

The potential impact of a prophylactic vaccine for human papillomavirus on the current cervical screening programme in Hong Kong

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- Objectives** To review and summarise current controversies in cervical screening in Hong Kong and discuss the potential impact of prophylactic human papillomavirus vaccination.
- Data sources** Literature search of Medline to December 2006, the Hong Kong Cancer Registry, and Centre of Disease Control.
- Study selection** Key words search terms were: 'human papillomavirus', 'vaccine', 'cervical cancer', 'screening programme', and 'Hong Kong'.
- Data extraction** Original articles, review papers, books, and the worldwide web.
- Data synthesis** Cervical cancer is one of the most common cancers in Hong Kong, and can be prevented if detected at its pre-cancerous stage. Despite the huge disease burden this imposes on our society and robust advocacy by the academic sector, an appropriate screening programme is still not in place. Existence of a vaccine that could potentially reduce the costs of universal screening should prompt our government to re-consider subsidising such a programme. While a combined screening-vaccination programme may be more cost-effective than screening alone, the vaccine is still costly, and the government must consider all the pros and cons.
- Conclusion** The new human papillomavirus vaccine, combined with an organised screening programme, is probably a more cost-effective way of preventing morbidity and mortality due to cervical cancer than the current programme in Hong Kong. More research and cost-effectiveness analyses are needed to decide on the ideal ages for primary vaccination and the requirement for booster shots.

Introduction

Among the cancers that we commonly encounter, cervical cancer is one of the most exceptional. It is not any less aggressive than other neoplasm, but is one of the very few cancers that can be detected early and treated effectively at a pre-cancerous stage. The Papanicolaou (Pap) smear is a widely available, easily accessible, relatively inexpensive technique that can be easily performed. The Pap smear has been credited with the decline of cancer incidences and deaths of up to 75%, due to early identification and treatment of the disease.¹

Despite a decreasing incidence, cervical cancer is still the second most frequent female cancer worldwide, representing 10% of all such neoplasms. According to estimates worldwide, almost 500 000 new cervical cancers are diagnosed and 230 000 corresponding deaths occur annually.² In 2004, The Hong Kong Cancer Registry reported that cervical cancer is the fifth most common cancer in local women, responsible for more than 400 new cases (4.3% of all new female cancers) and 128 deaths. Whilst the incidence of cervical cancer has shown a subtle decreasing trend over the years, the International Agency for Research on Cancer cites Hong Kong as a 'high-risk' area for this malignancy.³ Moreover, in 2005, cervical cancer was reported as the ninth commonest cause of female cancer deaths in Hong Kong.⁴

Key words

Cervical intraepithelial neoplasia; Mass screening; Papillomavirus vaccines; Uterine cervical neoplasms; Vaccination

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The role of human papillomavirus in cervical cancer

Since the 1960s, the role of the human papillomavirus (HPV) in the oncogenesis of cervical cancer has been exhaustively researched. Consequently, there is now a general consensus that infection with high-risk HPV serotypes (especially 16 and 18) results in pre-cancerous and cancerous lesions in the cervix as well as the vulva and vagina.⁵ Research has also shown that in the United States, more deaths result from HPV and cervical cancer than from the sequelae of all other sexually transmitted diseases (STDs) combined (with the exception of HIV-AIDS).⁶ The relative risks of various risk factor-associated cancers also provide some interesting insights. For example, relative risk is estimated to be 10 for smoking and lung cancer, 50 for chronic hepatitis B virus (HBV) infection and hepatocellular carcinoma, and a startling 300-400 for HPV and cervical cancer.⁷ In 1995, the International Agency for Research on Cancer finally established HPV strains 16 and 18 as carcinogenic in humans,⁸ and in many countries this knowledge has been the catalyst for launching aggressive Pap smear screening programmes. Although a vaccine is only an indirect way of preventing cervical cancer (preventing persistent cervical dysplasia due to HPV infection), it is nonetheless a promising approach. However, to date there is no evidence that the vaccine actually lowers cervical cancer incidence. Intensive research and marketing have been invested in the new HPV vaccine, and it is hoped that it may prove to be the most effective 'vaccine against a cancer'.

