Current status and future direction of cervical cancer prevention program in Malaysia

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Introduction

Cervical cancer remains one of the major cancer burdens worldwide particularly in under-developed and developing countries. Cervical cancer continues to have a major impact on women not only physically but also socially and sexually. Cervical cancer affecting one of the most important reproductive organ and many of these patients were from the reproductive age group. Cervical cancer is the second most common women cancer in the world. It was estimated that almost 0.5 million cases of cervical cancer had been reported in the world in 2006 and WHO has estimated almost 300,000 women died every year due to this disease. Approximately 80% of all this cases were reported from developing countries with low resource setting. This article will summarizes recent research on cervical cancer prevention, exploring available preventive measures in particularly related to secondary prevention and studying cervical cancer prevention program implemented worldwide with special interest to countries with low resource setting. Apart from highlighting what is happening in other countries, this article will also review our past and current cervical cancer prevention program in Malaysia. Finally, at the end of this article, based on current evidences from large randomised study and resources that available in our country, we will decide what would be the most appropriate (practical and cost-effective) cervical cancer prevention strategy that we should adopt in order to effectively prevent cervical cancer and at the same time reducing the morbidity and mortality from this disease in future.

Health System and Human Resources in Malaysia

In Malaysia, both public and private sectors are important players in the healthcare delivery system. About 80 percents of the healthcare services are provided by the public sector, which is considered as one of the best in this region. The public sector is heavily subsidized and focuses on healthcare promotion as well as rehabilitation and curative care at the primary, secondary, and tertiary levels. No one is denied access to healthcare in the government facilities regardless of his nationality or affordability to pay. With the exemption process, services for the disadvantaged group such as the poor, the pensioner and the elderly, are provided free of charge in the government healthcare facilities. The revenue earned by the government from fees collected for healthcare services only contributes to about 3% to 5% of the Ministry’s Annual Budget (1,2,3).

There are four types of public hospitals in Malaysia: 1) Public Main Hospitals; 2) Public District Hospitals; 3) Teaching Hospitals and 4) Private Hospitals. Each of Malaysia’s sixteen state capitals has a general hospital, with the number of beds averaging from 600 to 700 each and they provide full range of healthcare services. Because of their size and comprehensive range of care, general hospitals are the most preferred public hospitals in Malaysia. District Hospitals, which are much smaller, with the number of beds averaging from 250 to 400 each, provide more basic diagnostic and
The smallest unit in Malaysian healthcare services is called the Rural Health Clinic or “Klinik Desa”. There are many Rural Health Clinics under one District Hospital and in each Health Clinic, there are one Staff Nurse, one Community Nurse and a Midwife. The Health Clinic is covered by a visiting Doctor from District Hospital to run the Maternal and Child Health Clinic. Other than these clinics, there is also Community Polyclinics or “Poliklinik Komuniti”. The Community Polyclinics provide comprehensive primary health care services whereas the secondary and tertiary healthcare services are provided by all the hospitals. Under the Ministry of Health, there were at least 122 hospitals with a total number of more than 34,000 beds (providing secondary and tertiary care) and more than 1,800 Rural Health Clinics in 2004. There were also 6 Special Medical Institutions. In addition, there were 222 Private Hospitals and Private Maternity Homes in Malaysia. Currently, a number of modern and new Public Hospitals are being built to cater for the increase demand in healthcare services in Malaysia. Concurrently, the Government is also making efforts to increase the number of healthcare workers. In 2005 (Table 1), there were a total of 20,105 doctors from both Government Hospitals and Private Healthcare Centres. Basic healthcare through health facilities is currently available and accessible to more than 95 percents of the population in Peninsular Malaysia and about 70 percents of the population in Sabah and Sarawak (4).

Table 1 : Human Resource 2005 in Malaysian Health System (Source: Information And Documentation System Unit (IdS), Ministry Of Health, Malaysia)

<table>
<thead>
<tr>
<th></th>
<th>Public</th>
<th>Private</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors</td>
<td>10,943</td>
<td>9,162</td>
<td>20,105</td>
</tr>
<tr>
<td>Dentists</td>
<td>1,263</td>
<td>1,488</td>
<td>2,751</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>955</td>
<td>3,057</td>
<td>4,012</td>
</tr>
<tr>
<td>Nurses</td>
<td>32,580</td>
<td>11,540</td>
<td>44,120</td>
</tr>
<tr>
<td>Midwife/Comm Nurse</td>
<td>15,408</td>
<td>210</td>
<td>15,618</td>
</tr>
<tr>
<td>Medical Assistant</td>
<td>6,113</td>
<td>596</td>
<td>6,709</td>
</tr>
</tbody>
</table>

