Cervical Cancer Prevention with HPV Vaccines

Chaivanee Kaosayapandhu, B.Sc.Pharm.
Department of Pharmacy, Faculty of Medicine Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Cervical cancer is the most common malignancy in Thai women with 70% of all cases caused by Human Papillomavirus (HPV) 16, 18 and transmitted by sexual intercourse. Cervical cancer can be prevented by screening tests and HPV vaccines. In Thailand HPV vaccines currently are available in 2 types which are Bivalent, which has HPV 16,18 antigen and AS04 immunizer resulting in high immunization, and Quadrivalent, which has HPV 16,18 antigen and HPV 6,11 antigen which are not the cause of cervical cancer but of genital warts. The result of the study shows the differences of both types of vaccines in immunization mechanism, efficacy, cross-link prevention and indications. Both vaccines are certified for their safety. No severe side effects are found. Mild frequent side effects such as swelling, aching, redness will resolve spontaneously. HPV vaccines are most useful in female adolescents. However, women over 26 years of age or those who have sexual intercourse still benefit from vaccination especially when combined with annual Pap smear screening.

Keywords: Cervical cancer, Human Papillomavirus (HPV), Pap smear, HPV Vaccine, Bivalent vaccine, Quadrivalent vaccine

Siriraj Med J 2013;65:149-152
E-journal: http://www.sirirajmedj.com

Cervical cancer is the second most common cancer of women worldwide with approximately 275,000 deaths per year.[1] In Thailand, there are on average 9,999 new patients and 5,216 deaths per year.[2] The disease is most prevalent in women age 30-50 years. The most common cause of cervical cancer is the infection by Human Papillomavirus (HPV virus), which is responsible for 99.73 percent[3] of the cases. There are more than 100 strains of HPV virus. The most common causes of cervical cancer HPV are types 16 and 18[1] , which are responsible for 70 percent of the cases. Early stages of cervical cancer often show no symptoms, but the abnormal cells can be detected by Pap smear cervical cancer screening. If cancer cells are detected in the early stages, it can be treated and prevented from metastases.

At present, it is found that vaccination against HPV infection is another effective way, in addition to Pap smear, to prevent precancerous cervical cancer lesions, including cervical intraepithelial neoplasia (CIN) grade 2, 3 and adenocarcinoma in situ (AIS).

Correspondence to: Chaivanee Kaosayapandhu
E-mail: chaivanee@gmail.com
Received 3 September 2013
Revised 17 September 2013
Accepted 17 September 2013

Groups at risk for the disease

HPV virus is the main cause of cervical cancer, although, other factors[4] that increase susceptibility to infection or prone to cause cervical cancer have been shown in Table 1.

Transmission

HPV can be transmitted easily by touching the genital area. The majority is caused by having sexual intercourse. It is estimated that 50 to 80 percent of women who are sexually active will get infected with HPV at least once in their lifetime.[4,5] Women with only one partner can also have a chance of infection with HPV virus. A study in the USA found that 46 percent of women with only one partner were infected with HPV virus within 3 years.[6] Among about 80 to 90 percent of women infected with HPV virus, the virus will be naturally cleared. For the rest, 10 to 20 percent, the virus will remain in their body .When conditions are optimal such as when the body is weak or low immunity, the HPV virus will become persistent infection and develop into cervical cancer.

How can cervical cancer be prevented

The screening of cervical cancer with the Pap smear. This is to early detect abnormal cervical cells before the invasive stage and is considered as secondary prevention. It is suggested that this should be checked regularly, especially

TABLE 1. Risk factors.

Types of risk factor	Groups at risk for the disease
Gynecologic risk factors	Having sexual intercourse at an early age. (If younger than 18 years, the risk is higher). Having multiple partners. Multigravidity or multiparity. Having a history of sexually transmitted diseases. Never had cervical cancer screening before. Long time use of contraceptive pill.
Male risk factors	Husband with penile cancer. Women married to a man who had an ex-wife with cervical cancer. Man having history of sexually transmitted diseases. Man who had multiple partners or often changed partners.
Non-gynecologic risk factors	Smoking. (Depending on the amount and duration of smoking) Physical conditions with low immunity, such as AIDS or HIV infection or receiving immunosuppressant for a long time.

when starting sexual intercourse. If a pre-invasive lesion can be detected early, it can be cured. Pap smear is easy to check. However, the result from Pap smear can have a false negative rate as high as 20 to 30 percent.[7] Thus it is recommended to check annually.

The cervical cancer vaccine is also known as the HPV vaccine. This is used to directly prevent HPV virus from entering the body and is considered as primary prevention.