Human papillomavirus strains and their implications for vaccine research

Human papillomavirus represents the aetiological agent in nearly all cervical carcinomas and squamous intra-epithelial lesions, and approximately 40 of the more than 100 HPV types that are described have been identified in the cervix.⁹ In a large study published in 1995 involving 1000 cases of invasive cervical cancers collected in 22 countries,¹⁰ HPV DNA was detected in approximately 93% of patients. The most commonly encountered strains were HPV 16, 18, 31, and 45 (in 75% of tumours), of which HPV 16 was the most prevalent (found in about 50% of all cancers). Important co-factors in cancer associated with HPV include smoking, multiparity, and co-infection with chlamydia or HIV.¹¹

In Hong Kong, about 20% of young females in their 20s are infected with HPV.¹² Elsewhere, incidences have been reported to be as high as 30% before the age of 30 years, with seven of 10 women exposed at least once to HPV in their lifetimes.^{13,14} Human papillomavirus 16 is the most common genotype found in cervical cancer in Hong Kong, occurring in 61.7%, followed by HPV 18 in 14.8%,¹⁵ implying that

人類乳頭瘤狀病毒預防性疫苗的應用對香港目前子宮頸癌篩查計劃的可能影響

目的 檢討並總結香港目前有關子宮頸癌篩查的爭議，以及討論人類乳頭瘤狀病毒預防性疫苗的應用可能帶來的影響。

資料來源 2006年12月以前的Medline系統、香港癌症資料統計中心、疾病控制中心的文獻檢索。

研究選取 以'human papillomavirus'「人類乳頭瘤狀病毒」、「vaccine」「疫苗」、「cervical cancer」「子宮頸癌」、「screening programme」「篩查計劃」、「Hong Kong」「香港」為關鍵詞檢索文獻。

資料選取 論著、綜述、書刊以及萬維網。

資料綜合 子宮頸癌是香港其中一種最常見的癌症，如果能在癌症前期偵測到，是可以預防的。儘管這種疾病給社會造成沉重的負擔，而學術界又大力支持進行篩查，可是到目前為止，香港仍然沒有一套合適的計劃。一種能降低普查成本的新疫苗的出現，應能促使政府重新考慮資助這類計劃。雖然篩查和疫苗接種相結合的計劃會比單純的篩查計劃更有效，但目前疫苗仍然相當昂貴，因此，政府必須考慮正反兩面的論點。

結論 相比香港目前實行的計劃，把人類乳頭瘤狀病毒的新疫苗與有系統的篩查計劃相結合，相信是目前預防子宮頸癌發病和致死的成本效益最高的方法。我們需要做更多研究和成本效益分析來決定最適合進行疫苗接種的年齡，以及追加注射的條件。

a vaccine against HPV 16 would be more beneficial.

Considering the efficacies of the vaccines demonstrated by the Merck and Co and Glaxo-SmithKline (GSK) phase II and III trials (discussed later), such a vaccine could prove to be an important complement to established screening programmes, and conserve costs in resource-constrained societies by savings achieved through delaying the age of beginning screening and screening less frequently.¹⁶

Cervical screening in Hong Kong

Possibly due to resource constraints, there is currently no universal screening programme for cervical cancer in Hong Kong. An opportunistic 'record-and-recall' screening programme was launched in March 2004, but it is far from optimal for two main reasons.

First, there is no call-recall rationale to this method of screening, meaning that high-risk women will not be targeted if attendance is haphazard.³ Studies worldwide have shown that the majority of cervical cancer cases and deaths occur among women who have never been screened or treated.^{17,18} In Hong Kong too it is low-risk population who tend to be screened more frequently, with 79% of women aged older than 60 years never having had a cervical smear.³

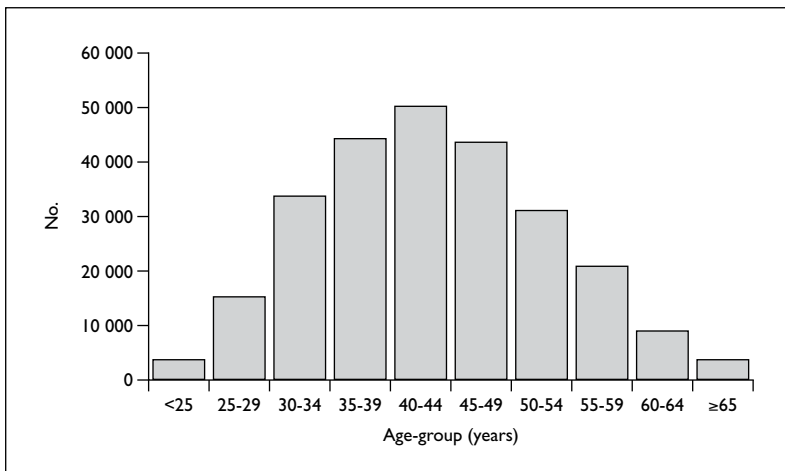


FIG. Number of women registered with the cervical screening programme by age²²

This kind of suboptimal opportunistic screening has been thoroughly analysed and commented on by local public health experts¹⁹ in the context of Hakama et al's 1985 definition of an 'ideal programme'.²⁰ Benefits of optimal coverage by a systematic method of call-recall over an opportunistic approach have also been demonstrated in large randomised control trials.²¹ In Hong Kong, as of November 2006 (after the new opportunistic screening programme had operated for 32 months), only 254 265 (<10%) of an eligible female population of 2.5 million (aged 21 to 69 years) had been registered, in contrast to 42 to 60% of local women who reported ever being screened in the past 5 years (Fig).²²

