A Review of Cervical Cancer Research in Malaysia

Zaridah S, MOG UKM

Gynecology oncologist, Obstetric & Gynaecology Department, Hospital Tuanku Fauziah, Kangar, Jalan Kolam, 01000 Kangar, Perlis.

SUMMARY

Despite cervical cancer being potentially preventable, it is the second most common cancer among women in Malaysia. One hundred and five articles related to Cervical Cancer were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. Fifty seven articles were selected and reviewed for the articles' clinical relevance and future research implications. This article reviews the various aspects of cervical cancer in Malaysia, mainly persistent infection of high risk human papillomavirus (HPV), primary prevention (HPV vaccination), screening method (Pap smear issues), and the attitude and knowledge of various groups of Malaysian women that contributed to the failure to reduce the incidence and mortality of cervical cancer. Most of the studies focused on prevention, Pap smear issues, HPV DNA testing, HPV vaccination and various recommendations for prevention of cervical cancer. Secondary prevention by screening is still an important aspect because even with HPV vaccination, screening still plays an important role as vaccination does not cover all high risk HPVs. There is a need to seriously consider a properly organised screening programme, taking into consideration what we already know about the attitude and knowledge of Malaysian women, economic factors and psychosocial issues of the screening method. There is also a large gap in clinical studies on the outcome, management and survival of cervical cancer patients in Malaysia.

KEY WORDS: *cervical cancer Malaysia, prevention, screening, HPV vaccination*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY/INCIDENCE

The Malaysian National Cancer Registry Report (2003) found that the most frequently occurring cancers in Malaysian women (in descending order) cancers of the breast, cervix, colon, ovary, leukaemia, and lungs. Cervical Cancer caused about 12.9% of all female cancers (an age standardised incidence rate of 19.7 per 100,000) in Malaysia. This was higher than other Asian and Western countries, and even globally (National Cancer Registry, 2003). Deaths from cervical cancer are rare amongst young women but its incidence increased from the age of 30 years and peaked at 60-69 years. Half (54.7%) of the cases involved women ages 40-59 years. Incidence rates were, in general, highest among Chinese women (28.8/100,000), followed by Indians (22.4/100,000) and the lowest amongst the Malays (10.5/100,000)[1].

The Ministry of Health Malaysia reported an average of 2000 to 3000 hospital admissions of cervical cancer cases per year in the country; most of them presenting late into the disease[2]. The annual cervical cancer death rate is 5.6 per 100,000 (Cervical Cancer Incidence and Mortality Rates 2011). The mortality rate due to cervical cancer in Malaysia is more than two times higher than the Netherlands, United Kingdom and Finland. Even with the introduction of screening programmes and immunisation against cervical cancer, the mortality rate has not decreased to a desirable level. The economic burden due to cervical cancer is enormous. It costs about RM312 million (USD76 million) to manage cervical cancer (from prevention to managing invasive diseases) annually in Malaysia. A big proportion (67%) of this is spent to manage invasive cancer cases[3].

Syed M AlJunid discussed the burden of cervical cancer in Malaysia and the potential cost and consequences of human papillomavirus (HPV) vaccination[4]. Since cervical cancer is treated primarily within regional hospitals, while precancerous lesions are treated within an ambulatory care set up, the burden was estimated as the direct, indirect and total annual costs associated with cervical cancer and precancerous lesions in Malaysia. This retrospective study to estimate the burden associated with cervical cancer was conducted at four hospitals[4]. A total of 444 hospital admissions attributable to cervical cancer were identified. Treatment for preinvasive disease is much cheaper. The average cost of atypical squamous cell of undetermined significant (ASCUS), cervical intraepithelial neoplasia 1 (CIN1), and CIN 2/3 in Malaysia were RM898, RM1453, RM1948 respectively compared to RM10,540 for cervical cancer. A prevalence-based model that used 1-year cross-sectional data was developed to estimate the number of events (cases of precancerous lesions, cervical cancer and genital warts) and costs (direct+indirect) that could be avoided by vaccination, Data from World Health Organization (WHO) and Global cancer incidence, mortality and prevalence (GLOBOCAN) estimated 4696 prevalent cases of cervical cancer annually in Malaysia. Based on this, Syed M AlJunid found the estimated treatment cost to be RM37,652,528 for inpatients and outpatients. There were 1372 cases estimated for precancerous lesions (ASCUS, CIN 1 and CIN 2/3), with the cost of outpatient treatment calculated as RM1,501,171, making the direct total management of HPV related disease to be RM39,153,699, with an additional RM12.4 million in indirect costs due to lost productivity[4].

Shanti et al, in her supplementary paper, recommended that the bulk of effort in managing cervical cancer should be allocated for preventive strategies – mainly screening, followed by combined screening-vaccination. The Malaysian government spends RM150 million annually to operate the nation's HPV immunisation programme but it takes only RM 32 million to operate the Pap smear screening program[5].

Corresponding Author: dr_zaridah@yahoo.com.sg

RISK FACTOR

Human papillomavirus and cervical cancer

The World Health Organization (WHO) had linked persistent high risk HPV infection, particularly HPV 16 and 18, to cervical cancer. Human papillomavirus infection is cleared within two years in most women. It is the persistent high risk HPV infection that puts the infected individual at high risk to develop CIN 3 and cervical cancer later on 6. Many studies in Malaysia also showed this association (Table I).

An independent, prospective, multi-centred, hospital-based cross-sectional studies involving Malaysia, Vietnam, Singapore, South Korea and the Philippines evaluate the prevalence of human papillomavirus (HPV) in women older than 21 years old with invasive cervical cancer (ICC) and high-grade precancerous lesions[9]. Out of 500 women confirmed with ICC, the HPV types detected were HPV 16 (36.8%-61.3%), HPV 18 (12.9%-35.4%), HPV 52 (5.4%-10.3%), and HPV 45 (1.5%-17.2%), whereas among the CIN 2/3/AIS cases, HPV 16 (29.7%-46.6%) was the most commonly observed type followed by HPV 52 (17.0%-66.7%) and HPV 58 (8.6%-16.0%)[9].

The prevalence of HPV infection were demonstrated in these two studies by Chong PP and Tay *et al* (Table II). Tay et al studied the prevalence of high-risk HPV DNA among 2364 women[10]. The overall prevalence of high risk HPV DNA was 25.6%. The prevalence of high risk HPV showed the peak age to be in women between 20-24 years old (49.1%) and a second peak prevalence in women 50-54 years old (30%). This pattern of peak prevalence is similar to the general trend published from other parts of the world. High risk HPV DNA detection was associated with 2.44-3.18 fold higher risk of developing cervical cytology abnormality or 9.8 fold higher risk for HSIL compared to HPV-negative women. In this study, the natural history of high-risk HPV infection showed that 90% of HPV infection regressed within the first 12 months of follow-up. Therefore, recommended implementation of a comprehensive cervical cancer screening and anti-HPV-16/18 vaccination program is an important and urgent measure for reducing the burden of cervical cancer in Malaysia and Singapore[10].

