Effectiveness and Cost-effectiveness of Human Papillomavirus (HPV) Vaccines in Cervical Cancer Prophylaxis

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Abstract— **Human papillomavirus (HPV) infection is the main cause of cervical cancer. Cervical cancer patients go through painful long-term treatments and high medical costs. Prevention is better than cure. Hence, regular cervical screening is recommended for Hong Kong women to prevent this disease. Some studies have been conducted in Western countries to show that cost-effectiveness can be achieved by combining HPV vaccines with regular screening. The study is guided by three research groups on the future implication of the cost-effectiveness of three cervical cancer prevention strategies: (1) annual Pap smear for women aged 25–42, (2) HPV vaccination at age 12, and (3) HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42. The three groups are compared in terms of their total lifetime cost, cost-effectiveness ratio and incremental life expectancy. The Markov model software is used as the main analytical tool. After analyzing, annual Pap smear screening is a cost-effective method to prevent cervical cancer that the total lifetime cost was approximately USD145.69; cost-effectiveness ratio was USD8.80/DALY; and incremental life expectancy was 2.72 years. Moreover, HPV vaccination combined with annual Pap smear screening is an effective way to prolong the life expectancy of women regardless of race that the total lifetime cost was approximately USD545.12; cost-effectiveness ratio was USD29.56/DALY; and incremental life expectancy was 2.84 years. Such result provides important insight for the formulation of a health care policy to prevent cervical cancer. This policy can save lives and reduce local treatment costs.**

Keywords- HPV vaccine, Cervical cancer, Cervical screening, Cost-effectiveness analysis

BACKGROUND

Cervical carcinoma is the second most common cancer found in women. Each year, 500,000 new cases of cervical cancer are reported, resulting in 250,000 deaths [1]. The World Health Organization (WHO) predicted that female mortality all over the world would be around 340,000–480,000 in the next 5–20 years [2]. In Hong Kong, the overall age-standardised morbidity and mortality rates of cervical cancer are 9.4 and 2.4 per 100,000, respectively, according to 2006 figures [3].

There is evidence that cervical carcinoma develops as a result of infection with high-risk genotypes of human papillomavirus (HPV). Epidemiological studies show that 70% of cervical cancer cases are related to HPV 16 and 18 infections. Studies also indicate that HPV infection is strongly interrelated with sexual activity [4, 5]. Women can be infected with HPV during their lifetime. HPV infections can clear spontaneously within one year. However, HPV infections can develop into cervical intraepithelial neoplasia (CIN) and cervical carcinoma when the infections persist and remain untreated [6].

The prevention of cervical cancer is currently managed in Hong Kong through a cervical screening programme launched in 2004. Women aged 25 and above are recommended to undergo a Pap smear screening every three years [7]. Regular cervical screening is an important cervical cancer preventive strategy, although the screening alone cannot protect a person from acquiring HPV infection.

The efficient use of resource is a major element in the health care system. Decisions on resources distribution, efficacy, and safety of new interventions and treatments are of utmost importance. However, the costs and cost-effectiveness of these new interventions and treatments must be considered. Hence, the present study focuses on examining the potential effectiveness and cost-effectiveness of prophylactic annual cervical screening, HPV vaccination, and HPV vaccination combined with annual cervical screening in Hong Kong.

Clients' demands are unlimited. Therefore, health policy makers should consider how to use health resources in an effective and efficient manner. Cost-effective analysis (CEA) provides an approach determines the most efficient method of utilising limited resources to maximise health benefits. Health effects result from the minimisation of resources [8]. The WHO Commission on Macroeconomics and Health points out that a cost-effectiveness ratio less than three times the gross domestic product (GDP) per capita is cost-effective [9]. In other words, a health care programme is cost-effective if the cost of each disability adjusted life year (DALY), which DALYs measure the difference between current health status and ideal health status, is either less than three times of the GDP per capita. Otherwise, the health care programme is identified as not cost-effective.

PURPOSE, METHODS AND MATERIALS

The study is guided by three research groups on the future implication of the cost-effectiveness of three cervical cancer prevention strategies: (1) annual Pap smear for women aged 25–42, (2) HPV vaccination at age 12, and (3) HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42. Two research questions guided the study:

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1. What is the future implication of the effectiveness and cost-effectiveness of each of the three cervical cancer prophylaxis strategies provided to 12-year-old females in Hong Kong?

2. How do the three cervical cancer prophylaxis strategies compare with one another in terms of cost-effectiveness ratio and incremental life expectancy?

