

New vaccines for prevention of HPV infection

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Abstract

Cervical cancer, which is caused by sexually transmitted human papillomaviruses (HPV), is the second most common cause of cancer deaths in women worldwide. In addition to cervical cancer, HPV is also a causative factor for vaginal cancer, vulvar cancer and anal cancer. Therefore, HPV is threatening the health of women in the world. In fact, different cytological screening tests have been launched to reduce the incidences of invasive cervical cancer in many countries. However, the sensitivity of those tests is relatively low and the cost effectiveness in repeat testing for indeterminate cases is debatable. The detection of HPV DNA is more sensitive than cytology for the detection of cervical cancer, therefore, it is recommended as an adjunctive test for cases with equivocal cytology. However, the methods for the diagnosis of cervical cancer cannot offer sufficient protection to women, as a result, the development of prophylactic HPV vaccines becomes a superior way in preventing HPV infections in human. Two drug companies, GlaxoSmithKline (GSK) and Merck, have developed HPV vaccines that offer protection against several HPV subtypes and help to prevent cervical cancer and genital warts. In Hong Kong, the licensure of these vaccines has recently been granted for clinical use. Perhaps, through the comprehensive application of the vaccines to the population, we can optimistically anticipate that the health condition of Hong Kong women against cervical cancer and some HPV-related diseases will be greatly improved.

Key words: Human papillomavirus; vaccines; cervical cancer; prevention.

Introduction

Cervical cancer is the second most common cancer in women after breast cancer worldwide.¹ Based on the statistics of the World Health Organization (WHO), there are more than two million women have cervical cancer in the world, and it is shocked that around 650 women died from cervical cancer daily in 2006. This fact has raised an alarming attention from the public for the prevention of this disease nowadays.

There are many studies showing that human papillomavirus (HPV) infection is the most obvious cause for cervical cancer, though other risk factors are also involved, including smoking and the use of oral contraceptives.^{2,3}

Laboratory tests have been employed for the diagnosis of cervical cancer. The Papanicolou (Pap) smear, which is introduced by Papanicolou and Traut in 1943, has been used for many years. This test aims to detect abnormal cells termed as “koilocytes” in cervix. However, several limitations are encountered which may lead to low sensitivity with false negative results.⁴ Since HPV infection is one of the causes for the cervical cancer progression, molecular methods to detect the presence of HPV DNA are also practical for cancer diagnosis. Polymerase chain reaction (PCR) can rapidly detect HPV specific DNA sequences, which indicates HPV infection of the patient.

Therefore, HPV DNA can be used as a marker of disease progression.⁴ However, these methods can have a high value for diagnosis, but are not effective for the prevention of cervical cancer. Perhaps, the development of vaccines against HPV infection is a better way to prevent this disease and will be discussed later.

What is HPV?

HPV are members of the family *Papillomaviridae*, and are sexually transmitted among human.¹ They cause genital warts and other anogenital cancer (cervix, vagina, vulva, penile, anus).⁵ HPV have a circular genome that codes for six early proteins (E1, E2, E4, E5, E6 and E7) and two late proteins (L1 and L2).⁴ The function of L1 and L2 proteins is to build up the outer capsid of the virus.⁶ E6 and E7 proteins are found to play major role in the malignant transformation of cervical cells.^{7,8} E6 proteins accelerates the degradation of p53 and lead to loss of control of cell cycle arrest and apoptosis, while E7 proteins stimulate genes expression which are required for cell cycle progression and DNA replication through E2F proteins.^{9,10} As a result, the invasion of HPV will lead to the malignant transformation of the cervical cells.

