

## The accuracy and cost-effectiveness of triple screening tests in cervical neoplasia

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**Objective :** Ideal cancer screening program should be not only accurate but also cost-effective. However, in Korea, the two aspect of cervix cancer screening program was not yet evaluated. Thus we conducted this study to evaluate the cost-effectiveness and accuracy of various screening methods for detecting uterine cervical neoplasia.

**Methods :** We used various methods (conventional Pap smear, cervicography and HPV test) to detect cervical neoplasia on 255 women who visited the Seoul National University Hospital from Dec. 1996 to Jul. 1997 and analyzed the accuracy and cost-effectiveness of each method along with various combinations of methods using Bayesian theorem. The accuracy was judged by the final histopathologic diagnosis.

**Results :** Sensitivity (SE) and specificity (SP) of each method to detect cervical intraepithelial neoplasia (CIN) 1 or above were 83.0% and 69.4% in Pap smear, 53.7% and 85.2% in cervicography, and 57.8% and 80.6% in HPV test, respectively. The combination of Pap smear with cervicography or with HPV test for detecting CIN 1 or above had same SE and SP of 89.1% and 62.0% respectively. The combination of cervicography and HPV test had SE of 78.9% and SP of 70.4%. Three methods combination showed 93.9% SE and 54.6% SP. The estimated cost per method was highest in three methods combination (117,000 won) and lowest in Pap smear alone (12,000 won). The cost for detection of one case of cervical neoplasia was highest in combination of cervicography and HPV test (241,907 won) and lowest in Pap smear alone (25,385 won).

**Conclusion :** The combinations of each method showed increased SE. These combinations, however, had low SP and high cost than individual method. Cervicography or HPV test alone should not be considered as an alternative to Pap smear for cervical cancer screening because its cost-effectiveness is not significantly better than that of Pap smear.

**Key Words :** Cervical neoplasia, Screening, Cost-effectiveness

## INTRODUCTION

Cervical cancer is the second most common cancer of women worldwide.<sup>1</sup> Invasive cervical cancer incidence has been decreased during last decade along with increase of pre-cancerous disease - cervical intraepithelial neoplasia (CIN) - in Korea.<sup>2</sup> Development of screening program and public education has led to increased detection rate of CIN, while invasive cancer incidence and mortality have dramatically decreased by effective treatment of CIN. Because cervical cancer can be cured when detected

early, continuous and active research for cervical cancer screening program is very important part not only in gynecologic oncology but also in national health affair.

Conventional cytology is relatively simple and cheap method of cervical cancer screening and eventually has led to decreased cervical cancer incidence and mortality.<sup>3</sup> However, 25-35% of false negative rate of Pap smear is need to be overcome,<sup>3-5</sup> and there have been substantial effort to develop a novel screening method.<sup>6</sup>

Colposcopy magnifies 6 to 40 times the lesion and application of acetic acid to the lesion is great help in discriminating between normal cervix and pre-invasive/invasive cervical disease. It also has a merit that directed biopsy is possible during colposcopy.<sup>7</sup> Cervicography, developed by Staff et al. in 1981, provides permanent, objective documentation of normal and abnormal cervical

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patterns.<sup>8</sup> The projected cervicogram is comparable to direct visual colposcopic magnification and resolution. The cervicogram can be obtained by a technician and sent to an expert for evaluation. Therefore cervicography possibly be used as a mass screening method by its comparable simplicity and accuracy.<sup>9,10</sup>

The primary cause of cervical cancer development is human papillomavirus (HPV).<sup>11</sup> Because HPV infections are necessary, if not sufficient, causes of cervical cancer, various methods have been developed and used for HPV detection. Various studies revealed that the combination of HPV DNA test and Pap smear had almost 100% sensitivity and negative predictive value to detect high-grade CIN.<sup>12</sup> At last the American College of Obstetricians and Gynecologists (ACOG) announced in 2003 that the combined use of a cervical cytology and FDA-approved test for high-risk types of HPV is an acceptable option of cervical cancer screening for women older than 30. Once women test negative on both tests they should be re-screened with the combined tests no more frequently than every 3 years. If only one of the tests is negative, however, more frequent screening will be necessary.

However, the most cost-effective method or combination is quite different in each country because it must have been affected by the disease prevalence, available medical resources and medical insurance system of individual country. Thus, we performed this study to find the most effective method(s) for cervical cancer screening in Korea.

