UNIT NO. 5

HPV VACCINE – A PARADIGM SHIFT IN THE PREVENTION OF CERVICAL CANCER

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ABSTRACT

The role of HPV in cervical cancer development is well proven[7,8]. Epidemiological studies showed that the odd ratio of cervical cancer among women with persistent HPV-16 infection is more than 100, compared to an odd ratio of 15 with cigarette smoking in lung cancer. Most HPV infection in men and women occurs soon after sexual debut[10]. The impact of HPV vaccines with either Gardasil or Cervarix is greatest if the vaccination is administered before the woman acquires the HPV infection. In all practical purposes, this means that the vaccine has to be given prior to a girl's sexual debut, that is, in the early teens. Widespread immunisation with these vaccines in girls before sexual debut can significantly prevent persistent infection by these HPV subtypes and their related pre-cancers and cancer. The change in the focus of attention – from secondary prevention of cervical cancer among mature women after 25 years old to prophylactic vaccination of young girls in the teens – in preventing development of the precursors of cervical cancer is indeed a major paradigm shift in the effort to prevent and to reduce the burden of cervical cancer in the 21st century.

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INTRODUCTION

Cervical cancer is the second commonest cancer in women world-wide. Every year, approximately 500,000 women are diagnosed with cervical cancer and 270,000 women die from it. It is projected that more than one million women will be suffering from it every year by 2050[1-3]. More than 80% of these women are from the developing countries, 105,000 cases in Latin America, 140,000 cases in Africa, 310,000 cases in Asia, and 110,000 cases in north America and Europe.

CURRENT CERVICAL CANCER PREVENTION PROGRAMME

The technique for screening of cervical cancer and its precursor lesions or intraepithelial neoplasia (CIN) by vaginal exfoliated cell cytology was first described by Dr George Papanicolaou in New York in 1923. The adoption of "Pap smear screening programme" in developed countries has evolved into organised public health scheme in the last 50 years. The programme typically consists of a well-established infrastructure to register women at risk and runs a call-and-recall system aiming to screen 80% or more of the women from 25 years to 65 years old at three to five yearly interval. Women with high-grade or repeatedly low-grade cytological abnormalities are then referred to specialised clinics for colposcopy for further evaluation and biopsy for histological diagnosis of the cervical lesions (Figure 1). In ideal situation, colposcopy, cytology and histological services require accreditation to maintain a high standard of practice. Women treated for CIN undergo long term followed up cytological surveillance. National statistics from a number of countries have demonstrated a very dramatic downward trend in the incidence and mortality rate from cervical cancer (Table 1).

An organised Pap smear screening programme for cervical cancer is expensive financially and in medical manpower. It is beyond the reach of most, if not all developing countries. Not surprisingly, the incidence and mortality rate of cervical cancer show a widening gap between developed and developing worlds. Even in developed countries, it has not been able to achieve screening of the whole population of women at risk.

Pap smear screening is not able to prevent development of cervical neoplasia, though adequate treatment of CIN prevents development of invasive cervical cancer. In this context, Pap smear screening programme is a secondary prevention programme for cervical cancer. There is a growing concern among health providers and policy makers on the cost and morbidity of treatment of CIN, and emotional and pyscho-sexual morbidity of having abnormal Pap smears associated with secondary prevention[4-6].

