Cost-Effectiveness Analysis of Different Management Strategies for Detection CIN2+ of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) Pap Smear in Thailand

Tanitra Tantitamit1*, Wichai Termrungruanglert1, Shina Oranratanaphan1, Somchai Niruthisard1, Patuou Tanbirojn1, Piyalamporn Havanond2

Abstract

Background: To identify the optimal cost effective strategy for the management of women having ASC-US who attended at King Chulalongkorn Memorial Hospital (KMCH). Design: An Economical Analysis based on a retrospective study. Subject: The women who were referred to the gynecological department due to screening result of ASC-US at King Chulalongkorn Memorial Hospital, a general and tertiary referral center in Bangkok Thailand, from Jan 2008 - Dec 2012. Materials and Methods: A decision tree-based strategy was constructed to evaluate the cost effectiveness of three follow up strategies in the management of ASC-US results: repeat cytology, triage with HPV testing and immediate colposcopy. Each ASC-US woman made the decision of each strategy after receiving all details about this algorithm, advantages and disadvantages of each strategy from a doctor. The model compared the incremental costs per case of high-grade cervical intraepithelial neoplasia (CIN2+) detected as measured by incremental cost-effectiveness ratio (ICER). Results: From the provider’s perspective, immediate colposcopy is the least costly strategy and also the most effective option among the three follow up strategies. Compared with HPV triage, repeat cytology triage is less costly than HPV triage, whereas the latter provides a more effective option at an incremental cost-effectiveness ratio (ICER) of 56,048 Baht per additional case of CIN 2+ detected. From the patient’s perspective, the least costly and least effective is repeat cytology triage. Repeat colposcopy has an incremental cost-effectiveness (ICER) of 2,500 Baht per additional case of CIN2+ detected when compared to colposcopy. From the sensitivity analysis, immediate colposcopy triage is no longer cost effective when the cost exceeds 2,250 Baht or the cost of cytology is less than 50 Baht (1USD = 31.58 THB). Conclusions: In women with ASC-US cytology, colposcopy is more cost-effective than repeat cytology or triage with HPV testing for both provider and patient perspectives.

Keywords: ASC-US - cost effectiveness - PAP smear - colposcopy - HPV testing - ICER

Introduction

Cervical cancer is the second most common cancer in the world and the most common gynecological cancer in Thailand. In 2009, the prevalence and mortality rate were 24.5 and 12.8 cases per 100,000 per year (WHO/ICO Information Centre, 2010). Fortunately, the optimal strategy for screening and management precancerous lesion would decrease both morbidity and mortality of cervical cancer.

The most common cytological abnormality is atypical cells of undetermined significance (ASC-US), 2.8% of all PAP smear results in US (Katic et al., 2013). It carries the risk of CIN2 6.9%, CIN3 2.6% and cervical cancer 0.1% (Katic et al., 2013). Where as the incidence of ASC-US in Thailand is 0.6-1.75% (Chichareon et al., 2002; Chichareon et al., 2005; Limpvanuspong et al., 2008), and 1.5% in our institution. It has a relatively high prevalence of high grade lesions from several previous studies in Thailand (10-18%) (Chichareon et al., 2002; Chichareon et al., 2005; Kantathavorn et al., 2008; Limpvanuspong et al., 2008; Sunthonlamsiri et al., 2010; Poomtavorn et al., 2011).

The optimal strategy for ASC-US triage should identify those women who require treatment and avoiding unnecessary procedures. The management of ASC-US is controversial. Clinical data from ALTS has demonstrated that two repeat cytology performed at 6 months interval, testing for HPV DNA and a single colposcopy are effective approaches to management the women with ASC-US (Wright et al., 2007).

Colposcopy with directed biopsy is a gold standard strategy for detection CIN. From several studies in Thailand revealed that the incidence of high-grade lesions detected from ASC-US was higher than other studies in Europe and US (Chichareon et al., 2002; Chichareon et al., 2005; Limpvanuspong et al., 2008).

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The repeat cytology is commonly used as a follow up method because it is not expensive and easy to do. The sensitivity of repeat cytology is 75% (Yarandi et al., 2009). The disadvantages are time consuming, increasing anxiety, patient’s discomfort, poor compliance and delaying management in high-grade lesion patients. The HPV triage is an accepted approach and has a higher accuracy than repeat cytology method (Arbyn et al., 2013). Approximately 40 percent of women with ASC-US Pap smear had a negative result for high risk HPV. Those patients can avoid an unnecessary colposcopy (Solomon et al., 2001). HR-HPV is a high sensitivity test and considered as the most cost-effectiveness strategy from several previous studies (Lytwyn et al., 2000; Kim et al., 2002; Kulasingam et al., 2006; Sheriff et al., 2007; Vanni et al., 2011).

Although HPV testing was a preferred method from previous economic studies, it may not an appropriate option in Thailand because of the difference in cost and detection rate. For this reason, we conduct this study to evaluate the most effectiveness and the most economical strategy for management of ASCUS women to detect the lesions of CIN 2 or greater.