Despite growing numbers of healthcare centres and healthcare providers, Malaysia is still facing a serious shortage of human resources as the number of population is increasing and the demand for better healthcare is escalating. According to statistics from the O&G Society of Malaysia, by 2008, there are a total of 647 O&G Specialists registered in Malaysia and if the country is aiming for O&G Specialist:Population ratio of 1:25,800, we need to have at least 250 more O&G Specialists. The total number of Clinical Oncologists in Malaysia is only 45 in 2008 and if the targeted doctor:population ratio of 1:100,000 is to be achieved, Malaysia has to produce another 150-200 Clinical Oncologists to meet the demand. What about Pathologists? There are a total of 103 Pathologists in Malaysia and hence, at least 400 more need to be produced in order to achieve the target of 1 Pathologist for every 42,300 populations (5). These figures have clearly shown that we are currently facing a serious shortage of human resources to run the health program especially in the government sector and these issues should be given the top most priority if we want to see more success in the implementation of any health program including cervical cancer prevention.
Cervical Cancer in Malaysia

The first report of Malaysian National Cancer Registry (NCR) was published in 2002 and the latest is the third report which is NCR 2005. All our NCR were merely descriptive in nature and there was no morbidity and mortality data. All reports were also confine to Peninsular Malaysia and did not include data from East Malaysia i.e Sabah and Sarawak.

Cervical cancer is the second most common women’s cancer, next to breast cancer and the most common gynaecological cancer in Malaysia. According to the National Cancer Registry 2005, a total of 4,057 cases of cervical cancer had been reported from 2003 until 2005. The ASR of cervical cancer was 16.1 per 100,000 populations. Cervical cancer incidence rate increased with age after 30 years. It has a peak incidence rate at ages 60 - 69 years, and declined thereafter. Chinese women had the highest ASR of 23.2 per 100,000 populations, followed by Indians with ASR of 16.4 per 100,000 populations and Malays with ASR of 8.7 per 100,000 populations (6). Compared to Chinese women in other Asian countries, the incidence of cervical cancer in the Malaysian's Chinese is among the highest.

<table>
<thead>
<tr>
<th>Site</th>
<th>No</th>
<th>%</th>
<th>Crude incidence rate</th>
<th>ASR</th>
<th>CumR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>11952</td>
<td>31.3</td>
<td>41.3</td>
<td>47.3</td>
<td>5</td>
</tr>
<tr>
<td>Cervix</td>
<td>4057</td>
<td>10.6</td>
<td>14</td>
<td>16.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Large bowel</td>
<td>3791</td>
<td>9.9</td>
<td>13.1</td>
<td>16.8</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1627</td>
<td>4.3</td>
<td>5.6</td>
<td>6.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1414</td>
<td>3.7</td>
<td>4.9</td>
<td>5.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Lung</td>
<td>1387</td>
<td>3.6</td>
<td>4.8</td>
<td>6.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1306</td>
<td>3.4</td>
<td>4.5</td>
<td>5.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Corpus Uteri</td>
<td>1253</td>
<td>3.3</td>
<td>4.3</td>
<td>5.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Thyroid Gland</td>
<td>1194</td>
<td>3.1</td>
<td>4.1</td>
<td>4.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>1014</td>
<td>2.7</td>
<td>3.5</td>
<td>4.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

ASR : Age Standardized Incidence
CumR : Cumulative Risk

Cervical Cancer Prevention Program in Malaysia

Primary Prevention

Primary prevention against cancer is under the National Cancer Control Program. The activities conducted include healthy lifestyle and wellbeing program, aiming to increase public awareness on cancer. Policies that have been developed are cancer prevention through dissemination of information on cancer prevention methods, early detection, treatment and also through legislative changes such as control of tobacco use (7,8). Hepatitis B vaccination program aims at preventing liver cancer whereas anti-smoking campaign is targeted at the prevention of lung cancer. Healthy lifestyle campaign includes an education on healthy and safe sex. The Human Papilloma Virus (HPV) Quadrivalent Vaccine was approved by the Malaysian Drug Authority on 20th October 2006 while the Bivalent Vaccine was approved in 2007. Currently HPV vaccination is only provided by the Private Healthcare Centre. This issue will be further discussed in the later part of this article.
Cervical Cancer Screening Program in Malaysia: Current Status

Pap Smear and Colposcopy

Cervical cancer is a preventable disease. In countries with population based and organized Pap smear screening program, the incidence and mortality due to cervical cancer can be significantly reduced. In places where screening quality and coverage areas have been high, Pap smear has been shown to reduce the incidence of invasive cervical cancer by as much as 80 percents (9). Pap smear screening frequency of 3 yearly is able to reduce the cumulative risk of woman from invasive cervical cancer by 91 percents (10). Cervical cancer screening program in Malaysia was implemented in 1969 and the modality of screening is conventional Pap smear. Until today, Pap smear screening program in Malaysia is based on opportunity. There are various agencies that provide Pap smear services such as National Population and Family Development Board (NPFDB), private clinics and hospitals, university hospitals, army hospitals as well as non-governmental organizations such as Federation of Family Planning Association of Malaysia (FFPAM). According to the National Cervical Cancer Guidelines 2003 and also Guidebook in Pap smear 2008, all sexually active women age between 20 to 65 years should undergo Pap smear screening annually for two consecutive years and if the Pap smear is normal on both occasions, they can continue the screening test once every three years. Malaysian’s Ministry of Health had allocated 3.55 millions Malaysian Ringgit in 2003 for the Pap smear screening program. Women who obtain Pap smear test from Public Hospital or other public health services do not need to pay for the services. Majority of the Pap smear test is conventional Pap smear and only a few Public Health Services and Private sectors are offering liquid based cytology.