A vaccine is a compound substance injected into the body to stimulate immunity to disease or infection. Vaccines used today compose of major components in two parts which are:

- Antigen protein on the surface of bacteria which can stimulate the body to produce antibodies against a specific disease.

- Supplements to help boost immunity (Adjuvant) which are chemical compounds supplemented into a vaccine to stimulate the body to produce an antibody response in a higher amount.[8]

HPV vaccine is made from a protein shell called the HPV virus-like particles (VLPs) through a purification method. Then the number of the proteins is amplified. The VLPs can reunite themselvesm automatically resulting in a structure like the HPV prototype with no DNA, thus it cannot cause cancer. VLPs have the ability to greatly stimulate the immune system (Antigenic properties).

We still do not know the exact mechanism of action of the HPV vaccine nowadays. However, there is a relationship with the creation of neutralizing antibodies. The vaccines will stimulate the body to produce Immunoglobulin G (IgG) specific for the HPV virus to release into the bloodstream. Then it is absorbed into the mucous secretions or mucous in the cervix, which will serve to prevent HPV virus to enter the body.[9]

This vaccine has been certified as safe with no serious side effects. The commonly found adverse symptoms are pain and swelling at the injection area which are mild and will heal spontaneously.

In Thailand, HPV vaccines are currently available in 2 brands which are: HPV Vaccine with 2 strains of HPV (Bivalent) produced from the gene L1 of HPV introduced for formation in baculovirus, which are extracted, purified, and then bind themselves to particles similar to virus like particles (VLPs) which is composed of HPV types 16 and 18 at 20 micrograms each. The addition of AS04 adjuvant, which comprises of aluminium hydroxide and 3-desacylated monophosphoryl lipid A (MPL), results in a fast early immune response, stronger immunity levels, and longer persistence both for cell mediated immunity and humoral mediated immunity.[10] The trade name is "Cervarix™."

HPV Vaccine with 4 strains of HPV (Quadrivalent) produced by Saccharomyces cerevisiae yeast comprising types 6, 11, 16, and 18 at 20, 40, 40, and 20 micrograms each, respectively. Types 6 and 11 have been added to prevent genital warts. This vaccine contains AAHS comprising amorphous aluminium hydrophosphate sulfate as an adjuvant with the trade name "Gardasil™."

The similarities and differences of two types of vaccines have been shown in Table 2.

Efficacy of the vaccine against cervical cancer

In a study to evaluate the efficacy of the vaccine against cervical cancer, one cannot use invasive cervical cancer as an end-point as leaving the subject with cervical cancer without any treatment is unethical. The efficacy of the vaccine is obtained from an assessment of preventing precancerous lesions generally, so precancerous of lesions (CIN 2 +) prevention is applied as an end-point. Presently, tumor CIN 3 + is used for assessment because this lesion is close to invasive cervical cancer with a very low chance for regression. Therefore, it is more accurate than using CIN2 + as an end-point. The Bivalent and Quadrivalent vaccines are 93 and 43 percent[12,13] effective in preventing CIN3+ regardless of any types of HPV types respectively in the subject, whose HPV infection has been undetected before.

Both Bivalent and Quadrivalent vaccines are more than 90 percent effective in preventing lesions before they become cervical cancer which are CIN 2, CIN 3 and adenocarcinoma in situ (AIS) caused by infection with HPV types 16 and 18 in women who have not been infected with those viruses before. The vaccine can also prevent infection with other carcinogenic HPV types that are not contained in the vaccine such as types 31, 33 and 45 because the genetic codes of these species are similar to HPV types 16 and 18. The study showed that both the Bivalent and Quadrivalent vaccines are effective in preventing lesions CIN2 + caused by HPV types 31, 33,

TABLE 2. Both types of vaccines are similar and different in some aspects.

	Bivalent vaccine	Quadrivalent vaccine
Company	GSK	MSD
Antigen	HPV 16/18	HPV 6/11/16/18
Adjuvant	AS04*	AAHS
Cell production	Baculovirus	Saccharomyces cerevisiae type of Yeast
Injection schedule	At 0, 1st, and 6th month	At 0, 2nd, and 6th month
Age recommended for the vaccine	9-55 years	9-26 years
Immunogenicity[11] (in female aged 18-45 years)	Higher than Quadrivalent vaccine 2.4-5.8 times for HPV-16 and 7.7-9.4 times for HPV-18	Lower than Bivalent vaccine
Efficacy in preventing of CIN III or more caused by HPV types16 and 18 in those who were not previously infected by HPV virus[12,13]	100 percent	100 percent
Effective in preventing of CIN in the 3rd stage or more regardless of any HPV strain in those who were not found to be infected by HPV virus before[12,13]	93 percent	43 percent

*Remark: AS04 is to bring the existing additive adjuvant which is aluminum salt (aluminium hydroxide) and added 3-desacylated monophosphoryl lipid A (MPL), a purified bacterial lipid, to enhance the immunogenicity of the vaccine as well with high immunity and can last longer.

