韓國疫學會誌 : 第30卷 第2號
Korean Journal of Epidemiology
Vol.30, No.2, Dec, 2008, 178-187

원 저

Diagnostic accuracy of conventional Pap test, liquid-based cytology and human papillomavirus DNA testing in cervical cancer screening in Korea: a meta-analysis

Jin-Kyoung Oh[1], Hai-Rim Shin[1,2], Gyungyub Gong[3], Jin Hee Sohn[4], Shin Kwang Khang[3]

National Cancer Control Research Institute, National Cancer Center, Goyang, Republic of Korea[1]
International Agency for Research on Cancer, Lyon, France[2]
Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea[3]
Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea[4]

Introduction

Screening is the main strategy for secondary prevention of uterine cervical cancer. Cytological screening, Pap test, has led to a significant reduction in the incidence of and mortality from cervical cancer[1].

Conventional Pap test was introduced into Korea in the late 1950's and has contributed to early detection of precancerous lesions and cervical cancer. Korean National Cancer Screening Program recommends that women of age 30 or more receive the Pap test biannually, whereas the Korean Society of Obstetrics and Gynecology recommends that women of age 20 or more receive the test annually[2].

Although Pap test has the merit of being convenient, reasonably specific and inexpensive, the sensitivity have been questioned. A low sensitivity of Pap test would put women at risk to develop invasive cervical cancer. Considerable variation in the sensitivity and specificity of Pap test has been reported[3]. In attempt to improve sample quality, interest has shifted to use liquid-based cytology (LBC). Although not included as a screening method in Korea, LBC has been rapidly popular among clinicians.

Received : 2008.10.2 Accepted : 2008.12.15
Correspondence : Hai-Rim Shin
International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France.
Tel : +33 4 72 73 84 18 Fax : +33 4 72 73 80 22
E-mail : hrshin@ncc.re.kr
Acknowledgement : This study was supported by a grant of the National R&D Program for Cancer Control, Ministry of Health, Welfare & Family Affairs, Republic of Korea (grant no. 0720580)

In view of the importance of human papillomavirus (HPV) in the etiology of cervical cancer, HPV DNA testing to allow women to be classified as high-risk HPV-positive or negative could be used as an adjunct to Pap test. Currently there is no recommendation for HPV testing in cervical cancer screening guidelines. However, the National Health Insurance Corporation has approved HPV testing to confirm cervical dysplasia or carcinoma resulting from an abnormal Pap.

Estimations sensitivity and specificity of screening test are important because they may be used to determine policy decisions, such as recommendations for optimal frequency of screening, management of mild abnormalities, and use of newer methods. To compare the accuracy of Pap test and other alternative screening tools (i.e., LBC and HPV testing), Korean studies that reported accuracy of each screening methods were intensively reviewed and the pooled estimates for sensitivity and specificity was calculated by meta-analysis.

Materials and methods

Articles published between 1995 and March 2008 were retrieved from the electronic bibliographic databases, MEDLINE and KoreaMed, using the following search terms (pap OR liquid OR cytology OR HPV) AND (sensitivity OR accuracy), AND (Korea OR Korean) for MEDLINE. Articles written in Korean or English were included.

For the meta-analysis, the threshold for the defini-

tion of an abnormal cytology was atypical squamous cells of undetermined significance or worse (ASCUS+). The results were converted to the nearest equivalent in the Bethesda System. Disease status should be verified by using biopsy (and/or colposcopy) as gold standard. Histological findings were categorized into normal, CIN1 (including koliocytosis, ASCUS or mild dysplasia), CIN2 (including low-grade squamous intraepithelial lesion (LSIL) or moderate dysplasia), CIN3 (including high-grade squamous intraepithelial lesion (HSIL), carcinoma in situ (CIS) or severe dysplasia) and invasive cancer. Histologically confirmed cervical intraepithelial neoplasia 2 or worse (CIN2+) was considered as true cervical diseases. The numbers of true positives, false negatives, false positives and true negatives defined at the considered thresholds (i.e., ASCUS+) and true disease (i.e., CIN2+) were extracted from each study, and sensitivity and specificity were re-calculated. Studies that the numbers to calculate sensitivity and specificity were not described on the paper were excluded in the meta-analysis.