In 1981, the service was extended to all family planning acceptors. The importance of Pap smear screening was emphasized through 1995 Healthy Life Style Campaign with the theme ‘Cancer’. Since the campaign, Pap smear screening was made available for all female aged between 20 and 65 years, once every three years.

From 1996 until 2005, the total number of Pap smear taken in Malaysia ranged from 350,000 to 400,000 annually and there was no significant increase in the numbers over the years. Majority of these Pap smears were performed at the Public healthcare services. Women’s awareness regarding Pap smear in Malaysia is still relatively low. The coverage of Pap smear screening program in 1996 was 26 percents (National Health and Morbidity Survey 1996, Institute of Public Health, Kuala Lumpur, Ministry of Health 1999) and the actual Pap smear coverage in the recent years is unknown as there is no Pap smear registry in Malaysia. Looking at the pattern of total number of Pap smear taken over the past few years, the actual coverage of Pap smear in the recent years may be in the range of 26 to 45 percents.
Public Health Clinics and Government Hospitals contribute approximately 69 percents of all Pap smear screening test, while Private Hospitals and Clinics contribute 20.6 percents of total Pap smear taken in 2005 (11). The overall positive detection rate (abnormal Pap smear) for the year 2005 was 0.86 percents while overall unsatisfactory Pap smear in the same year was 3.1 percents (11).

At present, there is no Pap smear registry in Malaysia and the data on the number of Pap smears were obtained from manual data collection done by the all the cytopathological laboratories around the country. The actual number of woman undergoing Pap smear screening are unknown because many Pap smears taken were not reported (especially if the Pap smear was done in the private health centre) and the same woman may be contributing for more than one smear. Currently, reporting of Pap smear is based on the Bethesda 2001 reporting system. According to the Guidebook for Pap Smear, a woman is advised to have Pap smear screening if she is between 20 – 65 years of age and has been sexually active. All new cases need to be screened yearly for two consecutive years. If the results were normal, screening needs to be repeated once every three years.

The volume of colposcopic procedures is limited due to limited number of abnormal Pap smear. Cancer prevention programme will be a wasted effort if not complemented with training in colposcopy. JKKPOG with the assistance from GO subcommittee of OGSM has come up with a structured colposcopic training programme to train as many specialists to be able to perform colposcopy and its related procedures competently. This training includes a structured colposcopy workshop and the participants will be assessed at the end of the workshop. The candidates are also required to log in 50 cases and perform at least 10 colposcopic procedures. Having successfully completed the logbook, the candidate will be considered to be given certificate of acknowledgement as Colposcopist. The very first of such workshop was conducted in Kuala Terengganu in October 2007. Seven O&G Specialists from Terengganu and Pahang have registered under this training
programme. The second workshop was held in Kangar, Perlis in March 2008 and another 10 trainees had been recruited.

Currently, without an organized population-based screening program and adequate number of trained colposcopist, we do not expect any positive impact on overall cervical cancer incidence and mortality in Malaysia at least for the next few years to come. An effort is being carried out by the Ministry of Health to initiate the population-based screening program. The demonstration project on call-recall system is currently being carried out in Klang, Selangor and Mersing, Johor in both the government organizations and private sectors. This pilot project is funded by the Ministry of Health (Family Health Development Division) and is an on-going project since 2006. This project involves usage of a networking computer system with Pap smear databases. Pap smear performed is a conventional type and Private Pathologists are also involved in interpreting the Pap smear to overcome shortage of public laboratories and high volume of smears. This project aims to achieve 75 percents Pap smear coverage among women age between 20 to 65 years. The main objective of this project is to study the feasibility and cost-effectiveness of organized screening program through call and recall system in reducing the incidence of invasive cervical cancer. This project is also an important platform to develop the national Pap smear registry. This demonstration project is expected to be completed by the year 2011(12).

Conventional versus Liquid-Based Cytology

Although liquid-based cytology has been shown to be more accurate in detecting high grade cervical lesion, until today there is no data to show that it is more effective in reducing the incidence and mortality from cervical cancer as compared to conventional pap smear. Interestingly, a recent systematic review and meta-analysis (analysis of published studies from 1991 - 2007) have shown that liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia compared with the conventional Pap test (13).

