

RESEARCH ARTICLE

Performance of HPV DNA Testing with Hybrid Capture 2 in Triage of Women with Minor Cervical Cytologic Abnormalities (ASC-US/LSIL) in Northern Thailand

Surapan Khunamornpong¹, Jongkolnee Settakorn¹, Kornkanok Sukpan¹, Jatupol Srisomboon², Prapaporn Suprasert², Sumalee Siriaunkgul^{1*}

Abstract

Background: Minor cervical cytologic abnormalities include atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL). Approximately 10-20% of women with minor cytologic abnormalities have histologic high-grade squamous intraepithelial or worse lesions (HSIL+). In Thailand, women with minor cytologic abnormalities have a relatively high risk of cervical cancer, and referral for colposcopy has been suggested. A triage test is useful in the selection of women at risk for histologic HSIL+ to reduce the colposcopy burden. The aim of this study was to assess the performance of high-risk HPV DNA test in triage of women with minor cytologic abnormalities in northern Thailand. **Materials and Methods:** All women with ASC-US/LSIL cytology who were referred to our colposcopy clinic from October 2010 to February 2014 were included. HPV DNA testing was performed using Hybrid Capture 2 (HC2). All patients received colposcopic examination. Accuracy values of HC2 in predicting the presence of histologic HSIL+ were calculated. **Results:** There were 238 women in this study (121 ASC-US and 117 LSIL). The HC2 positivity rate was significantly higher in the LSIL group than in ASC-US group (74.8% versus 41.0%, $p < 0.001$). Histologic HSIL+ was detected in 9 women (7.4%) in the ASC-US group and 16 women (13.7%) in the LSIL group ($p = 0.141$). There was no histologic HSIL+ detected among HC2-negative cases (sensitivity and negative predictive value of 100%). The performance of HC2 triage was highest among women aged >50 years with ASC-US cytology. An increase in the cut-off threshold for positive HC2 resulted in a substantial decrease of sensitivity and negative predictive value. **Conclusions:** HPV DNA testing with HC2 shows very high sensitivity and negative predictive value in triage of women with minor cervical cytologic abnormalities in northern Thailand. An increase of the cut-off threshold for HC2 triage is not recommended in this region.

Keywords: Cervical cancer - cytology - ASC-US - LSIL - triage - HPV DNA test - Thailand

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Introduction

Cervical cancer is the third most common cancer in women worldwide, but over 85% of the disease burden occurs in developing countries (Ferlay et al., 2010). Cervical cytology screening reduces the incidence of cervical cancer by detection of precancerous lesions (high-grade squamous intraepithelial lesion [HSIL]/cervical intraepithelial neoplasia [CIN] 2-3 or adenocarcinoma in situ) and early stage cancer, which can be successfully treated (Castle et al., 2007). The Bethesda system terminologies for cervical cytology reporting, introduced since 1988 with the most recent modification in 2001, helps stratify the risk for the presence of precancerous lesions (Solomon et al., 2002). Women with cytology result of atypical squamous cells, cannot exclude HSIL (ASC-H) or worse should be immediately referred for

colposcopy because of a sufficient risk of having high-grade cervical lesions (Massad et al., 2013)

Atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) are related cytology categories with overlapping morphologic characteristics and may be grouped as minor cervical cytologic abnormalities (Solomon et al., 2002; Arbyn et al., 2013a). Approximately 10-20% of women with minor cytologic abnormalities have histologic HSIL or worse lesions (HSIL+) (ALTS Group, 2003b; Fujii et al., 2014; Kietpeerakool et al., 2014; Poomtavorn et al., 2014). The management policy for women with these cytology results may be variable in different institutions or regions ranging from follow-up cytology to referral for colposcopy, which is particularly preferred in the areas with high cervical cancer incidence (Kietpeerakool et al., 2014). However, referral of all women with minor

¹Department of Pathology, ²Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand *For correspondence: sumalee.cmu@gmail.com

cytologic abnormalities to colposcopy results in a large burden for gynecologists. Triage test is useful for selection of women at risk for histologic HSIL+ while reduce the colposcopy burden.

