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Research progress and preventive strategy of HPV and cervical cancer and other related cancers

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Abstract. This paper comprehensively reviews the research on the relationship between HPV and cervical cancer and other cancers and expounds the pathogenesis of cancer caused by HPV and its negative impact on the body. The screening methods and their effectiveness are reviewed, and the relevant research and latest developments of vaccines are summarized. First, the basic knowledge about HPV (including the structure and typing of the virus and the mechanism of infection of the virus) is introduced, and the screening method and its effectiveness are explored. Furthermore, the relationship between cervical cancer and HPV infection (including the mechanism of occurrence, the type of virus that causes cervical cancer, and the characteristics after infection) is discussed emphatically. Subsequently, the relationship between HPV infection and other cancers (including the mechanism of infection, classification and post-infection characteristics) was further explored, such as oral cancer, anal cancer, and reproductive organ cancer (except cervical cancer that has been introduced above). In the end, the current research results on HPV prevention and the challenges to be met from the current point of view are summarized, and the outlook and some suggestions for the research direction of future vaccines are made.

Keywords: HPV, vaccines, cancer.

1. Introduction

Human papillomavirus (HPV) is one of the most common human diseases. According to WHO statistics, more than 50% of all people who have sex have more or less HPV infection. It is worth noting that among all infected patients, patients infected with high-risk HPV accounted for 50% of all HIV patients, and most of the high-risk HPV types in these patients were 16 and 18 types [1]. The frightening thing is that these high-risk HPVs will not only affect human health but also cause some related diseases. At present, how to reduce the tumors caused by HPV infection in the world is still a big challenge. Cervical cancer caused by HPV is still a huge problem, especially for low- and middle-income groups. However, in developed countries such as the United States, head and neck cancers have surpassed cervical cancers and become the most common HPV-related malignancies. Therefore, head and neck cancers have gradually become the largest burden of HPV-related cancers in the United States and other developed countries. Therefore, studying HPV and its related cancers can help us better understand and prevent them, thereby safeguarding human health. This article will review the relevant research and data on HPV, analyze the harm of HPV, the way of transmission and the pathogenesis of related diseases, so as to understand the harm of HPV to human beings. At the same

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time, by analyzing the deficiencies of the current preventive measures, suggestions for improvement measures are put forward. It is hoped that through the elaboration of this article, it can provide certain references and hints for research in related fields, and also hope to provide scientific protection suggestions for the public.

2. Basic knowledge of HPV virus

2.1. Shape of HPV virus

HPV is a double-stranded circular DNA virus with 72 nucleic acid fragments. Each coat shell contains two or more capsid proteins (L1, L2), which are pentamers of the main capsid protein L1 [1-3]. The capsid of each virion contains approximately 12 copies of the minor capsid protein. The total diameter of the virus is about 55 nanometers. The genome consists of double-stranded circular DNA and contains eight to nine open reading frames (ORFs). The protein coding sequences of these ORFs are restricted to one strand. When HPV parasitizes the host, they replicate at the specific location of the host and co-evolve with the host. They persist in replicating in dividing cells, manipulate the cellular environment and evade immune detection by hijacking key host cellular processes, and produce virions in cells that shed from the host [4].

2.2. Gene and gene division of HPV virus

In this process, the genome of the virus is divided into three regions: the early region, the late region and the remote control region (or upstream regulatory region). The early-onset zone (E) is primarily located in dendritic cells (also known as dendritic cells). Including E1 (Replication), E2 (Replication and transformation), E4 (probably for virus release), E5 (possibly for virus conversion), E6 (Transformation) and E7 (Transformation) genes. These genes are not only key to the viral cycle, but are also involved in cellular transformation processes including viral replication and tumor formation [1, 3]. The late region (L) is a kind of inclusion body which is highly expressed only in the host epithelium, and its main components are L1 and L2. Long-control (LCR) / uprinciple-regulator (URR) is a non-coding region containing replication starting point and transcription factors, which plays an important role in regulating DNA replication in the regulatory region of the virus. Although the number and size of reading regions of various HPV proteins are not the same, they all contain a highly conserved core gene, which plays a vital role in the replication and assembly of HPV. Other genes also play roles in driving cell cycling, virus release, and immune escape. In addition, the newly discovered and unknown HPV typing early regions E6, E7 and late region L1 have less than 90% sequence identity with the corresponding known HPV genotypes [1].