In the meta-analysis, LBC was restricted to ThinPrep (Cytyc Corporation, Marlborough, MA, USA) and SurePath (BD, Franklin Lakes, NJ USA). Although there are some other LBC, for example, MonoPrep (MonoGen, Inc. Lincolnshire, Il, USA) and CellPrep (Medimex, Seoul, Korea), ThinPrep and SurePath were only approved from Food and Drug Administration (FDA) in the United States and generally used as a reliable method in Korean clinical settings. HPV testing was restricted to Hybrid Capture 2 (Digene Corporation, Gaithersburg, MD, USA) as same reasons. However, HPV DNA Chips (Biomedlab or MyGene, Korea) have been widely used in clinics recently and additionally included in the meta-analysis. All of these thresholds, standard of true disease and inclusion criteria were used in the international systematic reviews and meta-analyses of cervical cancer screening [4,5].

Meta-DiSc version 1.4, software which developed for meta-analysis of test accuracy data[6] was used. Sensitivity and specificity was pooled by the Der Simonian Laird method (random effects model) to incorporated variation among studies and computed a weighted average.

Results

A total of 26 literatures that reported accuracy of Pap, LBC or HPV testing were retrieved but 2 studies

Table 1. Sensitivity and specificity of conventional Pap test, liquid-based cytology and HPV DNA testing (Korean studies)

Reference	Study subject	Prevalence	Threshold	Detection	Pap		LBC		HPV	
					Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
(24)	626 women who visited Catholic Univ. Holly Family Hospital, 2004-2007	HPV 44% ASCUS+ 83%	HSIL+	CIN2+	53.4	69.2			76.9 *Chip*	70.8
(47)	252 women who referred to Chosun Univ. hospital	HPV 68% ASCUS+ 65%	LSIL+	CIN1+			76.4 *ThinPrep*	68.1	79.8 *HC2*	62.3
(31)	2358 women who were referred to Chonnam Univ. Hospital, year was not mentioned	HPV 41% Cytology not mentioned	HSIL+	CIN2+			79 *ThinPrep*	98	84 *Chip*	72
(30)	406 women who visited Catholic Univ. Hospital, 2004-2006	HPV 70% ASCUS+ 64%	ASCUS+	LSIL+	62.6	96.1	91.7 *SurePath*	75.9	78.9 *HC2*	78.0
(16)	256 and 101 women who visited Yonsei Univ. Hospital, 2003-2004	Pap ASCUS+ 44% ThinPrep ASCUS+ 63%	ASCUS+	CIN1+	64.0	79.5	86.0 *ThinPrep*	66.0		

Table continues

Table 1. continues

(25)	176 women who visited Korea Univ. Guro hospital, 1999-2000	HPV 59% ASCUS+ 80%	ASCUS+ LSIL+	CIN1+	78 29	19 96			87 *HC2*	63
(13)	255 women who visited Seoul National Univ. Hospital, 1996-1997	HPV 42% ASCUS+ 61%	ASCUS+ HSIL+	CIN1+ CIN2+ Cancer CIN23+ Cancer	83.0 86.3 86.8 62.1 50.9	69.4 63.4 46.0 90.1 94.6			57.8 64.5 69.8 *HC2*	80.6 80.2 65.8
(23)	30 women who visited Seoul National Univ. Hospital with R/O cervical cancer	ASCUS+ 50%	ASCUS+	mild dysplasia+	73.7	90.9	78.9 *MonoPrep2*	81.6		
(22)	593 women who visited Korea Univ. Guro Hospital, 2000-2001	HPV 91% ASCUS+ 77%	ASCUS+	CIN2+	76.3	65.8			92.4 *HC2*	52.4
(14)	116 women who visited Dankook Univ. Hospital in 2003	ASCUS+ 13%	ASCUS+	Koilocytosis +	71.4	94.3				
(18)	156 women who visited Ajou Univ. Hospital, 2002-2003	ASCUS+ 81%	ASCUS+	LSIL+	87.2	43.6	94.9 *MonoPrep*	92.3		
(9)	294 women who visited Yonsei Univ. Hospital, 2003	ASCUS+ 56%	ASCUS+	CIN1+	72.0	64.6				
(12)	1235 women who visited Pohang St. Mary's Hospital, 1992-2001	ASCUS+ 31%	Not mentioned	CIN1+	82.7	95.5				
(21)	149 women who visited Soonchunhyang Univ. Hospital, 2002-2003	HPV 66%		Condyloma & CIN1+					HC2 94.6 Chip 83.7	HC2 78.9 Chip 89.5
(17)	1594 and 1339 women who visited Chonnam Univ. Hospital, 1998-2000	Pap ASCUS+ 22% ThinPrep ASCUS+ 50%	HSIL+	HSIL+	62.0	96.5	85.1 *ThinPrep*	98.3		
(29)	1023 women who visited Korea Univ. Guro Hospital for screening, 1994-1999	HPV 11% ASCUS+ 15%	ASCUS+	LSIL+	71.2	89.5			63.0 *HC1*	93.1
(27)	203 women who visited Korea Univ. Guro Hospital for general OBGY exam, 2000	HPV 26% ASCUS+ 41%	ASCUS+	Moderate dysplasia+ Mild dysplasia+	72.2 54.4	75.6 85.0			95.8 85.2 *HC1*	37.4 47.1
(28)	150 women who visited Samsung Medical Center for annual health check-up, 1996	HPV 4% ASCUS+ 12%	ASCUS+	CIN1+ ASCUS+	94	78			78 *PCR, 4HR types*	89
(15)	514 women who visited Catholic Univ. Hospital, 1996-1999				83.1	88.3		(N=82)	78.6 *HC1 or HC2*	76.5
	2285 women who visited Korea Univ. Hospital, 1996-1999				70.5	72.8		(N=1023)	62.1 *HC1*	86.1
	1031 women who visited Screening Center of Catholic Univ. Hospital, Pochon CHA Univ. Hospital and local clinics, 1996-2000				55.6	83.0			66.2 *HC1*	74.8
(19)	158 women who visited Seoul National Univ. Hospital	ASCUS+ 71%	ASCUS+	CIN1+	89.6	69.8	82.8 *ThinPrep*	83.0		
(11)	346 women who visited Hanyang Univ. Hospital, 1997-1998	ASCUS+ 42%	HSIL+	CIN2+	87.0	97.0				
(26)	699 women who visited Chungnam Univ. hospital, 1997	ASCUS+ 13%	LSIL+	Mild dysplasia+	81.8	(98.0)				
(20)	233 women who visited Chosun Univ. Hospital, 1995-1996	LSIL+ 30%	LSIL+	CIN1+	87.5	93.5			72.7 *HC1*	91.7
(10)	161 women who visited Soonchunhyang Univ. Hospital, 1998-1998	LSIL+ 29%	LSIL+	CIN1+	67.7	86.2				