Follow-up repeat cytology is a triage strategy for minor cytologic abnormalities, but this could result in a delayed diagnosis in some patients (Arbyn et al., 2013b). As HPV infection is a necessary cause of almost all cervical cancers, testing for high-risk human papillomavirus (hrHPV) DNA has been used for triage of women with minor cytologic abnormalities (Arbyn et al., 2013b; Massad et al., 2013). Many studies have been reported on the triage performance of Hybrid Capture 2 (HC2) which is the most widely used hrHPV DNA test approved by the US Foods and Drugs Administration (Arbyn et al., 2013b). A recent meta-analysis study reported a higher sensitivity of HC2 in the triage of minor cytologic abnormalities compared to repeat cervical cytology (Arbyn et al., 2013b). However, there is very limited information on the use of HC2 triage from Southeast Asia. In Thailand, there is only one previous study on HC2 triage of 90 women with ASC-US cytology (Kiatpongsan et al., 2006). Furthermore, there are only few studies that evaluated the triage performance of HC2 using different viral load cut-off thresholds, and such information has not been available in this region. The aim of this study was to assess the performance of HC2 in the detection of histologic HSIL+ in women with minor cervical cytologic abnormalities in northern Thailand.

Materials and Methods

This study was approved by the institutional ethic committee. Women with ASC-US/LSIL cytology results who were referred to colposcopy clinic at Chiang Mai University Hospital, in northern Thailand, from October 2010 to February 2014 were included into the study after an informed consent was obtained. Women who were pregnant, had previous hysterectomy, or had a previous history of any cervical lesion, abnormal cytology, or positive HPV testing were excluded. The majority of study population (69%) represented women who received conventional cervical cytology screening (Pap test) from outside clinics, whereas the remainder consisted of women from a population-based screening using liquid-based cytology (LBC) and HC2 (co-testing) performed in the Department of Pathology, Chiang Mai University (Siriaunkul et al., 2014). LBC slides were prepared using ThinPrep method (Hologic, Marlborough, MA, USA) and examined by 2 cytopathologists (J.S. and K.S.)

For the patients who had only referral Pap test results

available, cervical specimen for HPV DNA test was collected at colposcopy using a plastic spatula and a cytobrush. The sample was transferred from the collecting device into PreservCyt solution (Cytoc Corporation, Boxborough, MA, USA). The samples were tested for hrHPV DNA using HC2 test (Qiagen, Hilden, Germany) according to the manufacturer's instructions. HC2 test is designed to detect 13 hrHPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The quantitative viral load expressed in a relative light unit/positive control (RLU/PC) ratio was recorded. Positive HC2 test was defined with an RLU/PC ratio ≥ 1.0 . For the patients who already had LBC and HC2 tests performed in Chiang Mai University, the test results were collected.

All patients received colposcopic examination by gynecologic oncologists within 3 months after abnormal cytology results. Cervical tissue was obtained by biopsy or LEEP conization for histologic examination. Histologic diagnoses of all specimens were made by a team of gynecologic pathologists. In the cases that cervical tissue was not obtained, negative colposcopic diagnosis was considered only in women with satisfactory colposcopic examination and no suspicious lesion. The diagnoses after colposcopy were categorized for analysis as negative (absence of epithelial lesions), histologic LSIL, and histologic HSIL+.

Correlation was made between patient age group, cytology type and result, HC2 result and RLU/PC ratio, and the histologic diagnosis. Accuracy values of HC2 in predicting the presence of histologic HSIL+ were calculated, with reference to different age groups and RLU/PC ratio cut-off values. The data were analyzed by STATA version 11 (StataCorp LP, College Station, TX, USA). Differences of the results were tested by Fisher Exact test or T-test as appropriate. A p value <0.05 was considered statistically significant.