2.3. Classification of HPV virus

There are many types of HPV. At present, HPV can be divided into two types according to its virulence: low-risk type and high-risk type. Both types can infect the skin and mucous membranes. Low-risk HPVs (also known as non-oncogenic) generally only infect the skin and mucous membranes (replication of viral DNA occurs mainly in the spinous and granular layers), and rarely cause cancer and other diseases. However, some low-risk HPVs can induce epithelial proliferation in body parts such as the throat, genitals, and anus, resulting in thickening of the epidermis, accompanied by hyperplasia of the spinous layer and keratinization of the epidermis. Proliferation of the epithelium forms papillary tumors (warts). These warts are usually benign lesions such as condyloma acuminatum (genital warts), plana (flat warts) and keratopapulosis (acanticular keratosis). High-risk HPV can cause many types of cancer. Existing studies have shown that HPV has a high correlation with cervical cancer, oropharyngeal cancer and other reproductive organ cancers.

2.4. Pathway of HPV virus infection

The vertical transmission of HPV virus has always been a controversial topic. Generally, people with HPV do not have signs or symptoms, but they can still pass the viral infection on to others. The main

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route of transmission of HPV is mainly sexual transmission. At the same time, it can also be transmitted by skin contact (touching the relevant lesion area). In addition, the vertical transmission of HPV in utero has been a very controversial topic, and the specific mechanism of vertical transmission of HPV in utero is still unclear, but it is still a possible transmission route [1].

2.5. Classification of HPV viruses

After HPV infection, the body's immune system will begin to recognize and eliminate the virus. Generally, the virus will disappear on its own within two years. But in people with persistent infections, chronic infections, people with high-risk HPV infections, or people with weakened immune systems, this persistent, non-clearing infection can lead to health problems. For example, the E6 and E7 proteins in the HPV virus can interfere with the normal function of cells, promote the development and proliferation of a field of cells, and lead to the development of precancerous lesions. E6 protein can interact with p53 protein, thereby inhibiting the function of p53 (regulating cell cycle, monitoring and repairing DNA damage, preventing cell canceration). E7 protein can interact with Rb protein, which will lead to the impairment of Rb function and loss of inhibitory effect on CDKs, resulting in uncontrolled entry of cells into the S phase, resulting in abnormal cell proliferation and tumor development. At the same time, studies have shown that E6 and E7 proteins are closely related to the occurrence of high-risk HPV, so these can be used as markers of HPV precancerous lesions and can help prevent and treat them by detecting their expression levels. Precancerous lesions are abnormal changes in cells or tissues. It usually takes many years to develop from precancerous changes to cancer—several years to more than ten years. Like a tumor or abnormal cell disease, these lesions are often considered early stages of cancer development, but it does not always develop into cancer [5].

3. HPV and cervical cancer

3.1. The concept, statistics and classification of cervical cancer

According to statistics, there are about 529,800 new cases of cervical cancer and about 275,100 deaths in the world every year. There are two main types of cervical cancer, one is squamous cell carcinoma, the other is adenocarcinoma, , which accounts for about 10-20%. There are also a few fewer common tumors, such as adenosquamous carcinoma, anaplastic carcinoma, and small cell carcinoma. Up to now, HPV infection has been identified as the main factor leading to cervical cancer. One of the leading causes of high-risk HPV infection, particularly HPV18 and HPV18, which are the most common and considered high-risk HPV types that primarily contribute to the development of cervical cancer. Others such as HPV31, HPV22 and HPV45 are also high-risk HPVs associated with cervical cancer. For some patients with HPV virus persisting in the body, their cervical epithelial cells may be abnormally changed. These changes usually occur in the transition zone of the cervical surface, the area where the squamous epithelium of the outer cervix transitions to the columnar epithelium of the inner cervix. These abnormal changes and persistent HPV infection may be an important reason for the carcinogenesis of the epithelial cells of cervical cancer [1, 5, 6].

3.2. Other cervical cancer risk factors

In addition, there are many reasons that can lead to cervical cancer. For example, a person who is immunocompromised due to factors such as multiple pregnancy and smoking, has a compromised immune system, or is co-infected with one other sexually transmitted infection (such as HIV) or possibly with a high-risk HPV type. According to the survey, women who smoke are twice as likely to suffer from cervical cancer than non-smokers. Therefore, smoking cessation can also prevent cervical cancer [1].