Previous studies have established that 12-year-old girls are suitable participants in the CEA of HPV vaccines [11-23]. The objective of this study is to determine the effectiveness and cost- effectiveness of Hong Kong's vaccination programme, where HPV vaccines are administered to girls aged 12 years in addition to the current cervical screening programme. A total of 40,853 samples came from the Hong Kong Special Administrative Region Government data [10]. A Markov model was used to perform the cost-effectiveness analysis in the study. The Markov cohort analysis was employed for data analysis. The range used for the transition probabilities, costs and utilities are shown in Table 2.

RESULTS

The total lifetime costs and cost-effectiveness (CE) ratio of the three cervical cancer prevention strategies in different periods of life among clients were calculated using the computer-based Markov model. The calculation was based on women assumed to have been infected by HPV 16/18 and have natural immunity as well as those assumed to have been infected by other high-risk HPV genotypes and have no natural immunity. The cost and CE ratio estimation for the three strategies were based on the strategies in different periods of life and situations.

Cost of preventive strategies

The total lifetime costs trended downwards in the three strategies following the age of clients. Total lifetime costs spent in the annual Pap smear screening only at age 25–42 were around USD110-190 in different periods of life. Total lifetime costs spent in HPV vaccination at age 12 only were USD430-450 in different periods of life. Total lifetime costs spent in HPV vaccination at age 12 combined with annual Pap smear screening at age 25-42 were USD510-590 in different periods of life.

In Tables 1, comparing the result of the total lifetime costs in the three strategies, HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42 is the most expensive strategy in cervical cancer prevention. Annual Pap smear screening is the cheapest method for cervical cancer prevention. The results show that the costs for HPV vaccination only and the annual Pap smear screening were not equal to the cost for HPV vaccination combined with annual Pap smear screening. This discrepancy can be explained that HPV vaccination, annual Pap smear screening, and HPV vaccination combined with annual Pap smear screening are not substitutes for each other.

Cost-effectiveness ratio of preventive strategies

The CE ration trended downwards in the three strategies following the age of clients. CE ration decreased from 27 to 1 USD/DALY in the strategies of annual Pap smear screening only at age 25–42. CE ration decreased from 64 to 2 USD/DALY in the strategies of HPV vaccination at age 12 only. CE ration decreased from 83 to 3 USD/DALY in the strategies of HPV vaccination at age 12 combined with annual Pap smear screening at age 25-42. In Tables XX, comparing the result of the CE ratio in the three strategies, the ratio of HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42 was the highest.

Life expectancy of preventive strategies

Life expectancy of the three cervical cancer prevention strategies increased compared with the life expectancy in no intervention. Life expectancy would be increased by 2.715 years if women had Pap smear screening every year. Life expectancy would be increased by 2.767–2.834 years if women had HPV vaccination at age 12. The results did not vary, whether the client was infected by HPV 16 and 18 or by other high-risk HPV genotypes. A very slight difference occurred in the cervical cancer prevention strategy of HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42. The incremental life expectancy of this strategy was 2.835 years if women assumed to have been attacked by HPV 16 and 18 and have natural immunity received HPV vaccination as well Pap smear screening every year. The incremental life expectancy of the strategy was 2.832 years if women assumed to have been attacked by other high-risk HPV genotypes and have no natural immunity received HPV vaccination as well as Pap smear screening every year. The difference was merely 0.003 years. The summary of the results of life expectancy of the three cervical cancer prevention strategies is shown in Table 1.

Integrated results

The integrated results, including average total lifetime costs, average cost-effectiveness ratio, and incremental life expectancy in each cervical cancer prevention strategy, are presented in Table 1. Life expectancy increased in direct proportion to total lifetime costs and cost-effectiveness ratio in the three cervical cancer prevention strategies. The trend shows that the extension of life expectancy is related most to the total lifetime costs and the CE ratio used spent in cervical cancer prevention. Comparing the three strategies, HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42 can extend life expectancy the most. However, the total lifetime cost is naturally the most expensive. Comparing the three strategies, annual Pap smear screening only at age 25–42 is the cheapest method. However, incremental life expectancy is the lowest. These results were proven not only in the analysis of clients assumed to have been infected by HPV 16 and 18 and have natural immunity but also in the analysis of clients assumed to have been infected by other high-risk HPV genotypes and have no natural immunity (Table 1).

DISCUSSION

Effectiveness to reduce the risks of cervical cancer

According to previous studies, the strategy of HPV vaccination combined with annual cervical cancer screening can reduce a lifetime risk of cervical cancer by 95%–98% [17, 22, 24-25]. Assuming that HPV vaccines provide protection in the community commensurate to the efficacy results from clinical trials, vaccination should be administered in the teenage years before girls become sexually active, followed by an annual cervical cancer screening. If the sensitivity of Pap smear screening drops substantially in a vaccinated population, but its specificity remains stable, then Pap smear screening may eventually become an attractive option for women of all ages. If high levels of vaccine coverage are attained among teenage girls, cervical cancer mortality in Hong Kong will decrease. If low levels of vaccine coverage are preponderant among teenage girls, but mature women who are not infected by HPV undergo vaccination and participate in cervical cancer screening annually, and there is no change in the specificity of Pap smear screening, then cervical cancer mortality in Hong Kong will decrease.