ASCUS, atypical squamous cell of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology; HPV, human papillomavirus; HC, Hybrid Capture.

that specimens were collected with inadequate tool (i.e., cotton swab)[7] and completely duplicated[8] with a previous literature[9] were excluded to review. Table 1 is a summary table containing study population, year at sample recruitment, prevalence of cytologic abnormalities or HPV positivity in study population, cytologic cutoff, detection level, sensitivity and specificity of each screening method, and brand name of LBC or HPV testing. Sensitivity and specificity of each screening method was widely divergent among individual studies. Moreover, cytologic cutoffs, detection levels and test kit manufactures were also varied (Table 1).

Sensitivity of Pap test was varied from 53.4% to 94.0%, and specificity was 43.6%-97.0% [9-30]. Although it was also varied among individual studies, sensitivity (76.4%-94.9%) and specificity (66.0% to 98.3%) of LBC were relatively higher than those of Pap test. Sensitivity and specificity of HPV test were 57.8%-95.8% and 37.4%-93.1%, respectively. Generally, sensitivity and specificity of LBC were relatively higher than those of Pap test. Sensitivity of HPV DNA test was higher than that of Pap test but specificity was lower.

There were 15 studies on Pap test [11-15,17-19, 22,23,25-27,29,30], 3 studies on LBC[17,19,30] and 4 studies on HPV[13,22,25,30], which met the criteria for meta-analysis. As shown in Figure 1 and Figure 2, pooled sensitivity and specificity of Pap test for CIN2+ was 76% (95% CI=75%-78%) and 76% (95% CI=75%-77%), respectively. However, significant heterogeneity was observed across studies ($p<0.0001$) (Fig. 1, Fig. 2).

Table 2 shows pooled accuracy of each screening methods. Pooled sensitivity and specificity of LBC (i.e., ThinPrep & SurePath) for CIN2+ was 92% (95% CI=90%-94%) and 79% (95% CI=76%-81%), respectively. Pooled sensitivity and specificity of HPV testing (i.e., HC2) for CIN2+ was 83% (95% CI=80% -86%) and 59% (95% CI=55%-63%), respectively. There was significant heterogeneity among these studies' results ($p<0.0001$), except for pooled sensitivity of LBC ($P=0.682$).

