

RESEARCH ARTICLE

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Cervical Cancer Detection between Conventional and Liquid Based Cervical Cytology: a 6-Year Experience in Northern Bangkok Thailand

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Abstract

Objectives: To determine the prevalence of abnormal Papanicolaou (Pap) smear, cervical intraepithelial neoplasia (CIN) 2 or higher and cancer between conventional Pap smear (CPP) and liquid based Pap smear (LBP). **Methods:** This retrospective study was conducted at Bhumibol Adulyadej Hospital, Bangkok, Thailand between January 2011 and December 2016. Data was collected from medical records of participants who attended for cervical cancer screening test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for detecting CIN 2 or higher were evaluated by using the most severity of histopathology reports. **Results:** A total of 28,564 cases were recruited. Prevalence of abnormal Pap smear from CPP and LBP were 4.8 % (1,092/22,552) and 5.7 % (345/6,012), respectively. Percentage of unsatisfactory smears in CPP (52.3%) was higher than LBP (40.5%). From CPP and LBP, cervical cancer percentages were 0.2 and 0.1, respectively. Sensitivity, specificity, PPV, NPV and accuracy of CPP and LBP for detection cancer were 42.5 vs 26.1%, 99.9 vs 100.0%, 69.8vs 75.0%, 99.7 vs 100.0 % and 99.7 vs 99.7%, respectively. **Conclusion:** Prevalence of abnormal cervical cytology and cancer from CPP and LBP were 4.8/0.2 and 5.7/0.1 percent, respectively. Unsatisfactory smear of LBP was less than CPP. Sensitivity, specificity, PPV, NPV and accuracy of CPP and LBP for detection CIN 2 or higher and cancer were comparable.

Keywords: Cervical cancer- Papanicolaou smear- liquid based- conventional

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Introduction

Cervical cancer is the second most common cancer in Thailand, secondary to breast cancer. Age standardized incidence rate (ASR) was 16.7/100,000 person-year (Khuhaperma et al., 2013). Cervical cytology screening recognized as the most successful way to reduce the incidence of cervical cancer. The original conventional Papanicolaou smear (CPP) was introduced in year 1943. This method examines of exfoliated cell from the cervix by scraping, manual spreading the cells on the glass slides, fixing the cells and finishes by Papanicolaou staining. The slide was then examined under a microscope by a cytopathologist. The problem of the CPP was the inhomogeneous slide preparation technique from scraping, spreading and staining. Liquid-based cytology (LBP) was introduced in the mid-1990s to correct poor slide preparation. LBP was the collection of cervical exfoliated cells transferred into liquid media. The debris was removed by microfiltration. Specimen was the spreaded on the glass slide by automatic machine and the staining was achieved

by the same technique as CPP. The finished slide was examined under a microscope by a cytopathologist as well.

Bhumibol Adulyadej Hospital (BAH) currently uses both CPP and LBP for cervical cancer screening. During year 2011-2014, LBP in BAH was processed under license of Liqui-Prep™ (LMG International Inc., Florida, USA). Liqui-Prep™ was approved by the US FDA, CE Mark, Thai FDA and has been available internationally since 2004. It was a reagent system for general cytology of various specimens, including fine needle aspirations from cervix, anus, pleura and oral cavity. The specimen was collected and transferred in collection vial containing a low-alcohol NON-HAZMAT preservative (George et al., 2017). In January 2015, a new LBP technique was introduced to a new license by PathTezt™ (Biocytch Corporation Sdn.Bhd., Perak, Malaysia). PathTezt™ is an automated computer-controlled device designed to prepare standardized thin-layer cytological cell preparation using a filtration system. The cervical cytological results were reported in the Bethesda system format.

The purpose of this study was to determine the

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prevalence of abnormal Pap smear, cervical intraepithelial neoplasia (CIN) 2 or higher and cancer in comparison between CPP and LBP.