Problems with Pap Smear in Malaysia

If organized Pap smear screening program is carried out in Malaysia, we must overcome the following problems:

a. **Lack in human resources.** Table 1 have shown that we do not have enough manpower to support an organized Pap smear screening program. Cytologic testing is known to involves many procedures, time consuming, low reproducibility and labour intensive. Currently, our cytoscreener is very limited and majority of them are not full-time screener. A total of 95 trained cytoscreeners are available but only 25 percents are fulltime. There are approximately 6.9 million women aged between 20 and 65 years in Malaysia. If we want to achieve 80 percents Pap smear coverage within three-year period, we have to screen 1.07 million women every year. Average optimal workload for each cytoscreener is 5000 slides/year. From this figure, we need at least 213 cytoscreeners. Other than cytoscreener, more Pathologists are needed to assist particularly in dealing with abnormal cytologic reporting and management of preinvasive as well as invasive cervical cancer. In addition, the number of trained colposcopist in Malaysia is very limited and our colposcopic training program is still in an infancy stage. If the abnormal pap smear rate is 1%, we will expect a total number of 32,100 colposcopic procedure have to be done if organized screening program using pap smear is to be implemented. With this volume of colposcopic procedure, we need a least 65 trained Colposcopists in our country ( 80% pap smear coverage and workload of 500 procedure/colposcopist). Currently, all trained Colposcopists are also a Gynaecological Oncologist. There is no Gynaecologist in Malaysia who had been certified as
Colposcopist (Gynaecologist who complete full training program with exit certification in colposcopy).

b. **Pap Smear and Cancer Registry.** Currently we do not have Pap smear registry. Without Pap smear registry, we do not know the exact number and percentage of women in Malaysia doing a screening test. More importantly, Pap smear registry will provide platform for auditing and assessing the effectiveness of screening program. Call-recall system should be implemented nationwide. Apart form Pap smear registry, we also need a Cancer registry to address the issues of cancer morbidity and mortality which is still not available even in our recently released NCR 2005.

c. **Infrastructures.** Organized screening program requires adequate infrastructures including laboratory and colposcopic equipment. All hospitals must be equipped with complete colposcopic equipment both for diagnostic as well as therapeutic purposes. Implementation of call-recall system and Pap smear databases require appropriate infrastructures, software and computer networking.

d. **Training.** Training for all categories of staffs must be done. Training program should include technique of Pap smear taking, management of abnormal Pap smear, colposcopy and treatment of preinvasive disease. Training certainly needs financial support, equipments and trainers.

e. **Lack of research and demonstration project.** There are limited numbers of research pertaining to cervical cancer prevention in Malaysia. We have to engage with many more researches and demonstration projects to study the most cost-effective cervical cancer screening program in Malaysia.

f. **Lack of public awareness.** One of the most important predictor of success in any preventive program is the level of awareness among the target population with regards to the disease. All category of community must be educated regarding cervical cancer, its aetiology, its relation with HPV and how to prevent it. Public must be educated and inform regarding the danger and burden imposed by cervical cancer not only to the individual but also to family, community and to the country. Public awareness campaign must be intensified and carried out on a regular basis, all members of the community must have access to the information and actively involved in the campaign.

Apart from solving the above listed problems in relation to Pap smear, we must not ignore the potential benefits of other screening tests which had been studied extensively in other developing countries. Some had been completed and published and many more studies are being carried out in countries like Thailand, Indonesia, India, China and South Africa. All these studies focused on two main screening tests namely **visual inspection with acetic acid (VIA)** and **HPV testing.**

**Visual Inspection of Acetic Acid (VIA)**

Pap smear screening program has its own limitation especially in low resource setting. Pap smear requires laboratory support, manpower and time consuming. Patient with abnormal Pap smear requires proper treatment and this will involve availability of colposcopic facilities for both diagnostic as well as therapeutic purposes. All these involve a significant amount of financial and infrastructures supports. VIA or visual inspection of Acetic Acid is an innovative test for many years but currently has re-emerged as a reliable alternative to Pap smear test in cervical cancer screening particularly in low resource setting.

VIA had been shown in many studies to be an effective screening tool in low resource setting (14,15,16). One of the study was performed in Thailand on safety, acceptability and feasibility of a single visit approach of VIA and cryotherapy (17). This study concluded that a single visit approach with VIA and cryotherapy seem to be safe, acceptable and feasible in rural Thailand, and is a
potentially efficient method of cervical cancer prevention in such settings. In Malaysia, until recently, VIA is only utilized for the research purpose and there is no large study on VIA being conducted. However, following the bi-regional consultation on strategy to prevent cervical cancer meeting held in Pattaya, Thailand in April 2007, Malaysia has agreed to explore the role of VIA either as an alternative to Pap smear or as a part of single visit approach (SVA) in prevention of invasive cervical cancer. This study is currently being carried out in Sik, Kedah where women age between 25 and 50 years are offered visual inspection with 5% acetic acid as a screening test for cervical cancer. This project is funded by the WHO and Family Health Development Division, MOH with the cooperation from the Department of O&G, Sultanah Bahiyah Hospital. Women with positive test will be referred for colposcopy and cryotherapy if suitable. Both procedures are performed in one of the Health Clinics in same the district. Colposcopic and cryotherapy services are provided by the O&G Specialists from Hospital Sultanah Bahiyah and by the Family Medicine Specialist. All staff involved in this project had undergone training in VIA. Currently, the project is running well with more than 1,400 women had participated. This project is expected to be completed by March 2009. Preliminary results have shown an encouraging success in terms of practicality with high women’s satisfaction. The official and final report from this study will be released by middle 2009.