## MATERIALS AND METHODS

Two hundred and fifty five women who visited the Department of Obstetrics and Gynecology, Seoul National University Hospital to participate in the annual screening program for gynecologic cancer or referred to the hospital for their abnormal Pap smear results performed at other clinics were enrolled in this study. Informed consent was obtained from each participant. Before beginning this study, the study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

All participants had Pap smear, cervicography, and

HPV DNA test. After the three tests, histopathological confirmation was done by colposcopy directed punch biopsy or large loop excision of the transformation zone (LLETZ).

Conventional Pap smear was done as usual procedure using cytobrush, glass slide, and 95% alcohol as fixative. The 1991 Revised Bethesda System was used for judging the slides.

Cervicography was done using cervicoscope provided by NTL Asia (National testing Lab, Asia). After the application of 5% acetic acid to cervix for 15 sec, first shot of cervicography was taken and second shot was taken within 10 sec of first shot. Licensed evaluator of cervicography, approved by NTL Worldwide (National Testing Laboratory, Worldwide) and Medical College of Wisconsin, judged the cervicography to negative, atypical, positive (P0, P1, P2, P3), and technically defective. Positive results mean as follows; P0: probable normal variant, P1: low grade lesion, P2: high grade lesion, P3: cancer.

HPV DNA test was done using the Hybrid Capture<sup>®</sup> 2 system (Digene corporation) which can detect the high risk HPV type 16, 18, 31, 33, 35, 45, 51, 52, and 56. Sample collection was done at cervix, transformation zone, posterior fornix of vagina using sterilized speculum and cytobrush.

After the sequential application of 5% acetic acid and iodine solution to cervix, a gynecologic oncologist observed the cervix focused on atypical vascular pattern, white epithelia, punctation, and mosaicism with colposcopy (OMPI 6-SH, Carl Zeiss, Germany), and biopsied the cervical tissue for histopathological diagnosis.

LLETZ was done as follows. Following colposcopic assessment with the application of 5% acetic acid, the stroma of the cervix outside the transformation zone was infiltrated with 8 mL of a local anesthetic (2% lidocaine with 2-4 unit of vasopressin). A Radiofrequency Surgical Unit (Surgiton, Ellman Co., U.S.A) was used, together with a wire loop of appropriate size to excise the transformation zone, with the generator set on both cutting and coagulation.

Histopathological diagnosis for the tissue obtained from colposcopy directed punch biopsy and LLETZ was done by a specialized pathologist as following criteria; normal,

low-grade CIN (CIN 1), high-grade CIN (CIN 2, 3), and cancer.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each method (Pap smear, cervicography, HPV DNA test) and their combinations using histopathological diagnosis of colposcopy directed punch biopsy and LLETZ as a reference. The cost to detect a patient with cancer or CIN by each method and their combinations was calculated using sensitivity, specificity, PPV, and NPV according to the standard charge of National Health Insurance of Korea and compared each other. In various combinations of three methods, at least one abnormal result among them was considered as screening positive because an abnormal finding can induces further investigation.

## RESULTS

Pap smear revealed 39.2% of normal cytology, 13.3% of ASCUS, 12.2% of LSIL, 20.4% of HSIL, and 14.9% of cancer. Cervicography showed 54.9% of normal, 7.8% of atypical, 12.5% of P0, 7.5% of P1, 9.0% of P2, and 8.2% of P3. High risk HPV positive patients were 41.6%. Histopathological diagnosis results were 42.4% of normal, 9.0% of low-grade CIN, 27.8% of high-grade CIN, and 20.8% of cancer (Table 1).

ASCUS or above in Pap smear had sensitivity of 83.0%/86.3%/86.8% to detect low-grade CIN or above/high-grade CIN or above/cancer, respectively. When cut-off was raised to HSIL in Pap smear, the sensitivity to detect high-grade CIN or above was lowered to 62.1%. P0 or above in cervicography had sensitivity of 53.7%/57.3%/60.4% to detect low-grade CIN or above/high-grade CIN or above/cancer, respectively, and high risk HPV positive had sensitivity of 57.8%/64.5%/69.8% to detect low-grade CIN or above/high-grade CIN or above/cancer, respectively. Specificity of Pap smear was lower than cervicography or HPV test while there was no significant difference between cervicography and HPV test (Table 2).

Combination of Pap smear with cervicography, Pap smear with HPV test, and cervicography with HPV test showed that the sensitivity of 89.1%/91.9%/90.6%, 89.1%/92.7%/94.3%, and 78.9%/84.7%/86.8% to detect low-

grade CIN or above/high-grade CIN or above/cancer, respectively. Specificity was not significantly different between the each combination of two tests (Table 2).

