cells. All participants were invited to undergo 2 procedures: vaginal self-sampling (SS) using the Aptima Multitest Swab Specimen Collection Kit (Hologic Inc., Marlborough MA, USA) and physician-collected cervical sampling (PS) using ThinPrep specimen collection medium (Hologic Inc., Marlborough MA, USA). Each woman was instructed on how to use the vaginal self-sampling brush using picture-based instructions and video demonstration given by the researchers. After SS, all women underwent their scheduled gynaecological examination. The cytobrush was used by the gynecologist for collection of cervical material for HPV test, which was also used for liquid-based cytology (LBC). Both SS and PS specimens were immediately placed in collection tubes for HPV detection, stored at room temperature, and sent to the pathology laboratory within 3 hours.

HPV testing

The HPV mRNA test from either sample was performed using APTIMA (Hologic Inc., Marlborough, MA, USA) technology, which could detect E6/E7 mRNA expression of 14 hr-HPV types. The samples positive on APTIMA were further tested for mRNA of HPV types 16, 18, and 45 by the APTIMA genotype assay, which does not differentiate between HPV 18 and 45. The adequacy of sample was confirmed by the detection of human beta-globin protein. All the cervical specimens (physician-collected) were tested for Liquid-based cytology (LBC) (Hologic Inc., Marlborough, MA, USA) and interpreted by a cytopathologist at the NCI Bangkok. In case the LBC results were ASCUS, these women were referred for colposcopy. Women tested positive on any of the HPV tests and/or cytology (at ASCUS threshold) were referred for colposcopy. Biopsies were directed from any visible lesion on the cervix. Random biopsies were also taken from apparently normal cervix at the discretion of the colposcopists.

Statistical Analysis

Data were entered in the spreadsheet package EXCEL for Windows XP (Microsoft Corp.) and statistical analysis was performed using STATA software, version 17.0 (Stata-Corp, College Station, TX, USA). Participant socio-demographic and clinical characteristics were presented as proportions for categorical variables and as median with their interquartile range and/or mean with their standard deviation (SD) for the continuous variables. Cohen's Kappa statistic was used to compare the agreement between the SS and PS test results grouped in two categories (negative and positive) and in four categories (negative, Other HPV types excluding 16, 18 and 45, HPV 18 and/or 45 and HPV 16). CIN detection rates of the screening tests were obtained by dividing the number of cases detected after positive tests by the total number of women screened. Comparison of detection rates between the screening tests was done by estimating P values from the discordant pairs using the exact McNemar significance probability test.

Results

A total of 268 women were recruited for the study. The socio-demographic characteristics of all participants are shown in Table 1. The mean age of participants was 47.5 years (SD 8.3), with 45.5% of them aged > 50 years. Most of the participants (85.4%) were degree or diploma holders and 64.9% were currently married.

Table 2 presents the overall HPV prevalence. Of 268 participants, 20 (7.5%) were HPV-positive on the physician-collected samples. Among these screen-positive women, only two (0.7%) had HPV 18 and/or 45 and none had HPV 16 infections. For the self-collected samples, 4 participants had invalid HPV test results. Of the remaining 264 women with valid test results on self-collected samples, 29 (11.0 %) were HPV-positive, of whom, two (0.8%) were infected with HPV 16 and one (0.4%) with HPV 18 and/or 45 infections.

The agreement between self-sampling and physician-sampling HPV test results (when two HPV results categories were considered) was 92. 8% with a moderate Kappa value of 0.57 (Table 3).

Overall, any CIN was detected in 13.3 (35/264) per 100 women screened (10.6 [28/264] and 2.7 [7/264] per 100 women screened for CIN 1 and CIN 2 and/or 3 lesions respectively) (Table 4). The two HPV sampling modalities concurrently detected any CIN in 4.5 (12/264) per 100 women screened (3.8 [10/264] for CIN 1 and 0.8 [2/264] for CIN 2 and/or 3). Self-sampling alone additionally detected more CIN 2 and/or 3 compared to physician sampling modality (0.8 [2/264] versus 0.4 [1/264], respectively), though the differences were not statistically significant because of the small numbers.

