

Detection Rate of High-Grade Cervical Neoplasia and Cost-Effectiveness of High-Risk Human Papillomavirus Genotyping with Reflex Liquid-based Cytology in Cervical Cancer Screening

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Abstract

Introduction: This study aimed to determine the prevalence of cervical intraepithelial neoplasia grade 3 or worse ($\geq$ CIN3) and cost-effectiveness of human papillomavirus (HPV) genotyping with reflex liquid-based cytology (LBC) for cervical cancer screening in Singapore. **Materials and Methods:** Women who were $\geq$ 25 years old and undertook co-testing with LBC and HPV-genotyping (Cobas-4800, Roche, USA) for HPV-16, HPV-18 and 12 high-risk HPV types in a single institution were studied retrospectively. A single cervical smear in ThinPrep® PreservCyt® solution (Hologic, USA) was separated for tests in independent cytology and molecular pathology laboratories. The results were reviewed by a designated gynaecologist according to institutional clinical management protocols. Those who tested positive for HPV-16 and/or HPV-18 (regardless of cytology results), cytology showing low-grade squamous intraepithelial lesions (LSIL) or high-grade SIL (HSIL), or atypical squamous cells of undetermined significance (ASCUS) with positive 12 high-risk HPV types were referred for colposcopy. Colposcopy was performed by experienced colposcopists. Cervical biopsy, either directed punch biopsies or excisional biopsy, was determined by a colposcopist. The diagnosis of $\geq$ CIN3 was reviewed by a gynaecologic pathologist. Cost-effectiveness of HPV-based screening in terms of disease and financial burden was analysed using epidemiological, clinical and financial input data from Singapore. **Results:** Of 1866 women studied, 167 (8.9%) had abnormal cytology ($\geq$ ASCUS) and 171 (9.2%) tested positive for high-risk HPV. Twenty-three CIN were detected. Three of the 10 $\geq$ CIN3 cases had negative cytology but positive HPV-16. Compared to cytology, HPV genotyping detected more $\geq$ CIN3 (OR: 1.43). HPV+16/18 genotyping with reflex LBC was superior in terms of cost-effectiveness to LBC with reflex HPV, both for disease detection rate and cost per case of $\geq$ CIN2 detected. **Conclusion:** Compared to cytology, HPV+16/18 genotyping with reflex LBC detected more $\geq$ CIN3 and was cost-effective for cervical screening in Singapore.

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Key words: Co-Testing, Incidence trend, Mortality, Intraepithelial neoplasia, Pap smear

Introduction

In Singapore, the age-standardised incidence rate (ASR) of cervical cancer, which has been declining since 1974, was 7.0 per 100,000 from 2010 to 2014, ranking it the tenth most common cancer among women during this period.¹ The apparent rate of decline between each 5-year period was the most dramatic from 1995/1999 to 2000/2004 with 22.8%, and from 2000/2004 to 2005/2009 with 21.4%. However, this rate of decline diminished by more than half to 9.1% from 2005/2009 to 2009/2014. The lacklustre decline in the incidence of cervical cancer may be attributable to a low participation rate of cytology screening since 2004.^{2,3}

To sustain a continual improvement in cervical control in the short term before the impact of human papillomavirus (HPV) vaccination is seen, it would necessitate a change in screening strategy. Screening tests with good sensitivity for high-grade neoplasia, which allows for the prevention of the development of invasive disease and, on the other hand, a longer interval between screens for those with negative screening test, may overcome the limitation of screening by cytology alone.

