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ORIGINAL ARTICLE

The impact of cytology screening and HPV vaccination on the burden of cervical cancer

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Abstract

***Aim*:** To evaluate the impact of different strategies of human papillomavirus (HPV) vaccination on the burden of cervical cancer in Singapore.

***Methods*:** The incidence of cervical cancer was calculated using a Markov model with inputs based on Singapore data for the prevalence of HPV infection, socioeconomic characteristics and screening prevalence. The evaluation was performed for 10 scenarios: no screening, current opportunistic cytology screening, ideal optimal screening, universal adolescent HPV vaccination at 12-years old alone and with catch-up cohorts and combinations of screening and vaccination.

***Results*:** (1) The model prediction showed that cervical cancer cases were reduced by 6.5% using opportunistic screening, by 34.3% using optimized screening and by 63.9% with a universal HPV vaccination at 12 years of age. (2) Adding optimized screening, but not opportunistic screening, to a universal adolescent HPV vaccination program caused a moderate further reduction in cervical cancer cases. (3) No difference was discernable in the impact of vaccination introduction between the age groups <20, 20–24 and 25–29 years old. (4) The time required to halve the incidence of cervical cancer was 42 years for universal vaccination at the age of 12 but could be shortened by including catch-up cohorts of women up to 40-years old.

***Conclusion*:** A universal HPV vaccination program introduced between the ages of 12–29 is superior to cytology screening in reducing the burden of cervical cancer. However, in the next four decades of post-vaccination era, optimizing the screening program remains the most important measure for cervical cancer prevention.

Key words: Cervarix, cost-effectiveness, Gardasil, HPV infection, universal vaccination.

INTRODUCTION

Cervical cancer is the second most prevalent cancer in women worldwide.[1] Every year, 493 243 new cases are diagnosed and 273 505 women die from it.[2] In Singapore more than 200 women are diagnosed with cervical cancer every year and of these, more than 100 die from it.[3] Efforts to reduce the burden of cervical cancer with cytology screening in the last 50 years have had limited success. Undeniably, countries with well-organized screening programs have witnessed substantial drops in the incidence and mortality rate of cervical cancer. However, such programs are costly in terms of both finances and manpower. Furthermore, a large proportion of women at risk of cervical cancer have no access to screening. In Singapore, a national screening program was launched in 2004. Although more than half of the eligible women have had at least one cytology test within the last 3 years, many do not participate in regular screening.[4] The implementation of screening in Singapore has yet to be optimized.

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Cervical cancer is caused by high-risk (oncogenic) human papillomavirus HPV subtypes of which HPV-16 and HPV-18 are the most important as they collectively cause 70% of all cervical cancer.[5] The current vaccines, Gardasil (Mercik & Co.) and Cervarix (GlaxoSmith Kline), are prophylactic vaccines against HPV-16 and HPV-18 and have been shown to be extremely effective in clinical trials in protecting vaccinated girls against HPV-16- and HPV-18-related high-grade cervical intraepithelial neoplasia (CIN).[6,7] Despite the obvious benefits of these vaccines, many questions regarding their exact implementation remain unanswered. The aim of the present study was to examine, using a mathematical model, the possible outcomes of introducing HPV vaccines to women at different ages, catch-up intervals and in combination with different screening programs in Singapore.

METHODS

Summary of model

A Markov model was used to simulate the pathological progression of cervical cancer through the stages of HPV infection, CIN, cervical cancer or death or hysterectomized (Fig. 1). In this model, the simulation traced a cohort of 100 000 women from 12-years old to death.

The key computational equation used in this simulation was the Chapman–Kolmogorov differential equation as shown below:

$$P(t) = Be^{Qt}$$

B represents the original distribution of people (100 000 in the normal state only), e is the natural constant, Q represents the transition matrix. This matrix contains all the model parameters for the age-specific probability of a transition from one state to another. Time is represented by t, and is 5 in this instance, to represent a span of 5 years. It is assumed that the unit time for a transition from one state to another is 1 year.

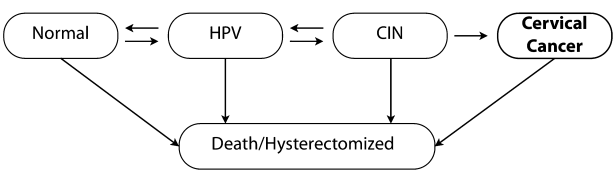

Figure 1 Model representation of disease progression from normal to HPV, (human papillomavirus), CIN, (cervical intraepithelial neoplasia) and cervical cancer.

