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# Cervical cancer prevention through cytologic and human papillomavirus DNA screening in Hong Kong Chinese women

## Key Messages

1. Since the launch of the cervical screening programme, the ever-screened rate has increased significantly from 37% in 2003 to 64% in 2008.
2. Using Hong Kong specific data on age-specific human papillomavirus (HPV) prevalence and cervical cancer incidence, the first cost-effectiveness analysis of the role of adjunctive HPV DNA testing was conducted.
3. Based on the principle that revision to current practice should not reduce effectiveness, the cost-effectiveness analysis suggests that 1,1,3-yearly cytology screening with HPV DNA testing is an optimal testing paradigm.

## Introduction

In March 2004, the Department of Health (DH) launched Hong Kong's first organised population-based cytologic (conventional or liquid-based) screening recall programme for women aged between 25 and 64 years. Women are recommended to undergo screening every 3 years following 2 consecutive annual negative cytologic smear results ("1,1,3-yearly smear cycle").<sup>1</sup> However, there has not been any formal evaluation of DH's cervical screening programme, and there is a need to investigate whether and by what factors this programme would result in higher screening coverage.

Given that persistent infection with high-risk human papillomavirus (HPV) subtypes is a necessary precursor to cervical carcinogenesis, the Hong Kong College of Obstetricians and Gynaecologists (HKCOG) suggested using HPV DNA testing as an adjunct to routine cytology screening.<sup>2</sup> Before widely adopting this strategy, its cost-effectiveness needs to be carefully evaluated using local-specific data.

This study aimed to (1) assess intermediate outcomes of the DH's cervical screening programme in terms of overall population coverage, stratified by socioeconomic determinants (ie equity of access), using a pre-post survey design; (2) predict the medium-to-long-term clinical effectiveness conferred by such population coverage patterns by fitting empirical parameters from objective 1 into a previously developed age-period-cohort projection model;<sup>3</sup> and (3) adapt and extend our previous state-transition Markov cost-effectiveness model<sup>4</sup> to include HPV DNA testing as an adjunct to conventional or liquid-based cytology.

## Methods

This study was conducted from June 2007 to July 2009.

### Objective 1

We used a pre-post survey design to assess the population coverage of cervical cytologic screening. We used the 2003 Population Health Survey<sup>5</sup> (coded PHS-2003) to extract data on the baseline coverage pattern before the launch of the cervical screening programme in 2004. To assess the current coverage, we designed a similar survey (coded SHS-2008) and conducted telephone interviews by random-digit dialling of all fixed, land-based telephone lines and sampling all women aged at least 25 years in the household.

We compared SHS-2008 with PHS-2003 to assess the impact of the cervical screening programme. We used multivariate logistic regression to generate adjusted odds ratios (ORs) for potential personal characteristics that were associated with the tendency of cervical cancer screening.

### Objective 2

We adapted a previously developed maximum likelihood age-period-cohort (APC) model<sup>3</sup> to project the likely avertable disease burden associated

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with the level and pattern of screening uptake after the implementation of the cervical screening programme as assessed in objective 1.

Data on cervical cancer incidence and mortality from January 1972 to December 2006 were based on the Hong Kong Cancer Registry. Statistics on population figures were obtained from the Census and Statistics Department. Incidence data were grouped from 1972-76 to 2002-06 into 5-year periods and 5-year age-groups from 25-29 to 80-84 years to give synthetic birth cohorts centred at 5-year intervals since 1892. Age-groups of <25 and >85 years were omitted due to small numbers.

We fitted the data by Poisson regression to compute 15-year projections of incidence rates to the period 2017-21.<sup>3</sup> We applied linear extrapolation of the seven observed periods and the seven most recent birth cohorts based on data from 1972 to 2006. This set of projected rates would reflect a continuation of the status quo of opportunistic screening in Hong Kong through 2021 (base case).

Population mortality rates were combined with incidence rates to derive age-period-specific mortality to incidence (M/I) ratios using observed data from 1972-76 to 2002-06. Assuming no change in cancer-specific survival over the projected time horizon, we applied a constant set of age-period-specific M/I ratios that were based on the two most recent observed periods and were smoothed using moving averages. To assess the impact of the new organised screening programme, we computed the number of cancer cases under different screening frequencies by applying the risk reduction estimates as per the International Agency for Research on Cancer (IARC). We derived these figures by calibrating the original IARC estimates, which were based on the comparator scenario of no screening, to Hong Kong's status quo of opportunistic screening.<sup>3</sup> Projected incident case numbers obtained from the APC modelling were adjusted downwards based on these cancer incidence reduction figures, beginning from the period 2007-11, assuming that all Hong Kong women would derive a similar level of benefit from screening compared with populations in the IARC study and irrespective of age and other characteristics. We assumed that the full benefit of the organised screening programme would only begin from 2007. The numbers of cancer-related deaths were then scaled pro rata according to the procedure using age-period-specific M/I ratios as specified above.