Materials and Methods

The retrospective study was approved by institutional review board, Bhumibol Adulyadej Hospital (IRB: 029/60). Data were reviewed from medical records in computerized program. Participants in this study were the women who attended the gynecologic clinic at Bhumibol Adulyadej Hospital during the study period (2011-2016). Known cases of pre-invasive, invasive cancer, hysterectomized and pregnant women were excluded from the present study. Specimens were collected by residents and staff members of the Department of Obstetrics and Gynecology.

Demographic data collected were age, menstrual status, underlying diseases, coitarche, number of partners, parity, education, contraception, history of sexual transmitted disease (STD) including human immunodeficiency virus (HIV), smoking and alcohol consumption.

Participants who had abnormal Pap reports as ASC-US (atypical squamous cells of undetermined significance), LSIL (low grade squamous intraepithelial lesion) were counselled to undergo colposcopic directed biopsy and/or endocervical curettage. The alternative option was a repeated cervical cytology within 6 months preferring with HPV testing. Those with atypical squamous cells cannot exclude high grade squamous intraepithelial lesion (ASC-H), High grade squamous intraepithelial lesion (HSIL) or cancer were recommended to undergo colposcopy with cervical biopsy and/or endocervical curettage. The investigation procedure was performed by certified gynecologic oncology specialist. After colposcopy, patients were further managed either by a closed follow up or a surgical procedure namely loop electrosurgical excision procedure, conization and hysterectomy, following the ASCCP guideline.

Continuous variables were expressed as mean and standard deviation (SD). Category data were expressed as number and percentage. Pearson Chi-square and Fisher's exact test were used to analyze the data when appropriate. Analytic program in this study was the SPSS statistic version 18 (SPSS, Chicago, IL, USA). The p-value of 0.05 or less was considered to be statistical significance.

Results

During the study period, a total of 28,564 medical records were examined. There were 22,552 and 6,012 cases in CPP and LBP group, respectively. The mean age of women participating in this study was 39.2 years old. One fifth of cases were of post-menopausal status. The demographic characters in this study were presented in Table 1.

Prevalence of abnormal cervical cytology from CPP, LBP by Liqui-Prep™ and PathTezt™ were 4.8, 5.6 and 5.9%, respectively. Rate of specimen inadequacy of CPP was 52.3%. It was more than that of LBP at 40.5% with statistical difference as represented in Table 2.

Prevalence of cervical cancer from CPP and LBP in this study were 0.2 % (53/22,552) and 0.1% (8/6,012), respectively. There were 142 cases of HSIL report in this study. Twenty-eight of cancer cases were diagnosed from CPP (20) and LBP (8). Around twenty percent (28/142) was the prevalence of cancer from the HSIL report. No cancer was found in LSIL group as represented in Table 3.

Comparison of sensitivity, specificity, PPV, NPV and accuracy of CPP and LBP was represented in Table 4. When the cytological report were HSIL+ (HSIL or worse), the sensitivity of CPP, Liqui-Prep™ and PathTezt™ were 65.5, 66.7 and 54.5, respectively. PPV of CPP, Liqui-Prep™ and PathTezt™ were 35.4, 38.1 and 28.6, respectively. Nearly one-hundred percent of specificity, NPV and accuracy of all three techniques were similar.

When the cytological report were cancer, the sensitivity of CPP, Liqui-Prep™ and PathTezt™ were 42.5, 33.3 and 18.2, respectively. The specificity, NPV and accuracy were nearly one-hundred percent. Positive Likelihood Ratio of all three techniques were extremely high.

Discussion

Cervical cancer is number one in mortality rate. Screening for cervical cancer is the best way to detect the preinvasive or early invasive cervical cancer. The prevalence of abnormal cervical cytology in Thailand from the CPP varied between 1.7-8.1% (Laiwejpithaya et al., 2009; Kituncharoen et al., 2015; Tanabodee et al., 2015; Kingnate et al., 2016) and from LBP were 3.70-12.30% (Laiwejpithaya et al., 2009; Kituncharoen et al., 2015; Tanabodee et al., 2015; Tangjitgamol et al., 2016), respectively.