The computation was done using Mathematica (Wolfram, Champaign, IL, USA) software. The computation output of the simulation was plotted against the actual cancer statistics for validation purposes. This model computation was performed to simulate different base scenarios for different screening and vaccination programs.

Model input

The transition probabilities for different disease steps in the cervical cancer development are summarized in Table 1.[8–17] The input data were based on available local statistics where possible. This included data for death from other causes and hysterectomy. In other cases, established international data were used as referenced appropriately.

The efficacy of the vaccine was assumed to be 100% against HPV-16 and HPV-18 and the duration of the protection was lifelong.[18] We ignored potential cross-protection for other HPV subtypes by the vaccines because the other subtypes individually contributed to only a small proportion of cervical cancer.

Model validation

Cancer statistics for validation of model statistics were obtained from the Singapore Cancer Registry.[19]

Model simulation of different scenarios

The model was run for a number of different scenarios with different vaccination and screening programs, as shown in Table 2. Two cytological screening strategies were incorporated in this simulation study: the current opportunistic screening approach and an ideal optimized vigorous screening. Under an opportunistic approach to screening, 55% of the eligible women in Singapore had had a cytology test in the last 3 years.[4] An annual screening rate of 17% (55% divided by 3) and an efficacy of 30% were calculated. It was assumed that an optimized screening would reach an annual screening rate of 80% of eligible women between the ages of 25 and 60 years and would provide an efficacy of 50%.[18]

RESULTS

The model predicted 230 cases of cervical cancer for the entire cohort of women over a span of 65 years (Fig. 2). This closely matched the actual number of 239 cases obtained from the Singapore Cancer Registry for the cohort born in 1948.

Table 1 Transition rates for model input

Age group	Normal → HPV rate[8]	HPV → normal rates[9]	HPV → CIN rates[10–12]	CIN → normal rate[13]	CIN → cervical cancer rate[14,15]	Death + hysterectomy rate[16,17]
<20	0.20000	0.8000	0.00110796	0.50000	0.0099	0.00387
20–24	0.50000	0.8000	0.00110796	0.50000	0.0099	0.00111
25–29	0.31408	0.8000	0.00110796	0.50000	0.0099	0.00117
30–34	0.23802	0.8000	0.0151241013	0.50000	0.0099	0.00260
35–39	0.23606	0.8000	0.0151241013	0.50000	0.0099	0.00580
40–44	0.23803	0.8000	0.0151241013	0.50000	0.0099	0.01176
45–49	0.22403	0.8000	0.0151241013	0.50000	0.0099	0.01533
50–54	0.29032	0.8000	0.0151241013	0.50000	0.0099	0.01665
55–59	0.26908	0.8000	0.0151241013	0.50000	0.0099	0.02088
60–64	0.15882	0.8000	0.0151241013	0.50000	0.0099	0.03163

Table 2 Different screening and vaccination scenarios evaluated

Scenario	Screening and vaccination characteristics
1	No screening + no vaccine
2	Current screening + no vaccine
3	Optimised screening + no vaccine
4	No screening + universal vaccine at 12 years of age
5	Current screening + universal vaccine at 12 years of age
6	Optimised screening + universal vaccine at 12 years of age
7	Current screening + universal vaccine at 12 years of age + catch up vaccination to 25, 30, 35, 40, 45, 50, 55, 60 and 65 years of age
8	No screening + universal vaccine at 12 years old starting at the age of 12, then at 25, 30, 35, 40, 45, 50, 55 and 60 years of age
9	Current screening + universal vaccine at 12 years of age starting at the age of 12, then at 25, 30, 35, 40, 45, 50, 55 and 60 years old
10	Optimised screening + universal vaccine at 12 years of age starting at the age of 12, then at 25, 30, 35, 40, 45, 50, 55 and 60 years old

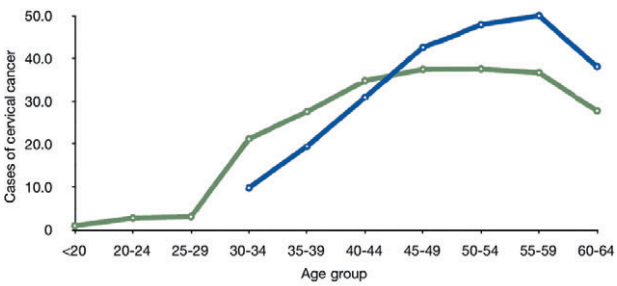

Figure 2 (o) Real and (o) predicted incidence of cervical cancer at various age groups.