There are over hundred of HPV types being identified. For those associate with cervical cancer, they are classified to either high-risk or low-risk type, depends on their prevalence in the induction of cancer. The high-risk types includes type 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82, while low-risk types includes type 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81.⁴ Many studies suggest that HPV16 and HPV18 are highly associated with cervical cancer.^{11,12,13}

HPV and cervical cancer progression

As mentioned before, cervical cancer is a type of cancer that is caused by persistent infection with HPV, especially the high-risk types. Cervical cancer begins in the cervix and becomes gradually more invasive.¹⁴ Unfortunately, the early stages of cervical cancer usually show very minor symptoms, including an abnormal vaginal bleeding and an unusual discharge from the vagina outside the period of menstrual cycle. Although HPV has been proved to be

highly associated with cervical cancer development, other factors might also contribute, including the young age of sexual activity, high number of pregnancies, smoking of cigarette, long-term use of oral contraceptives and infection of other sexually transmitted bacteria such as Chlamydia Trachomatis (CT) and Herpes Simplex Virus type 2 (HSV-2).^{15,16,17} The result of diagnosis suggests that the number of cases of cervical cancer is highest among women aged 35 to 44, but is extremely rare in women under the age of 20. It is highly recommended that women have to receive a regular Pap smear that checks for abnormalities in the cells that line the cervix. In case the Pap smear shows an uncertain result, molecular methods, like PCR, which determine the presence of HPV DNA, can be employed as supplementary test.⁴ However, these diagnostic tests can only be considered as the second-line of defence against cervical cancer, vaccination against HPV infection will be a proper method for the first-line of defence.

HPV vaccines

Prophylactic vaccines against HPV have been developed. They are based on discoveries that L1 proteins, which are the structural proteins of the outer capsid of HPV, are capable to assemble into virus-like particles (VLP).¹⁸ The VLP are effective in inducing high titers of virion-neutralizing antibodies after injection, with the advantages that it is non-infectious and non-oncogenic.¹⁹

Gardasil[®] and Cervarix[®], which are manufactured by Merck and GlaxoSmithKline (GSK), respectively, have been demonstrated to be effective against HPV infection.¹ Gardasil[®] is the first vaccine developed to protect cervical cancer and received the approval from the US Food and Drug Administration (FDA) in June 2006. It is a tetravalent vaccine contains not only the VLP of HPV16 and HPV18, but also the VLP of HPV6 and HPV11, which are classified as non-oncogenic but cause about 90% of cutaneous genital warts. Different from Gardasil[®], Cervarix[®] is a bivalent vaccine contains VLP of HPV16 and HPV18. Cervarix[®] is waiting for approval from FDA.¹

The HPV vaccine is administered by three intramuscular injections. The second and third doses are recommended to be administered 1 or 2 and 6 months after the first

dose.²⁰ This protection could last for at least 4.5 years and booster dose is not necessary. The recommended age for vaccination in women with ages between 15 and 25, but the strongest immune response were observed in pre-pubertal children. According to published studies, vaccine can be administered as young as in 9 years old children before any sexual activities.²¹ The vaccine injection did not show significant serious side effects but it is not recommended for women in pregnancy. The vaccine is well tolerated, though redness at the site of injection and mild to moderate pain may be developed.²⁰

However, issues remaining to be questioned like duration of protection, efficacy for prevention of cervical cancer, optimal age of immunization, effectiveness in immunocompromised or already infected individuals, the ideal combination of vaccine genotype and impact on cervical screening program are still unresolved.²² Moreover, the expensive cost of the vaccine may limit its implementation in developing countries.²³

Conclusion

Cervical cancers are developed gradually through a series of abnormal changes in the lining cells of the cervix. Regular screening Pap test is an important tool to detect these neoplastic changes. PCR and other molecular method like Hybrid Capture II are also employed as adjunct methods for cervical screening. However, these are only for HPV detection but not for prevention of HPV infection.

The development of both prophylactic HPV vaccines, Gardasil[®] and Cervarix[®], is an important milestone in the prevention of HPV infection. These prophylactic vaccines seem to offer a preventive method to the women at large and can reduce the death rate of cervical cancer and the treatment of pre-cancerous lesions.

Although the vaccines are still in the early dates of clinical implementation, it is hopeful that it will provide a powerful cervical cancer prevention if this approach is successful. Perhaps, with further studies, the development of therapeutic HPV vaccines will strengthen the prevention of cervical cancer in the future.

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