**Table 1. Results of different screening tests and final diagnosis**

Results of Screening tests	Number of objects (%)
Pap	
Normal	100 (39.2)
ASCUS	34 (13.3)
LSIL	31 (12.2)
HSIL	52 (20.4)
Cancer	38 (14.9)
Cervicography	
Negative	140 (54.9)
Atypical	20 (7.8)
P0	32 (12.5)
P1	19 (7.5)
P2	23 (9.0)
P3	21 (8.2)
HPV test	
Negative	149 (58.4)
Positive	106 (41.6)
Biopsy results	Number of objects (%)
Normal	108 (42.4)
Low-grade CIN	23 (9.0)
High-grade CIN	71 (27.8)
Cancer	53 (20.8)

When three methods were combined altogether, the sensitivity to detect low-grade CIN or above/high-grade CIN or above/cancer was increased to 93.9%/96.8%/96.2%, respectively. However, the specificity was lower than each method or combinations of two methods (Table 2).

The analysis of cost-effectiveness was summarized in Table 3. The cost for detection of one case of low-grade CIN or above/high-grade CIN or above/cancer using Pap smear alone was 25,385 won/39,952 won/112,317 won, respectively and this was lowest among other methods and their combinations. Combination of cervicography and HPV DNA test was most expensive method to detect low-grade CIN or above and cancer while HPV DNA test alone was most expensive method to detect high-grade CIN or above. Combination of three methods had the cost of 180,469 won/207,113 won/542,960 won to detect a case of low-grade CIN or above/high-grade CIN or above/cancer, respectively.

**Table 2. Sensitivity, specificity, positive predictive value and negative predictive value of different screening tests and their combinations according to various criteria**

Tests	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)
PAP only				
ASCUS+				
LGCIN+	83.0	69.4	78.7	75.0
HGCIN+	86.3	63.4	69.0	83.0
Cancer	86.8	46.0	29.7	93.0
HSIL+				
HGCIN+	62.1	90.1	85.6	71.5
Cancer				
Cancer	50.9	94.6	71.1	88.0
Cervicography only				
P0+				
LGCIN+	53.7	85.2	83.2	57.5
HGCIN+	57.3	81.7	74.7	66.9
Cancer	60.4	68.8	33.7	86.9
P2+				
HGCIN+	30.6	95.4	86.4	59.2
Cancer				
Cancer	32.1	98.0	81.0	84.6
HPV only				
HPV (+)				
LGCIN+	57.8	80.6	80.2	58.4
HGCIN+	64.5	80.2	75.5	70.5
Cancer	69.8	65.8	34.9	89.3
PAP+Cervicography				
ASCUS+/P0+				
LGCIN+	89.1	62.0	76.2	80.7
HGCIN+	91.9	55.7	66.3	88.0
Cancer	90.6	38.6	27.9	94.0
HSIL+/P2+				
HGCIN+	71.0	87.0	83.8	76.0
Cancer/Cancer				
Cancer	62.3	92.6	68.8	90.3
PAP + HPV				
ASCUS+/HPV (+)				
LGCIN+	89.1	62.0	76.2	80.7
HGCIN+	92.7	56.5	66.9	89.2
Cancer	94.3	39.6	29.1	96.4
HSIL+/HPV (+)				
HGCIN+	87.9	74.0	75.7	84.3
Cancer/HPV (+)				
Cancer	84.9	65.8	40.5	94.3
Cervicography+HPV				
P0+/HPV (+)				
LGCIN+	78.9	70.4	78.4	71.0
HGCIN+	84.7	67.2	70.9	82.2
Cancer	86.8	49.5	31.1	93.5
P2+/HPV (+)				
HGCIN+	74.2	77.1	75.4	75.9
Cancer/HPV (+)				
Cancer	81.1	64.4	37.4	92.9
PAP+Cervicography+HPV				
ASCUS+/P0+/HPV (+)				
LGCIN+	93.9	54.6	73.8	86.8
HGCIN+	96.8	48.9	64.2	94.1
Cancer	96.2	32.7	27.3	97.1
HSIL+/P2+/HPV (+)				
HGCIN+	88.7	71.0	74.3	86.9
Cancer/cancer/HPV (+)				
Cancer	88.7	64.3	39.5	95.6

\*PPV, positive predictive value; \*NPV, negative predictive value.