CERVICAL CANCER PREVENTION

Cervical cancer is a potentially preventable disease. There is a need to look into why this easily prevented and detected disease still has high prevalence and mortality. Many studies done in Malaysia revolved around cervical cancer prevention. There are three modalities of cervical cancer prevention: primary prevention by preventing HPV infection, sexual abstinence and healthy lifestyle, and HPV vaccination. Secondary cervical cancer prevention is through the detection and treatment of precancerous or preinvasive lesion; and tertiary prevention is the detection and treatment of the early stage of cancer.

Primary prevention

The prophylactic HPV vaccine was licensed in our country in November 2006, and recommended for routine use in girls aged 11 to 12 years and permissive use for females aged 9 to 26 years. According to the Annual Report of Malaysia Ministry of Health (2012), the immunisation coverage of a complete three dosage of HPV vaccine was achieved (87.12%) among 13 year old girls in year 2011.

HPV vaccination: knowledge and attitude

The studies on knowledge, attitude and practices on HPV infection and vaccination were conducted in various groups including secondary school, children, teachers, university students, and other groups of women from various level of education. All the studies below concluded that overall knowledge on HPV infection, vaccination and cervical cancer is poor and that knowledge and attitude translated to vaccine acceptance. There is a need to improve women's awareness and knowledge, and improve their attitude towards HPV vaccination.

Teenagers

Two cross-sectional studies on teenagers' knowledge of cervical cancer and its prevention were conducted; one in Sarawak involving 76 students[12] and the other involving eight schools in Kuala Lumpur*13*. In Sarawak, 61.8 % had poor knowledge of cervical cancer and its prevention, and 60.5 % of students were aware of cervical cancer (the highest rate of awareness involving the Chinese students). The main source of cervical cancer information were their parents (25.9 %). Race, socioeconomic status, father's education level, mother's education level and cervical cancer awareness were associated with the knowledge of cervical cancer prevention ($p< 0.05$). Not many students (22.3%) accepted HPV vaccination.

In the Kuala Lumpur study, although 80.4% have heard about cervical cancer, 74.4% had low knowledge of cervical cancer, 70.4% had low knowledge of the preventive measures of cervical cancer. Most students (69.3%) agreed to take the vaccination if the service was available in schools, 82.2% agreed that the vaccination of teenagers should be made compulsory. Both studies concluded that most students had low knowledge of cervical cancer and its prevention but they had a positive attitude toward vaccination. The Kuala Lumpur students agreed that vaccination should be made compulsory. Therefore, suitable educational programmes should be developed to improve the knowledge of secondary school students on the prevention of cervical cancer.

A study among secondary schools in Melaka looked into the HPV vaccination practice. The study involved a total of 612 secondary school girls aged from 13 to 17 years old from six secondary schools in Melaka, majority were from rural areas and with a family income of RM3000 or less. In this study, the prevalence of HPV vaccination was 77.9%. About 69% knew about cervical cancer and 77.6% knew about HPV vaccine. This study concluded that vaccination in schools significantly influenced vaccine uptake. Vaccine uptake were also improved with encouragement from healthcare workers and teachers (49.3%), parents (28.6%); and friends (0.2%)[14].

Hersham et al concluded that medical students had the highest level of knowledge of cervical cancer, HPV infection and HPV vaccination compared to dentistry and pharmacy students[15]. The studies recommended enhancing their knowledge level by organising educational and awareness programs in University campuses.

Women

In a survey among 233 young women (majority had tertiary education), 82.4% reported having knowledge of HPV, and 71.7% knew that having multiple sex partners increase the risk of HPV. Majority of the participants knew that sex before the age of 16 years increase the risk of HPV (58.4%). More than half of them have been vaccinated (51.5%). The paper concluded that promoting HPV and HPV vaccine campaigns all over Malaysia, especially in schools and through public campaigns, are crucial to raise the awareness and knowledge[16].

A questionaire which assessed the knowledge and attitudes of 449 young rural women in Malaysia towards HPV, HPV vaccination, and cervical cancer revealed extremely poor

knowledge emphasising the importance of educating rural residents on HPV. Acceptance of HPV vacination was significantly associated with knowledge of cervical screening and cervical cancer risk factors. Reasons for vaccine refusal include doubts about its safety and efficacy (27.4%); and the perceived embarrassment of receiving an STI vaccine (20.7%). Twenty percent perceived that they were not at risk for HPV infection. Most (90%) of the study participants reported that they required more information on the need for vaccination and who would need to be vaccinated (85.3%), as well as the potential risks or side effects of HPV vaccination (85.7%)[17]. Wong LP et al also revealed that 21.7% have heard about HPV and 10.3% have heard about the new HPV vaccine[18].

A cross-sectional study conducted among 300 Malaysian women in the obstetrics and gynaecology outpatient clinic in a selected hospital in Bangi, Selangor also found that educating the public on vaccination was highly recommended and the barriers to being vaccinated should be dealt with seriously. Only 12% to 25% correctly answered the questions but half of the respondents (53%) had a positive attitude toward HPV vaccination. Age, marital status, and level of education were significantly associated with this attitude[19].

A questionnaire was distributed among mothers in May 2007 in the University of Malaya Medical Centre, in Kuala Lumpur, Malaysia. A total of 362 mothers were included in the study. The study showed low knowledge of HPV and HPV vaccine. Although 57.3% were worried of the side effect, 65.7% accepted HPV vaccination for their daughters. Many of the mothers (83.9%) were unwilling to vaccinate their children if they had to pay, but if it was routine and freely available, acceptability rate increased to 97.8%[20].

Choice of HPV vaccine

The Malaysian government approved HPV vaccination program with three doses of HPV vaccine freely given to all 13-year-old girls from public or private schools on 21st February 2008; and the cabinet approved the budget on 19th August 2009[21]. World Health Organization (WHO) recommended that routine HPV vaccination be included in National Immunisation programmes.

Sharifah ezat compare and look at cost effectiveness of HPV vaccination in prevention of cervical cancer in Malaysia.This cross sectional economic burden study with 502 respondents were interviewed from six public Gynecology-Oncology hospitals in 2006-2009. In this study, cost effectiveness options were compared for three programs i.e. screening via Pap smear; modeling of HPV vaccination (Quadrivalent vaccine (QV) and Bivalent vaccine (BV) and combined strategy (screening plus vaccination). A scenario based sensitivity analysis was conducted using screening population coverages (40-80%) and costs of vaccines (RM 100-200/dose) were calculated. This study concluded vaccination increase life expectancy with better Quality of life (QOL) of women when cancer can be avoided. Cost effective strategies will include increasing the Pap smear coverage to 70% or higher. Since Malaysian women attitude regarding screening is doubtful , vaccination of young women is a more cost effective strategy against cervical cancers. The QV combined strategy was more cost effective (CE) than any method including Pap smear screening at high population coverage[3,22].