When the two HPV testing methods, HC2[13,22, 25,30] and HPV DNA Chip[24,31], were pooled together, pooled sensitivity and specificity was not

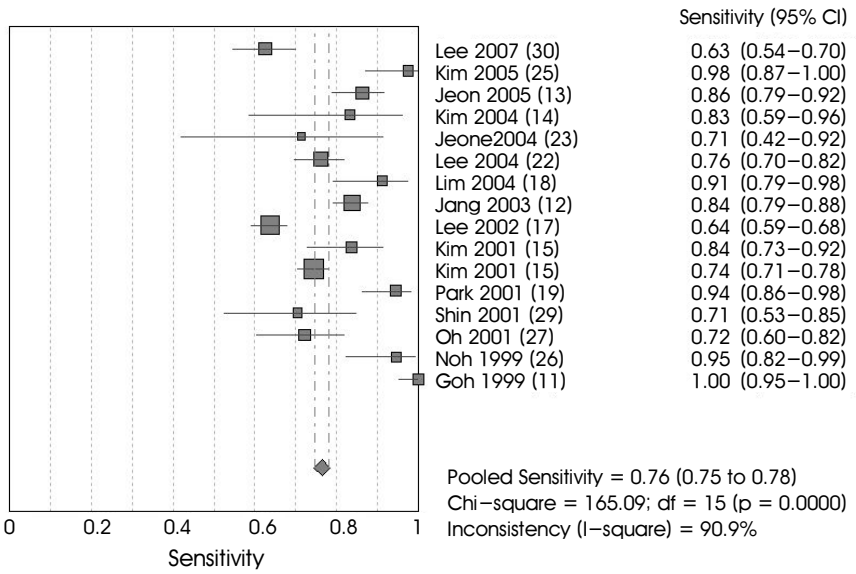

Fig. 1. Pooled sensitivity of conventional Pap test at the threshold of ASCUS for detection of CIN2+.
* Kim et al. 2001 (15) was a multiinstitutional study and provided 2 independent data set.

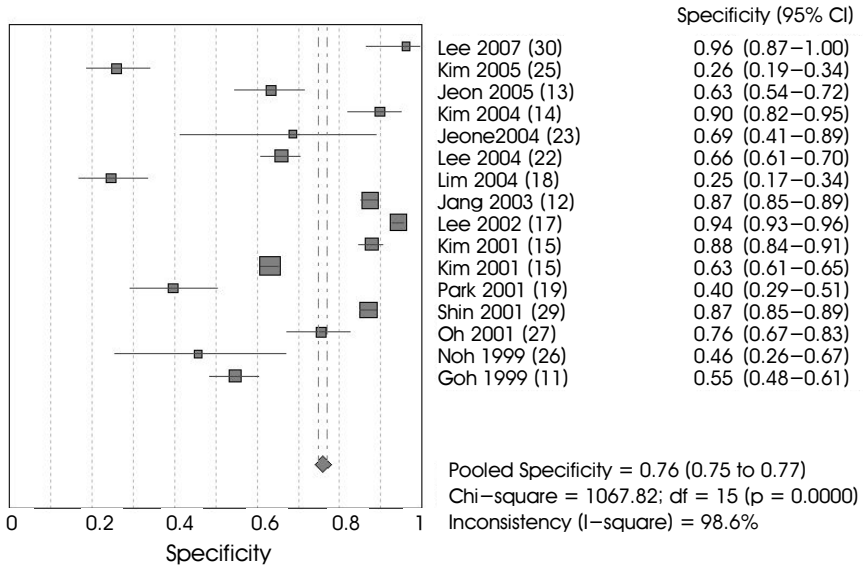

Fig. 2. Pooled specificity of conventional Pap test at the threshold of ASCUS for detection of CIN2+.
* Kim et al. 2001 (15)was a multiinstitutional study and provided 2 independent data set.

significantly different between two methods (data not shown).

Discussion

Uterine cervical cancer is one of the major cancers in Korean women. According to a recent report of Korean Central Cancer Registry, Cervical cancer accounted for 6.5% of new cancer cases from 2003 to 2005 and approximately 4,000 invasive cervical cancer cases (ICC) and 4,000 cervical carcinoma in situ (CIS) were diagnosed in each year. The age-standardized incidence rate for cervical cancer steadily declined from 19 per 100,000 women in 1993 to 13 per 100,000 women in 2005[32]. The Korean National Statistical Office reported that 987 women died from cervical cancer in 2007[33]. The age-standardized cervical cancer mortality rate also declined from 5.2 to 3.9 in 100,000 women in last decade[34]. On the other hand, the overall five-year relative survival rate for cervical cancer patients was steadily increased from 77.5% (in 1993-1995) to 81.1% (in 2001-2005) [32].