Figure 1. Algorithm for management of abnormal Pap smears

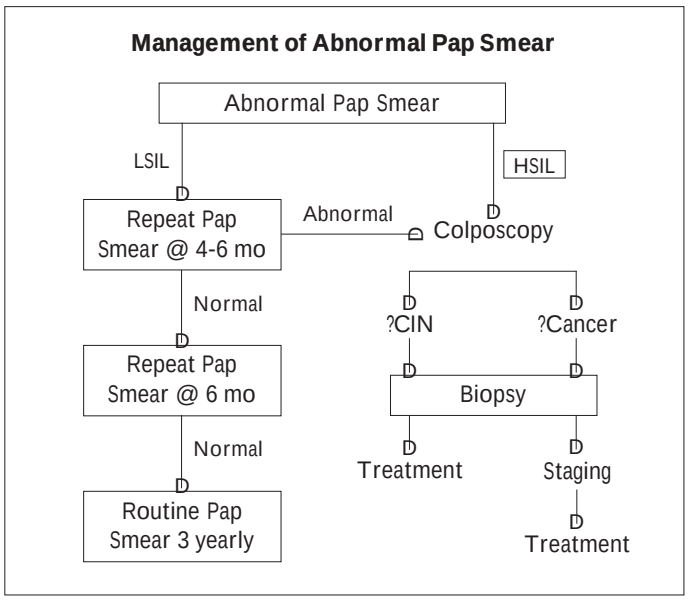

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Table 1. Incidents of adverse effects of Gardasil and placebo injections

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N=5088) %	Placebo (N=3790) %	Placebo combined the aluminium and saline placebo group		(Saline) Placebo (N=320) Incidents
Pyrexia	13.0%	11.2%	=	424.5	35.7
Nausea	6.7%	6.6%	=	250.1	21.0
Nasopharyngtis	6.4%	6.4%	=	242.6	20.4
Dizziness	4.0%	3.7%	=	140.2	11.8
Diarrheoa	3.6%	3.5%	=	132.7	11.1
Vomiting	2.4%	1.9%	=	72.0	6.0
Myalgia	2.0%	2.0%	=	75.8	6.4
Cough	2.0%	1.5%	=	56.9	4.8
Toothache	1.5%	1.4%	=	53.1	4.5
Upper respiratory tract infection	1.5%	1.5%	=	56.9	4.8
Malaise	1.4%	1.2%	=	45.5	3.8
Arthralgia	1.2%	0.9%	=	34.1	2.9
Insomnia	1.2%	0.9%	=	34.1	2.9
Nasal Congestion	1.1%	0.9%	=	34.1	2.9

HPV IN CERVICAL CANCER DEVELOPMENT

Human papillomavirus (HPV) is a large family of small DNA viruses. HPV infection has a predilection for epithelium, particularly the squamous epithelium. Of the 200 family members, 25 HPV subtypes infect the human genital tract. Only 13-15 subtypes are associated with cervical cancer and are aptly known as the high-risk oncogenic HPV subtypes. The others may be associated with genital warts or cervical inflammation or low-grade CIN are collectively known as the low-risk HPVs. There is a remarkable consistency across the globe in the frequency of distribution of the most prevalent high-risk HPV subtypes in cervical cancer: 53.5% HPV-16, 17.2 % HPV-18, 6.9% HPV-45 and 2.6% HPV-31 (Figure 2).

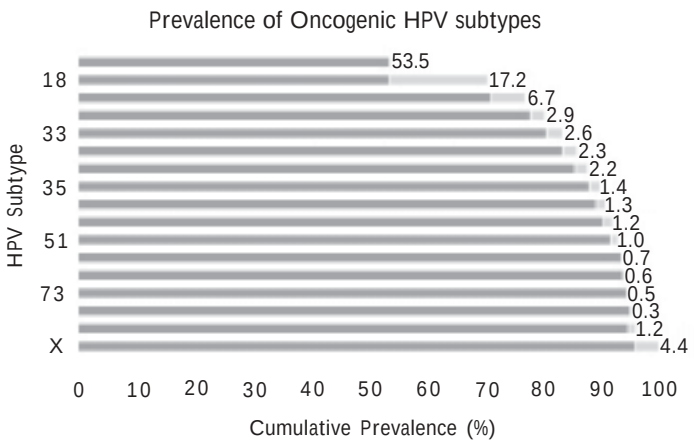
The role of HPV in cervical cancer development is well proven[7,8]. Epidemiological studies showed that the odd ratio of cervical cancer among women with persistent HPV-16 infection is more than 100, compared to an odd ratio of 15 with cigarette smoking in lung cancer. In high-grade CIN and invasive cancer, HPV DNA is integrated into the host genome. Molecular studies have identified the roles of HPV-16 E6 and E7 oncoproteins in neoplastic transformation of HPV-16 or HPV-18 infected cells. E6 oncoprotein binds to intracellular p53 protein and promotes p53 degradation. E7 oncoprotein exerts its oncogenic effect through its binding to Rb protein and drives the cell into active dividing cell cycle. While high-risk oncogenic HPV infection is a necessary agent in cervical cancer development, it is not able to cause cancer on its own. Some other factors are needed as co-factors in the development of cervical cancer.