Secondary prevention of cervical cancer: Screening

Cervical cancer fulfills the criteria for an effective screening program because it is a major health problem, has a preinvasive stage, and is treatable at an early stage. Cervical cancer screening had shown to be a cost-effective mean of controlling the cancer and Pap smear screening is recognised for secondary prevention. The procedure is easy, and inexpensive with acceptable sensitivity and specificity.

Pap smear screening in Malaysia

In Malaysia, Pap smear screening started in the 1960s, and available for free in government health facilities since 1995. Many healthy life style campaign and publicity were made to promote this procedure, yet it did not achieve above 70-80% coverage of the population to reduce cervical cancer morbidity and mortality[23]. World Health Organization recommends that routine HPV vaccination should be included in national immunisation programmes if prevention of cervical cancer constitutes a public health priority, taking into account that vaccine introduction is programmatically feasible and financing can be secured[24]. It would be a great challenge for Malaysia to provide HPV vaccination for the entire adolescent populations. A cross-sectional study among 116 participants from Penang shows that only 42.2% have heard of the HPV vaccine and they were only willing to pay an average of RM96.7 for the full course of vaccine (actual price RM1200). This mean that screening will still remain an important strategy to combat cervical cancer and every effort is needed to ensure that the investments made in screening are effective and efficient[25].

Pap smear challenges

1. Coverage

Pap smear failed to achieve a broad coverage because it is only done opportunistically and poor awareness[23]. There were many studies addressing various issues of Pap smear. Although it is simple, cheap, safe and readily acceptable by Malaysian women, Pap smear is never popular.

Pap smear coverage was less than 2% in 1992, 3.5% in 1995, 6.2% in 1996 to 47.3% in 2006; this low coverage was caused by lackluster nationwide Pap smear campaign. The public is largely unaware of the benefits of screening[19,26]. Many papers highlighted that poor coverage was caused by human factors (i.e. the negative attitude of women and health care providers, including unfriendly service). Malaysian women still had poor knowledge and awareness of cervical cancer and screening [27,28].

An article on the challenges of cervical cancer screening in Malaysia revealed that the lack of manpower and facilities of health care system contributed to poor Pap smear coverage[23]. The average doctor to (total) population ratio in Malaysia is 1:1400. The public sector hospitals, which provide care for the majority (80-90%) of the population, have shortages of specialists, doctors, nurses, and technologists. Although the service in public hospitals is free, the long waiting time affected working womenPrivacy issue, screening test procedure, unsystematic approach of follow up and result notification, call-recall system and limited resources are other reasons for the poor coverage. The focus should be on policies, improving awareness and the screening infrastructure, and making the service better accessible to women[23].

A quality Pap smear should be taken from the transformation zone (an area between the old squamocolumnar junction and the new squamocolumnar junction), and sampling should include the ecto- and endocervix. This paper quoted several papers that showed 42.8% to 70.4% of the Pap smears done in Hospital Universiti Sains Malaysia and Kota Bharu hospital was not taken from the transformation zone of the cervix, where 95% of preinvasive lesions and cervical cancers occur[26].

Eleven policy makers and health care providers from the Ministry of Health in Malaysia from October 2009 to May 2010 were interviewed. Interviewees' perceptions were explored on current and organised cervical screening program based on their expertise and experience. In their opinion, the opportunistic cervical screening program failed to address the needs assessment of the program mainly in four aspects: 1) the receiver i.e. the women's needs, accessibility and affordability, 2) providing the providers need, 3) allocating resources, coverage and providers correct attitude. Poor quality health management in terms of leadership, motivation, communication, time management and resources planning, make the service seems unfriendly, leading to failure and missed opportunities for health care providers to screen women[29].

Pap smear subsequent visits or follow up

One of the approaches that fulfilled all these criteria is an organised cervical screening program with a systematic call, recall, follow-up and surveillance system .A prospective randomised controlled study of 250 women in Klang who attended cervical screening and had a normal Pap smear in the previous year, and were due for a repeat smear were recruited and randomly assigned to four different methods of recall for repeat smear. The rates of recall messages reaching the women were 79% when using letter, 87% with registered letter, 66% with SMS and 68% with phone calls. However, direct communication via phone call was better for recalls as the positive responses to recall by telephone call was 50.9% compared to 23.9% by letter, 23.0% by registered letter, and 32.9% by phone messages ($p<0.05$)[30].

2. Knowledge and attitude

Generally, women's attitudes and beliefs towards cervical cancer and the importance of screening test will affect their uptake and compliance of Pap smear. Studies in various group of women of different ages, involving rural, urban and even university students to assess knowledge on cervical cancer, Pap smear screening, HPV infection and HPV vaccination, in the hope that the results can be used to plan strategies to prevent a potentially preventable cervical cancer. Most studies showed that the lack of knowledge seriously impacted preventive measures and attitude (Table III).

Another questionnaire survey was done on 221 cervical cancer patients at eight hospitals with gynaeoncologist, in women aged 25-85 years. Majority (56.3%) had none or only primary education and 61.1% had a household income of RM1000 or less. Forty eight percent reported never having had a Pap smear, whereas 95% did not have a smear within the past three years. The main responses for not having had a Pap smear were "Never heard about it" (36.2%), "Shy" (10.4%), "Afraid to do it" (13.1%), "Think the test is not important"(8.1%) and "No encouragement from family" (4.5%). A large majority (95.9%) of the patients did not know the optimal interval. The survey concluded, a large number of cervical cancer patients had inadequate knowledge and had not had a Pap smear within three years preceding cancer development.27The result strongly showed the need for an effective cervical screening program which is proactive, consistent, and has a systematic follow up.

Publicity / Source of Information

In one study, more than half of the participants (57.7%) mentioned that doctors/hospitals/clinics were their sources of information on Pap smear test, and 43.7% got their information from printed media such as newspapers, magazine, books and flyers, and 31.7% from electronic media such as radio and television. The workplace was the least common source (12.7%)[30]. Despite the government posting open invitations and flyers advising free Pap smear in all government clinics and hospitals and other public places, radio and television and awareness programmes organised by MOH, 96% of patients reported not knowing the recommended Pap smear screening intervals[27].

In a study among rural Southeast Asian women, half (45.7%) have heard about the vaccine from friends. The second most common source of information was the public media (31.4% television, 20% newspapers, 17.1% radio, and 10.0% magazines)[34]. In a cross-sectional study conducted from July 2008 to September 2008 in Universiti Kebangsaan Malaysia, female students of two different faculties (pharmacy and allied health science), who participated reported receiving their information from the mass media (59.1%), through health education (48.6%), and from posters in University campus (39.4%)[37].