3.3. Cervical cancer screening and symptoms

Worldwide, the number of cervical cancer cases and deaths is also slowly decreasing. According to the data, from 1975 to 2010, the number of newly diagnosed cervical cancer patients fell by half. But

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unfortunately, from 2017-2019, approximately 0.7% of women will still be diagnosed with cervical cancer. Because early-stage cervical cancer often does not cause noticeable symptoms, regular screening (HPV DNA and Pap smears) is extremely important for women to prevent the development of cervical cancer by detecting precancerous changes that may lead to cancer. If the disease develops to a certain extent, different clinical manifestations may appear, such as irregular vaginal bleeding, abnormally increased secretions or foul-smelling secretions. Or symptoms such as edema, anemia, weight loss, fever, and fatigue appear throughout the body [7].

In addition to cervical cancer, high-risk HPV can also cause cancers in other body parts, such as oral cancer, anal cancer, and other reproductive organ cancers.

4. HPV and oral cancer

4.1. Classification of HPV-caused oral cancer and other co-acting risk factors

Oral tumors include tongue, lips and cheeks, etc. It is one of the most common head and neck tumors. Tumor cells generally show a flat, thin shape (scale). Tumor cells generally show a flat, thin shape (scale). Tumors are mainly distributed inside the mouth, so most mouth tumors are squamous. Infection with HPV does not necessarily directly lead to oral cancer, but it is one of the main risks of oral cancer (especially the two high-risk grades of HPV 16 and 18). In addition, smoking, alcoholism, poor oral hygiene, oral inflammation, etc. are also risk factors for head and neck cancer [6].

4.2. Survey data on oral cancer caused by HPV

According to the Centers for Disease Control, HPV accounts for 70% of oral tumors in the United States, and new cases are on the rise. At the same time, it is well known that globally, about 3.6% of women and 10% of men are infected with human papillomavirus. From 2017 to 2019, data released by the National Institutes of Health show that about 1.2% of people will be diagnosed with throat or oral cancer at some point in their lives. In addition, the American Society of Oncology points out that men are twice as likely to develop oral cancer as women, and this is the highest among people over the age of 50. Conclusion: in clinic, male patients should pay attention to HPV infection and prevention and treatment of oropharyngeal carcinoma. After human papillomavirus (HPV) infection, tumor progression often takes many years to develop, but whether HPV virus infection alone can cause oropharyngeal cancer or other causes, such as smoking, drinking and so on, is uncertain. Oral cancer generally has clinical manifestations such as oral growth and pain. If oral and pharyngeal tumors can be diagnosed in time, the 5-year survival rate is 84%. Once the tumor spreads to the tissue, organ or lymph node, the five-year survival rate is only 65%. Therefore, it must be investigated comprehensively and systematically.

5. HPV and anal cancer

5.1. Anal cancer locations and symptoms

Anal cancer is a rare tumor that is located at the end of the rectum. Symptoms include anal and rectal bleeding, pain, itching in the anal area, or growths and lumps. The initiation of anal cancer is closely related to the infection and transmission of HPV [8].

5.2. HPV research data on anal cancer

A survey shows that 84% of human papilloma specimens can detect high-risk HPV, especially HPV-16. Another survey of squamous cell tumors in Denmark and Sweden showed that HPV-positive patients have a high rate, so most rectal cancers are caused by HPV. Therefore, HPV is considered to be the most common cause of anal cancer. According to the statistics of the National Institutes of Health from 2017 to 2019, about 0.2% of the population will develop rectal cancer, and the number of new cases and deaths is on the rise year by year [9].

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6. HPV and other genital cancers

HPV can also cause cancers of other reproductive organs, such as penile, vulvar, and vaginal cancers, which are rare cancers (vaginal cancers are even rarer when they are primary). HPV is responsible for 70% of vulvar cancers, 75% of vulvar cancers and more than 60% of penile cancers [8].

6.1. HPV and vulvar cancer

Vulvar cancer is a common malignant tumor, and its incidence rate accounts for 0.6% of all cancers in women. Typically, symptoms of vulvar cancer are rashes or bumps that can cause itching on the skin (the itching doesn't get better). Most patients are found in the elderly population (more than 80 percent of patients are over 50 years old, and more than 50 percent of patients are over 70 years old), but vulvar cancer can appear at any age.

Vulvar tumors are divided into two types, one is vulvar squamous cell carcinoma, the other is vulvar melanoma. Vaginal squamous cell carcinoma begins with vaginal squamous epithelium, and most of them are squamous cell carcinoma. Human papillomavirus (HPV) is the most important cause of oral squamous cell carcinoma (OSCC), and the inactivation of p53 and RGC in E6 and E7 is closely related to the malignant transformation of OSCC. The incidence of HPV-positive throat squamous cell carcinoma is between 18% and 75%. Vulvar melanoma is caused by something black on the vulva skin, mostly in the lesser labia and clitoris [8].