A large cluster-randomized trial on visual screening on cervical cancer incidence and mortality done in Tamil Naidu, India involving more than 50,000 women have shown that VIA screening, in the presence of good training and sustained quality assurance, is an effective method to prevent cervical cancer in developing countries (hazard ratio incidence of 0.75, 95% CI: 0.55-0.95 and hazard ratio mortality of 0.65, 95% CI:0.47-0.89)(18). The International Agency Research in Cancer with collaboration of a few Cancer Centres in India had just completed (unpublished) of a more interesting randomized control study to compare efficacy between VIA, HPV testing (CareHPV) and conventional Pap smear in the District of Osmanabad, India. This later study evaluated all the three modalities of cervical cancer screening test and compared them with no screening test (control) and their final outcome was cervical cancer incidence and mortality. More than 131,000 women participated in the study and the results were presented during the 12th Biennial Meeting of the International Gynaecological Cancer Society (IGCS) in Bangkok on 24th to 28th October 2008. The study have shown that HPV testing (using Digene FastHPV) was the most superior in preventing cervical cancer (hazard ratio of 0.47, 95% CI :0.32-0.69) and reducing mortality (hazard ratio of 0.52, 95% CI : 0.33-0.83) as compared to Pap smear and VIA. The study also showed that there was no difference between Pap smear and VIA in term of their effectiveness in preventing cervical cancer and reducing mortality rate (hazard ratio 0.86 versus 0.89). Women with negative test for both cytology and VIA also had similar lower incidence of developing cervical cancer as compared to control group. In all these studies, cryotherapy was one of treatment modalities is women with positive screening test.

New Technology for Cervical Cancer Screening

New technologies for cervical cancer screening includes Truscan, Automated System, Speculoscopy, HPV Testing and novel molecular marker, all of which are not available in Malaysia. These new technologies can be an adjunct to the existing Pap smear or as an alternative. In country like Malaysia, cost of implementing any new technology needs a very important consideration. Many of these new technologies have not been extensively evaluated. There is no randomized controlled study to show that Truscan and speculoscopy could reduce the cervical cancer incidence and mortality rate, while novel molecular marker is still investigational. Furthermore, Malaysia still has to address the problems of inadequate resources in term of manpower and infrastructures which need to be improved and strengthened in order to support these new technologies. Among all these new technologies, perhaps HPV testing is the most interesting and worth exploring. HPV testing using Hybrid Capture 2 was approved by the FDA in April 2003 as a primary screening test for women age
more than 30 years and it has been incorporated into the National Screening Program in the USA. Clavel C, et al conducted a study on 7932 women with the median age of 34 years who had a Pap smear done and HPV testing using Hybrid Capture 2 Digene, followed by colposcopic examination in selected patients. The study had shown that the sensitivity of HPV testing in detecting a histologically proven HGSIL was 100%, higher than that of conventional (68.1%) and liquid-based (87.8%) cytology. The specificity of HPV testing was found to be higher in women age more than 30 years (19). In 2005, the International Agency for Research on Cancer (IARC)/World Health Organization (WHO) recommended that HPV-DNA testing can be used for primary screening instead of cytology (20). Patients with negative HPV testing can be reassured and have less frequent screening interval. The earlier HPV testing needs laboratory support and time consuming but currently there are two new technologies on HPV testing which are faster and potentially as reliable as the former HPV testing. Two new HPV testing are Digene FastHPV (CareHPV) and Arbo Vita E6 Strip test. Currently Digene FastHPV (CareHPV) is being tested in the demonstration projects in China and large cluster randomised control trial in India (see above). Digene FastHPV test is expected to be available commercially in 2008 - 2009. In our Malaysian context, Arbo Vita E6 strip test is an interesting HPV testing that can be explored if it is found to be reliable and sensitive as a primary screening tool. Arbo Vita E6 strip test is a rapid test whereby the result can be obtained in less than 20 minutes as compared to Digene FastHPV which takes about 2.5 hours. Arbo Vita E6 strip test is testing against the E6 oncoprotein as compared to major capsid protein in Digene FastHPV. E6 oncoprotein is said to be more sensitive marker for the risk of malignant transformation.

