Review

Review of Research on the Prevention of HPV Infection and Cervical Cancer

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Abstract

Worldwide, cervical cancer remains as one of the most common malignancies that threaten women's health. An epidemiological survey has shown that high-risk chronic HPV infection is the leading cause of cervical cancer. Thus, the prevention of HPV infection is the main approach to the prevention and treatment of cervical cancer. Sexual behavior, individual immunity, and age are important cofactors in the promotion of HPV infection. Preventive measures that have been gradually implemented worldwide have significantly decreased the incidence of cervical cancer in recent years. These measures include preventive vaccination against common high-risk HPV and cervical cancer screening, which includes HPV testing. HPV testing in cervical cancer screening has received increased attention and provides the basis for the prevention and treatment of cervical cancer. Given that HPV infection rates significantly vary from region to region, procedures for cervical cancer screening should be improved based on regional differences.

Cervical cancer is a unique cancer given its clear cause and preventability. Nevertheless, cervical cancer remains a common malignancy that seriously threatens women's health. Worldwide, the incidence of cervical cancer ranks third and is second only to those of colorectal and breast cancers. The mortality rate of cervical cancer ranks fourth among other malignant tumors and is second only to those of colorectal, lung, and breast cancers. In 2008, international cancer-related agencies reported that annually, 529,512 women are diagnosed with cervical cancer and that 274,967 women die of cervical cancer [1]. Denny [1] reported a gap between the incidence and mortality of cervical cancer in different regions. The incidence of cervical cancer in low-income countries and regions is nearly 10 times that in developed countries and regions. An epidemiological survey showed that high-risk HPV infection is the leading cause of cervical cancer. Alam *et al* [2] reported that 99.7% of tissue samples from cervical cancer cases are positive for HPV infection and that more than 50% of cervical cancer cases are co-infected with HPV16 or HPV18. Studies on HPV infection have expanded in recent years. Measures for the prevention and control of HPV have been gradually implemented and have helped decrease the incidence of

cervical cancer.

HPV characteristics

Molecular biology characteristics of HPV

HPV, a pathogen associated with cervical neoplasms, belongs to the Papillomavirus genus of the papilloma multinodular vacuolar virus family. It is a naked, small, double-stranded RNA virus with a simple structure. HPV DNA encodes 5–8 open reading frames: E6, E7, E1(E8), E2, E4(E3), and E5. These ORFs are involved in the replication, transcription, translation, regulation and cell transformation of viral DNA. HPV is widely distributed in humans and animals, and has a high tissue and host specificity [3].

Type of HPV

More than 115 HPV genotypes have been identified. Approximately 40 HPV genotypes are associated with genital tract infection [4]. HPV is classified as high-risk HPV, possible high-risk HPV, and low-risk HPV based on structure, function, and pathogenicity [5]. The degree by which different HPV subtypes increase the risk of cervical cancer is different.

HPV16, 18, 31, 33, 45, 52 and 58 are closely associated with the incidence of cervical cancer and are considered as high-risk HPV subtypes. HPV16 and HPV18 account for more than 70% of HPV infection cases. HPV35, 39, 51, 58, 59, 68, 73, and 82 are related with the incidence of cervical cancer and are possible high-risk HPV subtypes. Low-risk HPV subtypes include HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89, and mainly cause benign proliferative lesions of skin mucosa, such as genital papilloma, exogenous genital warts and lesions, and low cervical intraepithelial neoplasia (CIN) [6]. HPV26, 53 and 66 have received limited research attention.

HPV16 is closely associated with cervical cancer and is present in more than 50% of cervical cancers. HPV16 variants have attracted increasing attention in recent years. HPV16 variants include six variants: European, Asian, Asian-American, North American, African-1, and African-2. Sanchez *et al* [7] confirmed that infection by HPV16 variants account for more than half of all cervical cancers. In addition, various variants exhibit different potentials to cause cervical cancer. For example, the European and Asian subtypes can increase the incidence of cervical squamous cell carcinoma by three times.

