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Comparative accuracy of Pap smear and HPV screening in Ubon Ratchathani in Thailand

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ABSTRACT

We evaluate the potential for using high-risk human papillomavirus (hr-HPV) testing-based screening for cervical intraepithelial neoplasia (CIN) in routine health services in Thailand; its accuracy in comparison to that of conventional cytology (CC); and the utility of HPV16/18 positive results and liquid-based cytology (LBC) triage for HPV-positive women in the detection of high-grade CIN. Women aged 30–60 years in Ubon Ratchathani province, Thailand were screened with CC and hr-HPV testing and those abnormal on either tests were referred for colposcopy and/or directed biopsies. The final diagnosis using COBAS was based on histology or colposcopy when histology was not available. Estimation of test accuracy parameters was done using latent class analysis using Bayesian models. Of the 5004 women were enrolled, 20 (0.4%) had abnormal CC and 174 (3.5%) women were HPV-positive. Among 185 women abnormal on CC or HPV-positive, 176 (95.1%) underwent colposcopy, of whom 101 (57.4%) had abnormal colposcopy findings. Ninety-seven women with abnormal and 69 with normal colposcopy had biopsies performed. All 21 women with histological CIN2 or worse had hr-HPV and none were abnormal on CC. The estimated sensitivity, specificity and positive predictive value were respectively 71.8%, 97.0% and 13.0% of HPV testing; 53%, 98.7% and 20.3% for triage of HPV-positive women with LBC; and 70.4%, 98.2% and 16.9% when test positivity was taken as HPV16/18 irrespective of LBC result or positive for hr-HPV non 16/18 types and LBC triage. Our study findings indicate poor performance of cytology screening and demonstrate the potential and utility of using HPV testing in public health services in Thailand as well as the utility of primary HPV testing and LBC triage in screening for cervical neoplasia.

1. Introduction

Cervical cancer is the second most common cancer among Thai women, with an estimated 8200 new cases annually around 2012 which is expected to increase to 9200 cases around 2020 [1]. The age-standardized incidence rates across Thailand ranged from a high of 24.6 per 100,000 women in Lamphun to a low of 10.4 per 100,000 in Khon Kaen [2]. Wide spread implementation cytology screening has substantially reduced cervical cancer incidence and mortality in high-income countries in Europe, North America and Australia [3–5]. In Thailand, opportunistic cervical cytology screening has been on-going for several years since 1985. In 2002, the Ministry of Public Health (MoPH) and the National Health Security Office (NHSO) commenced providing countrywide cervical screening to all Thai women aged 35–60 years under universal health care coverage insurance scheme at 5-year intervals and integrated it within the routine health services of Thailand. Over the last two decades the incidence of cervical cancer has been slowly declining in Thailand [6–12].

It has been well documented in recent years that providing quality assured and effective cervical cytology screening is a challenging task and cytology screening programs have been less successful in reducing cervical cancer burden in low- and middle income countries (LMICs) [13]. The challenges in introducing high-quality, frequently repeated cytology screening and the well documented low sensitivity of cytology to detect cervical cancer and its precursors CIN 2 and CIN3 (cervical intraepithelial neoplasia grades 2 and 3) lesions in various settings

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have led to the evaluation of alternative screening approaches such as human papillomavirus (HPV) testing-based screening [13–17]. HPV testing alone or with cytology triage is currently increasingly being used as a primary screening approach for cervical neoplasia.

The causal role of persistent high-risk HPV (hr-HPV) infection in cervical carcinogenesis, the high accuracy of HPV testing in detecting cervical neoplasia, recent development of assays that permits the detection of hr-HPV DNA in cervical specimens, the high negative predictive value of negative HPV tests for CIN 2 or worse lesions and the potential value of HPV testing as an objective screening test in the post HPV vaccination era prompted us to evaluate its test performance, feasibility and acceptability in a cross-sectional study in Ubon Rachathani province. Moreover, the findings from such a study will be useful for and guide eventual national scale up of HPV testing as a primary screening test in future.