**Figure 2.** Digene FastHPV or CareHPV is relatively new HPV testing which had been extensively studied in large randomised control trial in country with low resource setting. It is cheaper and the result will be available on site within 2.5 hours.
Human Papilloma Virus and Cervical Carcinoma in Malaysia

Human Papilloma Virus

Human Papilloma Virus (HPV) is a DNA virus. The virus does not have an envelope but it consists of shell called capsid. HPV DNA is circular and double-stranded. HPV DNA or genome has three major regions i.e Long Control region, E region and L region. Based on the sequence of genes in the E6, 7 and L1 regions, there are more than 200 HPV subtype and at least 13 of them are categorized as high risk HPV type because of their oncogenic properties. HPV has been attributed to many skin and mucosal diseases ranging from benign viral warts to a malignant disease such as cervical cancer, vulvar cancer, vaginal cancer, penile cancer, anal cancer and also a neck cancer. HPV is the primary aetiology in cervical cancer. HPV 16 and 18 have been attributed to at least 71% of invasive cervical cancer. High risk HPV is also responsible in preinvasive cervical lesions while low risks HPV especially Type 6 and 11 are responsible in at least 90% of anogenital warts. In invasive cervical cancer, high risk HPV has been attributed in 99.7% of cases (21).

The actual prevalence of HPV infection among Malaysian women is unknown. To date, there is no large study on Human Papilloma Virus in Malaysia. Large studies on prevalence of HPV infection have been conducted in other Asian countries and among those is a study by Clifford GM on the prevalence of HPV infection using PCR-based EIA on cervical smear sample in groups of women from four countries namely India, Vietnam, Korea and Thailand. The study showed that the age-standardized prevalence for any HPV is 8.7%, with the high-risk types representing a large proportion of the infected women (5.4%) (22).

A small study done locally by Tiang YP on women attending STD Clinics and District Health Clinic in the state of Selangor found that HPV DNA (using PCR method) was detected on Pap smear in 20 to 24% of women attending STD Clinics while only 1.3% in women attending District Health Clinics. He also found that 50% of those HPV detected were of high risk HPV 16 and 18 (23). However, the sample size was small with only 381 subjects and a confirmatory test was based on gel electrophoresis and not by more sensitive test i.e hybridization. Larger local study done by Anwar K, et al with larger samples (996) showed a very low prevalence of HPV in normal population (1.5%). Again, this could be attributed to the sample’s age group and the technique for HPV detection which was similar to the study done by Tiang YP.

Genital warts is a common skin disease caused by low risk HPV type 6 and 11 in 90% of cases. The prevalence of genital warts in Malaysia is unknown as majority of patients seek treatment from the private health centres and there is no reporting system for genital warts in Malaysia. Other than that, many women and men did not seek treatment as the disease is very minimal or they were asymptomatic. Small local study on type of HPV responsible in vulvo-vaginal wart (condylomata acuminata) was conducted in the National University of Malaysia. This study utilized in-situ hybridization using biotinylated probes to detect the HPV deoxyribonucleic acid (DNA) of types 6, 11, 16, 18, 31 and 33. All vulvar and vaginal lesions showed typical histopathological features of condylomatous changes. HPV 6 and HPV 11 were detected in 100% and 87.5% of all cases, respectively. HPVs 16, 18, 31 and 33 were not found in the sample study (24).

Studies on the prevalence of HPV type and preinvasive as well as invasive cancer in Malaysia are also scanty. The prevalence of preinvasive cervical lesion in Malaysia is grossly underestimated because of low Pap smear coverage. Study on the prevalence of HPV infection in this group of women is difficult due to inadequate samples. Small retrospective study on prevalence of HPV type in invasive carcinoma was done by Cheah PL. He conducted the HPV DNA testing using in-situ hybridization on 100 cases of squamous cell carcinoma. The study revealed the presence of HPV type 16 in 47% and
type 18 in 41% of cases. This gives an overall detection rate of 88% of the two HPV type 16 and 18 in invasive squamous cell carcinoma of cervix (25). Another study by Patmanathan A, using PCR followed by non-radioactive Southern hybridization with type-specific oligonucleotides for HPV 16 and 18 and monoclonal antibodies test for expression of HPV 16 L1 and HPV 18 E6 proteins, found that 57 out of 60 cervical carcinomas (95%) were positive for HPV 16 and 18 with equal proportion (26). These two studies highlighted the importance of HPV 16 and 18 in the aetiology of invasive cervical cancer in Malaysia. Unpublished data from study done in HUKM involving over 140 cervical cancer specimens (Prof Dr. Sharifah Nor Akmal) have shown that HPV 33 has emerged as one of the important HPV serotype in relation to cervical cancer among Malaysian women. We are still awaiting the final results of this ongoing study and hopefully will eventually have a clearer pattern of HPV serotype responsible for cervical cancer among Malaysian women.