### **Objective 3**

To conduct the cost-effectiveness analysis for cervical screening strategies and the inclusion of HPV DNA testing as a triage, we developed an individual-based stochastic model, which simulated the natural history of cervical cancer. Each stochastic realisation of this model corresponded to the life history of an individual. A simulated individual entered the model at the age of 10 years without HPV infection. Once infected, the individual was free of lesions (HPV-

infected) for some time and then either cleared the infection or progresses to cervical intraepithelial neoplasia (CIN) 1. After CIN 1 was established, the individual may regress to earlier stages (normal or HPV-infected) or progress to CIN 2,3. Similarly, with CIN 2,3, the individual may regress to earlier stages or progress to cervical cancer if the HPV causing the infection belonged to the high-risk group. Our assumptions regarding management of abnormal screening results were based on the Guidelines on Management of Abnormal Cervical Cytology published by HKCOG.<sup>2</sup>

To perform the cost-effectiveness analysis using the natural history model, we needed to estimate the age-specific probabilities of infection. We used two Hong Kong specific data sources for this procedure: (1) age-specific HPV prevalence data from a Hong Kong study conducted in 2002,<sup>6</sup> and (2) age-specific cancer incidence data from the Hong Kong Cancer Registry.<sup>7</sup>

We used the incremental cost-effectiveness ratio (ICER), defined as the marginal cost divided by the marginal health benefit compared with the next most effective non-dominated strategy, to evaluate the cost-effectiveness of different strategies. Strategies with ICER below a predetermined threshold (an ICER threshold) were considered to be cost-effective. In this study, we interpreted the cost-effectiveness of strategies in the context of the World Health Organization (WHO) threshold of three times the gross domestic product (GDP), which was equivalent to around US\$90 000 (the Hong Kong GDP was around US\$29 820 to 30 781 in 2007 to 2009).<sup>8</sup> We defined the optimal strategy as the strategy that yields the best health outcome among all cost-effective strategies.

## **Results**

### **Objective 1**

The telephone survey was conducted from December 2007 to March 2008. We contacted 1858 women and successfully interviewed 1023, which corresponded to a response rate of 55%. All comparisons were examined on weighted whole population samples, using age-specific weighting adjusted for the size of the land-based non-institutional population (excluding foreign domestic helpers). To assess the change in screening coverage since the launch of the DH's cervical screening programme, we compared the results of SHS-2008 to that of PHS-2003.<sup>5</sup>

In SHS-2008, 64% of the respondents reported to have had cytology smears in the absence of symptoms (ie preventive screening), which was substantially higher than the 37% in PHS-2003 (Table 1). In particular, the ever-screened rate increased sharply from 13% to 40% among those aged  $\geq 65$  years, and from 26% to 53% among those who did not have regular physical check-up.

Among those who had been screened without symptoms, 64% of the SHS-2008 respondents reported to have regular

screening, which was similar to that in PHS-2003 (60%). There was a significant decrease in regular-screening rate among those divorced/widowed (61% vs 37%) and significant increases among those economically active (Table 1).

Our multivariate regression analysis suggested that respondents in SHS-2008 were more likely to have had preventive screening (OR, 4.3). Women were more likely to have had preventive screening if they had a secondary education or above (OR, 1.4-1.6) or a monthly income of  $\geq$ HK\$20 000 (OR, 1.8). In contrast, women were less likely to have had preventive screening if they were currently non-married (OR, 0.27) or aged  $\geq$ 65 years (OR, 0.25). Among those who had ever had preventive screening, those who had regular physical check-up were more likely to have regular screening (OR, 6.8), whereas those who aged 45 to 64 years (OR, 0.7) or  $\geq$ 65 years (OR, 0.1) were less likely to have regular screening than those aged 25 to 44 years.