Overall, the decreased incidence and mortality rates of cervical cancer and increased survival rates

Table 2. Pooled accuracy for detection CIN2+

Test	Number of studies	Reference	Pooled sensitivity (95% CI), heterogeneity	Pooled specificity (95% CI), heterogeneity
Pap test	15	(11-15, 17-19, 22, 23, 25-27, 29, 30)	0.76 (0.75-0.78) p<0.0001	p<0.00010.76 (0.75-0.77) p<0.0001
LBC	3	(17, 19, 30)	0.92 (0.90-0.94) P=0.682	0.79 (0.76-0.81) p<0.0001
HPV	4	(13, 22, 25, 30)	0.83 (0.80-0.86) p<0.0001	0.59 (0.55-0.63) p<0.0001

CIN, cervical intraepithelial neoplasia; LBC, liquid-based cytology; HPV, human papillomavirus test (i.e., Hybrid Capture 2).

are probably due to the introduction of screening programs and effective treatment[35,36]. Cervical cancer screening using the Pap test was first introduced in the late 1950s and became more widely used in the 1980s. The overall participation rate including both opportunistic and national organized screening was estimated at 73.6% in 2007[37]. Although cervical cancer screening is widely expanded, the screening quality is questionable. Factors limiting sensitivity of conventional Pap testing include small lesion size, inadequate sampling, obscuring blood and debris, and variability of individual results. Considerable variation in the sensitivity and specificity of Pap test has been reported[3]. In this review of 23 Korean literatures, sensitivity of Pap test was varied from 53.4% to 94.0%.

LBC is supposed to have a number of advantages over conventional Pap test. These include a more representative transfer of cells from the collection device to the glass slide, a reduction in the number of unsatisfactory cytology specimens, the availability of residual cellular material for subsequent molecular testing or for making additional glass slides, and possibly increased detection of abnormal cytology. Many developed countries use LBC as a primary cervical cancer screening tool based on cost-effectiveness[38]. Despite of these advantages of LBC, majority of Korean clinicians prefer conventional Pap test to LBC because the price of conventional Pap test is much lower than of LBC [39]. In this meta-analysis, sensitivity and specificity of LBC was higher than those of Pap or HPV testing. In contrast with general understanding about higher sensitivity of LBC than of Pap test, a most recent literature of systematic review on diagnostic accuracy of Pap test and LBC reported that the pooled sensitivity of Pap test and LBC was not significantly different, and specificity was similar [4]. The pooled sensitivity of Pap test and LBC at ASCUS threshold for CIN2 or worse was 88.2% (95% CI=80.2%-93.2%) and 90.4% (95% CI=82.5%-95.0%), respectively. The pooled specificity of Pap test and LBC at ASCUS threshold for CIN2 or worse was 71.3% (95% CI= 58.3%-81.6%) and 64.6% (95% CI= 50.1%-76.8%), respectively.

According to dozens of large-scale clinical studies, sensitivity and specificity of HPV testing in primary screening for cervical cancer and its precancer lesions varied 46%-100% and 52%-96%, respectively, and generally higher than those of cytology[40]. HPV testing has shown to be an efficient alternative to repeated cytology in cases of uncertainty in the reading of Pap test, and is an appropriate way to follow women after treatment for abnormal cervical lesions. HPV testing has shown to provide clinically meaningful evidence to guide management of HPV positive women with normal cytology without compromising safety.

According to a most recent literature of systematic review conducted following the Cochrane Collaboration Guidelines, the pooled sensitivity of HPV DNA test (90.0%, 95% CI=86.4%-93.7%) was significantly higher than cytology (72.7%, 95% CI=63.9%-81.5%, at threshold of ASCUS), whereas the pooled specificity of HPV DNA test (86.5%, 95% CI=83.1%-89.8%) was significantly lower than cytology (91.9%, 95% CI=90.2%-93.6%, at threshold of ASCUS)[5]. In countries where cytology is of good quality, it has been suggested that HPV testing as the sole screening modality with cytology reserved for triage of HPV-positive women[41]. The most important obstacles to more widespread acceptance of HPV testing in cervical cancer screening are its high cost and the fact that the technology is not in the public domain, as it is for cervical cytology.

In this meta-analysis, the pooled sensitivity and pooled specificity of Pap test were both 76%. However these may have some difference from real accuracy of cervical cancer screening in Korea for several reasons. First, study subjects were highly selected high-risk group because they mostly referred women for further evaluation with abnormal cytology in primary cervical screening. Prevalence of abnormal cytology (12-83%) or HPV infection (4-91%) in study women was much higher than in general population (abnormal cytology 5%; HPV infection 10%, appro-

ximately)[42-44]. In most studies, the presence or absence of disease was not verified with colposcopy and histology in all women who attend primary screening leading to potential verification bias. It is likely that false negative results are missed for either test without adequate verification of test negative. This causes an overestimation of the sensitivity or false positivity rate.