Relationship between HPV and cervical cancer and characteristics of HPV infection

HPV is ubiquitous in the population: 40% of women will be infected with HPV during the first two years of their sexually active lives, and 80% of women over 50 years of age are infected with HPV [8]. However, 70% and 90% of the HPV load is automatically cleared by the body's immune system during the first year and the first two years after infection, respectively. Three years after infection, almost only 5% of the viral load is characterized as continuous infection, and then develops into cervical cancer [9]. Denny [1] believes that under the influence of persistent HPV infection, precancerous cervical lesions require 10–30 years to develop into cervical cancer.

According to an international study conducted by the International Cancer Research Association, HPV16 (53%), HPV18 (15%), HPV45 (9%), HPV31 (6%), and HPV33 (3%) are the most common HPV subtypes in the world. HPV16 is the subtype with the highest infection rate among all cervical lesions [10]. Denny [1] reported that the HPV16

subtype is more likely to develop into cervical squamous cell carcinoma, and that the HPV18 subtype is more likely to develop into cervical adenocarcinoma and adenosquamous carcinoma. Harper [9] reported that HPV16 (62%), HPV18 (8%), HPV45 (6%), HPV31 (5%), and HPV33 (4%) are the most common HPV subtypes of cervical squamous cell carcinoma. Nearly 90% of cervical adenocarcinoma cases are positive for infection with the HPV16, HPV18, and HPV45 subtypes.

According to the study data obtained by Vinodhini *et al* [11] in 2012, the worldwide HPV infection rate among females is 32.1%. The HPV infection rate in developing countries is 42.2%, which is 22.6% higher than that in developed countries. In Asia, especially eastern Asia (mainly including China and South Korea), the HPV infection rate is 57.7%. Europe exhibits the lowest HPV infection rate: western Europe exhibits the lowest infection rate at 3.7%, followed by southern Europe at 15.1%. In more developed countries, the most common HPV subtypes are HPV16, 18, 58, 52, and 31.

Risk factors for HPV infection

Sexual behavior

Sexual behavior is the most important cofactor in the promotion of HPV infection and cancer incidence. Sexual behavior provides patients with direct exposure to HPV. High-risk sexual behavior includes unprotected sex, multiple sexual partners, and young age during sex for the first time [11]. High-risk sexual behavior can maintain high viral loads in patients. In addition, the chemical composition of semen directly stimulates the cervix. Thus, up to 60% of sexually active women are infected with HPV [12].

Individual immunity

Low individual immunity is another crucial factor in the promotion of HPV infection. Immunodeficient individuals cannot clear HPV infection in a timely manner and are at increased risk for persistent HPV infection. Given that HIV-positive individuals have significantly lower T-cell counts than healthy individuals, the duration of development from cervical precancerous lesions to cervical cancer is significantly shorter, and incidence and mortality are higher [13]. HIV-positive individuals are more susceptible to infection by uncommon HPV subtypes. Rahman *et al.* [14] investigated the incidence of HPV among HIV-positive individuals and found that most common HPV subtypes are HPV52 (10.5%),

HPV39 (9.5%), HPV54 (9%), HPV45 (7.8%), HPV56 (7.2%), HPV53 (6.4%), HPV31 (6.2%), HPV42 (5.3%), HPV16 (5.1%), HPV51 (5.1%), and HPV68 (5.1%).

Age

Age is another important factor for the promotion of HPV infection. Women of reproductive age are more likely to be infected with HPV^[11]. Gita *et al.*^[12] found that the incidence of HPV infection is highest among women aged 35 to 44. Cercato *et al.*^[15] utilized questionnaires to identify the risk factors for HPV infection. Education, socioeconomic status, gynecological history, use of oral contraceptives, sexually transmitted diseases, working conditions, low body mass, low intake of vegetables, male factors, smoking, and drinking were included as items in the questionnaires.