Cost-effectiveness method in cervical cancer prevention

Focusing on cost and effectiveness, the age-based screening programme using annual Pap smear screening as a triage method among Hong Kong women has the potential to be more cost-effective than HPV vaccination alone, especially for girls aged 12, as well as HPV vaccination for girls aged 12 combined with applying annual Pap smear screening as a triage test for women aged 25–42. The total lifetime cost spent was USD146, with the target women participating in an annual Pap smear screening only at age 25–42 and not vaccinated. It is the cheapest cervical cancer preventive strategy compared with the others so far.

The importance of incremental life expectancy by three years

In current study, it has been found that the life expectancy would be increased around three years through the prevention strategy of HPV vaccination combined with annual Pap smear screening. Although the increase in life expectancy is three years, it is very important for the society because of four reasons. First, show a positive relationship between life expectancy and GDP. The increment of life expectancy affects GDP in a positive way because the productivity of the society will rise no matter population is in a good or bad health state. Palpably, productivity of individuals will increase if they have healthy life expectancy. Although individuals have unhealthy life expectancy, productivity of the society will also increase. It is because patients need drugs, treatments, nursing care and other allied health services. In the view of production, individuals produce more medical goods due to disease. Therefore, health has a first-order impact on economic growth [26]. Second, lift expectancy is an objective factor to present a subjective well-being. In Papavlassopulos & Keppler study [27], it pointed that life extension reflects an improvement of well-being, although subjective well-being can differ from person to person or culture to culture. Healthcare has as much impact on life expectancy as income. The appropriate income cost for access to healthcare if life expectancy is to increase. In addition, a market oriented healthcare system can deteriorate inequities in life expectancy as well as well-being. Third, to measure the effectiveness of medical interventions, the gain in life expectancy is a main element. Refer to the result of incremental life expectancy; physicians decide whether the benefits of an intervention outweigh its harm or the insurance companies consider whether or not cover a new medical intervention. The result also helps a pharmaceutical company concern whether a new drug is more effective than the standard drugs to be worth marketing. The most important is it helps the healthcare professionals or policy makers designing guidelines for clinical practice [28]. Last but not least, it is a global indicator to disclose whether changes are valuable for improving both physical and psychological health states of the population, for allocating resources, and for political programmes measurement [29].

Limitations

This study has several important limitations. First, the researcher could not model the natural history of multiple HPV infections. Therefore, vaccination against HPV 16 and 18 in this study was counted to reduce the total number of HPV infections. However, morbidity of cervical cancer caused by other high-risk HPV genotypes increased marginally because women are still at risk of acquiring other HPV types, whether or not they received HPV vaccination. Explaining the natural history of multiple infections and the effect of natural history of high-risk HPV genotypes when vaccine targets are eliminated is important [34]. Second, potential cross-protection from other high-risk HPV genotypes was not considered [34]. Third, herd immunity was not considered that the effect might be underestimated [30-32, 34]. Fourth, data depended on the preferences of clients and parents, likelihood of vaccine acceptability, and behavioural response (i.e., annual cervical cancer screening) to an intervention only partially effective against cervical cancer [17, 33-34]. Finally, the main uncertainties include the nature and duration of natural and vaccine-induced immunity against HPV, the effect of vaccine-induced immunity on mature women, the nature of the interactions between different types of HPV, the decline of the prevalence of HPV 16 and 18, and the presence of cross-protection in other high-risk HPV genotypes by the current HPV vaccination [6, 25, 35].

CONCLUSION

This study was conducted to assess the future implications of the cost-effectiveness of three cervical cancer prophylaxis strategies, namely, annual Pap smear screening only at age 25–42, HPV vaccination at age 12 only, and HPV vaccination at age 12 combined with annual Pap smear screening at age 25–42 provided to teenage girls in Hong Kong. Furthermore, it aims to help ascertain the most effective and cost-effective methods in cervical cancer prevention as well determine the best method to prolong life expectancy by comparing the strategies. It has been found that HPV vaccination can effectively stop HPV infection transmitted to CIN but cannot prevent all HPV genotypes. Cervical screening is the most cost-effective method in cervical cancer prevention, but it cannot stop the progress of CIN development. In the achievement of the goal of 100% reduction of cervical cancer, the frequency of cervical cancer screening after vaccination is the more important determinant for the clinical and economic outcomes of an HPV vaccination programme compared with screening only. Therefore, with the main aim of avoiding cervical cancer, an HPV vaccination programme using the currently available vaccines should only be considered if annual cervical cancer screening after vaccination can be maintained. The researcher attempted to offer methods of prolonging life expectancy by providing qualitative insight to policymakers regarding the consequences of utilizing the current cervical cancer screening strategy and HPV vaccination for cervical cancer prevention. This study showed prevention is much more cost-effective than medical treatment. That will make our scarce resource more cost-effective, and then produce better health for women, making a happy life for girls.