Barriers to cervical cancer prevention (HPV vaccination and pap smear barriers)

Psychosocial aspects

Both HPV vaccination and Pap smear had challenges and barriers as shown in various studies.

Malaysian men and women receive equal educational opportunities. In 2001, 95% of girls attended primary school, and 74% continued to secondary level. In 2005, 60% of women were part of the Malaysian labour force, primarily as sales workers and clerks, 27% were housewives, and 11% were in school. The unemployment rate among women has been below 4%, and fewer than 3% were hardcore poor. Among those married, 80-85% of their husbands were working, with an average monthly income of RM1500[23].

A bilingual questionnaire was sent to 1500 secondary school teachers from 20 urban schools in Malaysia; 1166 completed questionnaires were returned. From this group, 46.1% had never heard of HPV while 50.9% had never had a Pap smear. However, 73.8% have heard of the HPV vaccine with 75% of them agreeing to have it. Almost all (96%) considered themselves religious with 79.8% of them agreeing to have the vaccine. The highest factors that influence the teachers' decision to accept the vaccine was the safety of the vaccine (84%). Other factors that affected the acceptance were its risk (55.4%), effectiveness (55%) and doctor's advice (54.4%). Less than half (35.8%) considered the 'halal-ness' of the vaccine as a factor. Only 145 (12.7%) teachers felt they have enough knowledge to counsel parents, and 670 (58.7%) felt they did not have enough knowledge to do so. Majority of the teachers (n=1104; 96.8%) felt they needed to be given more information about the vaccine. Almost all (n=1077; 94.6%) of the teachers felt the government should provide more information to educate the public about cervical cancer and the vaccine. Many (n=822; 72.3%) teachers would encourage their students to take this vaccine and 781 (68.5%) teachers would be comfortable discussing the vaccine with their students/parents. Some (n=291; 25.5%) were unsure. This review concluded that a national school-based HPV immunisation program can be implemented effectively in a multiethnic, cultural and religious country despite limited knowledge of HPV-related pathology among teachers[38]. The focus group discussion of 47 participants also showed the same concern regarding safety and side effects, cost and Muslims concerned on the 'halalness' of the vaccine[39].

Al-Dubai et al in his paper looked into the barriers of HPV vaccine in 300 participants; 131 participants (43.7%) reported non awareness of the vaccine, 120 (40%) were concerned about the side effects of the HPV vaccine, 81 (27%) of the participants were afraid of needles and 71 (23.7%) of the participants were afraid of the social stigma related to HPV vaccination. Other barriers reported by the participants were 'no time to take the vaccine' (20.3%), 'vaccine was expensive' (15.7%), 'vaccine is not reachable' (11.7%), and'vaccination was not needed because they were not sexually active' (10.7%)[19].

Physicians' experiences in providing HPV immunisation were assessed by a mailed questionnaire and 41.4% responded. Malay Muslim physicians considered cultural sensitivity an issue when recommending HPV vaccines more than paediatricians and family physicians who were more likely to agree that acceptance is better if vaccines were recommended as prevention against cervical cancer rather than a sexually transmitted disease. Almost 70% had poor success in recommending HPV vaccines in their practice, with the majority of patients preferring to postpone immunisation. Physicians reported cultural disparities in vaccine uptake. Majority (95.5%) agreed that the HPV vaccines show great promise in cervical cancer prevention in the country. Many physician think (77.3%) cost is the commonest barrier for the vaccine acceptance followed by vaccine safety and effectiveness (13.8%). Many agreed (87.0%) that the Malaysian government should introduce a school based HPV vaccination program, and 74.5% agreed that HPV vaccination of all adolescent (girls) should be made mandatory[40].

The National Health Morbidity survey (NHMS) 2006 showed that the uptake of screening was particularly low among uneducated and low-income women. In 2007, 23% of cervical cancer patients who were surveyed had no education and 38% had only primary school education. Among these patients, 36% were not familiar with the screening test, 13% were afraid of taking it, 10% felt shy, and 3% did not have their screening because they could not find a female doctor. Improving screening coverage will remain an important strategy for combating cervical cancer in Malaysia.The focus should be on the policy-making context, improving awareness and the screening infrastructure, and making the service better accessible to women. Approaches to screening must look into these factors: women or population, provider, and program or service[23,28,41].

Twenty three medical students in Shah Alam, Malaysia discussed the procedure of the Pap smear test. They found the main barriers for not performing a Pap smear test is the lack of awareness 16 (70%), shyness 12 (52%) and the cost of the test 12 (52%). Another study cited the place of screening (15.5%) and the lack of time (11.3%), lack of a female doctor, the unavailability of a hospital or clinic close by, and the loss of virginity (2.1%) as barriers[31].

A study focused on the reasons for not screening given by different population subgroups . Indian women were the least likely to have had a Pap smear test (PST) and also the least likely to know the reasons why one should be screened. Malay women were less likely than Chinese women to have received a PST and were more likely to report embarrassment as the reason for not being tested. Urban women were less likely than rural women to have been tested and more likely to state the lack of time as the reason. These results suggest targeted interventions may be necessary to increase screening rates in Malaysia[42]. A possible solution may be to implement worksite cervical screening programs in which eligible women can be easily tracked and invited to have a Pap test[43].

Cervical cancer prevention cost

In Malaysia, only 10.3% (RM32 million) of the annual expenditure was allocated for Pap smear screening while 68% (RM167 million) were used for managing invasive cervical cancer. As the average monthly income for women is RM 500 ($125), this should be affordable since Pap smears were provided free in the public health care setting, and was between RM15 and RM 25 ($4.4 to $7.4) in private healthcare. Most Malaysians can easily access any healthcare provider by land, as 96% of the population live near paved land roads[23].

The introduction of widespread vaccination of females against HPV can potentially prevent 89% of cervical cancer cases at steady rate and this could potentially lead to an annual savings of over RM45 million in terms of HPV related treatment costs[3].

However, the ultimate success of HPV vaccines in reducing the incidence of cervical cancer will be dictated by its uptake and affordability since there are no health insurance coverage for HPV vaccines. Initially, two years after the first vaccine was released in Malaysia, the administration cost (actual cost of the HPV vaccine plus vaccine administration cost) was approximately RM400 per dose. Vaccination uptake of about 80% was required for "herd immunity." The median household monthly income in the present study population was RM1700. Their perceived savings per month was only RM205.69. The estimated cost of treatment was RM 1200 for the full course of vaccine and RM400 per injection, which is equal to almost 25% of their monthly income[28]. How many women can afford this?