Oncogenic or the high-risk subtypes of HPV are the necessary aetiological agents in the development of high-grade lesions and cervical cancer. HPV deoxyribonucleic acid

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(DNA) detection offers a great potential as a screening tool for the disease. Mayrand et al reported that the sensitivity of primary HPV DNA screening for cervical intraepithelial neoplasia grade 2 (CIN2) and CIN3 was 94.6%, compared to 55.4% for cytology test.⁴ Other randomised longitudinal studies in primary screening setting confirmed the superiority of HPV DNA test over cytology in the sensitivity for high-grade CIN ($\geq$ CIN2).⁵⁻⁷ In longitudinal trials involving multiple rounds of screening, HPV DNA test detected more $\geq$ CIN3 during the first round, thus allowing appropriate treatment to be performed in preventing the development of invasive disease during the interval between screens.⁸⁻¹⁰

The implementation of HPV DNA test in primary screening was slow because of its low specificity for $\geq$ CIN2. The management of women who tested positive for HPV was uncertain and referral of all these women for colposcopy would lead to unnecessary tests and over-treatment of less severe lesions with low malignant potential. One approach to resolve this dilemma is to separately test for HPV-16 and HPV-18 which are, by far, the most common HPV subtypes in $\geq$ CIN3 and invasive cervical cancer.¹¹⁻¹⁴ In this regard, the Athena trial which used a test system with outputs for HPV-16, HPV-18 and 12 other high-risk HPV types confirmed the superiority of HPV DNA test over cytology.¹⁵ More importantly, it yielded useful clinical information on the absolute risk of $\geq$ CIN2 and $\geq$ CIN3 for women who tested positive for HPV-16 and HPV-18 among women whose cytology was negative. These results allowed for the development of clinical management strategy based on the detection of HPV-16 and HPV-18. The system has since been approved by the United States Food and Drug Administration (USFDA) and is recommended in guidelines for primary screening for cervical cancer.^{16,17}

Cost-effectiveness is a major budgetary concern in introducing HPV DNA primary screening for cervical cancer. A study using data from the ATHENA trial reported that HPV 16/18/12 high-risk HPV test system was cost-effective in primary cervical screening in the United States of America (USA).¹⁸ This result is encouraging but it is well recognised that cost-effectiveness is the result of a complex dynamic process involving the operating cost of the test, further investigations and treatment of abnormal results, prevalence of HPV subtypes and burden of high-grade lesions and cervical cancer in the community. It should, therefore, be assessed by individual countries before a decision is made on its implementation.

In 2013, a pilot project that co-tested with HPV+16/18 genotyping and liquid-based cytology (LBC), and performed in 2 independent laboratories for screening of cervical cancer, was introduced in our institution. The present study aimed to determine the detection rate of $\geq$ CIN3 and cost-effectiveness of HPV+16/18 genotyping with reflex

cytology for cervical cancer screening in Singapore.

Methods and Materials

This retrospective study was approved by the Institutional Review Board.

Subjects

Women 25 years or older who attended a single institution for gynaecologic services and had undertaken co-testing for cervical cancer screening were identified. Women on follow-up for prior abnormal cervical cytology and those who reported a history of treatment for CIN, cervical or other lower genital tract cancers were excluded.

Co-Testing

Each individual had a single cervical scrape taken in ThinPrep® PreservCyt® solution. In the laboratory, each sample was divided into 2 aliquots – one was for HPV DNA testing using Cobas 4800 HPV test (Roche, USA) carried out according to the manufacturer's protocol in the molecular pathology laboratory, and the second was sent to the cytology laboratory for routine LBC analysis. Each laboratory reported the results independently. The results were reviewed by a designated gynaecologist for management decision, including colposcopy referral, in accordance with the institutional protocol (Fig. 1). Colposcopy was performed by experienced gynaecologic colposcopists. The final diagnosis was based on colposcopy directed punch biopsies, or cervical tissues obtained by loop electro-excision procedure, cervical conisation or hysterectomy.

Data Collection

This study was confined to the initial round of co-testing. Data on age, cytology and HPV DNA status, referral to colposcopy and final histological diagnosis were recorded.

Data Analysis

Descriptive data were tabulated for detection rate of abnormal cytology and HPV DNA subtypes, and rate of colposcopy referral. Cross-tabulation was performed based on the detection of CIN according to cytology and HPV categories.