Second, the sensitivity and specificity of Pap test in local clinics may be lower than in these studies because most of these studies were conducted in university hospitals with high quality health professionals and well-trained laboratory personals. Actually, more than 60% of cervical cytology have been tested in commercial laboratories, which have limited pathologists and laboratory personals[45].

Third, although error occurs at the beginning of cervical specimen collection and one of the advantages of LBC is to reduce inadequate specimens than in conventional Pap test, all 24 reviewed studies did not included inadequate specimens for their analysis. Sensitivity of Pap test in real setting possibly lower than the pooled sensitivity, 76%, for these reasons.

Fourth, the number of studies on LBC or HPV testing included in this meta-analysis was small and these studies conducted in recently compared to studies on Pap test. The accuracy of LBC or HPV testing is possibly higher than of Pap test because these new technologies have been recently equipped and the laboratory personals also have been recently trained. In contrast, Pap test has been widely used for several decades and the studies included in this meta-analysis were based on relatively older data than LBC or HPV testing.

Finally, significant heterogeneity was observed across studies in the meta-analysis ($p<0.0001$), excepting for pooled sensitivity of LBC ($P=0.682$), and subgroup analysis was not possible. Therefore, the pooled sensitivity and pooled specificity in this meta-analysis have limit to present accuracy of Pap test, LBC and HPV testing as a primary cervical cancer screening tools in Korea.

In conclusion, because enhancing cervical cancer screening coverage and improving the quality of cervical cancer screening are part of an important strategy for secondary prevention[46], accuracy and cost-effectiveness of cervical cancer screening methods should be further evaluated.

Reference

1. Stewart BW, Kleihues P. World Cancer Report. Lyon: IARC; 2003.
2. Park SY, Khang SK. Guidelines for the screening of uterine cervical cancer. J Korean Med Assoc 2002;45(8):1005-14.
3. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10):810-9.
4. Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol 2008; 111(1):167-77.
5. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review andmeta-analysis of non-randomized studies. Gynecol Oncol 2007;104(1):232-46.
6. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.
7. Jeon HW, Bum BK. Clinical Significance of a Cervical Cytologic Diagnosis of Atypical Squamous Cells of Undetermined Significance: Qualitification and HPV DNA Detection. Korean J Gynecol Oncol Colposc 2000;11(4):381-388.
8. Kim YT, Kim JW, Kim SH, Kim YR, Kim JH, Yoon BS, et al. Clinical usefulness of cervicogram as a primary screening test for cervical neoplasia. Yonsei Med J 2005;46(2):213-20.