Materials and Methods

Study design

This is an economical analysis study based on retrospective data reviewed from medical record of women with ASC-US cytology who attended at OPD at King Chulalongkorn Memorial Hospital (KCMH), a general and tertiary referral center in Bangkok Thailand, from Jan 2008 to Dec 2012. We use the colposcopy with directed biopsy to detect CIN 2+ as a gold standard method. Primary screening was performed by using the conventional method. The results were reported based on Bethesda 2001 system. If there is any abnormal result, the patients will be called to see the gynecologists. They will receive the details about management algorithm, advantage and disadvantages of each strategy in order to make a decision by themselves.

Three treatment strategies consists of colposcopy arm, HPV testing (Hybrid Capture 2® High-Risk HPV DNA Test TM) and repeat conventional cytology sampling. Women in the immediate colposcopy arm were referred to colposcopy and biopsy, those in the HPV triage arm were referred to colposcopy if high-risk HPV types were detected and those in repeat cytology arm which follow up at 6 and 12 months were referred to colposcopy if a repeat abnormal result occurred.

Cost data

We conducted the analysis from both health care provider (hospital) and patient’s perspective. The recent cost data in 2013 were used and expressed in Thai Baht. (1USD = 31.58THB). We use only direct medical costs, which were provided by Center of Health Assurance at KCMH. The unit costs consist of the material costs such as HPV test cost, physician assessment, cytopathological laboratory test and electricity cost. Capital cost and labor cost were also included. Indirect costs such as loss of productivity and transportation costs were assumed to have the same among patients.

Clinical data and cost effectiveness analysis

A decision tree was developed to predict the clinical management algorithm. Base case values used in the model were mainly based on data from a retrospective study from Jan 2008 to Dec 2012. Effectiveness was expressed as the number of CIN2+ cases detected by different methods. The results of cost-effectiveness analysis were represented by incremental cost-effectiveness ratios (ICERs) per detected CIN 2+ case.

ICER is calculated from this formula; ICER = (C1 - C2) / (E1 - E2)

C1-C2 = additional cost of method 1 compare with method 2
E1-E2 = additional case of CIN2+ detected of method1 compare with method 2

Results

Clinical data, cost data and base case analysis

From retrospective data of women referred to gynecological investigation due to Pap smear screening result of ASC-US. The total number of ASCUS diagnosed women was 1,401, but only 1,117 women followed up at gynecologic clinic of KCMH. There were 391, 157 and 569 women decided to undergo immediate colposcopy,
HPV testing and repeat cytology respectively. All of these, 69 cases were proved to be CIN2+ through following pathological reports (6.71%).

Figure 1 presents the CIN 2+ detected rate of each strategy. Colposcopy was the most effective method. The detected rate of CIN2+ cases was 9.7% whereas the detected rate of HPV-testing and PAP smear were 5.1% and 4.1% respectively. Repeat cytology was the strategy that has the highest rate of noncompliance patients (13.1%)

Directed medical cost used in both base case and sensitivity analysis was shown in Table 1

Table 2 presents the base-case effectiveness. Table 3 and Figure 2, present base-case incremental cost effectiveness result. In provider’s perspective, both HPV testing and cytology triages were strongly dominated by colposcopy, that is, colposcopy constituted the least costly and most effective follow up strategy. Compare the repeat cytology with HPV triage; repeat cytology triage is less costly than HPV triage, whereas HPV triage provides more effective option at an incremental cost-effectiveness ratio (ICER) of 56,048 Baht per additional case of CIN 2+ detected.

In the patient’s perspective, the least costly and least effective is repeat cytology triage. Repeat cytology has an incremental cost-effectiveness (ICER) of 2,500 Baht per additional case of CIN2+ detected when compare to colposcopy.

Figure 2. Base-case Incremental Cost Effectiveness Results: Provider’s Perspective

Table 3. Base-Case Incremental Cost Effectiveness Results

Table 1. Direct Medical Costs Baseline Values and Ranges used in Sensitivity Analysis*

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>COST (Baht)</th>
<th>Base case</th>
<th>Patient’s perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy</td>
<td>357</td>
<td>640</td>
<td>250-3200</td>
</tr>
<tr>
<td>HPV testing</td>
<td>1,121.58</td>
<td>1,127.12</td>
<td>300-2300</td>
</tr>
<tr>
<td>Cytology</td>
<td>561.1</td>
<td>500</td>
<td>150-1550</td>
</tr>
</tbody>
</table>

*Ranges used in sensitivity analysis for costs were obtained from a survey of laboratories from various government and private hospitals in Thailand