In present study, the prevalence rate of abnormal cervical cytology from the CPP and LBP were 4.8 and 5.7%, respectively. The population in this study came from all over Thailand. Even though it was hospital based study, this area was the suburban area that located in the north part of Bangkok. This may represent the exact prevalence of abnormal Pap smear in the different socio-economic status and education.

In this study, the satisfactory rate of specimen from LBP was higher than CPP with statistical difference (59.5 and 47.7%). It was similar to previous literatures that LBP can significantly decrease unsatisfactory rate of smears (Akamatsu et al., 2012; Sigurdsson., 2013; Singh et al., 2015; Gupta et al., 2016; Jeong et al., 2017). However, the adequacy rate of specimen in this study was still lower than Lopez-Alegria's work form Brazil that reporting around 95% (Lopez-Alegria et al., 2015). Nowadays, there are many LBP commercial kit in Thailand. LBP technique can increase the adequacy rate of specimen obtaining. Disadvantages of CPP were suboptimal smears with insufficient squamous cells, dense inflammation, mucin, presence of obscuring blood and thick smears. Overlapping epithelial cells decrease their sensitivity to as low as 50% with rising false negative rate ranging 14-33% (Sharma et al., 2016).

During the period of record reviewing, it was the transitional period from CPP to LBP in Bhumibol

Table 1. Characteristics of Women Participating in the Study

Characteristics	CPP (n = 22,552)	LBP (n = 6,012)	p-value
Age (years)	39.73+16.20*	38.63+13.58*	0.603
Age group			0.101
< 20	2,255 (10)	300 (5)	
20-39	9,697 (43)	3,427 (57)	
> 40	10,600 (47)	2,285 (38)	
Menstrual status			0.228
Pre-menopause	16,914 (75)	4,930 (82)	
Menopause	5,638 (25)	1,082 (18)	
Underlying disease			0.221
No	18,718 (83)	5,351 (89)	
Yes	3,834 (17)	661 (11)	
Sexual intercourse			0.561
No	225 (1)	120 (2)	
Yes	22,327 (99)	5,892 (98)	
Coitarche (years)			0.087
< 20	13,982 (62)	3,006 (50)	
> 20	8,570 (38)	3,006 (50)	
Number of sexual partners history			0.480
0-1	17,591 (78)	4,930 (82)	
> 2	4,961 (22)	1,082 (18)	
Parity			0.395
0-1	12,855 (57)	3,066 (51)	
> 2	9,697 (43)	2,946 (49)	
Education			0.047***
< Bachelor	11,953 (53)	2,345 (39)	
Bachelor or above	10,599 (47)	3,667 (61)	
Occupation			0.103
Government officer	2,255 (10)	902 (15)	
Employee	8,345 (37)	1,864 (31)	
Housewife	4,510 (20)	1,443 (24)	
Student	2,255 (10)	120 (2)	
Others	5,187 (23)	1,683 (28)	
Contraception			0.466
No	16,688 (74)	4,208 (70)	
Oral contraceptive pills	677 (3)	120 (2)	
Others	5,187 (23)	1,684 (28)	
HIV			0.246
No	21,875 (97)	6,012 (100)	
Yes	677 (3)	0 (0)	
Smoking			0.121
No	21,650 (96)	6,012 (100)	
Yes	902 (4)	0(0)	
Alcohol consumption			0.369
No	21,650 (96)	5,952 (99)	
Yes	902 (4)	60 (1)	

*: mean + SD (standard deviation), **: n(%), ***: The result is significant at p < .05, CPP: conventional cervical Pap smear, LBP: liquid based cytology, HIV: human immunodeficiency virus

Adulyadej Hospital. Siriraj University Hospital, the foremost research hospital in Thailand, upgraded all their

cervical cytology screenings to their in house liquid-based technique (Laiwejpithaya et al., 2009). BAH, still uses