**Table 3. Cost per screening for the detection of one case of cervical neoplasia**

Method	Cost per screening method	Cost for detecting one case	Multiples of PAP test cost in each diagnosis
<b>Cancer</b>			
PAP only	12,000	112,317	1.00
Cervicography only	25,000	377,207	3.36
HPV only	80,000	551,088	4.91
PAP+Cervico	37,000	187,727	1.67
PAP+HPV	92,000	454,701	4.05
Cervico+HPV	105,000	604,675	5.38
PAP+Cervico+HPV	117,000	542,960	4.83
<b>HGCIN</b>			
PAP only	12,000	39,952	1.00
Cervicography only	25,000	238,908	5.98
HPV only	80,000	289,934	7.26
PAP+Cervico	37,000	95,155	2.38
PAP+HPV	92,000	192,867	4.83
Cervico+HPV	105,000	274,643	6.87
PAP+Cervico+HPV	117,000	207,113	5.18
<b>LGCIN</b>			
PAP only	12,000	25,385	1.00
Cervicography only	25,000	116,502	4.59
HPV only	80,000	239,821	9.45
PAP+Cervico	37,000	70,095	2.76
PAP+HPV	92,000	157,608	6.21
Cervico+HPV	105,000	241,907	9.53
PAP+Cervico+HPV	117,000	180,469	7.11

## DISCUSSION

The effectiveness of Pap smear in reducing morbidity and mortality from cervical cancer is undeniable.<sup>3</sup> However, the false-negative rate of Pap smear for detecting cervical cancer and precancerous lesions is variably reported from as low as 10% to as high as 60%.<sup>13-16</sup> False-negative Pap tests result from sampling error, screening error, and interpretive error. To overcome this limitation of Pap smear, Navratil combined Pap smear and colposcopy and reported the increase of the diagnostic accuracy for cervical lesion.<sup>17</sup> However, colposcopy is not suitable for population screening because it is expensive, time consuming, and need specialized expert.

Ferris et al. reevaluated the women with a recent smear demonstrating cytologic atypia using cervicography, and concluded that the cervicography may be used as an effective, inexpensive intermediate triage test for the evaluation of women with atypia.<sup>18</sup> However, Baldauf et al. suggested that cervicography should not be considered

as an alternative to cytology for cervical cancer screening since its accuracy is not significantly better and its rate of technically defective tests is significantly higher.<sup>19,20</sup> De Sutter et al. reported that the overall detection of CIN is improved when cervicography and Pap smear are used jointly and concluded that cervicography must be considered as a complementary test to cytology.<sup>21</sup> In addition, HPV DNA test alone also had a low sensitivity of 63.6% to detect cervical cancer.<sup>22</sup>

In this study, as like as the Guanacaste Project,<sup>22</sup> the detailed result criteria for each method were used and compared with histopathologically confirmed results. As a result, each combination of methods had higher sensitivity and lower false-negative rate than the sole method. Combinations of methods which contain cervicography showed low sensitivity in detecting low-grade CIN and invasive cancer. This must have resulted from the low accuracy of cervicography and suggest that the cautious interpretation of cervicography. It is also noted that the majority of subjects included in this study were patients

with abnormal Pap smear result referred from primary health care provider to our hospital and this should have influenced the high rates of high-grade CIN and invasive cancer and the low accuracy of cervicography also.

The cost to detect a low-grade CIN or above was lowest in Pap smear alone. HPV test alone was expensive than the three methods combination to detect a low-grade CIN or above probably because of the much higher cost of HPV test than Pap smear and rather low sensitivity and specificity of HPV test than the three methods combination. As expected, similar results were shown in cost analysis to detect a high-grade CIN or above and invasive cancer and these suggest that the Pap smear is the most appropriate method for cervical cancer screening in Korea. In accordance with our study, Kaufmann et al. reported that HPV test is not a cost-effective triage for patients referred with Pap smears reported as showing ASCUS or LSIL because the cost of HPV test was nearly double that of triage based on repeat cytologic testing alone.<sup>23</sup>

According to the announcement of ACOG, Pap smear and HPV test combination could be used every 3 years for cervical cancer screening when both tests are negative. However our cost analysis showed that Pap smear could detect a cancer patient with less than a quarter cost of the combination of Pap smear and HPV test. Therefore if we could get substantial evidence for the increased sensitivity and specificity of the Pap smear and HPV test combination in the future studies, we could recommend a suitable screening interval to Korean women with the combination.

Matsunaga et al. performed the cost-effectiveness analysis for cervical cancer screening in Japan to estimate the cost per life-year saved by the screening; cost-effectiveness ratio (CER).<sup>24</sup> The analysis was made using a simulation model to estimate long-term cost and effectiveness of the screening programs. CER of cervical cancer screening was estimated to be US\$ 40,604. If the incidence rate becomes 85% of the current figure in 2015, CER would be US\$ 48,176 and it was suggested that the cervical cancer screening would remain reasonably cost-effective until the year 2015. However, the cost analysis of our study had not included the decrease of incidence and mortality by the cancer screening test. In

addition enrolled subjects of the present study were relatively small and selected at a referral institute (Seoul National University Hospital) and thus may have been unrepresentative of general population participating in cervical cancer screening program. Therefore the disease incidence in general population and prognosis after treatment should be considered in the future studies with large number of subject.