Table 2. Base case analysis of costs and outcome of evaluation of ASC-US

<table>
<thead>
<tr>
<th>PROVIDER’S PERSPECTIVE</th>
<th>Cost (Baht)</th>
<th>CIN2+ Detected per 100</th>
<th>CIN2+ Detected per case</th>
<th>C/E (Baht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colposcopy</td>
<td>357</td>
<td>9.7</td>
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<td>HPV testing</td>
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<tr>
<td>Cytology</td>
<td>561.1</td>
<td>4.1</td>
<td>0.041</td>
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<table>
<thead>
<tr>
<th>PATIENT’S PERSPECTIVE</th>
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<td>9.7</td>
<td>0.097</td>
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<tr>
<td>HPV testing</td>
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<td>0.051</td>
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<td>Cytology</td>
<td>500</td>
<td>4.1</td>
<td>0.041</td>
<td>12,195</td>
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</tbody>
</table>

Table 3. Base-Case Incremental Cost Effectiveness Results

<table>
<thead>
<tr>
<th>PROVIDER’S PERSPECTIVE</th>
<th>IC (Baht)</th>
<th>IE (CIN2+ detected per case)</th>
<th>ICER (Baht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy</td>
<td>(561.1)</td>
<td>-0.056</td>
<td>Dominated</td>
</tr>
<tr>
<td>HPV testing</td>
<td>(1121.5)</td>
<td>-0.046</td>
<td>Dominated</td>
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<tr>
<td>HPV testing</td>
<td>(1121.5)</td>
<td>0.01</td>
<td>56,048</td>
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<thead>
<tr>
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<th>ICER (Baht)</th>
</tr>
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<tbody>
<tr>
<td>Colposcopy</td>
<td>(640.0)</td>
<td>0.056</td>
<td>2,500</td>
</tr>
<tr>
<td>HPV testing</td>
<td>(1121.1)</td>
<td>-0.046</td>
<td>Dominated</td>
</tr>
<tr>
<td>HPV testing</td>
<td>(1127.1)</td>
<td>0.01</td>
<td>62,712</td>
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ICER is calculated according to the following equation: ICER = (Cost of screen strategy A - Cost of screening strategy B) / (Effectiveness of screen strategy A - Effectiveness of screening strategy B). Dominated strategies are those with higher costs and lower clinical efficiency than other strategies, IC: Incremental cost, IE: Incremental effectiveness, ICER: Incremental cost effectiveness ratio

ASC-US: Atypical Squamous Cells of Undetermined Significance, CIN: Cervical intraepithelial neoplasia, C/E: Cost/Effectiveness
Sensitivity analysis

Table 4 presents the one-way sensitivity analysis of costs for follow up strategies. The model results were most sensitive to change in colposcopy costs. The cytology triage will become the most cost-effectiveness option when the cost of colposcopy exceeds 2,250 Baht or the cost of cytology less than 50 Baht.

When vary HPV testing cost, HPV testing remains dominated by colposcopy. However, when the cost of HPV testing was less than 300 Baht, there was no longer a dominated alternative and provided more cost effective than cytology triage at ICER 7,712 Baht.

Discussion

There were 69 CIN2+ cases from 1,117 ASC-US results detected by all of the three strategies (6.71%). This detection rate is lower than other previous studies in Thailand that show a prevalence of high grade CIN in women with ASC-US was 12-26% (Chichareon et al., 2002; Kantathavorm et al., 2008; Limpvanuspong et
The study found that colposcopy was the most effective method, with 97.9% (95% CI: 96.0-99.2) CIN2+ cases detected, compared to 95.6% (95% CI: 93.6-97.3) by HPV testing. The cost-effectiveness of each strategy was evaluated, with the most cost-effective strategy being HPV testing in women with ASC-US smear results, followed by colposcopy. The results suggest that for women with ASC-US smear results, HPV testing is the most cost-effective strategy, followed by colposcopy.

References


rate of CIN2+ cases obtained from a retrospective study in the single institution that cannot represent the entire population in Thailand. Third, high rates of loss to follow up might interfere the effectiveness of cytology and HPV testing. Fourth, lack of information on the quality of life related to the different strategies may be considered. Although colposcopy was the most effective method, it might cause negative psychological effect associated with an examination. The HPV testing and colposcopy triages might cause anxiety because they need a period of time to follow up and do not completely avoid the unnecessary to perform colposcopy. Last, there are also other factors that may affect the effectiveness of each strategy such as the experience of physicians, the reliability and accuracy of laboratory and pathological interpretation which are difficult to access.

To clarify the accurate cost-effectiveness of each triage, future study should be a prospective study from multicenter in Thailand. It also would be valuable to obtain and compare QALYs of the women who diagnosed ASC-US smear results after performed different strategies. Currently, the follow up protocol was changed as ASCCP 2012; reflex HPV testing is preferred and extends the follow up period of cytology triage. Adjustment of the economic model is necessary to give better information for decision making in the future.

In conclusion, the results of the study may guide the physicians in counseling and management the women with ASC-US cytology for the optimal management in low-resource countries and may be benefit for health policies and resource management of the hospitals.
Tanitra Tantitamit et al