DIAGNOSIS AND PATHOLOGY

HPV DNA testing

HPV DNA testing can be used as triage. This study compared the performance of nested MY/*GP* Polymerase Chain Reaction (PCR) and FDA approved-Hybrid Capture II (HClI) using clinical cervical scrapings from 40 patients. It was found that PCR was more sensitive (81.8%) compared to HCII (36.4%) in detecting HPV, but the specificity of HClI was much higher (96.6%) than PCR (58.6%). The Negative Predictive Value (NPV) of both the techniques were quite similar but Positive Predictive Value (PPV) of HClI was much higher (80.0%) compared to PCR (42.9%). While the HCII method showed good specificity for HPV detection, it is less sensitive than PCR[44]. Another study of 200 cervical swab samples by Chong also concluded that PCR was a reliable method to detect HPV[11]. Both studies concluded that PCR was an ideal and reliable method for detecting HPV from clinical samples.

A study that compared conventional Pap smear to split sampling using ThinPrep® smears, found split sampling from discarded sampling devices after conventional Pap smear retain adequate sample cells for diagnostic purposes[45].

Biomarkers in cervical cancer

Proteomics in cancer research may uncover potential biomarkers of cervical cancer. This study identified 18 proteins to be differentially expressed in the plasma of CIN 3 and SCC stage IV samples. The expression of cytokeratin 19 and tetranectin could be explored for further role in cervical cancer treatment and monitoring[46].

A clinicopathological immunohistochemistry study from 40 hysterectomy specimens to predict the aggressiveness of adenocarcinoma of cervix found that certain subset p21WAF1 expression is significantly associated with infiltration of the corpus and lymph node metastasis. p27Kip1 expression is significantly associated with lymph node invasion. The presence of lymph node metastasis is strongly associated when p16INK4a and p27Kip1 expressions are analysed in combination[47].

In a study of 109 cases of 29 low squamous intraepithelial lesion (LSIL), 27 high squamous intraepithelial lesion (HSIL) and 53 squamous cell carcinoma (SCC), diffuse continuous staining with p16INK4a involving >75% of LSIL or HSIL and SCC was noted in 1 (3.4%) LSIL, 24 (88.9%) HSIL, 46 (86.8%) SCC. The increased p16INK4a immunopositivity in HSIL and SCC appears in line with the integrated existence of the hrHPV and may provide more insightful information on risk of malignant transformation of cervical squamous intraepithelial lesions than mere hrHPV detection[48].

Immunohistochemical stain was used to study the involvement of Bcl-2 and Bax proteins in cervical carcinogenesis. Sixteen low grade (LSIL), 22 high grade (HSIL) squamous intraepithelial lesions, 28 invasive (13 stage I and 15 stage II-IV) squamous cell carcinoma (SCC) and 15 benign cervices were immunohistochemically studied. 4-µm sections of the cases were immunostained for Bcl-2 (Clone 124: Dako) and Bax (Dako) and staining intensity was rated as 1 (light), 2 (moderate) and 3 (strong) and percentage cellular staining as 0 (negative), 1 (1-25%), 2 (26-50%), 3 (51-75%) and 4 (>75%). Bcl-2 and Bax appeared to be upregulated at different stages of cervical carcinogenesis, Bcl-2 in HSIL and Bax after invasion. Intensification of staining of Bcl-2 at the basement membrane in some HSIL and SCC may augur for increased aggressiveness[49].

In a retrospective study on 61 cases of cervical neoplasms comprising 25 cases of CIN 3 and 36 SCC, all cases were evaluated by immunohistochemistry using Ki-67 and p53 monoclonal antibodies. Results showed that the differences of Ki-67 and p53 expression between CIN 3 and SCC were statistically significant. In conclusion, Ki-67 and p53 may serve as helpful adjuncts to routinely-stained histological sections in differentiating between CIN 3 and SCC[50].

An automated cervical pre-cancerous diagnostic system was proposed to be developed to reduce detection error due to poor diagnostic skill of the cytotechnologists and cytopathologists. The automatic diagnostic system used a new algorithm that is referred as region-growing- based features extraction (RGBFE) to extract the features of cervical cell (i.e. size of nucleus, size of cytoplasm, grey level of nucleus and grey level of cytoplasm). These features will then be fed into the H2MLP network, which classify the cervical cells into normal, LSIL or HSIL cell. The effectiveness of the proposed diagnostic system has been demonstrated empirically using 550 reported Pap smear tests[51].

In a study evaluating Fourier transform infrared (FTIR) spectroscopy as a new tool for screening of cervical cancer compared with cervical cytology (gold standard), a total of 800 cervical scrapings were taken by cytobrush and placed in ThinPrep medium. The samples were dried over infrared transparent matrix. Beams of infrared light were directed at the dried samples at frequency of 4000 to 400 cm-1. The absorption data were produced using a Spectrum BX II FTIR spectrometer. Data were compared with the reference absorption data of known samples using FTIR spectroscopy software. The results showed the sensitivity was 85%, specificity 91%, positive predictive value 19.5% and negative predictive value of 99.5%. This study suggests that FTIR spectroscopy could be used as an alternative method for screening for cervical cancer[52].

Role of imaging

This retrospective study that was aimed at evaluating the role of CT scan in predicting parametrium involvement in the early stage of cervical carcinoma was conducted in a Gynaecologic Oncology Centre, Hospital Alor Star from January 2004 till December 2008. All 104 patients with operable stage I and II cervical cancer had pelvic CT scan for evaluation of parametrium involvement. Parametrial streakiness or presence of infiltration suggested local invasion. Following radical hysterectomy, the specimens were sent for histological confirmation, and the correlation between CT scan finding and the histopathology result was studied. The result revealed the sensitivity and the specificity of CT scan in assessing parametrial involvement was 33.3% and 84.8%, respectively; indicating that CT scan had high specificity but low sensitivity in determining parametrial involvement in early stage of cervical cancer[53].

PRESENTATION AND TREATMENT

A questionnaire survey showed that 181/221 stages known cases, 76% of all cases were diagnosed in FIGO stage 2 or higher[23,27]. A USM study showed only 21% was diagnosed at stage 1 with majority of the cases were diagnosed at stage II onwards[54]. A retrospective study of 444 cervical cancer patients by Al Junid et al showed that 64.4% of cases were at either stage I or stage II disease and the occurrence of disease is strongly related to age[3]. This study showed that 34.5% of cases occurred in women aged 50-59 years old compared to NCR peak age 60-65 years old. Al Jashamy reported a retrospective study of 77 cervical cases from the histopathology laboratory of Ipoh hospital from 1st January, 2005 to 31st December, 2006This study showed cervical intraepithelial neoplasia (CIN) was found in 33/77 (42%) cases, cervical carcinoma in 12/77 (15.6 %)cases and metastatic squamous cell carcinoma in 10 /77 (13.0%) cases and adenocarcinoma in 13/77(17%)cases, CIN III accounting for 27%, and 5% each for CIN I, CIN II and CIN II-III. The highest rate for CIN was in the 41-50 year age group (43%) and the lowest rate was in the group aged 61-70 years (6%)55. Another study among 8 major hospitals showed squamous cell carcinoma was commonest (76.1%) and adenocarcinoma was 17.6%[27].