Second, opportunistic screening is not cost-effective. For example, a local study showed that the current ad-hoc screening "over-screens low-risk women, and at best its effectiveness is still worse than an organised programme with 10-yearly screening and only 60% coverage, but costs much more".²² In the United States, more than USD6 billion is spent each year on evaluating and treating low-grade lesions with a high chance of spontaneous regression without intervention.²³ These huge monetary burdens are not readily visualised in Hong Kong, because they are dispersed in both the private and public sectors, and with no shared patient database it is hard to monitor the costs of services and rates of follow-up in the private sector.

Determining the ideal age to begin screening is crucial to the implementation of a successful screening programme in Hong Kong. Based on evidence from case-control studies, cohort studies, and ecological studies, in 2001 it was suggested that local women aged 25 to 64 years who have ever had sex, should have Pap smears every 3 years after two normal consecutive annual smears.²⁴ However, the international view on the screening policy is still not

BOX. Pitfalls of the current cervical screening programme in Hong Kong

1. Low cover of the target population (high-risk individuals)
2. Not cost-effective
3. Costs are difficult to monitor in the private sector
4. Will eventually become obsolete due to lack of recommendations including human papillomavirus vaccine in the protocol

unified. For example, The United States Preventative Services Task Force, the Canadian Task Force on Preventative Health Care, the American Cancer Society, and the American College of Obstetrics and Gynecology recommend starting smears at the age of 18 years; the United Kingdom guidelines suggest screening from the age of 20 years, while the European guidelines suggest screening at the latest before the age of 30 years. Nevertheless, all of these various guidelines suggest screening should be started earlier for individuals having earlier vaginal intercourse.²⁵ A recent report from Hong Kong recommends 4- to 6-yearly screening with target coverage of 80%, in order to maximise cost-effectiveness³ (yearly screening would increase effectiveness by 5%, but at five times the cost). The Box summarises the pitfalls of the current cervical screening programme in Hong Kong.

All of the above recommendations were based on screening programmes without a vaccination policy. In light of the new HPV vaccines, important questions to address now include: (i) Would combining vaccination and screening help the Hong Kong government save costs? (ii) Will the vaccine be used for prophylactic or therapeutic purpose, or both? (iii) Will there be competition for resources from other new and upcoming vaccines, such as the pneumococcal or meningococcal vaccines? (iv) Should vaccination coverage be population-based (school-based or in a women's wellness programme), or paid for by individuals in an elective setting? Finally, (v) what are the social implications of a vaccine against an STD in a Chinese population, which tends to be more reluctant than westerners to discuss sexual practices?

The vaccine

An effective prophylactic vaccine is considered by many as the ultimate public health tool against widespread diseases. Infection by high-risk HPV is now considered a necessary part of the natural course of nearly all cervical cancers. Together with a high incidence of HPV infections in the general population, the rationale for a prophylactic HPV vaccine seems justified. Support for such a policy also requires good host-immune responses to HPV, as well as easily targeted carcinogenic HPV strains.

Currently, prophylactic HPV vaccines are

TABLE 1. Factors influencing successful vaccination against human papillomavirus (HPV)

Favourable	Unfavourable/uncertain
1. Good host-immune response	1. No long-term studies
2. Specifically targetable strains of HPV	2. Unknown duration of protection
3. Minimal adverse effects	3. Costly
4. High efficacy in preventing pre-cancerous and cancerous lesions	4. Lack of universal consensus on vaccination schedule

manufactured by Merck and Co and GSK. The vaccines are tetravalent (against HPV 16, 18, 6, and 11) and bivalent (against HPV serotypes 16 and 18) respectively, and based on the recombinant capsid protein L1, with the aim of eliciting neutralising antiviral antibodies to protect against future infection. Reportedly, the vaccine induces an immune titre approximately 50-fold greater than natural immunity.²⁶ In addition, therapeutic vaccines are also under development. These vaccines may be able to induce cell-mediated immune responses by infusing viral oncogenic proteins E6 and E7, hence eliminating the transformed tumour cells.²⁷ Both the Merck and GSK prophylactic vaccines have undergone successful phase III clinical evaluations (randomised controlled trials on large patient groups), and in June 2006 the Advisory Committee on Immunization Practices recommended that the first vaccine should be developed for prophylaxis of cervical cancer. The Food and Drug Administration (FDA) recently licensed the Merck quadrivalent vaccine Gardasil (www.cdc.gov), which is now included in the 2006-07 WHO recommendations for vaccinations.²⁸