Cost-Effectiveness Analysis

The incremental cost-effectiveness ratio (ICER) based on cost per quality-adjusted life-year (QALY) and clinical impact were analysed with an Excel-based Markov cohort

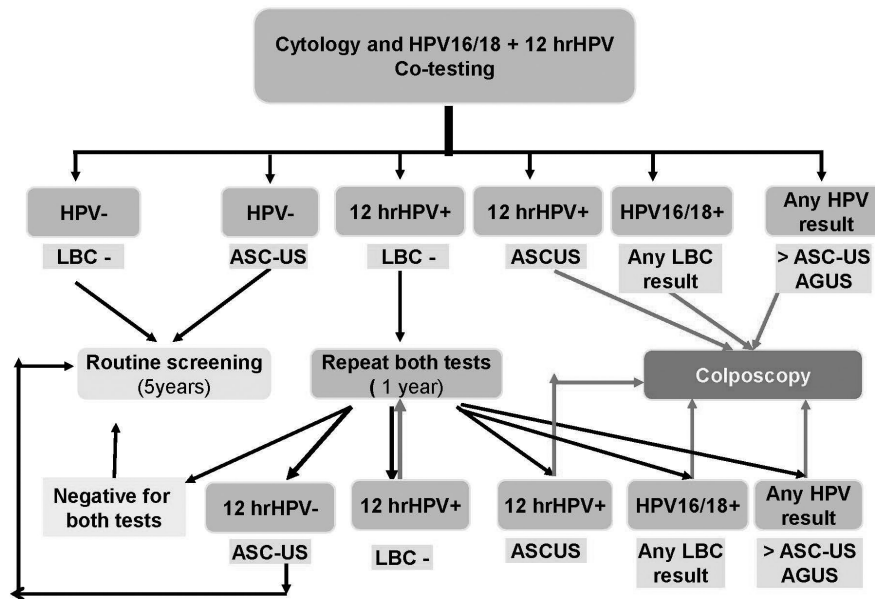


Fig. 1. A management algorithm for cervical cancer screening by co-testing.

model as described by Huh et al.¹⁸ The model inputs were based on data derived from Singapore sources for prevalence of HPV genotypes,¹⁹ prevalence of CIN1, CIN2, and CIN3, the cost of diagnosis and treatment of CIN and invasive cancer,²⁰ demography of women population and participation rate of cervical screening.^{2,3} It was assumed that the non-attenders of screening were most likely to be the same individual during the screening cycles for each strategy. The sensitivity of CIN detection was based on data revealed in this current study by cytology and co-testing. The absolute details of model inputs are summarised in Table 1. For this analysis, 2 screening scenarios were compared to no screening – LBC with reflex HPV for atypical squamous cells of undetermined significance (ASCUS) and HPV+16/18 genotyping with reflex LBC for 12 high-risk HPV-positive cases.

Results

Within the study period, 1866 women, aged between 25 and 75 years, were screened by co-testing. Of 1866 co-tests, 1684 (90.2%) tested negative for intraepithelial lesion and malignancy (NILM), 167 (8.9%) were abnormal with changes of ASCUS or more severe lesions, and 171 tested positive for high-risk HPV (9.2%) (Table 2). HPV genotype distribution was 1.8% for HPV-16, 0.6% for HPV-18, and 6.8% for 12 high-risk HPV. There were 95 women who fulfilled the criteria and were called for colposcopy. By the date of this analysis, 88 (92.6%) had been examined by colposcopy and 23 women had a diagnosis of CIN on

histopathology. Of the entire cohort, 10 (0.54%) cases of $\geq$ CIN3 were detected; 7 were from women with both abnormal cytology and positive HPV tests. Three cases of $\geq$ CIN3 had NILM and positive HPV-16; 1 of these was diagnosed as CIN3 with a focus suspicious of microinvasion (Table 3). Compared to LBC with reflex HPV, the odds ratio of detecting $\geq$ CIN3 by HPV+16/18 with reflex LBC was 1.43 (95% CI, 0.54 to 3.77).