The model predictions showed that there was a significant decrease in the total number of cases of cervical cancer annually after the entire female cohort of 12-year olds had been vaccinated (Fig. 3). Comparing the impact of single strategy individually, cancer cases were reduced by 63.9% with a universal HPV vaccination at 12-years old alone, by 34.3% with an optimized screening program and by a mere 6.5% with the current opportunistic screening strategy. Combining a universal HPV vaccination at 12-years old with cytology screening at the current participation rate did not have an additional impact on the burden of cervical cancer. However, a further moderate reduction in cancer cases was seen if the additional screening was optimized.

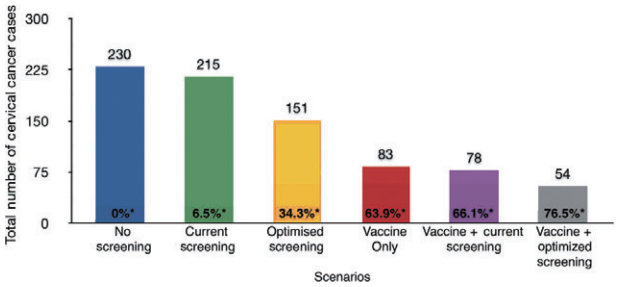

Figure 3 Predicted number of cases of cervical cancer in various scenarios. *indicates percentage reduction compared to no screening.

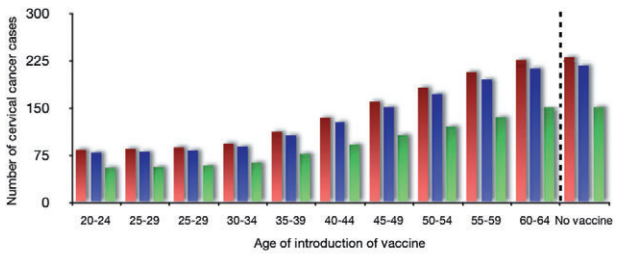

Figure 4 Number of cervical cancer cases for (■) no screening, (■) current screening and (■) rigorous screening against age of introduction of vaccine.

Analysis for age of entry of universal vaccination with three different screening strategies (no screening, current screening, optimized screening) showed that there was no discernible difference in the total number of cervical cases for vaccination introduced between the following age groups: <20, 20–24 and 25–29 (Fig. 4). In contrast, the impact of mass vaccination declined rapidly if introduced after the age of 30.

The time interval required to reduce the cervical cancer cases in Singapore by half is shown in Figure 5. This interval was 42 years for a universal vaccination at the age of 12 years. The interval was shortened with inclusion of catch-up cohorts of women for vaccination. There was a significant reduction with every 5-year cohort of catch-up included until the age of 40 years. Thereafter, inclusion of additional catch-up cohorts had a diminishing impact.

DISCUSSION

The principle of the model used in this study has been extensively reported and appeared to have performed

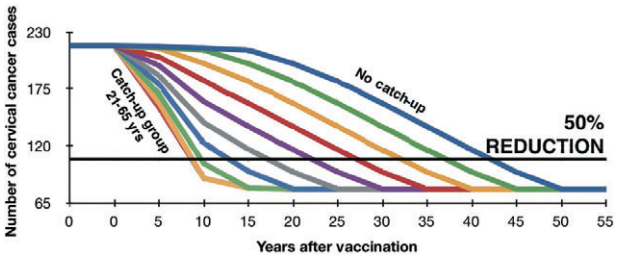

Figure 5 Total number of cases of cervical cancer in (—) no catch-up, (—) catch-up group 21–30 years, (—) catch-up group 21–25 years, (—) catch-up group 21–30 years, (—) catch-up group 21–35 years, (—) catch-up group 21–40 years, (—) catch-up group 21–45 years, (—) catch-up group 21–50 years, (—) catch-up group 21–55 years, (—) catch-up group 21–60 years, (—) catch-up group 21–65 years,

well in our study. The model output was verified against real data from the cervical cancer cases reported in the Singapore National Cancer Registry. Data from the 1948 birth cohort were selected in this study because the total number of cervical cancer cases up to the 65-years old was available and complete and was deemed the most applicable for comparing the model output for a vaccinated cohort from 12-years to 65-years old. The apparent difference between the observed and the predicted incidence of cervical cancer in the older age groups can be explained by the sharp increase in hysterectomy rates over the last few decades. In the birth cohort from 1948 hysterectomies were far fewer than today. Hence, compared to the historical data from the cancer registry, the model predicted fewer cervical cancer cases in the older age group in whom hysterectomies were most often performed.