As mentioned in previous paragraph, HPV DNA test had low sensitivity to detect CIN in this study as shown in the Guanacaste Project.<sup>22</sup> However there were numerous studies which showed very high sensitivity of HPV DNA test to detect cervical neoplasia.<sup>25-28</sup> Low sensitivity of HPV DNA test in this study, although the exact cause of such results is unknown, must have influenced the final cost analysis and, therefore, our results should be cautiously interpreted and large well-designed future studies are mandatory as well.

In conclusion, the combinations of each screening method increase the sensitivity at the price of decreasing specificity and cost-effectiveness. Cervicography or HPV test alone should not be considered as an alternative to Pap smear for cervical cancer screening because its cost-effectiveness is not significantly better than that of Pap smear. Pap smear and HPV test combination could be considered as a non yearly-based screening method after large and wide prospective studies in Korea.

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## 자궁경부 종양에서 다중선별검사의 비용효과 분석

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전용탁<sup>1</sup>, 김용범<sup>1</sup>, 김재원<sup>2,3</sup>, 박노현<sup>2,3</sup>, 송용상<sup>2,3</sup>, 강순범<sup>2,3</sup>, 이효표<sup>2,3</sup>

**목적** : 이상적인 선별검사의 조건은 정확하고 비용효과가 좋아야 한다. 자궁경부암 선별검사에 대하여 이 두 측면에 관한 연구는 우리나라에서 매우 드물다. 이에 자궁경부암 선별검사에 사용될 수 있는 여러 가지 방법들과 그 조합들에 대한 정확성과 비용효과에 대하여 알아보고자 하였다.

**연구 방법** : 1996년 12월부터 1997년 7월까지 서울대학교병원 산부인과를 방문한 255명의 여성을 대상으로 하였다. 질확대경 하 조준생검 또는 자궁경부 원추절제술을 시행하여 얻은 결과를 최종 진단으로 정하고 세포도말검사, 자궁경부 확대촬영검사, 인유두종바이러스검사 중 한 가지 검사만을 시행한 경우와 두 가지 검사를 조합한 경우, 마지막으로 세 가지 검사를 모두 시행한 경우에 있어서 각각 검사방법의 민감도와 특이도, 위양성률과 위음성률을 계산하였다. 또한 이 결과를 바탕으로 Bayes 이론에 의한 계량진단법을 이용하여 비용효과 분석을 시행하였다.

**결과** : 경증 자궁경부 이형성증 이상을 진단하는데 있어 각 한 가지 방법을 사용하였을 때 민감도와 특이도는 세포도말검사가 83.0%와 69.4%, 자궁경부 확대촬영검사가 53.7%와 85.2%, 인유두종바이러스검사가 57.8%와 80.6%였다. 세포도말검사에 자궁경부 확대촬영검사 혹은 인유두종바이러스검사를 병용한 경우 경증 자궁경부 이형성증 이상을 진단할 수 있는 민감도와 특이도는 두 조합 모두에서 89.1%와 62.0%를 보였다. 자궁경부 확대촬영검사와 인유두종바이러스검사를 병용할 경우 민감도는 78.9%, 특이도는 70.4%였다. 세 가지 검사를 모두 시행한 경우의 민감도는 93.9%, 특이도는 54.6%로 나타났다. 세포도말검사의 비용은 12,000원인데 비하여 세 가지 검사를 동시에 시행할 경우 비용은 117,000원이었고, 자궁경부 이형성증 1예를 발견하기 위한 비용은 자궁경부 확대촬영검사와 인유두종바이러스검사를 병용한 경우가 가장 비쌌고(241,907원) 세포도말검사가 가장 저렴하였다(25,385원).

**결론** : 자궁경부암의 선별검사로써 세포도말검사와 자궁경부 확대촬영검사, 그리고 인유두종바이러스검사 각각을 단독으로 시행하는 경우보다 두 가지 혹은 세 가지 검사를 같이 시행하는 경우가 진단의 민감도를 높이고 위음성률을 낮추는 결과를 얻었으나, 비용효과 면에서는 정확도의 향상이라는 장점에 비하여 과도한 비용 상승을 보여주었다. 따라서 일반 인구집단을 대상으로 하는 선별검사로써는 세포도말 단독 검사가 현재로써는 가장 적절할 것으로 보인다.

**중심단어** : 자궁경부암, 선별검사, 비용효과