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Table 1 Total lifetime costs, cost-effectiveness ratio, and incremental life expectancy in the three cervical cancer prevention strategies

	Women attacked by HPV 16 and 18 and having natural immunity						**Women attacked by other high-risk HPV genotypes and not having related natural immunity**					
	Total lifetime cost (USD)		**Cost-effectiveness ratio (USD/DALY)**		**Life expectancy (years)**	**Incremental life expectancy (years)**	**Total lifetime cost (USD)**		**Cost-effectiveness ratio (USD/DALY)**		**Life expectancy (years)**	**Incremental life expectancy (years)**
Method	**Range**	**Average**	**Range**	**Average**			**Range**	**Average**	**Range**	**Average**		
No intervention	0	0	0	0	15.1655	---	0	0	0	0	15.1655	----
Annual Pap smear screening only at age 25–42	186.41-111.06	145.69	26.51 - 0.56	8.80	17.8806	2.7151	186.41-111.06	145.69	26.51 - 0.56	8.80	17.8806	2.7151
HPV vaccination at age 12 only	447.14-428.89	437.27	63.60 - 2.15	23.05	18.0000	2.8345	447.14-428.89	437.27	63.60 - 2.15	23.05	17.9334	2.7679
HPV vaccination at age 12 + annual Pap smear screening at age 25–42	585.13-511.11	545.12	83.23 - 2.57	29.56	18.0000	2.8345	585.20-511.15	545.18	83.24 - 2.57	29.56	17.9975	2.8320

Table 2 Probabilities, costs and utilities used in the model

Model variables: probabilities and ranges used in sensitivity analysis			
Variables	Median	Range	Source
Normal to CIN 1	0.0211	0.0004–0.0418	[36]
CIN 1 to CIN 2, 3	0.00525	0.0007–0.0098	[36]
CIN 2, 3 to local invasive cancer	0.0050	0.0020–0.0080	[36]
Regression of CIN 1	0.0145	0.0034–0.0256	[36]
Regression of CIN 2, 3	0.00365	0.0015–0.0058	[36]
Progression of invasive cancer stage			
Local to regional	0.0250	0.0100–0.0400	[36]
Regional to distant	0.0375	0.0250–0.0500	[36]
5-year cervical cancer survival rate			
Local	0.865	0.80–0.93	[36]
Regional	0.47	0.28–0.66	[36]
Distant	0.185	0.04–0.33	[36]
Annual probability of symptom detection			
Local	0.38	0.10–0.66	[36]
Regional	0.60	0.36–0.84	[36]
Distant	0.835	0.68–0.99	[36]
Test characteristics			
Sensitivity of conventional cervical cytology	0.75	0.5–1.0	[36]
Specificity of conventional cervical cytology	0.95	0.9–1.0	[36]
Reduction in HPV incidence and conditional (caused by HPV 16, 18) on immune response after having HPV vaccination	1	N/A	[36]
Probability of diagnosing the disease and treating it well	1	N/A	[36]
Cost data for the study (USD)			
Cost of three doses of HPV vaccines#	402	N/A	[41]
Direct medical cost*			
Conventional cervical cytology	115	40-190	[36-39]
Test cost	55	10-100	[36-39]
Office visit	13.5	7-20	[36-39]
Time cost	33.5	17-50	[36-39]
Travel cost	13	6-20	[36-39]
Aggregate cost*			
Colposcopy and biopsy	275	150-400	[36-39]
CIN 1	350	200-500	[36-39]
CIN 2, 3	700	500-900	[36-39]
Local invasive cancer	15,750	9,500-22,000	[36-39]
Regional invasive cancer	20,350	11,700-29,000	[36-39]
Distant invasive cancer	47,085	12,670-81,500	[36-39]

Note: * Cost data were Hong Kong data in 2000 [36-39] and were the base cases considered as the market prices. These data were adjusted by the rate of inflation and deflation from 2001 to 2009 that inflation and deflation were taken from the Census and Statistics Department, HKSAR; and with 3% annual discount, which it was recommended by WHO-CHOICE [40], from 2010 to 2036. # Data came from a US study [41].