Table 2. Comparison of Cervical Cytology Results

Results	N	CPP	LBP	
			Liqui-Prep™	PathTezt™
Specimen				
Satisfactory**	14,331 (50,2)	10,751 (47,7)	1,440 (52,5)	2,140 (65,4)
Unsatisfactory	14,233 (49,8)	11,801 (52,3)	1,301 (47,5)	1,131 (34,6)
Cervical Cytology				
NILM	27,127 (94,9)	21,460 (95,2)	2,586 (94,4)	3,081 (94,1)
LSIL	244 (0.9)	179 (0.8)	31 (1.1)	34 (1.0)
HSIL	142 (0.5)	108 (0.5)	16 (0.6)	18 (0.6)
Atypical smear	990 (3.5)	752 (3.3)	103 (3.7)	135 (4.2)
Cancer	61 (0.2)	53 (0.2)	5 (0.2)	3 (0.1)
Total	28,564 (100)	22,552 (100)	2,741 (100)	3,271 (100)

*n(%), NILM: negative for intraepithelial lesion or malignancy, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, CPP: conventional cervical Pap smear, LBP: liquid based cytology, **: The result is significant at $p < .001$, Atypical smear: included ASC-US: atypical squamous cells of undetermined significance, ASC-H: atypical squamous cells cannot exclude high grade squamous intraepithelial lesion, AGC: atypical glandular cells, AGCFN: atypical glandular cells favor neoplasia

Table 3. Correlation of Cervical Cytology and Histopathology

Cytology	CPP			LBP			PathTezt™			N
	≤ CIN 1	CIN2/3	Cancer	Liqui-Prep™			PathTezt™			
				≤ CIN 1	CIN2/3	Cancer	≤ CIN 1	CIN2/3	Cancer	
LSIL*	164 (91.6)	15 (8.4)	0(0)	29 (93.6)	2 (6.4)	0 (0)	33 (97.0)	1 (3.0)	0 (0)	244
HSIL*	44 (40.7)	44 (40.7)	20 (18.6)	5 (31.3)	7 (43.7)	4 (25.0)	8 (44.4)	6 (33.3)	4 (22.3)	142
Cancer*	10 (18.9)	6 (11.3)	37 (69.8)	1 (20.0)	0 (0)	4 (80.0)	1 (33.3)	0 (0)	2 (66.7)	61
Total	218	65	57	35	9	8	42	7	6	447

*n(%), LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, ≤ CIN 1: cervical intraepithelial neoplasia grade 1 or less, CIN 2/3: cervical intraepithelial neoplasia grade 2, 3, CPP: conventional cervical Pap smear, LBP: liquid based cytology

Table 4. Cancer Detection Rate of Cervical Cancer Screening

	CPP		LBP			
	HSIL+	Cancer	Liqui-Prep™		PathTezt™	
			HSIL+	Cancer	HSIL+	Cancer
Sensitivity*	65.5	42.5	66.7	33.3	54.5	18.2
	(54.5-75.3)	(31.9-53.5)	(34.8-90.0)	(9.9-65.1)	(23.3-83.2)	(2.2-51.7)
Specificity*	99.5	99.9	99.5	100	99.5	100
	(99.4-99.6)	(99.8-99.9)	(99.1-99.7)	(99.8-100.0)	(99.2-99.7)	(99.8-100)
PPV*	35.4	69.8	38.1	80.0	28.6	66.7
	(30.0-41.1)	(57.2-79.9)	(23.8-54.7)	(32.5-97.1)	(16.0-45.5)	(16.3-95.3)
NPV*	99.8	99.7	99.8	99.7	99.8	99.7
	(99.8-99.9)	(99.7-99.8)	(99.6-99.9)	(99.5-99.8)	(99.7-99.9)	(99.6-99.7)
Accuracy*	99.4	99.7	99.4	99.7	99.4	99.7
	(99.3-99.5)	(99.6-99.7)	(99.0-99.6)	(99.5-99.8)	(99.0-99.6)	(99.4-99.8)
LR+*	141.5	597.1	139.9	909.6	118.5	592.7
	(110.7-180.8)	(345.4-1032.2)	(71.3-274.5)	(109.5-7553.6)	(56.6-248.1)	(57.8-6069.9)
LR-*	0.35	0.58	0.33	0.67	0.46	0.82
	(0.26-0.46)	(0.48-0.69)	(0.15-0.75)	(0.45-0.99)	(0.24-0.87)	(0.62-1.08)

HSIL+: high-grade squamous intraepithelial lesion or worse, PPV: positive predictive value, NPV: negative predictive value, LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio, *% and (95% Confidence Interval), CPP: conventional cervical Pap smear, LBP: liquid based cytology

both CPP and LBP. We consider upgrade all to liquid based technique in the near future when LBP cost is reduced.