OUTCOME

A retrospective study by Hospital Universiti Sains Malaysia to determine the five-year survival rate among patients with cervical cancer who were treated, found that the overall five-year survival was 39.7% (median survival time of 40.8 months). The log-rank test showed that there were significant survival differences between the groups, stage at diagnosis (p=0.005); and primary treatment (p=0.0242). Late stage (III-IV) had the lowest survival (18.4%) compared to stage I (54.7%) and II (40.8%).The five-year survival was statistically significantly higher in patients who received surgery (52.6%) compared to non-surgical treatment[54].

In one study review of 55 patients with FIGO IB1 lymph nodes negative cervical cancer managed from 1997-1999 post radical hysterectomy, adjuvant RT was tailored according to the Gynecology Oncology (GOG) risk score. Radiotherapy (RT) was omitted for patients with risk score < 40 (RS); RS >40 to <120 were given modified field RT; and RS > 120 were given standard field RT. This study showed the adjuvant RT to patients with RS 120 significantly improved their five-year recurrence rate and disease free survival[56].

Table I: Human papillomavirus and cervical cancer in Malaysia

	Summary	HPV detection	HPV 16	HPV 18
Cheah PL[7]	a. 29 invasive squamous cell carcinoma (SCC) (between 1 January 1991 and 31 December 1992)	17/29 (58.6%)	16 (55.1%)	1 (3.44%)
	b. 43 cases invasive SCC (between 1 January 1995 and 31 December 2000)	38/43 (88.4%)	21/43 (48.8%)	5/43 (11.6%)
Al Junid[4]	Data on HPV type and distribution were derived from Castellsague et al. 2007 and the WHO/ICO Information Centre on HPV and Cervical Cancer		74.9% detected HPV 16/18	
Sharifah Noor Akmal *et al*[8]	UKMMC-38 abnormal smear	95% HR HPV detected	9 (23.7%)	2 (5.2%)

Table II: Prevalence of HPV infection from cervical swab samples

		HPV detection	HPV 16	HPV 18
Chong *et al*[11]	200 cervical swabs (180 qualified for PCR analysis) from March 2007 until September 2007 from women who underwent Pap smear screening from the Gynaecology and Obstetrics Clinics in several hospitals in Southern Selangor and Health clinics.	84/180(46.6%)	72 (85.7%)	6 (7.1%)
Tay[10]	2364 cervical swab samples from women attending obstetric and gynaecological clinics in Southern Malaysia and Singapore.	280 (24.3%) HPV detected	606 (25.6%) positive for high-risk HPV DNA	
	1153 liquid base and HPV DNA simultaneously –(HPV DNA genotypes not performed)	25 (8.9%) has intraepithelial abnormalities 3HSIL (1.08%)		

Sivanesaratnam, in his review of pregnant mothers with malignant conditions, recommended colposcopy and a directed biopsy if an abnormality was detected at colposcopy. If this reveals normal histology, re-evaluation can be done 8 weeks after delivery. If the biopsy reveals CIN, repeat cytology and colposcopy every 6±8 weeks, repeat biopsy if disease progressed. Performing a cold knife cervical cone procedure during pregnancy can cause significant morbidity, excessive cervical bleeding in 5±15% and up to 25% spontaneous abortion rate. For stage 1B and early 11A lesions, radical hysterectomy and pelvic lymphadenectomy are the preferred method of treatment. Before 20 weeks of pregnancy, radical surgery is carried out without delay with the foetus in utero. Between 20 and 32 weeks' gestation, treatment may be delayed until the foetus has better survival, delivered via a high classical caesarean section before radical hysterectomy, avoiding surgery on the lower uterine segment and cervix during delivery. Vaginal delivery carries the risk of the dissemination of malignant cells into lymphatics or vascular channels. Radiotherapy is an effective therapy for cervical cancer in pregnancy; the complications were similar to those in non-pregnant patients[57].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Cervical cancer is preventable. A combination of HPV vaccination and Pap smear screening programmmes was shown to be cost effective to prevent cervical cancer. There is a large gap in knowledge, attitude and practices among Malaysian women on cervical cancer screening. Even with adequate knowledge, this was not translated to practice. There is a need to individualise/ personalise the approach as well as continue with public awareness to ensure the women come for the screening and also has support to do so.

The psychosocial aspect and economic burden formed a difficult barrier that affect cervical cancer screening and prevention programme. There is a need to find alternative approach to increase Pap smear coverage to 70-80%, improve follow-up or explore possibilities of screening for HPV infection as an alternative or additional to Pap smear. There is a need to look into incorporating healthcare activities, i.e. promoting and performing Pap smear or HPV DNA cervical sampling during home visits or work place visits, having a dedicated team, and following the school health team system.

The study's recommendations that should be considered include promoting awareness among medical practitioners, and including men in promotional campaigns. Employees (including men) from both government and private sectors should be reminded about screening. Another recommendation is linking with data of the National Registration Department, so that women could be invited for screening at regular intervals after they reach the eligible age[12].

SECTION 3: FUTURE RESEARCH DIRECTION

There is a large gap in clinical research on cervical cancer. Areas such as cervical cancer presentation, investigations and managements could be studied. In terms of cervical cancer treatment, patients should have more options, for example radical surgery and adjuvant chemotherapy, for women who refused radiotherapy. The taboos of modern treatment and belief in traditional complementary medicine can be explored to curb the misconception of cervical cancer treatment, as there were patients who, although were diagnosed early, delayed treatment for traditional options and only presented to hospital at an advanced stage; thus leading to poorer prognosis. There is also a need to explore other screening methods such as cervical smear self sampling for HPV DNA screening that could possibly increase screening coverage.

Table III: Summary of some of the studies on knowledge and attitude of Pap smear screening