Table 1. Participant Socio-Demographic Characteristics

Characteristics	Number*	Percentage**
Participants assessed	268	
Age (years)		
<30	54	20.1
40-49	92	34.3
≥50	122	45.5
Mean (SD; range)	47.5	(8.3; 28 – 61)
Education		
Primary	14	5.2
Secondary	25	9.3
Degree or Diploma	229	85.4
Marital status		
Married	174	64.9
Single	66	24.6
Separated, divorced, or widowed	28	10.4
Monthly income		
None	12	4.5
<29,999	84	31.3
30,000 – 49,999	88	32.8
≥50,000	84	31.3

*, The figures are frequencies unless otherwise specified; **, the figures are proportions unless otherwise specified; SD: standard deviation

Table 2. Prevalence of HPV from Self- and Physician sampling for HPV Testing

HPV test result	Number	Percentage
HPV result from physician-sampling		
Negative	248	92.5
Positive	20	7.5
Other HPV types excluding 16, 18 and 45	18	6.7
HPV 18 and/or 45	2	0.7
HPV result from self-sampling [$]		
Negative	235	89
Positive	29	11
Other HPV types excluding 16, 18 and 45	26	9.8
HPV 18 and/or 45	1	0.4
HPV 16	2	0.8

HPV, human papilloma virus; [$], 4 participants with invalid HPV test results

Discussion

In recent years, the mRNA based APTIMA test has been accepted in primary cervical cancer screening either in conjunction with cervical cytology (in the USA) or as standalone screening test (in south Sweden, Wales [UK], Basque Country [Spain], Scotland [UK], Australia, France, England (UK), Nigeria, and Zambia). Additionally, the recent update of the WHO guidelines stipulated A 5-year interval screening using HPV mRNA testing on clinician-collected specimens, as opposed to 5–10-year screening intervals recommended for the HPV DNA based testing. However, evidence of the utility of self-collected samples in HPV mRNA testing is still lacking.

Table 3. Agreement between the HPV Results from Self- and Physician Sampling

HPV results from self-collected samples	HPV results from physician-collected samples			
	Negative	Positive		
		Other HPV types excluding 16, 18 and 45	HPV 18 and/or 45	HPV 16
Negative	230	5	0	0
Positive				
Other HPV				
types excluding				
16, 18 and 45	14	12	0	0
HPV 18 and/or 45	0	0	1	0
HPV 16	0	1	1	0
Agreement when two categories are used*				
Agreement	92.8			
Kappa	0.57			
Agreement when four categories are used**				
Agreement	92.1			
Kappa	0.53			

HPV, human papilloma virus; *, The two categories used are negative and positive; **, The four categories used are negative, other HPV types excluding 16, 18 and 45, HPV 18 and/or 45 and HPV 16

Our findings show high agreement and moderate kappa between the testing results based on the self- and physician- collected samples. Other previous studies observed similar moderate agreement: one that tested for the 14 different HR-HPV mRNA observed a kappa value of 0.62 (good agreement) (Johnson et al., 2014); one that tested the samples for RT PCR based detection of HPV DNA observed a kappa of 0.46 (moderage agreement) (Phoolcharoen et al., 2018); one using a PCR based assay that tests for individual HPV types observed a moderate kappa of 0.54 (Castle et al., 2013); one that tested for HR-HPV DNA using hybridization assay observed a moderate agreement (kappa 0.54) among older (50+ years) but lower agreement (kappa 0.37) among younger (30-49 years) women (Karwalajtys et al., 2006). However, most of the other studies that tested for HPV DNA had good to excellent concordance (kappa range: 0.70-0.88) between the self- and provider-collected sampling technics, especially when RT-PCR based assays were used (Bhatla et al., 2009; Boggan et al., 2015; Gravitt et al., 2001; Madhivanan et al., 2021; Obiri-Yeboah et al., 2017; Safaeian et al., 2007; Sowjanya et al., 2009).