It is important to recognise that cervical cancer is a rare outcome of HPV infection. Studies of natural history of HPV infection show that while 10% of women infected with high-risk HPV develop cytological abnormalities, only 0.8% develop CIN 3 and 0.16% develop cancer[8,9].

HPV transmission

HPV can be transmitted easily through skin-to-skin genital contact, with or without penetrative intercourse[9]. Most HPV infection in men and women occurs soon after sexual debut[10]. The prevalence of oncogenic HPV infection rises rapidly to reach 20% for the 25 year-olds and, more than 50% of sexually active women would have been infected by it during their life

Figure 2. Prevalence of Oncogenic HPV subtypes in Cervical cancer



time[1,3]. As HPV infection tends to involve a wide area of the ano-genital region, condom only provides a limited protection, if at all, in sexual transmission of HPV[9].

HPV can display a long latent phase of several years before clinical manifestation. The detection of HPV-16 antibodies in the serum from children before sexual debut and in the prepuces of young children undergoing circumcision suggest that HPV infection may be acquired in some cases through vertical transmission from mother to the child[11].

HPV immunology

Host immune reactions are important for natural regression of HPV infection. It has long been recognised that regression of cutaneous warts is associated with intense infiltration of lymphocytes at the vicinity of the warts. However, the host humoral immune response to natural HPV infection is subdued. Naturally occurring anti-HPV antibodies are detectable in low level in the serum of some people with previous HPV infection. This is explainable by the fact that HPV readily evades the host immune system through two mechanisms. Firstly, as an epitheliotrophic virus, HPV infects cervical epithelium without assessing the blood circulation. HPV virions are assembled in mature epithelial cells at he surface of the epithelium and are discharged into the vagina lumen instead of blood circulation. Secondly, HPV interferes with interferon release in the infected epithelium and suppresses the antigen presenting Langerhans cells in cervical mucosa[12,13]. The resultant mucosal immuno-suppression favours persistence of HPV infection, a state necessary for the virus to exert its neoplastic transforming property.

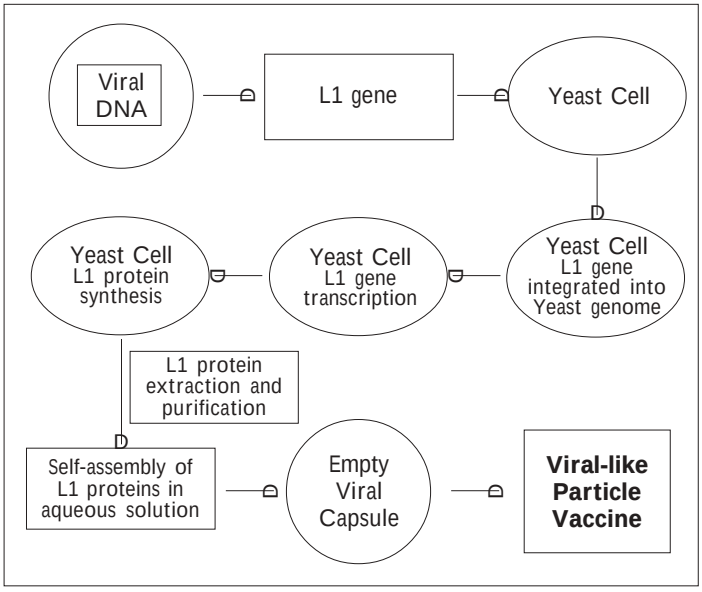
Nevertheless, natural regression of cervical HPV infection occurs in the majority of women. It has been found that 50% of young women clears their oncogenic HPV infection within 12 months and, cumulatively, 80% of them do so within three years.