Results

There were 238 women included in this study, 121 (50.8%) had ASC-US cytology and 117 (49.2%) had LSIL cytology. The patients' age ranged 19 to 68 years with a mean age of $44.0 \pm SD 9.4$ years ($46.1 \pm SD 8.4$ years in ASC-US group and 41.9 ± 10.0 years in LSIL group, $p < 0.001$). The RLU/PC ratio ranged 0.06 to 2,054.7 with a median of 4.4 (0.3 in ASC-US and 176.1 in LSIL). The overall HC2 positivity rate was 57.6%. The HC2 positivity rate was significantly higher in LSIL group than in ASC-US group (74.8% versus 41.0%, $p < 0.001$). The diagnoses after colposcopy were histologic HSIL+ in 25 women (10.5%, including 2 women with squamous cell

Table 1. Detection Rate of Histologic HSIL or Worse in 238 Women with ASC-US or LSIL Cytology Stratified by Age Groups

Age group (years)	Total cases		ASC-US cytology		LSIL cytology	
	No.	No. of HSIL+	No.	No. of HSIL+	No.	No. of HSIL+
≤ 40	84	9 (10.7%)	31	3 (9.7%)	53	6 (11.3%)
41-50	83	11 (13.3%)	46	4 (8.7%)	37	7 (18.9%)
> 50	71	5 (7.0%)	44	2 (4.5%)	27	3 (11.1%)
Total	238	25 (10.5%)	121	9 (7.4%)	117	16 (13.7%)

*HSIL+: histologic high-grade squamous intraepithelial lesion or worse lesions

carcinoma and adenocarcinoma each), histologic LSIL in 98 women (41.2%), and negative result in 115 women (48.3%). Cervical tissue biopsy was not obtained in 10 of the 115 women with negative colposcopic diagnosis.

Histologic HSIL+ was detected in 9 women (7.4%) in ASC-US group and 16 women (13.7%) in LSIL group (Table 1). The difference in the histologic HSIL+ detection rate between ASC-US group and LSIL group was not significant ($p=0.141$). Women aged >50 years tended to

Table 2. Comparison of Diagnoses and HC2 Results in Women with ASC-US and LSIL Cytology Stratified by Types of Cytology Specimens

	ASC-US cytology, n=121		LSIL cytology, n=117	
	LBC, n=46 (%)	Pap, n=75 (%)	LBC, n=27 (%)	Pap, n=90 (%)
HC2 result				
Positive	21 (45.7)	27 (36.0)	25 (92.6)	64 (71.1)
Negative	25 (54.3)	48 (64.0)	2 (7.4)	26 (28.9)
Colposcopic diagnosis/histology				
Negative	27 (58.7)	50 (66.7)	10 (37.0)	28 (31.1)
LSIL	16 (34.8)	19 (25.3)	13 (48.1)	50 (55.6)
HSIL or worse	3 (6.5)	6 (8.0)	4 (14.8)	12 (13.3)

*LBC: liquid-based cytology

have a lower rate of histologic HSIL+ in the ASC-US group, but the difference was not significant (Table 1). Histologic LSIL was detected in 35 women (28.9%) in ASC-US group and 63 women (53.8%) in LSIL group. The detection rate of histologic LSIL was significantly higher in LSIL cytology than in ASC-US cytology ($p<0.001$).

Table 2 shows a comparison between cytology specimen types (LBC and Pap test) among ASC-US group and LSIL group with regard to HC2 results and colposcopy results. The HC2 positivity rate was significantly higher in the LBC specimens than in the Pap specimens with LSIL cytology ($p=0.026$), whereas the difference was not significant in ASC-US group ($p=0.341$). There was no significant difference in the distribution of histologic diagnoses between LBC and Pap specimens among ASC-US group ($p=0.550$) and LSIL group ($p=0.784$).