9. Kim YR, Kim YT, Kim SH, Kim JW, Yoon BS, Chung DJ. Clinical Usefulness of Cervicogram as Primary Screening Test of Cervical Intraepithelial Neoplasia. Korean J Obstet Gynecol 2004;47(6): 1113-1119.
10. Do HS, Chang JY, Choi SD, Sunwoo JG, Bae DH. The correlation of result in Cervicography, Human papilloma virus test and cervical cytology as the screening tests of cervical neoplasia. Korean J Gynecol Oncol Colposc 1998;6(2):123-32.
11. Goh SH, Kim SR, Kim KT, Cho SH, Moon H, Lee JA, et al. Accuracy of Cervical Pap Smear. Korean J Gynecol Oncol Colposc 1999;10(2):156 -63.
12. Jang JH, Kim SH, Jang SH, An TS, Weon JC, Jung KW, et al. PAP Smear: Analysis of 10 Years Results (1992-2001). Korean J Obstet Gynecol 2003;46(9):1714-9.
13. Jeon YT, Kim YB, Kim JW, Park NH, Song YS, Kang SB, et al. The accuracy and cost-effectiveness of triple screening tests in cervical neoplasia. Korean J Gynecol Oncol 2005;16(3):221-8.
14. Kim HJ, Go JH, Park CH. PapSure Test for Cervical Cancer Screening - Papanicolaou Smear Cytology and Speculoscopy. Korean J Gynecol Oncol Colposc 2004;15(4):333-46.
15. Kim SJ, Park CK, Lee HP, Namkoong SE, Kang SB, Saw HS, et al. Multiinstitutional Study for the Development of Cervical Cancer Screening Model with New Cervicography, Pap Smear and HPV-DNA Test. Korean J Obstet Gynecol 2001;44 (5):911-37.
16. Kim YR, Kim YT, Kim SH, Kim JH, Kim JW, Park YW. Comparative analysis of conventional Papanicolaou smear, fluid-based thin-layer method and cervicography. Korean J Gynecol Oncol 2005;48(12):2932-40.
17. Lee KC, Choi HS, Kim HJ, Kim YS, Jeong KP, Park H, et al. The Comparison of Conventional Pap Smear with ThinPrep Pap Smear in detecting HSIL and Cervix cancer. Korean J Obstet Gynecol 2002; 45(5):753-8.
18. Lim YK, Lim JC, Kim JH, Lee JP, Chang KH, Ju HJ, et al. Comparison of Efficacy between MonoPrep(R) and Papanicolaou Smear for Cervical Cancer Screening. Korean J Obstet Gynecol 2004; 47(1):109-17.
19. Park IA, Lee SN, Chae SW, Park KH, Kim JW, Lee HP. Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of the histologic diagnosis: a clinical study of women with cervical abnormalities. Acta Cytol 2001;45(4):525-31.
20. Rho HG, Cho SM, Han SJ. The Clinical Evaluation of Triple Combined Test [Cytology, HPV DNA Test, Cervicography] for Uterine Cervical Cancer. Korean J Obstet Gynecol 1998;41(3):713-24.
21. Yeo SJ, Kim DS, Nam KH, Shin IK, Kim TH, Lee HH, et al. Detection of human papillomavirus in cervical neoplasia using HPVDNAChip and Hybrid Capture II system. Korean J Gynecol Oncol Colposc 2003;14(2):151-7.
22. Lee KJ, Lee JK, Saw HS. Can human papillomavirus DNA testing substitute for cytology in the detection of high-grade cervical lesions? Arch Pathol Lab Med 2004;128(3):298-302.
23. Jeon YK, Kim OR, Park KW, Kang SB, Park IA. Liquid-Based Cytology Using MonoPrep2(TM) System in Cervicovaginal Cytology: Comparative Study with ConventionalPap Smear and Histology. Korean J Cytopathol 2004;15(1):33-39.
24. Kahng J, Lee HJ. Clinical Efficacy of HPV DNA Chip Test in the Era of HPV Vaccination: 1,211 Cases, A Single Institution Study. Korean J Lab Med 2008;28(1):70-78.
25. Kim MK, Sohn JH, Kim CH, ChoiJS. The Usefulness of Concomitant High-Risk Human Papillomavirus Test and Colposcopy in Combination with the Papanicolaou Test in ASCUS Patients. Korean J Cytopathol 2005;16(1):18-24.
26. Noh HT, Lee SS. The Efficacy of Cervicography Combined with Pap Smear in Cervical Cancer Screening. Korean J Gynecol Oncol Colposc 1999; 10(1):13-23.