HPV L1-particle vaccines

HPV is a simple DNA virus. The viral genome consists seven early genes (E1 – E7) and two late genes (L1 – L2). The early genes regulate viral DNA replication and growth control while the late genes encode the viral capsid proteins. The discovery that L1 proteins synthesised by genetic engineering technique undergo self-assembly in aqueous solution into viral like particles opens a new floodgate for studies of HPV immunology. It is found that these viral-like particles share the same morphology and immunological properties as the natural HPV viral particles[14]. It permits vaccination with a "false" virus which carries no biological risk of viral activation or viral cytopathic effects in the host.

HPV L1 gene is highly conserved in the evolution of the virus. Variation in L1 gene forms the basis for classification of HPV subtypes. L1 viral-like particles are therefore subtype specific. L1 viral-like particles can be synthesised for different HPV subtypes. In phase III clinical trials, the quadrivalent

Figure 3. Synthesis of L1-Viral-like Particles



HPV vaccine (Gardasil) from Merck contains viral-like particles for HPV-6, HPV-11, HPV-16 and HPV-18, whereas the bivalent HPV vaccine (Cervarix) from GlaxoSmithkline contains viral-like particles for HPV-16 and HPV-18. HPV-6 and HPV-11 are the subtypes responsible for genital warts. HPV-16 and HPV-18 are responsible for 71% of all cervical cancers.

L1 capsid proteins are arranged in pentamers which make up the rosette-like external structure of HPV virion. The host immune reactions to epitopes on these molecules can be enhanced with other molecules known as immune adjuvants. Immunological enhancing effect seems to vary with different adjuvants. The quadrivalent HPV vaccine (Gardasil) from Merck uses aluminium hydroxide while the adjuvant used in the bivalent HPV vaccine (Cervarix) from GlaxoSmithkline is ASO4, a compound comprising 500 mg of aluminium hydroxide and 50 mg of 3-deacylated monophosphoryl lipid A.

Intramuscular injections of these vaccines in three separate doses over a span of six months have demonstrated a seroconversion rate of 100% in phase II clinical trials of Gardasil and Cervarix[15,16]. The geometric mean level of IgG antibodies in the serum of vaccinated women was 17-fold higher than that found in natural HPV-16 infection and 18-fold higher than natural HPV-18 infection. These levels of antibody titre were maintained up to a follow-up period of 45 months. These immunoglobulin-G antibodies are secreted into cervical mucus and, by neutralising any free HPV virions, offers an opportunity as a first-line defence against viral infection of the epithelial cells. The neutralising antibodies also prevent these HPV infections when the targeted HPV subtypes gain access to the blood circulation through micro-traumas on the vulva, vagina and other ano-genital cutaneous tissue with no natural body fluid secretions.

PRIMARY PREVENTION OF CERVICAL CANCER

The final results of two phase III prospective, double-blind, placebo-controlled randomised clinical trials with Gardasil on young women between 15 to 26 years old from 29 countries were recently reported[17,18]. After an average follow-up of three years, no cases of HPV 6-, 11-, 16- and 18-related VIN 1-3, VaIN 1-3 and genital warts were observed in the vaccine group (n=2,261) compared to 60 cases in the placebo group (n=2,279). Gardasil was 100% protective for these diseases. Results from the second trial showed that GARDASIL was 98 percent effective in preventing high-grade cervical pre-cancers associated with HPV types 16 and 18; one case of CIN 3 was observed in the vaccine group (n=5,305) compared to 42 cases in the placebo group (n=5,260). Gardasil did not alter the course of HPV lesions in women who had HPV infection at the time vaccination was carried out.