Additionally, more high-grade CIN and CIN of any grade were detected using the self- than the physician-collected samples in our study, though the difference did not reach statistical significance. Of the total three high grade CIN one was detected through self-sampling only. Other studies using the HPV DNA testing did observe higher detection rates of CIN 2/CIN 3 for the self-collected sampling (Bhatla et al., 2009; Boggan et al., 2015; Johnson et al., 2014; Obiri-Yeboah et al., 2017; Sowjanya et al., 2009). However, most studies observed no difference between provider-collected and self-sampling for the detection of high-grade cervical lesions (Bhatla et al., 2009; Boggan et al., 2015; Johnson et al., 2014; Sowjanya et al., 2009).

Table 4. CIN Detection by Use of Physician and Self-Collected HPV Samples

		CIN diagnosis on colposcopy/histopathology		
		CIN 1 n (Detection rate [per 100 women screened])	CIN 2/3 n (Detection rate [per 100 women screened])	Any CIN n (Detection rate [per 100 women screened])
Women screened (n = 264)				
Women detected with CIN		28 (10.6)	7 (2.7)	35 (13.3)
HPV result				
Physician- collected	Self- collected			
Negative	Positive	2 (0.8)	1 (0.4)	3 (1.1)
Positive	Negative	2 (0.8)	0 (0.0)	2 (0.8)
Positive	Positive	10 (3.8)	2 (0.8)	12 (4.5)
Total		14 (5.3)	3 (1.1)	17 (6.4)
Self- versus physician-collected samples				
Ratio		1.00	1.50	1.07
95% CI		(0.72 -1.39)	(0.67 -3.34)	(0.79 -1.45)
Exact p-value		1.00	1.00	1.00

CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus

A recent meta-analysis by Arbyn et al observed that similar cross-sectional sensitivity for high-grade CIN and slightly higher specificity for high-risk HPV RNA testing with APTIMA than DNA tests on clinician-collected cervical samples, while HPV RNA testing was less sensitive on self-collected samples compared to clinician-collected samples (Arbyn et al., 2022). However, the comparator in this meta-analysis was the standard HPV test modalities (HC2 and GP5+/6+ PCR). It is possible that if APTIMA was to be compared with the newer HPV DNA assays that are currently being used in the screening programmes, the clinical relative test accuracy would have been similar. The HPV mRNA assay used in this study targets transcripts of the HPV E6 or E7 genes, whose expression indicates increase in cellular transformation at the time of transition from HPV infection to cervical precancer. Hence detection of HPV E6 or E7 mRNA might signify infections transformation, as opposed to detection of viral DNA only signifies presence of the virus (Doorbar et al., 2012). Furthermore, a recent study observed that use of an mRNA based assay resulted in cost savings and reductions in unnecessary testing and procedures when compared to use of a DNA based assay (Dombrowski et al., 2022).

After the advent of the COVID-19 pandemic, more efficient, cost-effective cervical cancer prevention opportunities need to be promoted especially for the at high-risk under-screened women, more so in the low- and middle-income countries. Offering self-sampling kits has generally been proven more effective in reaching and increasing participation among the under-screened women than inviting them to be screened at a clinic (Arbyn et al., 2018). However, the participation rates varied a lot among settings and additionally depended on the self-sampling strategies used. Sending self-collection kits at home seemed to more effective in attracting under-screened women to participate, though it is likely to result in increased wastage of the kits. The opt-in strategy, in which women request a self-sampling kit, seems economic and ecological, though not much more efficacious in increasing participation in the under-screened women (Arbyn et al., 2018). Furthermore, for any strategy to be successful, it should be coupled with high adherence to follow-up investigations and/or treatment of the women after positive tests on self-collected samples. More larger studies need to be set up to further evaluate the utility of self-sampling in cervical cancer screening using HPV mRNA testing. Additionally, its acceptance and improvement on screening participation should be assessed in a local screening setting in Thailand before general roll out.

Author Contribution Statement

SS study concept and design, SP, PPl, PPa, and KS participants recruitment and coordination, data collection and sample collection, RM statistical analysis, PB manuscript drafting, and revision. All authors read and approved the final manuscript.

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Ethical Statement

This study was approved by the National Cancer Institute Research Ethics Committee

Disclaimer

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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