Prevalence of our cervical cancer by CPP and LBP

methods were 0.2 and 0.1%, respectively. Prevalence of cervical cancer from previous study in Thailand were found to be between 0.14-1.4% in CPP and 0.02-0.9% in

LBP method (Laiwejpithaya et al., 2009; Kituncharoen et al., 2015; Tanabodee et al., 2015; Kingnate et al., 2016; Tangjitgamol et al., 2016). This result showed quite low prevalence of cervical cancer comparing to the previous study in Thailand. BAH is the airforce hospital. The participants who attended the gynecological clinic were airforce officer, their family and the people who lived nearby the hospital. More than half of attendant had education level of bachelor or more.

When the efficacy of cervical cancer detection between CPP and LBP were compared in women with HSIL or higher, specificity, NPV and accuracy of CPP or LBP were comparable at nearly one hundred percent.

When Pap report was of HSIL or higher groups, sensitivity of CPP and LBP were around two-third. The sensitivity of CPP was similar to LBP at 60%. There was no difference between both types of LBP. PPV in present study was lower than that of previous studies by Laiwejpithaya et al., (2009) while the sensitivity and specificity were compatible with reports by Arbyn et al., (2008). Arbyn et al., (2008) compared test performance characteristics of conventional to liquid-based cervical cytology sample. Their work was a systemic review and meta-analysis, published between 1991-2007. Approximately 90% of the participants were European women. For HSIL or higher groups, sensitivity and specificity were similar for conventional and liquid-based preparation (55.2% vs 57.1%, 96.7% vs 97.0%).

In this study, the cytological reports of cancer from LBP were of small number of cases. Only 3 and 5 cases came from PathTeztTM and Liqui-PrepTM technique, respectively. Only 8 and 53 cases came from LBP and CPP methods. This caused the sensitivity of cancer cytology for CPP to be higher than that of LBP.

The performance of CPP in this study was compared to the result from work by 2016 work of Cobucci et al., (2016). The percentage of sensitivity, specificity, PPV and NPV for HSIL or worse groups in this study and Cobucci's work were 65.5/64, 99.5/84, 35.4/99 and 99.8/99, respectively. The results from this study were comparable to the previous study.

In the present study, the performance of CPP, Liqui-PrepTM and PathTeztTM were compared. The number of cases in Liqui-PrepTM and PathTeztTM method were 2,741 and 3,271 cases, respectively. The sensitivity, specificity, PPV, NPV and accuracy of all three were similar. This observation was supported by the Taoka's work on 1,551 specimens from Japan in year 2010 (Taoka et al., 2010). The performance of CIN 1 or CIN 2+ of CPP and SurePath methods were not statically significant.

The limitations of this study were its retrospective approach. Some demographic data were omitted in some reports. Specimen collectors performance also must be varied between medical student, resident and staffs.

In conclusion, the prevalence of abnormal cervical cytology at BAH were 4.8%, 5.6% and 5.9% in CPP, Liqui-PrepTM and PathTeztTM, respectively. Liquid based cytology gave the percentage of specimen adequacy compared to CPP. CPP and both techniques of LBP had high diagnostic performance for cancer

detection especially specificity, NPV and accuracy. CPP was comparable to liquid-based cytology for cancer detection. Cytological screening was still the important role for early cervical cancer detection. The conventional technique was still useful for cancer detection with the major problem of specimen adequacy. The liquid based technique was an alternative technique for specimen adequacy improvement.

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