6.2. HPV and vaginal cancer

Vaginal cancer is cancer that is located in the vagina (the muscular tube that connects the uterus to the reproductive organs), usually on the surface of the vagina. The initial symptoms are not obvious, but if they continue to worsen, there will be abnormal vaginal bleeding, lumps in the vagina, etc. Vaginal cancer mainly includes: the most common vaginal squamous cell carcinoma , and vaginal adenocarcinoma. As well as vaginal melanoma and vaginal sarcomas [8].

6.3. HPV and penile cancer

Penile cancer occurs in the skin and tissues of the penis. Its clinical manifestations include dysplasia, ulceration of the skin of the penis, or painful bleeding with discharge. The p16INK4A tumor suppressor gene is a biomarker recommended by the International Department of Urology (ISUP) for the diagnosis of penile cancer. Most penile tumors are squamous (epitheloid) carcinomas, but also: basal cell carcinomas, tumors, and melanomas. Basal cell carcinoma develops in the deep layers of the skin and grows slowly, so it is less likely to spread to other parts of the body. Tumors develop in blood vessels, muscle, fat, and other tissues. Melanoma is a tumor that arises from skin cells. Penile cancer is usually primary and rarely secondary, but it can spread to other parts of the body [8,10].

7. HPV vaccine and testing

Up to now, three vaccines have been launched to prevent high-risk HPV, namely Gardasil, Sevarix and Gardasil-9. According to WHO data estimates, HPV vaccines can prevent most cervical and anal cancers, more than half of vaginal cancers and nearly half of vulvar cancers, and they can also prevent some genital warts. Therefore, HPV vaccination is very important for both men and women. The best age for Sevarix and Gardasil-9 is 26. For those who have reached the age of 15, three injections are required after the first injection before they can be protected [11-13].

With regard to the examination of HPV and related tumors, cervical cancer is the only test method approved by the US Food and Drug Administration among the tumors caused by HPV. There are currently no FDA-approved assays for the detection of HPV infection or cellular changes caused by HPV in tissues such as the vagina, vulva, oropharynx, and anus. Research is ongoing on assays to identify treatments that can detect precancerous lesions at these sites or cancers found at an earlier, more treatable stage.

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8. Challenges and prospects

At present, there are still many challenges and problems about HPV prevention waiting to be broken through and solved through experiments and other means. For example, in terms of HPV vaccines, although three vaccines have been launched, these vaccines can only prevent part of the high-risk HPV, and most HPV types are not covered, especially some low-risk HPV. Although these low-risk HPVs will not cause obvious harm to the body under normal circumstances, they still have a certain probability of causing diseases such as papilloma or genital warts. At the same time, the currently launched HPV vaccine has been proved to be very effective in preventing related HPV through experiments, but whether the vaccine can maintain long-term immune effect remains to be explored. Therefore, future vaccine research also needs to pay attention to these undiscovered HPV types. At the same time, more experiments are needed to investigate the long-term immune effect of these vaccines. At the same time, there is still great resistance to the promotion of HPV vaccines. Due to economic development, religious and cultural issues in some areas, the promotion of HPV-related concepts and knowledge has been greatly hindered, and the popularization of vaccines has been severely limited.

With the progress and development of society, global medical technology and global health work are improving steadily. In recent years, great efforts have been made by health organizations to control the number of patients with HPV-related diseases. The emergence of HPV vaccine has greatly controlled the number of patients. With the conduct of follow-up research and the promotion of relevant knowledge, the effect of HPV vaccine will be further optimized and expanded with the experiments and explorations of researchers, and the popularity of vaccine will gradually increase.

9. Conclusion

This article studies the prevention and detection of HPV and related diseases and focuses on the relationship between cervical cancer and HPV, summarizes the structure of HPV virus and how to cause cancer, and integrates some papers related to HPV and its vaccines in recent years, summarizes the advantages and disadvantages, discusses the development direction of technology. Finally, in terms of vaccines, there are still some difficulties that need to be overcome (the popularization of vaccines and the development of vaccines). Hope this article can help in solving the problems. Subsequent research needs to design more reasonable and representative epidemiological research plans to obtaining accurate and credible results, gradually deepening people's understanding of the correlation between HPV and cancer.

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