In terms of efficacy, phase II trials²⁹⁻³¹ with HPV vaccines certainly show promise. The tetravalent vaccine was able to lower the combined incidence of persistent infection or disease with HPV 6, 11, 16, or 18 by 90% (95% confidence interval, 71-97%; $P=0.0001$), and for the bivalent vaccine corresponding figures were 91% (95% confidence interval, 65-98%). This contrasts with 100% of non-vaccinated persons having persistent infection with HPV 16/18. Published mathematical models predict that a vaccine that prevents 98% of persistent HPV 16/18 infections will reap an equivalent reduction in HPV 16/18-associated cancers, and a 51% reduction in all cervical cancers³¹ (Table 1). There is as yet no evidence to show that the vaccine prevents dysplasia of the cervix caused by other HPV genotypes.

The vaccine in Hong Kong

Vaccination is probably the second most important public health intervention of all time (the first being clean drinking water). Since about 1798, we have been benefiting from just a handful of vaccines that save millions of lives every year. Throughout the 'invention era' of vaccines at around the time of World War II, and the 'national immunisation era' from 1900 to

1973, industrialised countries have had tremendous success with large-scale disease control, culminating in the eradication of smallpox in 1980.³²

Since the WHO Expanded Programme on Immunization in 1974, Hong Kong has also jumped on the bandwagon of universal vaccination, and has enjoyed great success. This is largely attributed to our centralised health care (especially post-natal care) and education systems, which both provide platforms for universal immunisation programmes. The concept of school-based vaccination in Hong Kong is of particular importance, because if the HPV vaccine is to be recommended for teenage or prepubertal females (around the age of 12 years),³³ it could be readily and conveniently implemented. It could also reduce the fall-out due to embarrassment, cultural stigma, and ignorance about the disease.

In 2004, a Markov model performed in Hong Kong³⁴ measured cancer incidence reduction, years of life saved, lifetime costs, and incremental cost-effectiveness ratios. It concluded that even though our current 'opportunistic' model of screening already produces nearly 40% reductions in the lifetime risk of cervical cancer compared to no screening, organised screening every 3, 4, and 5 years might result in corresponding reductions of 90%, 87%, and 83%. Moreover, it was also inferred that an organised screening programme would provide substantial cost-benefits and cost reductions compared to opportunistic screening. Although this study provides strong evidence in support of organised screening, there are still no local data available regarding the implementation of universal screening combined with vaccination. Research in this area should be a priority.

A similar analysis based on a United States population compared three strategies for cervical cancer prevention: (i) vaccination only, (ii) conventional cytological screening only, and (iii) vaccination followed by screening.¹⁶ According to this study, the cost-effectiveness of vaccination depended on the age of vaccination, duration of vaccine efficacy, and the cost of the vaccine. Crucially, this theoretical cohort illustrated that vaccination alone is not cost-effective, and that optimal benefit in terms of both health and economic impact would entail vaccination plus biennial screening from the age of 24 years.

For Hong Kong vaccination alone may not

TABLE 2. Factors influencing the addition of vaccination against human papillomavirus to the current cervical screening programme

Pros	Cons
1. Delayed age to begin screening	1. Extra start-up costs
2. Less frequent screening	2. Stigma of taking a sexually transmitted disease vaccine
3. Improved overall cost-effectiveness	3. No local cost-benefit analytic studies
4. Possibly decreased cancer incidence, morbidity, and mortality	
5. School-based vaccination programmes are already in place	

be the most economically attractive, but may still be worthwhile compared to the current situation. Though difficult to perform (because the cost-effectiveness of the current Hong Kong system is not easily quantified), it would be of interest to compare efficiency curves of a 'vaccine only' strategy to 'no intervention'.

A combined programme

Published economic analyses of cervical cancer screenings have consistently shown that less frequent screening can dramatically reduce costs with relatively little loss in life expectancy.¹⁶ The possibility of combining such a programme with vaccination provides attractive alternatives to the current non-cost-effective system prevailing in Hong Kong. Costs can be saved by delayed onset screening, less frequent smears, reduced management of innocent lesions, and hopefully also a reduced overall incidence of cervical cancer.