The health economic model analysis showed that the incidence of cervical cancer was 19.21 per 100,000 population when no screening was performed, 13.25 per 100,000 population for screen strategy of LBC with reflex HPV testing, and 6.62 per 100,000 population for strategy involving HPV+16/18 genotyping with reflex LBC. Both screening strategies were cost-effective by ICER criteria (S\$2104 for LBC with reflex HPV testing and S\$3623 for HPV+16/18 genotyping with reflex LBC). There was a marginal advantage in incremental net monetary benefit towards screening with HPV+16/18 genotyping with reflex LBC compared to LBC with reflex HPV testing (S\$37,696 vs S\$37,233, respectively [Table 4]). The one-way sensitivity test showed that sensitivity of cytology and HPV genotyping had the greatest impact on the cost-effectiveness of screening (Fig. 2). In regard to impact on disease detection compared to cytology primary screening, HPV+16/18 genotyping primary screening increased detection of invasive cervical cancer from 47.5% to 83.1% and $\geq$ CIN2 from 56% to 80.3% respectively (Fig. 3). The number of missed and interval progression from $\geq$ CIN2 to invasive cancer was also reduced from 20 cases per annum in cytology screening programme

Table 1. Input Data to Model for Cost-Effectiveness Analysis

Annual Progression Rate	%	Annual Regression Rate	%
Well to high-risk HPV	4.2	From 12 high-risk HPV/NIML to normal	58.6
12 high-risk HPV to CIN 1	8.1	From 12 high-risk HPV/LSIL to normal	45.6
12 high-risk HPV to CIN 2	0.1	From HPV16/18 with NIML to normal	43.8
12 high-risk HPV to CIN 3	0.1	From HPV16/18/LSIL to normal	21.8
16/18 to CIN 1	9.9	From CIN 1 to well	21.2
16/18 to CIN 2	0.6	From CIN 1 to HPV	2.4
16/18 to CIN 3	1.5	From CIN 2 to well	9.4
CIN 2 to CIN 3	3.2	From CIN2 to CIN 1	9.4
CIN 3 to ICC	1.1	From CIN 3 to well	3.9
		From CIN 3 to CIN 1	1.6
Prevalence of HPV/CIN/Cancer		Test Sensitivity and Specificity	
Prevalence of high-risk HPV	8.2	Cytology sensitivity for CIN2+	53.2
Prevalence of HPV 16/18	2.1	Cytology sensitivity for CIN3+	57.7
Prevalence of CIN 1	0.3	Specificity of cytology	73.4
Prevalence of CIN 2	0.4	HPV sensitivity for CIN2+	86.6
Prevalence of CIN 3	0.5	HPV sensitivity for CIN3+	89.9
Prevalence of ICC	0.053	HPV specificity	62.7
% Population $\geq$ ASCUS	3.9	Colposcopy sensitivity	100
% Population Cyto+/HPV+	2.7		
Cost of Tests (2013)	SGD (\$)	Treatment Cost (2013)	SGD (\$)
Clinic visit	72.81	CIN2+	1500
Cytology screening	55.0	Cancer	25,000
HPV DNA	100		
Colposcopy/biopsy	286.14		
Screened Population		Screening Interval	No. years
Total population (women)	1,953,200	Cytology alone	3
Population ≥ 25 and ≤ 65 years old	63.7%	HPV with reflex with reflex cytology	5
% ineligible for screening	11.4	Attendance rate for managed algorithms	75%
Total eligible population	1,101,734		
Compliance rate of screening	50%		
Total screen population	550,867		

ASCUS: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial lesion; DNA: Deoxyribonucleic acid; HPV: Human papillomavirus; ICC: invasive cervical carcinoma; LSIL: Low-grade squamous intraepithelial lesion; NMIL: Negative for intraepithelial lesion or malignancy

Table 2. Cytology and HPV DNA Status of the Entire Cohort

Cytology Category	n	High-Risk HPV DNA Detection	
		n	%
Negative	1684	94	5.6
ASCUS	138	50	36.2
SIL	29	27	93.1
Unsatisfactory	10	0	0
Others	5	0	0
Total	1866	171	9.2

ASCUS: Atypical squamous cells of undetermined significance; DNA: Deoxyribonucleic acid; HPV: Human papillomavirus; SIL: Squamous intraepithelial lesion