### Objective 2

The maximum likelihood APC model predicted that there will be 5911 cervical cancer cases and 1428 deaths over the 15 years from 2007 to 2016 under the base-case scenario of opportunistic screening (Fig 1). From the APC model, 15-year projections from 2007 to 2021 estimated that if all women were screened every 1, 3, and 5 years, compared with the status quo of opportunistic screening, the incremental cumulative number of cases prevented (years of life saved) would be 5254 (32 000), 4655 (28 200) and 2322 (14 100), representing 89%, 79%, and 39% reductions, respectively (Fig 1).

### Objective 3

We performed a cost-effectiveness analysis to compare different combinations of cytology screening and HPV DNA testing from annually to 5-yearly. We assumed that cytology testing had a sensitivity of 70% and 80% for CIN 1 and CIN 2,3, respectively, and a specificity of 95%.<sup>9</sup> We also assumed that HPV DNA test had a sensitivity of 83% and a specificity of 93%.<sup>10</sup> We considered quality-adjusted life-year (QALY) and cancer incidence reduction as outcome measures of screening strategies. We also calculated the total cost including both the treatment cost for CIN 2,3 and cervical cancer and the cost for cytology and HPV DNA tests (Table 2). Both the QALYs and costs were discounted at an annual rate of 3%.

Table 3 shows the total cost, cancer incidence, cancer incidence reduction, QALY and ICER for different combination of strategies comprising cytology and HPV DNA tests. When there was no screening, the individual cost and QALY were US\$66 and 28.80812 years, respectively. In the baseline scenario (60% screening coverage), all strategies averted around 50 to 60% cancer cases and saved 8.94 to  $10.52 \times 10^{-3}$  QALYs (Table 3).

We performed a pair-wise comparison of screening strategies with and without HPV DNA testing (Table 3). The addition of HPV DNA testing to cytology-only strategies resulted in more QALYs at the expense of a higher costs and would be cost-effective for regular screening every  $\geq$ 3 years under the WHO ICER threshold (US\$90 000 per QALY). When considering all screening strategies, all the cytology-only screening strategies were dominated (Fig 2). The optimal screening strategy was regular, 4-yearly cytology screening with HPV DNA testing.

**Table 1. Comparison of screening practice between PHS-2003 and SHS-2008**

Variable	% of women who had been screened preventively		% of women who have regular screening among those who had been screened preventively	
	PHS-2003	SHS-2008	PHS-2003	SHS-2008
Overall	37	64	60	64
Age-group (years)				
25-44	41	65	63	73
45-64	44	74	58	61
$\geq$ 65	13	40	36	28
Marital status				
Single	18	25	53	61
Married	45	80	60	68
Divorced/widowed	27	51	61	37
Monthly income (HK\$)				
1-9999	38	61	57	64
10 000-19 999	40	53	63	74
$\geq$ 20 000	54	68	58	78
No income	34	67	60	58
Occupation				
Professionals	42	58	54	79
White-collar	40	63	61	70
Blue-collar	39	61	54	71
Economically inactive	34	67	60	58
Physical check-up				
Yes	65	79	79	78
No	26	53	43	41

**Table 2. Treatment and test costs in cost-effectiveness analysis**

Parameter*	Cost (US\$)
Treatment	
CIN 2,3 <sup>11</sup>	733
Local ICC <sup>11</sup>	13 172
Regional ICC <sup>11</sup>	14 098
Distant ICC <sup>11</sup>	22 580
Test	
Administration <sup>11</sup>	30
Cytology smear <sup>11</sup>	10
Human papillomavirus DNA <sup>12</sup>	49
Colposcopy and biopsy <sup>11</sup>	284
Health status	Utility <sup>13</sup>
No cancer	1
CIN 1	0.91
CIN 2,3	0.87
Local ICC	0.76
Regional ICC	0.67
Distant ICC	0.48
Cancer survivor	0.84

\* CIN denotes cervical intraepithelial neoplasia, ICC invasive cervical cancer

**Table 3. Cost-effectiveness analysis comparing different cytology screening and human papillomavirus (HPV) DNA testing strategies up to age 65 years**