In HC2-positive ASC-US group, the detection rate of histologic HSIL+ tended to be higher in LBC specimens than in Pap specimens (14.3% versus 8.0%, $p=0.712$), whereas this detection rate was similar in LBC and Pap specimens among HC2-positive LSIL cytology (16.0% versus 18.8%, $p>0.999$). There was no histologic HSIL+ detected among HC2-negative cases.

Table 3. The Performance of HC2 in Predicting Histologic HSIL or Worse Stratified by Age Groups

Age group (years)	No.	HC2-positive rate (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total cases	238	57.6	52.9	100	47.4	18.2	100
≤40	84	69.0	41.7	100	34.7	15.5	100
41-50	83	59.0	54.2	100	47.2	22.4	100
>50	71	42.2	64.8	100	62.1	16.7	100
ASC-US	121	41.0	67.8	100	65.2	18.8	100
≤40	31	58.1	51.6	100	46.4	16.7	100
41-50	46	45.7	63.0	100	59.5	19.0	100
>50	44	20.5	84.1	100	83.3	22.2	100
LSIL	117	74.8	37.6	100	27.7	18.0	100
≤40	53	75.5	35.8	100	27.7	15.0	100
41-50	37	75.7	43.2	100	30.0	25.0	100
>50	27	77.8	33.3	100	25.0	14.3	100

*NPV: negative predictive value, PPV: positive predictive value

Table 4. Comparison of the HC2 Performance Using Different RLU/PC Ratio cut-off Values In Predicting Histologic HSIL or Worse

Cut-off for positive test (RLU/PC ratio)	No. of positive test	No. of histologic HSIL+	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total cases, n=238							
1.0	137	25	52.9	100	47.4	18.2	100
2.0	127	23	55.5	92.0	51.2	18.1	98.2
4.0	121	21	56.0	84.0	53.1	17.4	96.6
10.0	110	19	59.2	76.0	57.3	17.3	95.3
20.0	106	17	59.2	68.0	58.2	16.0	93.9
ASC-US, n=121							
1.0	48	9	67.8	100	65.2	18.8	100
2.0	42	8	71.1	88.9	69.6	19.0	98.7
4.0	36	6	72.7	66.7	73.2	16.7	96.5
10.0	31	5	75.2	55.6	76.8	16.1	95.6
20.0	30	5	76.0	55.6	77.7	16.7	95.6
LSIL, n=117							
1.0	89	16	37.6	100	27.7	18.0	100
2.0	85	15	39.3	93.8	30.7	17.6	96.9
4.0	85	15	39.3	93.8	30.7	17.6	96.9
10.0	79	14	42.7	87.5	35.6	17.7	94.7
20.0	76	12	41.9	75.0	36.6	15.8	90.2

*NPV: negative predictive value, PPV: positive predictive value

Among different age groups (40 years or less, 41-50 years, and >50 years), HC2 positivity rate was significantly decreased by age in ASC-US group from 58.1% in the women aged 40 years or less to 20.5% in women aged > 50 years ($p=0.001$) (Table 3), whereas there was almost no change of HC2 positivity rate among LSIL cytology by age. The accuracy and the specificity of HC2 in the detection of histologic HSIL+ was significantly increased with age among ASC-US group ($p=0.007$ and $p=0.003$, respectively), while no significant difference was observed in LSIL group.

Table 4 shows a comparison of HC2 performance using variable cut-off value of RLU/PC ratio (from 1.0 to 20.0) and histologic HSIL+ as the triage aim among 238 patients with ASC-US or LSIL cytology. Increase of the cut-off value to 20.0 reduced the number of women with positive test by 22.6% (37.5% in ASC-US and 14.6% in LSIL). The accuracy and the specificity were increased (4.3-8.2% and 8.9-12.5% difference, respectively) in all patient groups (overall, ASC-US, and LSIL). However, in all groups, there was a decrease of the sensitivity (25.0-44.4% difference), particularly in the ASC-US group, and the negative predictive value (4.4-9.8% difference).