In one of the largest Phase III clinical studies involving 18,644 women aged 15 to 25 from 14 countries across Europe, Asia-Pacific and Latin and North America, Cervarix vaccine was reported to have shown 100 percent effective in preventing persistent HPV-16 and HPV-18 infection and their related precancerous lesions[19]. Furthermore, a significant cross-protection against six-month persistent infection caused by virus types 45, 31 and 52 was observed. Together with virus types 16 and 18, these types are collectively responsible for more than 80 percent of cervical cancer cases globally.

Both Gardasil and Cervarix vaccinations are well tolerated. The most significant adverse effect of vaccination is a mild to moderately severe pain at the site of injection of the vaccine in almost 90% of women. Other adverse reactions are uncommon but include pyrexia (13%), nausea (6%), nasopharyngitis (6%), Dizziness (4%), diarrhoea (3.6%), myalgia (2%), malaise (1.4%), Arthralgia (1.2%) and insomnia (1.2%). The incidence of these adverse effects of the vaccine was the same as in the group of women receiving placebo injections.

The extremely high efficacy of these recombinant vaccines in preventing persistent HPV-16 and HPV-18 infection and their related high grade pre-cancers of the cervix supports the rationale of primary prophylaxis of cervical infection by these two HPV subtypes, and in the case of Cervarix, also a significant protection against HPV-33, HPV-45 and HPV-52. It is estimated that the vaccination should reduce the incidence of low grade cytological abnormalities classified as "atypical squamous cells of undetermined significance" or ASCUS by 20-40 % and low-grade squamous intraepithelial lesions (LSIL) by 35% within months following the vaccination. The incidence of high-grade squamous intraepithelial lesions (LSIL) and invasive cancer should be reduced by 65% and 80% respectively in the years and decades after the vaccination. The effectiveness of preventing cervical cancer of this magnitude well surpasses the success of a well-organised "Pap Smear Screening Programme" over the last five decades. More importantly, the cost in treating the pre-invasive lesions can be greatly reduced.

The impact of HPV vaccines with either Gardasil or Cervarix is greatest if the vaccination is administered before the woman acquires the HPV infection. In all practical purposes, this means that the vaccine has to be given prior to a girl's sexual debut, that is, in the early teens.

The change in the focus of attention – from secondary prevention of cervical cancer among mature women after 25 years old to prophylactic vaccination of young girls in the teens – in preventing development of the precursors of cervical cancer is indeed a major paradigm shift in the effort to prevent and to reduce the burden of cervical cancer in the 21st century.

CONCLUSIONS

Cervical cancer contributes significantly to the global cancer burden. HPV-16 and HPV-18 are the most prevalent oncogenic HPV subtypes responsible for more than 70% of cervical cancers. Recombinant bivalent and quadrivalent viral-like particle vaccines, Cervarix and Gardasil, have been shown in large clinical trials to prevent cervical infection by these HPVs. Widespread immunisation with these vaccines in girls before sexual debut can significantly prevent persistent infection by these HPV subtypes and their related pre-cancers and cancer.

Table 2. Cervical Cancer Occurs Despite Established Screening Programs Example of Europe

Country	Recommendation		% regularly screened	Per100,000 women	
	Age range(years)	Interval(years)		Incidence	Mortality
Finland	30-60	5	93	6.2	3.0
England	25-64	3-5	83	10.5	5.1
Sweden	23-60	3	83	10.9	5.6
Belgium	25-64	3	78	12.8	6.2
The Netherlands	30-60	5	77	9.4	3.8
France	25-65	3	69	13.6	5.4