Prevention of HPV and cervical cancer

Since 2009, the incidence of cervical cancer has gradually decreased in Western Europe and the United States. Nadarzynski *et al.*^[16] proposed that this decrease mainly benefitted from two effective preventative measures: 1) The preventative vaccination of populations at high risk of HPV, including 12–13 year old girls. 2) The universal implementation of cervical cancer screening and HPV testing among women aged 25 to 64.

HPV vaccine

Vaccines specific for several HPV subtypes have been developed since the beginning of the 1990s^[6]. At present, two HPV prophylactic vaccines have been developed, including Cervarix and Gardasil. Cervarix is a HPV16 and 18-type divalent vaccine, whereas Gardasil is a HPV6, 11, 16, and 18-type quadrivalent vaccine. Both vaccines are licensed by the US Food and Drug Administration and the European Medicines Evaluation Agency^[17].

The period of sexual development is the most appropriate time for preventative vaccination against HPV. The Advisory Committee on Immunization Practice and Department of Obstetrics and Gynecology, American University, believe that HPV-infected individuals should be actively inoculated with HPV vaccines whether their Pap smears are abnormal or their HPV test results are positive^[18].

A clinical randomized controlled trial reported by Harper^[9] confirmed that the protection rate against HPV infection is

96% 5 years after vaccination with HPV6, 11, 16 and 18-type quadruple vaccines and 100% 9.4 years after vaccination with HPV16 and 18-type divalent vaccines. Given that cross-immunization between HPV types can decrease the infection rates of HPV31, HPV33, HPV45, HPV51 and HPV52, Tota *et al.*^[19] believed that the successful development of HPV vaccines has potentially decreased the likelihood of cervical cancer by 70%.

Brabin *et al.*^[20] estimated that by 2025, 70%–80 of the 12–13 year-old female population will be vaccinated against HPV, thus possibly decreasing the future incidence of cervical cancer in women aged 20–29 years by 55%–63%. Koliopoulos *et al.*^[3] also believed that if the vaccine is inoculated widely, the incidence of cervical cancer will be significantly reduced 20 years later.

HPV-related cervical cancer screening

HPV typing is a supplemental screening method that effectively improves the efficiency of cervical cancer screening. UK, US, South Africa, Thailand, and Germany advocate the inclusion of HPV testing in cervical cancer screening programs^[21]. A nationwide audit report in Sweden showed that 65% of Swedish patients who have been diagnosed with cervical cancer have never participated in cervical cancer screening, and that only 25% of cervical cancer patients have participated in cervical cancer screening with HPV subtype test. Given that most cases of cervical cancer were diagnosed at an early stage in these patients, most had a good prognosis^[22].

Del Mistro *et al.*^[23] reported that compared with other screening methods, such as cytology screening and colposcopy screening, HPV screening for cervical cancer has the best performance and highest sensitivity (92.3%) and specificity (78.6%). Gyllensten *et al.*^[22] found that the sensitivity difference between cytological screening and HPV subtype test among postmenopausal women is greater than that among women of other ages, whereas the sensitivity of HPV subtype screening is thrice that of cytological screening.

Saslow *et al.*^[24] reported a more detailed screening procedure for cervical cancer and proposed that cervical cancer screening should begin from the age of 21. Women aged 21 to 29 should undergo cytological screening every 3 years. Women aged 30 to 65 should undergo cytology screening every 3 years or HPV test combined with cytological screening every 5 years.

In conclusion, cervical cancer remains one of most serious malignant tumors that affect women's lives in the global context. In addition, high-risk HPV infection significantly promotes the development of cervical cancer. Understanding the distribution of HPV subtypes has guided the development of anti-HPV vaccines and the prevention of cervical cancer. At present, HPV vaccines are mainly inoculated in developed countries because of economic reasons. Future research on HPV and cervical cancer should aim to decrease the cost of HPV vaccines, improve the screening system for cervical cancer, and develop new approaches for the prevention of cervical cancer.

Declarations

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No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

T Wang made the literature analysis and wrote, discussed and revised the manuscript of this review.

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