Studies	Summary	Results	Reasons
Cross sectional descriptive study[31]	A convenience sample of 142 women aged 18 to 70 years at Tengku Ampuan Rahimah Hospital, Klang, in Selangor, Malaysia. Data collection in September 2011 till January 2012.	72.5% had heard about Pap smear test 57.7% got their information from doctors, 43% from printed material, and 31% from the media.	The barriers to Pap smear test include place of screening (15.5%) which was mentioned as the main barrier, followed by the lack of time (11.3%).
Focus group discussion-perception of medical students[32]	23 medical students from International Medical School, Management and Science University, Shah Alam.		Main barriers for women are the lack of awareness (n=16; 70%), followed by shyness (n=12;52%) and the cost of the test (n=12;52%).
Cross-sectional design[33]	A total of 287 female university students (response rate of 95.9%) from the Management and Science University (MSU), Shah Alam.	61-77% provided the correct answer.	The most common barriers were the worrying about the test (95.8%), followed by lack of encouragement or information from healthcare workers (61.2%).
A cross-sectional household survey[34]	231 women in Petaling Jaya city in 2007. The association between risk perceptions of cervical cancer and screening practice.	14% have had Pap test Women had limited knowledge on the established risks for cervical cancer.	Majority perceived certain types of food (instant noodles or chemical substances embedded in foods); smoking; taking drugs; family history; side effects of hormone replacement therapy; adultery; cleanliness of both husband and wife; environmental or air pollution; use of public toilets; poor feminine hygiene; contraceptive use, unclean abortion; frequent sex' and sexual activities against the norm of religion as risks for cervical cancer.
A questionnaire Survey[35]	403 female teachers from 40 public secondary schools in Malaysia selected by cluster random sampling Jan-March 2010.	62% never had Pap smear. This means that regardless of a participant's educational level and employment status, school teachers also perceived Pap smear screening test negatively, consistent with most of the studies which cited factors such as embarrassment, shyness, reluctance, and time-consuming service.	Reasons: shy, afraid, don't know, no information, no awareness 59-74%.
Cross sectional study[36]	280 women from Mukim Jaya Setia Kota Bharu, Kelantan.	51.4 % had Pap smear screening, Impact of Health care worker campaigns.	3 main reasons for not screening were unawareness (36.7%), unnecessary (23.7%), and lack of time (13.7%).

ACKNOWLEDGEMENT

I would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper. I wish to thank the Clinical Research Centre team for its contribution and support.

REFERENCES

1. Malaysian National Cancer Registry Report (2003). Ministry of Health, Malaysia.
2. Devi Beena CR, Tang TS, Gerard LC. Preliminary results from the pilot study on the National Cancer Patient Registry--Cervical Cancer. Med J Malaysia 2008; 63 Suppl C: 63-65.
3. Sharifa Ezat WP, Syed Aljunid. Cost-effectiveness of HPV vaccination in the prevention of cervical cancer in Malaysia. Asian Pac J Cancer Prev 2010; 11(1): 79-90.
4 Syed M Aljunid, Zafar A, Saperi S, *et al.* Burden of disease associated with cervical cancer in Malaysia and potential costs and consequences of HPV vaccination. Asian Pac J Cancer Prev 2010; 11(6): 1551-1559.
5. Shanthi V, Majdah M, Syed Aljunid, *et al.* Cervical cancer in Malaysia: can we improve our screening and preventive practice? BMC Public Health 2012; 12(Suppl 2): A17.
6. Gravitt PE. The known unknowns of HPV natural history. J Clin Invest 2011; 121(12): 4593-4599.
7. Cheah PL, Looi LM, Sivanesaratnam V. Human papillomavirus in cervical cancers of Malaysians. J Obstet Gynaecol Res 2011; 37(6): 489-495.
8. Sharifah Noor Akmal, Seeni A, Nurismah M, *et al.* Prevalence of human papillomavirus in abnormal cervical smears in Malaysian patients. Asian Pac J Cancer Prev 2009; 10(2): 303-306.
9. Quek SC, Lim BK, Domingo E, *et al.* Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical intraepithelial neoplasia across 5 countries in Asia. Int J Gynecol Cancer 2013; 23(1): 148-156.
10. Tay SK, Tay YK. The prevalence and significance of high-risk human papillomavirus DNA test in southern Malaysia and Singapore. Aust N Z J Obstet Gynaecol 2009; 49(3): 323-327.
11. Chong PP, Asyikin N, Rusinahayati M, *et al.* High prevalence of human papillomavirus DNA detected in cervical swabs from women in southern Selangor, Malaysia. Asian Pac J Cancer Prev 2010; 11(6): 1645-1651.