REFERENCES

1. Ferlay, J., Bray, F., Sankila, R., Parkin, D.M., EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union in 1998, version 5.0. IARC CancerBase No. 4. Lyon, IARCPress, 1999.
2. Max ParkinDM, Bray F, Ferlay J,Pisani P. Global Cancer Statistics, 2002.CA Cancer J Clin 2005; 55:74-108.
3. Global Cancer Rates Could Increase by 50% to 15 Million by 2020. IARC 2004.
4. Basen-Engquist K, Paskett ED, Busaglo J, Miller SM, Schover L, Wenzel LB, Bodurka DC. Cervical cancer. *Cancer* 2003; 98: 2009-14.
5. de Groot JM, Mah K, Fyles A, Winton S, Greenwood S, Depetrillo AD, Devins GM. The psychosocial impact of cervical cancer among affected women and their partners. *Int J Gynecol Cancer* 2005; 15: 918-25.
6. Wenzel L, Dogan-Ates A, Habbal R et al. Defining and measuring reproductive concerns of female cancer survivors.J *Natl Cancer Inst Monogr* 2005; 94-8;
7. Wallboomers JH, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, PetoJ, Meijer CJ, Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide.J *Pathol* 1999; 189: 12-9.
8. Bosch FX, Lorincz A, Munoz N, Meijeer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer.J *Clin Pathol* 2002; 55: 244-65.
9. McIntosh N. JHPIEGO strategy paper. 2000; 2.
10. Burk RD. Human papillomavirus and the risk of cervical cancer. *Hosp Pract (Off Ed)* 1999; 34: 103–11.
11. Tay SK. Genital oncogenic human papillomavirus infection: a short review on the mode of transmission. Ann Acad Med Singapore. 1995 Jul;24(4):598-601.
12. Tay SK, Jenkins D, Maddox P, Campion MC, Singer A. Subpopulations of Langerhans' cells in cervical neoplasia.Br J Obstet Gynaecol. 1987 Jan;94(1):10-5.
13. Tay SK, Jenkins D, Maddox P, Singer A. Lymphocyte phenotypes in cervical intraepithelial neoplasia and human papillomavirus infection. Br J Obstet Gynaecol. 1987 Jan;94(1):16-21.
14. 14B.L. Trus, R.B. Roden, H.L. Greenstone, M. Vrhel, J.T. Schiller and F.P. Booy, Novel structural features of bovine papillomavirus capsid revealed by a three-dimensional reconstruction to 9 A resolution, *Nat Struct Biol* 1997 (5), pp. 413-20.
15. Harper DM, Franco EL, Wheeker C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial.Lancet 2004; 364:1757-65.
16. Koutsky LA et al. A controlled trial of a human papillomavirus type 16 vaccine.N Engl J Med 2002; 347(21):1645-51.
17. Future II study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.NEJM 2007 May 10;356(19):1915-27.
18. Garland SM et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. NEJM 2007 May 10;356(19):1928-43.
19. Paavoven J, Jenkins D, Bosch FX et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial.Lancet. 2007;369(9580):2161-70.

LEARNING POINTS

- **Pap smear screening is not able to prevent development of cervical neoplasia, though adequate treatment of CIN prevents development of invasive cervical cancer.**
- **Cervical cancer is a rare outcome of HPV infection. While 10% of women infected with high-risk HPV develop cytological abnormalities, only 0.8% develop CIN 3 and 0.16% develop cancer[8,9].**
- **HPV can display a long latent phase of several years before clinical manifestation. HPV infection may be acquired in some cases through vertical transmission from mother to the child[11].**
- **Natural regression of cervical HPV infection occurs in the majority of women. It has been found that 50% of young women clears their oncogenic HPV infection within 12 months and, cumulatively, 80% of them do so within three years.**
- **HPV-16 and HPV-18 are the most prevalent oncogenic HPV subtypes responsible for more than 70% of cervical cancers. Recombinant bivalent and quadrivalent viral-like particle vaccines, Cervarix and Gardasil, have been shown in large clinical trials to prevent cervical infection by these HPVs.**
- **Gardasil did not alter the course of HPV lesions in women who had HPV infection at the time vaccination was carried out.**
- **The impact of HPV vaccines with either Gardasil or Cervarix is greatest if the vaccination is administered before the woman acquires the HPV infection – this means that the vaccine has to be given prior to a girl's sexual debut, that is, in the early teens.**