**HPV Vaccination in Malaysia**

HPV vaccine is a new paradigm in cervical cancer prevention program. Quadrivalent Vaccine (Gardasil) was approved by the FDA on 8th June 2006. On 29th June 2006, US Centres for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) voted to recommend Gardasil to be routinely given to girls when they are 11 to 12 years of age and it can also be given to girls at the age of 9. This vaccine was found to be very effective in preventing the type specific HPV infection and also preinvasive disease of the vulva, vaginal and cervix. The benefits of this vaccine were found to be sustained for at least 5 years. Based on the study, HPV vaccine is expected to prevent at least 71% of squamous cell carcinoma of the cervix and 96% of adenocarcinoma of the cervix. Currently this vaccine is available in more than 100 countries and Malaysia was one of the Asia Pacific countries that licenced the administration of HPV vaccine. Malaysian’s drug authority approved the Quadrivalent Vaccine on 20th October 2006 and currently it is available exclusively in the Private Health Centres. This vaccine is not available at the government hospitals. It is licenced for women age 9 to 26 years. Bivalent Vaccine called Cervarix had also been approved in 2007 and currently is recommended to women until the age of 45. The role of HPV vaccine in country like Malaysia is very promising but the issues of cost-effectiveness and long-term benefits are yet to be answered. Furthermore, there are few issues pertaining to HPV vaccine that has to be addressed such the duration of protection, local data on prevalence of type-specific HPV infection in relation to invasive cervical carcinoma, the need for booster, efficacy in older women and public perception with regards to prevention of sexually transmitted disease in young sexually naieve girls/boys. The most important question that need to be answered is on how cost-effective the HPV vaccines be if it is to be introduced into the National Immunization Program. To answer this important issue, a cost-effective analysis on the HPV vaccine is currently being carried out by a group of researchers in the department of Community Health, National University of Malaysia involving a few government hospitals. The study commenced in March 2006 and is expected to be completed in 2008. There is also an on-going study by a Professor of Cytopathology from the same institution in collaboration with MERCK on the Prevalence of HPV type and invasive cervical cancer. There are a few more studies awaiting approval by the ethic committee and one of them is study on HPV genotyping in abnormal cervical lesion using real-time PCR on thin prep sample.

A technical committee was given a responsibility to study and make recommendation on the role of HPV vaccine in Malaysia and the committee is the National Immunization Technical Committee under Disease Control Division of the Malaysian Ministry of Health. Currently, Ministry of Health, NGOs and Pharmaceutical company is actively involved in the health promotion in terms of knowledge on HPV and cervical cancer. This health promotion and education are delivered through mass media, media electronics, posters and pamphlets. By the year 2009, all major questions will be hopefully answered and if the HPV vaccine is going to be included into the National Immunization program, it may take place in 2009 or beyond.
As for the age of vaccination, HPV vaccine provides full benefits to young and sexually naïve vaccinees. Therefore, it is important to have a data on sexual initiation among the adolescents before deciding on when the vaccination should begin. In Malaysia, Lee LK has conducted a cross-sectional study on the prevalence of sexual intercourse among adolescents in 2001(27). The study aimed to describe the prevalence of premarital sexual intercourse and the determinants of sexual intercourse among Malaysian secondary school students (age 12 to 18 years). 4500 respondents were recruited in the study (see Table 3).

Table 3: Distribution of respondents by background characteristics (Lee LK. Singapore Med J 2006; 47(6):476-481)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sexual experience</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>All respondents</strong></td>
<td>4,500</td>
<td>100</td>
<td>4,243</td>
<td>93.8</td>
<td>242</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,089</td>
<td>46.4</td>
<td>1,892</td>
<td>91.7</td>
<td>172</td>
</tr>
<tr>
<td>Female</td>
<td>2411</td>
<td>53.6</td>
<td>2331</td>
<td>97.1</td>
<td>70</td>
</tr>
<tr>
<td><strong>Ethnic group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>2,332</td>
<td>51.8</td>
<td>2,182</td>
<td>94.5</td>
<td>127</td>
</tr>
<tr>
<td>Chinese</td>
<td>1,314</td>
<td>29.2</td>
<td>1,238</td>
<td>94.7</td>
<td>69</td>
</tr>
<tr>
<td>Indian</td>
<td>771</td>
<td>17.1</td>
<td>730</td>
<td>95.1</td>
<td>38</td>
</tr>
<tr>
<td>Others</td>
<td>83</td>
<td>1.8</td>
<td>73</td>
<td>90.0</td>
<td>8</td>
</tr>
</tbody>
</table>

The overall prevalence of sexual intercourse in adolescent was 5.4%. This figure was smaller compared to other countries (15% in Thailand and 60% in Great Britain) (28).

Figure 3: Age at first sexual intercourse among adolescent in Malaysia (Lee LK. Singapore Med J 2006; 47(6):476-481)
What is the financial implication of HPV vaccination program? Any national vaccination program required a large amount of financial supports. For example, if the Ministry of Health decided to initiate the HPV vaccination to girls age 13 years, it is estimated that about RM 300 million is to be spent in a year to cover approximately 250,000 13 year old girls.