2. Material and methods

2.1. Study population

Eligible population were apparently healthy women aged 30–60 years who underwent Pap smear screening in 50 primary healthcare units in 7 districts in Ubon Ratchathani province in northern Thailand in the setting of the national cervical cytology screening program. The women were invited by the nurses in the primary care units to participate in the study when they presented for routine cytology screening. The study was explained in detail and all participants provided written informed consent before entering the study. The participants were recruited during the period July 2014 to January 2015. This study was approved by the ethics committee of the National Cancer Institute, Bangkok, Thailand.

2.2. Collection of sociodemographic details

After obtaining written informed consent, sociodemographic details including marital status, age at first child birth, number of children and screening history were obtained from the participants using a structured questionnaire in direct interviews administered by the nurses before obtaining a Pap smear.

2.3. Sample collection and HPV genotyping

After obtaining sociodemographic history, the examination procedure was described in detail to the women. A speculum examination was carried out under bright light from a halogen lamp and the cervix was visually inspected for any abnormalities such as signs of inflammation, ulceration and growth. After naked eye visual inspection, cervical cells were collected using an Ayre's spatula, and a conventional smear was prepared by spreading the cells in the spatula on a prelabelled glass slide and fixed with spray fixative. Then the spatula was rinsed in a tube containing PreservCyt® solution (Hologic Inc., Marlborough MA, USA). A second cervical cell sample was collected using an endocervical brush, which was then rinsed and placed in the same vial containing the PreservCyt solution in order to collect more cervical cells.

2.4. Cytology evaluation

The cervical smear slides were transported to the provincial Government cytology laboratory in Ubon Ratchathani province where the smears were processed stained, read and reported. All the smears were initially read by a cytotechnician who categorised them as normal and abnormal smears. All abnormal smears and a 10% random sample of normal smears were then reviewed by a medically qualified cytopathologist and the results were reported using the Bethesda system. All women with cytological abnormalities at the atypical squamous cells of uncertain significance (ASCUS) threshold were referred for colposcopy by a gynaecology oncologist, and directed biopsies were obtained from colposcopically abnormal areas in women with colposcopic abnormalities. In those women with normal colposcopic findings cervical biopsies were randomly performed at 12 and 6 o clock positions.

Table 1
Characteristics of women screened in the project in Ubon Ratchathani province.

Characteristics	Number	Percentage
Women screened	5004	
Age		
30–39	1117	22.3
40–49	2340	46.8
50–59	1547	30.9
District		
Det Udom	393	7.9
Don Mot Daeng	296	5.9
Meuang	1107	22.1
Muang Sam Sip	2289	45.7
Samrong	315	6.3
Sawang Wirawong	197	3.9
Warin Chamrap	407	8.1
Marital status		
Married	4730	94.5
Widowed	135	2.7
Separated	99	2.0
Unmarried	40	0.8
Age at first child[a]		
< 18	372	7.7
18–21	2187	45.5
22+	2244	46.7
No. of children[a]		
1	484	10.0
2–3	4017	83.3
4+	322	6.7
Ever screened?		
No	236	4.7
Yes	4768	95.3
No of years since previous screening[a]		
< 5	3778	95.2
5+	189	4.8
Modality used in previous screening[a]		
Pap smear	4375	99.8
VIA	8	0.2
HPV	2	0.0
Knowledge about HPV		
No	1804	36.1
Yes	3200	63.9

VIA: visual inspection with acetic acid; HPV: human papilloma virus.
[a] Figures do not add up to total because of missing information.

2.5. HPV testing

The vials with cervical cell specimens in PreservCyt solution were stored at room temperature and were transported in room temperature to the National Cancer Institute (NCI), Bangkok for HPV testing using COBAS 4800 System (Roche Molecular Systems, Inc., Branchburg, NJ, USA). The COBAS 4800 HPV test simultaneously detects a total of 14 h-HPV types: HPV-16 individually, HPV-18 individually, and pooled high-risk (hr)-HPV genotypes other than HPV 16 and 18 (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (OHR), in addition to a separate high b-globin control. All HPV-positive samples were tested with reflex