It is most interesting that this model prediction showed that the current screening program in Singapore with an annual screening participation rate of merely 17% was blatantly ineffective. However, an optimized screening program to include 80% or more of the eligible women would reduce the number of cases of cervical cancer by 34.3%. Reports from the experience of a national screening program in the UK, where optimized screening was introduced in 1987, showed a 50% reduction in the total number of cervical cancer cases in the country.[20] This level of screening participation has been shown to be very difficult to achieve in most countries, including Singapore, where a national cytology screening program had been initiated since 2004. The low success rate of cytology screening in other parts of Asia is not dissimilar to Singapore.[3] This underscores the limitation of cytology screening and the importance of

alternative or additional cervical cancer prevention measures in Asia, where the burden of cervical cancer is the most significant.

In contrast, vaccination for the cohort of 12-years old alone was predicted to reduce the numbers of cervical cancer by 63.9%. The result was consistent with other modeling studies.[21] This estimation of cervical cancer reduction was conservative as it did not take into account the benefit of cross-protection of the vaccines against other oncogenic HPV subtypes.[7,18,22] A universal vaccination appeared to be distinctly superior to cytology screening. With the effectiveness of vaccination, our model predicted no further advantage of concurrent screening for the cohort, if screening was practiced at the current participation rate. Even with an optimized screening participation rate, concurrent cytology screening and universal HPV vaccination would only offer a moderate additional protection against cervical cancer because of the limited efficacy of cytology per se.[23] These results are important considerations for countries where organized screening programs have yet to be introduced.

It is notable that this analysis showed no difference in the impact of a vaccination program introduced in the group of 12–29-years of age. We believe this can be explained by the relatively high age of sexual debut in Singapore.[3] Whether this trend will change remains to be seen. For current considerations, one can postulate that Asian countries with characteristics similar to Singapore could introduce the vaccination for the female cohort as old as 29 years. However, for the logistics of vaccination delivery, programs involving schoolchildren may be the most efficient, as demonstrated by the experience from Australia and the UK.

It is obvious that the impact of vaccination of 12-year olds on the incidence of cervical cancer can only be seen in long term. However, the lag time could be shortened by introducing catch-up cohorts of women for vaccination up to the age of 40 years. The benefit of catch-up cohorts has been previously reported and implemented in some national vaccination programs such as Australia and the UK. However, the advantage of catch-up vaccination beyond 26-years old has not been reported from other countries, possibly because of the different age of sexual debut in women between countries. We believe that the experience in Singapore is largely applicable in many countries, most notably in Asia where cervical cancer is most prevalent and where screening programs do not exist.

Despite the inclusion of a catch-up cohort of women for vaccination, there remains a post-vaccination era of 3 to 4 decades during which a large group of women are at risk of cervical cancer. The evidence is compelling: an optimized screening program for CIN and early cervical cancer, whether based on cytology, HPV-DNA or visual inspection with acetic acid, remains the most significant life-saving public measure for these women.[24–26]

While the analysis of the impact of the HPV vaccination in this study is interesting and the results are promising, the introduction of such a program would require a further cost–benefit analysis. Several studies elsewhere have reported there are significant cost effectiveness and benefits to vaccination to control cervical cancer.[21] However, the study should be repeated for individual countries.

CONCLUSION

Using Singapore as a case-study model, our results demonstrate that a universal HPV vaccination program is superior to cytology screening for reducing the burden of cervical cancer. Mass HPV vaccination can be introduced to cohorts of girls between the ages of 12 to 29 years. For an adolescence vaccination program, an effective catch-up cohort could be included up to the age of 40 years. However, further cost-effectiveness analysis is warranted before its implementation in an individual country. Optimized screening should be continued as the immediate and the post-vaccination measure of a cervical cancer control program.

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