Discussion

Minor cytologic abnormalities account for approximately 5-7% of all cervical cytology reporting and comprise the majority of abnormal cytology results (ALTS Group, 2003b; Katki et al., 2013). ASC-US and LSIL have overlapping cytomorphology and risk for high-grade cervical lesions (Solomon et al., 2002; Castle et al., 2007; Fujii et al., 2014). In general, women with minor cervical cytologic abnormalities have less than 20% risk of histologic HSIL+ and a very low risk of cervical cancer (ALTS Group, 2003a; 2003b). The reported risk of cervical cancer was as low as 0.1% in a large recent US study (Katki et al., 2013). However, in previous ASC-US and LSIL studies in northern Thailand where the cervical cancer incidence is high, a relatively high risk for cervical cancer (1.9-2.4%) was reported (Kantathavorn et al., 2008; Kiatiyosnusorn et al., 2010). Considering the rather low cost of colposcopy and patients' compliance for follow-up in Thailand, referral these women for colposcopy has been recommended (Kietpeerakool et al., 2014).

The detection rate of histologic HSIL+ in minor cervical cytologic abnormalities in this study was lower than that previously reported from the same institution which were based on the cases collected before 2010 (13.9% in ASC-US and 32.2% in LSIL cytology) (Kantathavorn et al., 2008; Kiatiyosnusorn et al., 2010). However, the detection of histologic HSIL+ in ASC-US in this study is comparable to that in another 2 recent studies in Thailand (Ekalaksananan et al., 2011; Pothisuwan et al., 2011), and our result in LSIL is within the range reported from other institutions in the country (11.2-19.6%) (Kietpeerakool et al., 2014). The explanation for the difference is not clear as the cytology results in this study were obtained from our institution (using LBC) and other laboratories (using Pap test), and there was no significant difference in histologic HSIL+ detection rate regarding

the type of cytology specimen. As the results in this study should reflect the current cytology practice after a decade of implementation of 2001 Bethesda system, possible explanations might include the declining incidence of cervical cancer in Thailand over time by cancer screening or the modification of interpretation among cytology examiners through the development of educational and quality assessment processes in the country. Compared to recent reports from the developed countries with a low cervical cancer incidence, the detection rate of histologic HSIL+ in our study was slightly higher than that in the US study (6.1% of ASC-US and 11.6% of LSIL cytology) (Katki et al., 2013), but was lower than that of another Japanese study (17.6% in ASC-US and 19.2% in LSIL cytology) (Fujii et al., 2014). Variation in the training for cytology and/or histologic interpretation in different regions might partly contribute to variable detection rate of histologic HSIL+ among ASC-US and LSIL studies.

The prevalence of positive HC2 among samples with ASC-US or LSIL in this study (41.0% and 74.8%, respectively) was within the previously reported ranges (23-77% in ASC-US and 55-89% in LSIL) (Kiatpongsan et al., 2006; Arbyn et al., 2009; Kelly et al., 2011; Junyangdikul et al., 2013; Katki et al., 2013; Li et al., 2013; Laowahutanont et al., 2014). One previous study in northeastern Thailand using PCR detection of HPV DNA (either low- or high-risk types) reported a similar positivity rate in ASC-US (43.8%) and LSIL (76.9%) (Ekalaksananan et al., 2011).

There has been a controversial issue whether liquid-based cytology is more sensitive in the detection of cervical epithelial lesions than conventional Pap test (Sigurdsson, 2013). Although there was some difference of HC2 positivity rate between the LBC and Pap test in this study, the detection rate of histologic HSIL+ was comparable between both cytological methods either in the ASC-US group or LSIL group. The finding indicates that the outcomes of minor cytologic abnormalities in our region are not significantly affected by the types of cytology specimen used in the screening.