CERVICAL CANCER SCREENING PROGRAM IN MALAYSIA: FUTURE DIRECTION

Despite HPV vaccination, cervical cancer screening test must still be implemented because (1) HPV vaccination program will take time to fully implemented, (2) the impact of HPV vaccination on the final end-point will take more than a decade and (3), even with HPV vaccination program fully implemented, approximately 30% of women will not benefit from the vaccination. The question which still has no answer is what is the best cervical cancer screening program during HPV vaccination era? In Malaysia, lack of resources, manpower and geographical barrier will be the main hindering factors in the implementation of organized screening program using Pap smear alone perhaps at least in the next five to ten years. We need to explore the other modalities of cervical screening tests such as VIA and HPV testing. Both screening tests had been shown by large study to be at least as effective tool for cervical cancer prevention and in fact, there was a strong evidence that cheaper and faster HPV testing was more effective in preventing cervical cancer as well as reducing the mortality rate. Perhaps we can adopt what Thailand is currently implementing i.e the dual-tract screening program. The dual-tract screening program uses both conventional Pap smear and VIA as screening test in selected women age from 30 till 50 years old. The other alternative is to explore new HPV testing (Digene FastHPV) as a first screening test and those with positive test will be subjected to VIA which is more specific. Any woman with VIA positive will be treated during the same setting with cryotherapy. This model was actually proposed by International Agency of Research in Cancer. Please refer to Figures 4, 5 and 6 for an example of cervical cancer screening model that can be implemented in Malaysia.

Figure 4: Dual tract program : VIA – Cryotherapy and Conventional Pap Smear (Thailand Model). Different group of women will undergoing different screening test. Screening interval is 5 years and women with suspicious lesion and not suitable for cryotherapy will be referred to Hospital with O&G Specialist/Gynae-Oncologist. Women who had screening test using one method do not need to repeat the test using the other method.
Figure 5. A generic of proposed demonstration project in future for Malaysia

Information, education, and communication recruitment

Screening

FastHPV: Vaginal Sampling (optional by provider and/or client)
FastHPV: Cervical Sampling (by provider using a vaginal speculum)
Pap: (by provider using a vaginal speculum)
VIA

Negatives on all rapid tests (VIA, VILI, FastHPV). Told to return for rescreening in 3-5 years.

Anyone positive on any screening test (positives on Pap are contacted and brought back for colposcopy).

Colposcopy and biopsy as appropriate

Referral to regional referral hospital for further management
- Women with visually diagnosed or suspected cancer.
- Women with CIN lesions too large for cryotherapy.

Cryotherapy of all clients positive on at least one screening test

Test of cure one year later with colposcopy
SUMMARY

Cervical cancer is the second most common women cancer in Malaysia. With Age-Standardized incidence of 16.1 in 100,000 populations, the burden of cervical cancer in Malaysia is comparable with other developing countries such as Thailand, Myanmar, Vietnam, India and some countries in south America. More than 90% of women in Peninsular Malaysia have access to healthcare and if well organized population-based screening program is implemented and the problem of inadequate resources is overcome, the likelihood of success will be higher. However, currently Malaysia is still having the problems of lack of public awareness, inadequate human resources (paramedics, doctors, pathologist, cytotechnologist and colposcopist) and infrastructures to run the program. Apart from that, without Pap smear registry, the actual Pap smear coverage is unknown and because of low coverage of Pap smear, not many Gynaecologists are trained in colposcopy. Malaysia is currently taking an initiative to study the feasibility of call-recall system using call letter, computer networking and databases to increase the Pap smear coverage. If this project is successful, the system will be implemented in a larger scale to reach a wider population coverage. Being a large country geographically, there are still many localities where healthcare services are inaccessible in particularly in the East Malaysia i.e Sabah and Sarawak. Hence, the alternative to Pap smear as a primary screening test should be explored and perhaps, VIA with single visit approach using cryotherapy may be feasible and more practical in this area. The role of VIA in screening of cervical
cancer is undeniable and this has been proved by large cluster-randomized control trial. There is also strong evidence that with proper training and quality control, VIA is as effective as Pap smear in the prevention of cervical cancer. VIA has an advantage of being very cheap and the result is available almost immediately.

With the availability of cheaper and faster HPV testing, this can be incorporated into the existing screening program either as a single primary screening modality or in combination with other modality, particularly VIA. If this policy is to be implemented, the more sensitive screening test will be performed first and a second test which is more specific will be performed on those with positive test that requires treatment.

Vaccination against HPV infection is very promising. Although it has been approved in Malaysia since October 2006, the Ministry of Health is yet to implement a Government-funded Immunization Program. This is believed to be implemented in 2009 with target population of all girls aged 13 years old. Even with the implementation of HPV vaccination program, cervical cancer screening program must be strengthened as HPV vaccine will only prevent 70 to 80% of invasive cervical carcinoma and this impact can only be observed after 10 to 15 years or even longer. To have a significant reduction in the incidence and mortality of cervical cancer in the future, it does not only rely on screening program or vaccination but also on how successful the country is in promoting healthy lifestyle to the public such as consumption of a well-balanced diet, avoidance of smoking, regular exercises and healthy sexual practices.

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