Table 3. Pathological Diagnosis by Cytology and HPV Status

Cytology/HPV Status	n	No. of Colposcopy	CIN 1	CIN 2	CIN 3
SIL					
16 and/or 18 +	10	10	2	0	3
12 high-risk HPV+	17	15	3	0	2
HPV-	2	2	1	0	0
Subtotal	29	27	6	0	5
ASCUS					
HPV 16 and/or 18 +	14	13	2	0	1
12 high-risk HPV+	36	22	1	2	1
HPV-	88	5	1	0	0
Subtotal	138	40	4	2	2
Negative					
HPV 16 and/or 18 +	16	12	0	0	3
12 high-risk HPV+	78	7	1	0	0
HPV-	1590	2	0	0	0
Subtotal	1684	21	1	0	3
Overall	1866		11	2	10 (0.54%)

ASCUS: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial lesion; HPV: Human papillomavirus; SIL: Squamous intraepithelial lesions

to 12 cases in HPV primary screening programme. Cost per person per annum for screening test and cost per case of high-grade lesion detected showed advantage towards HPV primary screening than cytology screening (Fig. 3).

Discussion

Real-world experience of primary HPV test in population screening is not yet available. We presented in this study an institutionally-based setting of cervical cancer screening which reflected the real-world individual care scenario commonly seen in places with no structured population screening programme. HPV test with types 16 and 18 genotyping was introduced to the existing practice of screening by liquid-based cytology. The rationales of the co-testing were to avoid anxiety expressed by clinicians and women towards new screening tests and to garner local

laboratory and clinical experience in routine primary HPV test.

It is interesting to note the similar prevalence of abnormal test by cytology (8.9%) and HPV test (9.2%) individually. The prevalence of high-risk HPV detected was twofold higher than the rate in Singaporean women with normal cytology in a previous study, and the findings concurred with that of the ATHENA trial in the USA.^{15,19} In fact, the prevalence of $\geq$ CIN3 (0.54%) in this study was identical to that reported in the ATHENA trial. This reflected the burden of high-risk HPV and $\geq$ CIN3 in previously screened communities in the USA and Singapore.

Of the 10 $\geq$ CIN3 cases detected in this study, 7 had abnormal cytology and 3 had negative cytology. The increased detection rate of $\geq$ CIN3 (OR: 1.43) was within the reported range of longitudinal clinical trials comparing primary HPV test to cytology.⁸⁻¹⁰ One of the women with

Table 4. Comparison of Cost-Effectiveness of Different Scenarios of Screening Strategies

Screening Strategy	Strategy Characteristics	Incidence of Cervical Cancer/100,000 Women	Cost (SGD)	
			ICER	INMB
	No screening	19.21		139
A	LBC/Reflex HPV*	13.15	2104	37233
B	LBC/HPV+ 16/18†	6.62	3623	37696

LBC: Liquid-based cytology (thin-prep); HPV: Human papillomavirus; ICER: Incremental cost-effectiveness ratio; INMB: Incremental net monetary benefit

*High-risk HPV test for ASCUS cytology.

†Cobas 4800 system (Roche).

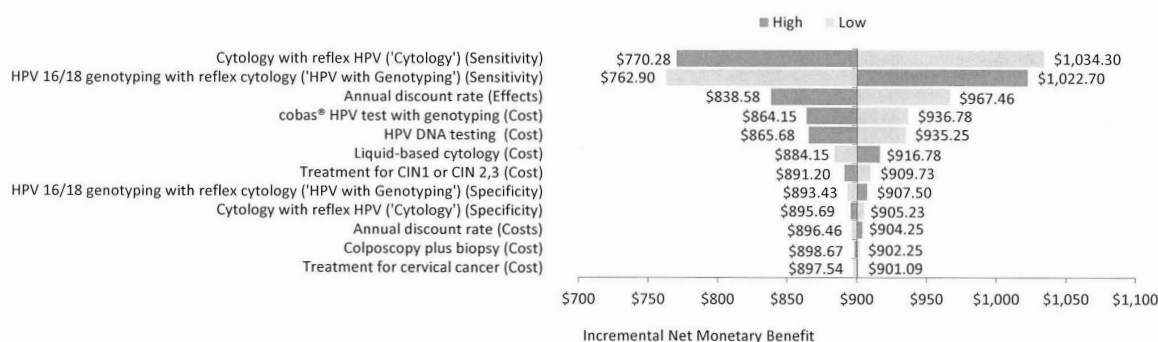


Fig. 2. A tornado diagram showing the results of a one-way sensitivity analysis.