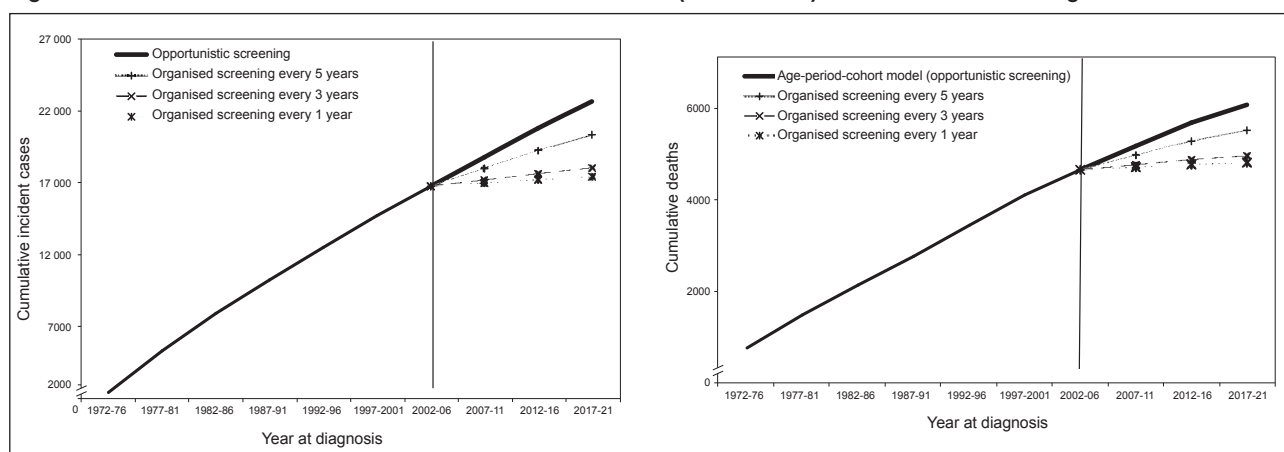
Strategy	Cost (US\$)	No. of cervical cancer cases per 100 000 women (reduction %*)	Quality-adjusted life-year saved (10 <sup>-3</sup> year)*	Incremental cost-effectiveness ratio <sup>†</sup>	Incremental cost-effectiveness ratio <sup>‡</sup>
No screening	66	1506	-	-	-
Cytology, 5-yearly	200	787 (48)	8.94	-	14 979
Cytology+HPV, 5-yearly	215	741 (51)	9.43	32 505	32 505
Cytology, 4-yearly	223	749 (50)	9.41	-	Dominated
Cytology+HPV, 4-yearly	241	707 (53)	9.75	52 139	78 902
Cytology, 3-yearly	262	708 (53)	9.83	-	Dominated
Cytology+HPV, 3-yearly	283	672 (55)	10.08	83 601	127 516
Cytology, 2-yearly	333	675 (55)	10.17	-	Dominated
Cytology+HPV, 2-yearly	360	646 (57)	10.31	191 352	345 363
Cytology, 1-yearly	532	645 (57)	10.44	-	Dominated
Cytology+HPV, 1-yearly	573	626 (58)	10.52	532 132	678 118

\* Calculated using 'no screening' as the reference

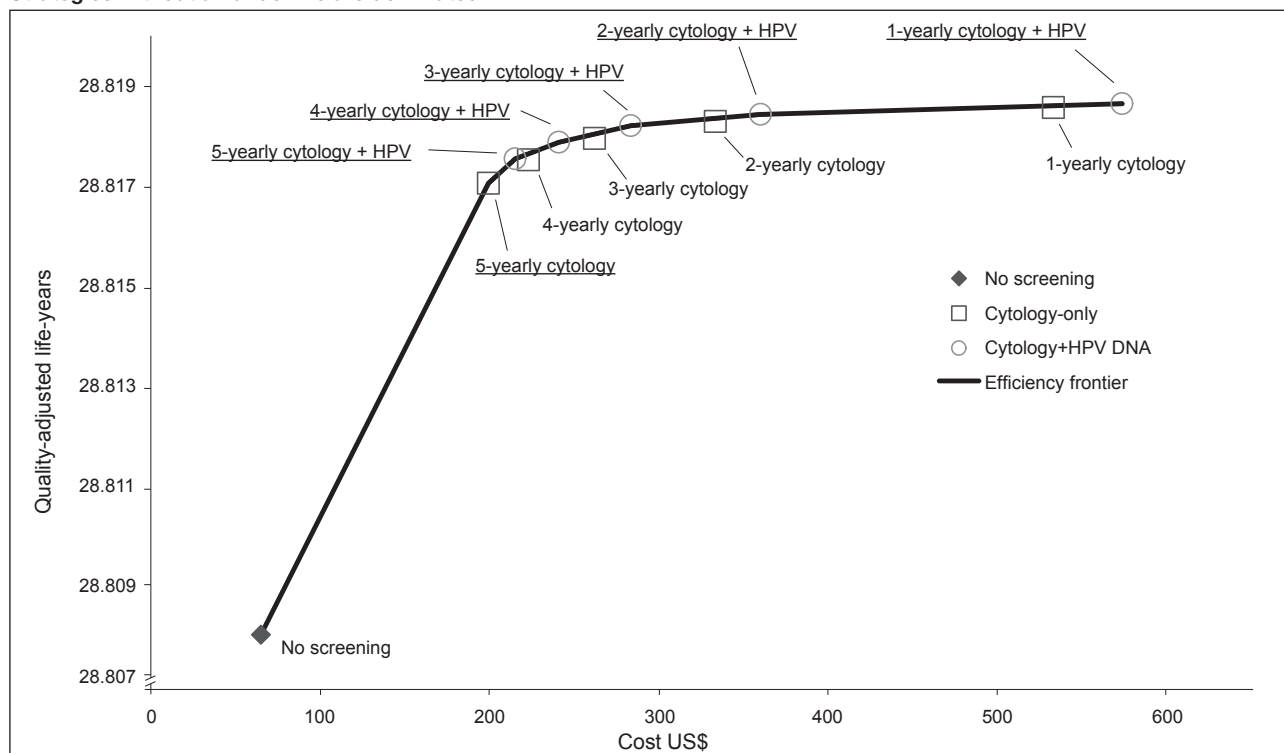
<sup>†</sup> Comparing cytology screening and HPV DNA testing strategies versus cytology screening only strategies at the same interval