Whether or not such a strategy can be implemented in Hong Kong requires thorough investigation. Issues concerning the duration of the vaccine efficacy, the requirement of booster shots and their timing, and the cost of the vaccine itself, all need to be addressed. Local epidemiological studies also document that the lack of public knowledge about cervical cancer is a leading reason for the low uptake of screening in Hong Kong.³⁵ Therefore public health education needs to be markedly improved, via population-based health promotion campaigns and school sex education (Table 2).

School-based vaccination

Compared with other developed countries like the United States or United Kingdom, Hong Kong has a much closer-knit public education infrastructure, with government and subsidised schools providing over 90% of education for children. Currently, vaccines given to schoolchildren include: booster doses for diphtheria-pertussis-tetanus (DPT), measles-mumps-rubella (MMR), and the polio trivalent booster. These are given in primary 1 and primary 6 classes (corresponding to ages 6 and 12 years). Ideally, the HPV vaccine could be given at the same time as the

second polio booster dose, so as to cover over 90% of 12-year-old girls in Hong Kong. By this means, costs pertaining to logistics (nurses, equipment, and work-days off etc) could also be conserved.

Further issues concerning the implementation of a human papillomavirus vaccine

Cost

The vaccine is expensive; in their November 2006 brochures, Merck and Co lists their tetravalent HPV vaccine (marketed as Gardasil) at HK\$898 per dose and a complete course entails three doses to be taken over 6 months. Cevarix from GSK involves similar costs, which are also escalated by booster shots.

Duration of the vaccine effect

Current evidence from the manufacturer's trials suggests that the vaccine will be effective for at least 4 years.^{29,30} As further cohort studies pertaining to the efficacy of the vaccines are performed, more will be revealed about the long-term effects of the immunisation. Booster shots will incur additional costs and will become a deterring factor for government subsidies. By comparison, the HBV vaccine requires three doses, polio six, DPT six, and MMR two.

Stigma

Unlike the HBV vaccine, which also protects against a pre-cancerous disease, the HPV vaccine is, in essence, a vaccine against an STD. This is liable to impose a stigmatising effect on those who receive it. By taking the vaccine, the recipients might be regarded as implying a need for it. Similarly the public might perceive this as a vaccine only for those who undertake high-risk sexual activities. Extrapolating this concept further, an individual who has already taken the vaccine may lapse in terms of healthy sexual practices and the recommended regular screening. All of the above issues are liable to be even more pertinent to the Chinese population, which tends to be more reticent about discussing sexual practices and STDs.

Prophylactic vaccination in older women

Prophylactic HPV vaccines are less likely to be indicated in older women, because they rarely acquire new infections. For them a therapeutic vaccine might be more meaningful. Therapeutic vaccines could also benefit this age-group more than others, because with ageing the transformation zone of the cervix recedes into the endocervical canal, and atrophy hinders cytologic interpretation, making regular screening less sensitive.¹⁷

Vaccination in human papillomavirus-infected women

Although the effectiveness of vaccinating women who are naive to infection is high (rendering a relative risk reduction of 98.5% for cervical dysplasia), the results are disappointing in those who are already infected. The FDA's Vaccines and Related Biological Products Advisory Committee has provided compelling evidence that the vaccine is no more effective than placebo in women who were already infected with the vaccine genotypes of HPV (both polymerase chain reaction-positive and seropositive).³⁶ As in the previous group of older women, therapeutic vaccines may well have a much greater role in this situation.

Conclusion

Cervical cancer is one of the most common malignancies in Hong Kong, and can be prevented if detected at its pre-cancerous stage. Despite the huge disease burden this imposes on our society and

robust advocacy by academics, a sound screening programme is still not in place. This could be due to difficulty in implementing it within the prevailing public-private health care system, as well as the high cost implications of universal screening. Thus, compared to other developed countries such as the United Kingdom, where a systematic call-recall screening programme covering 80% of the relevant population has been implemented since 1988,²¹ Hong Kong has much to do in this area.

Emergence of a vaccine that could potentially reduce the costs of universal screening should prompt the Hong Kong government to re-consider the notion of subsidising such a programme. Besides, the local public health infrastructure is well-enough equipped to accommodate such a strategy. Due to the excellent school-based vaccination programme already in place, the integration process should be straightforward.

While a combined screening-vaccination programme may be more cost-effective than screening alone, the vaccine is nevertheless costly, and subsidising it from public funds will be a challenge, especially as proof concept (that it can actually prevent cervical cancer) is still lacking. In which case initially at least, the use of HPV vaccine may be restricted to the private sector. For now, the need is for more cost-effectiveness analyses, as well as research into the ideal ages for vaccine delivery and the need (and timing) for booster shots. Hopefully, information from such studies will expedite the decision-making processes addressing this very important public health issue.

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