In this study, all women with histologic HSIL+ were HC2-positive, and the sensitivity and negative predictive value of HC2 triage was very high. However, the overall specificity and positive predictive value was rather low (47.4% and 18.2%, respectively). The specificity of HC2 test was higher in ASC-US cytology than in LSIL cytology (65.2% and 27.7%, respectively) and was comparable to the pooled specificity reported in the recent meta-analysis (58.3% for ASC-US and 27.8% for LSIL) (Arbyn et al., 2013b), whereas the positive predictive value is similarly low in both groups. The sensitivity of HC2 for detection of histologic HSIL+ among women with ASC-US cytology in our study was higher than the previous study in Thailand (100% versus 85.7%), whereas the specificity (65.2% versus 69.7%) and negative predictive value (100% versus 96.4%) were comparable (Kiatpongsan et al., 2006). However, the positive predictive value of HC2 was lower in our study (18.8% versus 34.3%), which was possibly related to a lower rate of histologic HSIL+ among ASC-US women (7.4% versus 15.6%) (Arbyn et al., 2013b). For LSIL cytology, HC2 triage was less effective due to

the high positive rate of HPV test in this group, similar to the previous observations (Arbyn et al., 2009).

Regarding the influence of age group, the performance of HPV triage was apparently improved among women aged >50 years with ASC-US cytology. The finding is in keeping with the previous reports (Arbyn et al., 2013b; Katki et al., 2013). In our previous population-based screening with HC2 test (Siriaunkgul et al., 2014), the proportion of HC2-positive women declines after age 50 years, and this may enhance the significance HC2 in women of this age group who have ASC-US cytology. For women with LSIL which reflects a productive HPV infection with a high viral load, the proportion of HC2-positive women was consistently high across different age groups. The specificity of HC2 triage of LSIL cytology was similar in all age groups. This finding is different from the pooled data in the meta-analysis study where the specificity of HC2 triage of LSIL is increased by age and is up to 43.7% in women aged >50 years (Arbyn et al., 2013b).

Increasing the cut-off threshold for positive HC2 was found to increase specificity of HC2 in triage of minor cervical cytologic abnormalities (Arbyn et al., 2013b). In an Italian study (Ronco et al., 2007), the sensitivity of HC2 triage was unchanged when the RLU/PC cut-off threshold was increased from 1.0 to 2.0, whereas the specificity was increased for 3-5%. In another UK study (Sargent et al., 2010), the use of RLU/PC cut-off of 2.0 for HC2 triage is suggested. In our study, although an increase of cut-off threshold from 1.0 to 2.0 helped decrease the number of cases for colposcopy by 7.3%, this resulted in missing 8.0% of histologic HSIL+. With increasing cut-off threshold, the overall accuracy and specificity increased. However, there was a substantial drop in the sensitivity and negative predictive value. At the threshold of 20.0, the sensitivity of HC2 was previously reported as 73.1% in ASC-US and 90.6% in LSIL (Arbyn et al., 2013b), which is much higher than that observed in our study (55.6% in ASC-US and 75.0% in LSIL). These findings suggest that the increase of cut-off threshold may not be suitable for HC2 triage of minor cervical cytologic abnormalities in northern Thailand.

Despite the high sensitivity and negative predictive value of HC2 in triage of minor cervical cytologic abnormalities, the positive predictive value is rather low. Several potential additional biomarkers are under investigations such as such as HPV 16/18 genotyping, HPV E6/7 mRNA test, p16/Ki67 dual immunocytochemistry, and DNA methylation (Arbyn et al., 2013a; Verdoodt et al., 2013; Chujan et al., 2014; Fujii et al., 2014; Ordi et al., 2014; Persson et al., 2014; Tezcan et al., 2014). Further studies are needed in the evaluation of the effectiveness of these tests in the population of this region.

In conclusion, hrHPV DNA testing with HC2 shows very high sensitivity and negative predictive value in triage of women with minor cervical cytologic abnormalities in northern Thailand. The performance of HC2 triage is highest among women aged >50 years with ASC-US cytology. An increase of the cut-off threshold for HC2 triage is not recommended in this region.

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