<sup>‡</sup> Comparing the next most-effective non-dominated strategy

**Fig 1. Cumulative incident cases and deaths from cervical cancer (1972 to 2021) under different screening scenarios**



**Fig 2. Cost-effectiveness of different combinations of cytology screening and human papillomavirus (HPV) DNA testing. Strategies without an underline are dominated.**



## Discussion

### Objective 1

The ever-screened rate in the absence of symptoms (ie preventive screening) increased from 37% in PHS2003 to 64% in SHS-2008 and an increase was uniformly observed when subjects were stratified by socioeconomic determinants. These results suggest that cervical screening programme has increased coverage in the general population and has been particularly successful in boosting the ever-screened rate among those with very low baseline tendency to do so (ie those aged  $\geq 65$  years and those with no regular physical check-up). However, the ever-screened rate among those aged  $\geq 65$  years remained low at 40%. The programme recommends that women aged  $\geq 65$  years undergo screening if they have never been screened before or if the most recent screening was performed a long time ago.<sup>1,2</sup> The low ever-screened rate among women aged  $\geq 65$  years may be due to their misconception that women who are sexually inactive or postmenopausal do not benefit from it.<sup>1</sup> Overall, while the ever-screened rate has significantly increased since the launch of the programme, the current rate of 64% should be further increased to maximise the benefits.

### Objective 2

In terms of policy implementation, the screening programme launched in Hong Kong in 2004 was really a government-operated programme, which provided a prospective record and recall function for those who had ever been screened.<sup>1</sup> The programme encouraged women to undergo regular cytologic examination through social marketing campaigns for the general public, via primary care and women's health providers on an opportunistic basis. For women who decided to get screened, they could be tested at public or private care providers on a full fee-for-service basis and these providers were then encouraged to enter the screened woman's details into a centralised database for subsequent automatic recall (every 3 years) and archiving of test results. For an ideal programme, it is important to explicitly anchor the screening to proactive and personalised invitations (initial 'call' function).

### Objective 3

Although HPV DNA testing could be used as an adjunct to cervical cancer screening,<sup>2</sup> its role has not been addressed by the cervical screening programme.<sup>1</sup> Using Hong Kong specific data on age-specific HPV prevalence and cervical cancer incidence, we provided the first cost-effectiveness analysis on this topic. Under the WHO ICER threshold (defined as three times the local GDP, which is US\$90 000), our cost-effectiveness analysis suggested that adding HPV DNA testing to cytology-only screening would be cost-effective if the regular screening interval was  $\geq 3$  years (Table 3). Therefore, our analysis supports adding HPV DNA testing to the current recommended 1,1,3-yearly screening strategy.

Our analysis suggests that among all screening strategies, screening with cytology and HPV DNA testing every 4 years is the optimal strategy. However, although the 1,1,4-yearly cytology with HPV DNA testing strategy was more cost-effective than 3-yearly cytology screening alone, the former was less effective in preventing cervical cancer. Based on the principle that revision to current practice should not reduce effectiveness, our analysis suggests that 1,1,3-yearly cytology screening with HPV DNA testing is optimal.

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