repeated negative cytology tests was found to be positive for HPV-16 and a final diagnosis of a high-grade lesion with a focus of suspicious microinvasion highlighted the benefit of HPV test which allowed this woman's lesion to be prevented from progressing to a clinical carcinoma of the cervix during the interval of screening. This capability of HPV test at the initial round of screen was previously reported by Ronco et al in the follow-up of 4 European longitudinal studies.²¹

The fact that LBC and HPV tests were carried out in 2 independent laboratories which reported the results separately allowed us to analyse the results in this study in the manner of primary HPV test with reflex cytology. Of the 10 CIN3+ cases, 7 would have been referred for immediate colposcopy because of positive test for HPV16/18, regardless of cytology. The remaining 3 cases would have been referred for colposcopy because of squamous intraepithelial lesions (SIL) on LBC in 2 cases and ASCUS with reflex positive high-risk HPV test in 1 case. Based on the rate of concurrent positivity on cytology and HPV in this study, 4.1% (77/1688) of the women would have been referred for colposcopy, with a detection rate of $\geq$ CIN3 in 1 out of 7.5 colposcopy referrals. This would substantially reduce the cost of screening tests without overburdening the colposcopy services.

Not surprisingly, health economic modelling has estimated a reduced incidence rate of cervical cancer with screening. More importantly, the incidence rate was lower in screening scenarios that employed HPV-based testing. Using criteria set by the World Health Organization that an ICER of onefold or less of the gross domestic product is cost-effective for medical intervention, the HPV+16/18 genotyping with reflex LBC proved to be highly cost-effective for Singapore. In terms of impact of screening on disease burden, HPV+16/18 genotyping detected more $\geq$ CIN2 and cervical cancer compared to LBC primary screening with reflex HPV test. Our findings concurred with studies from the USA and Europe.²¹⁻²³ These findings are in distinct contrast to early studies of primary HPV screening

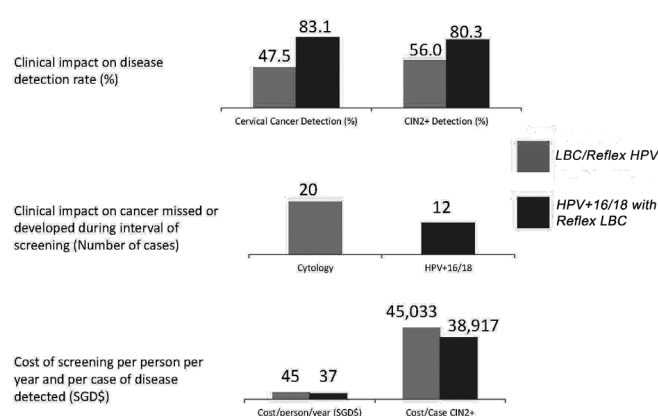


Fig. 3. Comparison of clinical and monetary cost of 2 screening strategies.

without cytology triage as HPV test has low specificity for high-grade lesions.²⁴

Because of the extension in screening interval from 3 years for cytology screening to 5 years for HPV-based screening, the net monetary savings in the cost of screening per person per year and costs of detecting $\geq$ CIN2 per case were lower for HPV-based screening. It is envisaged that (as shown in clinical trials in population screening) when subsequent rounds of screening detect fewer HPV-positive cases and $\geq$ CIN3, the number of reflex cytology tests would also substantially diminish.^{21,25} This would translate to further financial cost savings and improve the margin of cost-effectiveness in a sustained long-term screening programme.

Conclusion

The findings of the present study corroborated the reported results of clinical trials that HPV-based cervical screening is superior to cytology screening. In Singapore, HPV+16/18 genotyping with reflex LBC detected more $\geq$ CIN3 and was highly cost-effective.

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