45 for 89.4, 82.3, 100 percent and 70, 24, -51.9 percent respectively.[14,15]

The antibody levels after vaccination will increase to the maximun levels about one month after the third dose injection and gradually decrease until the 24th month, but are still higher than the antibody levels caused by natural infection.[5] For the safety of the vaccine, both vaccines have a common type of adverse reaction which is the pain at the injection area. Other adverse symptoms at the injection area include pain and swelling or other symptoms which may occur including dizziness, nausea, headache, fever, fatigue, and these are mostly found in adolescents more than in children and adults.

HPV vaccine is used to prevent HPV infection. It is, thus, useful in those who have never been infected with HPV virus before. In other words, it is useful for the people who have never had sexual intercourse, because HPV virus can infect easily by direct contact particularly by sexual intercourse. Therefore, the vaccine in children will give the maximum benefit as they have not been infected with the virus via sexual intercourse. In addition, children also have a higher response and higher immunity level.[16]

Suggestions and recommendations that should be informed before HPV vaccination

The persons should be informed of the following points, that the HPV vaccine cannot be used as a substitute for cervical cancer screening as cervical cancer can be caused by infection of other HPV types that the vaccine cannot cover. There is a need for cervical cancer screening together with the vaccination. The HPV vaccine might not prevent HPV infection for all pre-cancerous lesions and cervical cancer cases, and it does not completely prevent cervical cancer. Therefore, this does not mean that the vaccinated person will not develop cervical cancer, or a person who has not be vaccinated will all develop cervical cancer. The HPV vaccine cannot prevent abnormal Pap smear result and cannot be used as a treatment for pre-cancerous cervical lesions. The HPV vaccine cannot prevent other diseases of the sexual organs that are not caused by HPV infection such as herpes and vaginal bacterial infections of various kinds. In immunocompromised women, the antibody level might be lower than normal women, so after HPV vaccination, a barrier method such as condom should be considered to prevent HPV infection, and the course of vaccination should be completed.

SUMMARY

The cervical cancer vaccine is an alternative for prevention of cervical cancer. Vaccination in girls aged 11-12 years will render maximum benefit as they have never had sexual intercourse and the vaccine can stimulate the body's immune level 2 times higher than adults.[16] For women with previous sexual intercourse, the vaccine can also be effective in preventing the disease. It preferably should be done in conjunction with regular cervical cancer screening.

REFERENCES

1. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human papillomavirus and related cancers in world. Summary report 2010. [Accessed April 2013]. Available from: www.who.int/ hpvcentre
2. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human papillomavirus and related cancers in Thailand. Summary report 2010. [Accessed April 2013]. Available from: www. who. int/ hpvcentre
3. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-9.

4. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005 Mar;32 Suppl 1:S16-24.
5. Brown DR, Shew ML, Qadadri B, Neptune N, Vargas M, Tu W, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. J Infect Dis. 2005 Jan 15;191(2): 182-92.
6. Collins S, Mazloomzadeh S, Winter H, Blomfield P, Bailey A, Young LS, et al. High incidence of cervical human papillomavirus infection in women during their first sexualrelationship. BJOG. 2002 Jan;109(1):96-8.
7. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003 Jan;16(1):1-17.
8. Garçon N, Wettendorff M, Van Mechelen M. Role of AS04 in human papillomavirus vaccine: mode of action and clinical profile. Expert Opin Biol Ther. 2011 May;11(5):667-77.
9. Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. Drugs. 2010 Jun 18;70(9):1079-98.
10. Giannini SL, Hanon E, Moris P, Van Mechelen M, Morel S, Dessy F, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccineformulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. Vaccine. 2006 Aug 14;24(33-34): 5937-49.
11. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine andHPV-6/11/16/18 vaccine: follow-up from months 12-24 in a Phase III randomized study of healthy women aged 18-45 years. Hum Vaccine. 2011 Dec;7(12):1343-58.
12. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012 Jan;13(1):89-99.
13. Muñoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010 Mar 3;102(5):325-39.
14. Wheeler CM, Castellsagué X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012 Jan;13(1):100-10.
15. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis. 2009 Apr 1;199(7):926-35.
16. Pedersen C, Petaja T, Strauss G, Rumke HC, Poder A, Richardus JH, et al. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. J Adolesc Health. 2007 Jun;40(6):564-71.