27. Oh HS, Shin JH, Lee LH, Kim HS, Saw HS. The Prevalence of HPV Infection in General Population of Korea and Efficacy of HPV DNA Test as an Adjunctive Screening of CervicalCancer. Korean J Gynecol Oncol Colposc 2001;12(3):225-234.
28. Oh YL, Shin KJ, Han J, Kim DS. Significance of high-risk human papillomavirus detection by polymerase chain reaction in primary cervical cancer screening. Cytopathology 2001;12(2):75-83.
29. Shin JH, Lee JK, Chough SY, Hur JY, Park YK, Saw HS. Hybrid Capture System HPV DNA Test as a Screening Tool of Cervical Cancer. Korean J Gynecol Oncol Colposc 2001;12(1):31-38.
30. Lee KC, Jung CK, Lee A, Jung ES, Choi YJ, Park JS, et al. A Comparision of Surepath(TM) Liquid-Based Smear with a Conventional Smear for Cervicovaginal Cytology-with Reference to a Histological Diagnosis. Korean J Cytopathol 2007;18(1):20-28.
31. Lee HS, Kim KM, Kim SM, Choi YD, Nam JH, Park CS, et al. Human papillomavirus genotyping using HPV DNA chip analysis in Korean women. Int J Gynecol Cancer 2007;17(2):497-501.
32. NCC. (National Cancer Center). Cancer Incidence in 2003-2005. In; 2008.
33. NSO. (Korea National Statistical Office). Annual Report on the Cause of Death Statistics. Daejeon; 2008.
34. Shin HR, Park S, Hwang SY, Kim JE, Jung KW, Won YJ, et al. Trends in cervical cancer mortality in Korea 1993-2002: corrected mortality using national death certification data and national cancer incidence data. Int J Cancer 2008;122(2):393-7.
35. Chung HH, Jang MJ, Jung KW, Won YJ, Shin HR, Kim JW, et al. Cervical cancer incidence and survival in Korea: 1993-2002. Int J Gynecol Cancer 2006;16(5):1833-8.
36. Jung KW, Yim SH, Kong HJ, Hwang SY, Won YJ, Lee JK, et al. Cancer Survival in Korea 1993-2002: A Population-Based Study. J Korean Med Sci 2007;22(Suppl):S5-S10.
37. NCC. (National Cancer Center). Cancer Facts and Figures 2008. Goyang, Korea; 2008.
38. Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. Health Technol Assess 2004;8(20):iii, 1-78.
39. Chung HH, Kim JW, Kang SB. Cost is a Barrier to Widespread Use of Liquid-Based Cytology for Cervical Cancer Screening in Korea. J Korean Med Sci 2006;21(6):1054-9.
40. IARC. (International Agency for Research on Cancer). IARC handbooks of cancer prevention; cervix cancer screening. Lyon: IARC press; 2005.
41. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine 2008;26 Suppl 10:K29-41.
42. Oh JK, Franceschi S, Kim BK, Kim JY, Ju YH, Hong EK, et al. Prevalence of human papillomavirus and Chlamydia trachomatis infection among women attending cervical cancer screening in the Republic of Korea. Eur J Cancer Prev 2008;in press.
43. Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, Oh JK, et al. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. J Infect Dis 2004;190(3):468-76.
44. Shin HR, Lee DH, Herrero R, Smith JS, Vaccarella S, Hong SH, et al. Prevalence of human papillomavirus infection in women in Busan, South Korea. Int J Cancer 2003;103(3):413-21.
45. Park MH. Cervical cancer screening in Korea. Korean Journal of Cytopathology 2003;14(2):43-52.
46. Konno R, Shin HR, Kim YT, Song YS, Sasagawa T, Inoue M, et al. Human papillomavirus infection and cervical cancer prevention in Japan and Korea. Vaccine 2008;26 Suppl 12:M30-42.
47. Ahn TG, Park JS, Han SJ. The comparative evaluation of clinical screening in combined tests [cytology (ThinPrep(R)), HPV DNA test (Hybrid capture(R) II), cervicography] for uterine cervical cancer. Korean J Gynecol Oncol 2007;18(1):17-25.

=국문초록=

자궁경부암 검진 방법으로써 고식적 자궁경부세포검사, 액상세포검사, 인유두종바이러스 검사의 정확도 비교: 메타 분석

오진경[1], 신해림[1,2], 공경엽[3], 손진희[4], 강신광[3]

국립암센터 국가암관리사업단[1], 국제암연구소 생정통계 및 역학연구부[2],
울산대학교 의과대학 병리학교실, 서울아산병원 병리과[3], 성균관대학교 의과대학 병리학교실, 강북삼성병원 병리과[4]

목적: 우리나라에서 자궁경부암 조기검진 방법으로 사용되고 있는 Pap 검사, LBC(액상검사) 및 HPV 검사의 정확도를 파악하기 위함이었다.

연구대상 및 방법: MEDLINE과 KoreaMed를 통하여 1995년부터 2008년 3월까지 각 검사 방법의 민감도와 특이도를 보고한 논문을 검색하였음. 각 검사 방법의 민감도와 특이도의 대표값을 산출하기 위하여 메타 분석을 실시하였다. 조직학적 확진이 이루어진 사례만 메타 분석에 포함하였으며, CIN2 이상으로 진단된 경우를 질병으로 정의하였다. 세포 검사에서는 ASCUS 이상을 양성으로 간주하였다.

연구성적: 총 24편의 논문이 검색하였고, 이 중 Pap 검사는 15편, LBC는 3편, HPV 검사는 4편이 선정 기준에 부합하여 메타 분석에 포함하였으며, 메타 분석 결과 민감도는 LBC가 가장 높고(92%), HPV 검사(83%)와 Pap 검사(76%) 순이었고, 특이도는 LBC(79%)가 가장 높고, Pap 검사(76%)와 HPV 검사(59%) 순이었다. 그러나 LBC의 민감도(heterogeneity p-value=0.682)를 제외하고는 모두 연구간에 통계적으로 유의한 이질성을 보였다(p-value<0.0001).

결론: 각 연구의 이질성이 심하여 본 메타 분석 결과가 각 검사 방법의 정확도를 대표한다고 하기에는 제한적이며, 향후 보다 신뢰할만한 자궁경부암 조기검진 방법의 정확도 검증과 더불어 비용-효과 분석도 이루어져야 할 것이다.

Key Words: sensitivity, specificity, Pap, liquid-based cytology, human papillomavirus, meta-analysis