12. Hesham R, Syarif Husin L, Kiat AN. Knowledge of cervical cancer and acceptance of HPV vaccination among secondary school students in Sarawak, Malaysia. Asian Pac J Cancer Prev 2011; 12(7): 1837-1841.
13. Rashwan H, Ishak I, Sawalludin N. Knowledge and views of secondary school students in Kuala Lumpur on cervical cancer and its prevention. Asian Pac J Cancer Prev 2013; 14(4): 2545-2549.
14. Al-Naggar RA, Bobryshev YV, Al-Jashamy K, *et al.* Practice of HPV vaccine and associated factors among school girls in Melaka, Malaysia. Asian Pac J Cancer Prev 2012; 13(8): 3835-3840.
15. Hesham HR, Nur Zakiah, N Mohd Saat, Dahlia Nadira AM. Knowledge, attitude and practice of malaysian medical and pharmacy students towards human papillomavirus vaccination. Asian Pac J Cancer Prev 2012; 13(5) :2279-2283.
16. Al-Naggar RA, Bobryshev YV. Practice towards human papillomavirus vaccines among Malaysian women: a survey of a general youth population. Asian Pac J Cancer Prev 2011; 12(8): 2045-2049.
17. Wong LP. Knowledge and attitudes about HPV infection, HPV vaccination, and cervical cancer among rural southeast Asian women. Int J Behav Med 2011; 18(2): 105-111.
18. Wong LP, Sam IC. Ethnically diverse female university students' knowledge and attitudes toward human papillomavirus (HPV), HPV vaccination and cervical cancer. Eur J Obstet Gynecol Reprod Biol 2010; 148(1): 90-95.
19. Al-Dubai SAR, Alshagga MA, Al-Naggar RA, *et al.* Knowledge, attitudes and barriers for human papilloma virus (HPV) vaccines among Malaysian women. Asian Pac J Cancer Prev 2010; 11(4): 887-892.
20. Sam IC, Wong LP, Rampal S, *et al.* Maternal acceptance of human papillomavirus vaccine in Malaysia. J Adolesc Health 2009; 44(6): 610-612.
21. Saidatul Norbaya Buang, Introduction of National HPV immunization program: sharing Malaysia Experience presented at Global Meeting on cervical cancer prevention programme 29 Nov-2 Disember 2010.
22. Sharifa Ezat WP, Syed Aljunid. Comparative cost-effectiveness of HPV vaccines in the prevention of cervical cancer in Malaysia. Asian Pac J Cancer Prev 2010; 11(4): 943-951.
23. Nor Hayati O, Rebolj M. Challenges to cervical screening in a developing country: the case of Malaysia. Asian Pac J Cancer Prev 2009; 10(5): 747-752.
24. Woo YL, Omar SZ. Human papillomavirus vaccination in the resourced and resource-constrained world. Best Pract Res Clin Obstet Gynaecol 2011; 25(5): 597-603.
25. Khoo CL, Teoh S, Abdul Rashid Khan, *et al.* Awareness of cervical cancer and HPV vaccination and its affordability among rural folks in Penang Malaysia. Asian Pac J Cancer Prev 2011; 12(6): 1429-1433.
26. Nor Hayati O. Cancer of the cervix - from bleak past to bright future; a review, with an emphasis on cancer of the cervix in malaysia. Malays J Med Sci 2003; 10(1): 13-26.
27. Nor Hayati O, Beena CD, Halimah Y. Cervical cancer screening: patients understanding in major hospitals in Malaysia. Asian Pac J Cancer Prev 2009; 10(4): 569-574.
28. Wong LP, Wong YL, Low WY, *et al.* Cervical cancer screening attitudes and beliefs of Malaysian women who have never had a pap smear: a qualitative study. Int J Behav Med 2008; 15(4): 289-292.
29. Fauziah A, Su TT. Enhancement of the cervical cancer screening program in Malaysia: a qualitative study. Asian Pac J Cancer Prev 2010; 11(5): 1359-1366.
30. Rima Marhayu AR, Majdah M, Zaleha AH, *et al.* Is the phone call the most effective method for recall in cervical cancer screening? - results from a randomised control trial. Asian Pac J Cancer Prev 2013; 14(10): 5901-5904.
31. Al-Naggar, Practice and Barriers towards Pap Smear test from a public Hospital in Malaysia. J Community Med Health Edu 2012, 2:3.
32. Al-Naggar RA, Zaleha MI. Perception and opinion of medical students about Pap smear test: a qualitative study. Asian Pac J Cancer Prev 2010; 11(2): 435-440.
33. Al-Naggar RA, Low WY, Zaleha MI. Knowledge and barriers towards cervical cancer screening among young women in Malaysia. Asian Pac J Cancer Prev 2010; 11(4): 867-873.
34. Wong YL, Chinna K, Mariapun J, *et al.* Correlates between risk perceptions of cervical cancer and screening practice. Prev Med 2013; 57 Suppl: S24-6.
35. Fauziah A, Norlaili AA, Su TT. Factors related to poor practice of Pap smear screening among secondary school teachers in Malaysia. Asian Pac J Cancer Prev 2011; 12(5): 1347-1352.
36. Asmani AR , Aziah D Pap smear practice among women in Mukim Jaya Setia, Kelantan. Malaysia Journal of Public Health Medicine 2007,vol 7 (1): 20-24.
37. Tan YY, Hesham R, Qodriyah HM. Knowledge and attitude of university students in health sciences on the prevention of cervical cancer. Med J Malaysia 2010; 65(1): 53-57.
38. Woo YL, Sharina MR, Chong KR, *et al.* Does the success of a school-based HPV vaccine programme depend on teachers' knowledge and religion? -- A survey in a multicultural society. Asian Pac J Cancer Prev 2012; 13(9): 4651-4654.
39. Wong LP. Preventing cervical cancer through human papillomavirus vaccination: perspective from focus groups. J Low Genit Tract Dis 2009; 13(2): 85-93.
40. Wong LP. Physicians' experiences with HPV vaccine delivery: evidence from developing country with multiethnic populations. Vaccine 2009; 27(10): 1622-1627.
41. Mohd Rushdan MN. Current status and future direction of cervical cancer prevention program in Malaysia. 2008.
42. Richard A. Dunn , Andrew K.G. Tan Cervical cancer screening in Malaysia: Are targeted interventions necessary?Social Science & Medicine 71 (2010) 1089-1093.
43. Fauziah Abdullah, Michael O'Rorke, Liam Murray, and Tin Tin Su. Evaluation of a Worksite Cervical Screening Initiative to Increase Pap Smear Uptake in Malaysia: A Cluster Randomized Controlled Trial : BioMed Research InternationalVolume 2013 (2013), Article ID 572126, 7 pages http://dx.doi.org/10.1155/2013/572126
44. Saini R, Shen TH, Othman NH, *et al.* Evaluation of polymerase chain reaction (PCR) method and hybrid capture II (HCII) assay for the detection of human papillomavirus in cervical scrapings. Med J Malaysia 2007; 62(3): 206-209.
45. Norodiyah O, Othman NH. Adequacy of cellular material in split-sampling of cervical scrapings for routine cancer screening: an analysis of 702 smears. Malays J Pathol 2012; 34(2): 115-121.
46. Looi ML, Karsani SA, Rahman MA, *et al.* Plasma proteome analysis of cervical intraepithelial neoplasia and cervical squamous cell carcinoma. J Biosci 2009; 34(6): 917-925.
47. Farveen Marican AB, Nik Raihan NM, Nor Hayati O. Clinicopathological comparison of adenocarcinoma of cervix and endometrium using cell cycle markers: P16ink4a, P21waf1, and p27Kip1 on 132 cancers. Infect Dis Obstet Gynecol 2011; 2011: 857851.
48. Cheah PL, Looi LM, KH Teoh, KS Mun, Abdul Rahman Nazarina p16INK4a is a Useful Marker of Human Papillomavirus Integration and Risk Stratification Asian Pacific J Cancer Prev, 13, 469-472)
49. Cheah PL, Looi LM. Significance of Bcl-2 and Bax proteins in cervical carcinogenesis: an immunohistochemical study in squamous cell carcinoma and squamous intraepithelial lesions. Malays J Pathol 2006; 28(1): 1-5.
50. Tan GC, Sharifah Noor Akmal, Shiran MS, *et al.* Utility of Ki-67 and p53 in distinguishing cervical intraepithelial neoplasia 3 from squamous cell carcinoma of the cervix. Asian Pac J Cancer Prev 2008; 9(4): 781-784.
51. Mat-Isa NA, Mashor MY, Othman NH. An automated cervical pre-cancerous diagnostic system. Artif Intell Med 2008; 42(1): 1-11.
52. Shady G El –Tawil, Rohana A, Zaki N.Muhamed , Norhayati O. Comparative study between Pap smear cytology and FTIR spectroscopy:a new tool for screening for cervical cancer, Pathology (October 2008) 40(6), pp. 600–603.
53. Mohamad Nasir S, Nazimah I, Rushdan MN. The Role of Computed Tomography (CT) Scan in Assessment of the Parametrial Involvement in Early Stage Cervical Carcinoma. Journal of Surgical Academia 2012; 2(1): 14.
54. Nuradhiathy AR, Khattak M, Yong Zulina Z, *et al.* Estimating the five-year survival of cervical cancer patients treated in hospital universiti sains malaysia. Asian Pac J Cancer Prev 2013; 14(2): 825-828.
55. Al-Jashamy K, Al-Naggar RA, San P, *et al.* Histopathological findings for cervical lesions in Malaysian women. Asian Pac J Cancer Prev 2009; 10(6): 1159-1162.
56. Rushdan MN, Tay EH, Khoo-Tan HS, *et al.* Tailoring the field and indication of adjuvant pelvic radiation for patients with FIGO stage Ib lymph nodes-negative cervical carcinoma following radical surgery based on the GOG score--a pilot study. Ann Acad Med Singapore 2004; 33(4): 467-472.
57. Sivanesaratnam V. Management of the pregnant mother with malignant conditions. Curr Opin Obstet Gynecol 2001; 13(2): 121-125.