Review

Progress in the Research on the Relationship between Infection with Human Papillomavirus and Tumorigenesis

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Abstract

Human papillomavirus (HPV) is a DNA virus that infects the skin and mucous membranes of the human body. Approximately 80% of sexually active women are likely infected with HPV. Cervical cancer is one of the most common malignant tumors and is second in incidence only to breast cancer. Infection with high-risk HPV types is the main risk factor for cervical cancer, which is currently the only malignant tumor with a clearly defined etiology. HPV infection is also closely related to the incidence and development of other malignant tumors. In addition to cervical cancer, HPV can cause other urogenital tumors, as well as tumors in the digestive tract, lungs, eyes, skin, and other organ systems. This paper provides a review of the progress in HPV infection-related research and provides novel ideas for the study of tumor etiology and mechanisms.

Human papillomavirus (HPV) is a DNA virus that infects the basal epithelium of the skin and mucous membranes of the human body. It is ubiquitous among the population but its incidence is highest among sexually active young individuals. Approximately 200 types of HPV have been identified. These HPV types are categorized as high-risk or low-risk types based on their pathogenicity. The 13 high-risk HPV types are HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59m, and 68. HPV16 and HPV18 account for 50% to 60% of HPV cases, and are the most closely related with the incidence of malignant tumors. The risk of HPV infection is associated with age, gender, number of sexual partners, and other factors. The carcinogenic mechanism of HPV remains unclear and likely involves a multi-factorial, multi-step progressive process. Continuous, high viral load is the necessary condition for HPV-induced tumorigenesis. More than 10% of malignant tumors are related to HPV infection. Early studies have shown that HPV DNA is integrated into the host cell chromosome and interferes with the expression of vascular endothelial growth factor (EGFR) through E2 gene inactivation and the E5 gene, thus up-regulating the expression of the E6 and E7 proteins. The E6 and E7 proteins respectively inhibit the activity of

P53 and RB genes, activate the transcription of human cell telomerase, cause the abnormal differentiation of cells, lead to the immortalization of normal cells, and finally initiate tumorigenesis. Nevertheless, the immortalization of HPV-induced host cells cannot be explained merely by the lack of E2, the overexpression of E6 and E7, and host gene stability. In addition, integrated viral genes are not present in all HPV-related malignant tumors. Epidemiological studies have shown that some infections are associated with oral-genital contact. Viruses spread to other mucous membranes and initiate subclinical infection. After activation by certain unknown mechanisms, viruses will cause cancer and initiate malignant transformation. HPV infection has become a necessary condition for cervical cancer and may be a risk factor for other primary or secondary tumors.

HPV and urogenital malignant tumors

Cervical cancer

Cervical cancer is the cancer with the second highest incidence in women, and is closely related with HPV. Approximately 80% of sexually active women may be

infected with HPV. Each year, there are approximately 500,000 new cases of cervical cancer in the world and approximately 250,000 individuals die of cervical cancer. Studies have shown that HPV is present in tissue samples from 99.7% of cervical cancer cases. HPV16 and HPV18 account for 70% of cancer cases, and 50% of cervical cancer cases is caused by HPV16. HPV 6, 44, 53, and 54 appear in multiple infections, whereas all other HPV types are single infection. Infection with a single low-risk HPV type has not been found in cervical cancer tissues. High-risk HPV types are co-infected with low-risk HPV types. HPV16 is most closely related with cervical squamous carcinoma and HPV18 most likely causes cervical adenocarcinoma. Epidemiological research and evidence have identified HPV as the cause of cervical cancer. The cancerization of cells by HPV is caused by multiple factors that interact with each other. However, not all HPV infections will develop into cancer: the carcinogenesis of HPV is dependent on the body's immunity and persistent HPV infection.

Ovarian cancer

Ovarian cancer is closely related with HPV16 and HPV18, and is positively correlated with vascular endothelial growth factor ki-67. In 2012, Malisice *et al.* [2] studied 54 patients with ovarian cancer. They identified four cases of positive HPV16 infection based on the results of PCR detection and the clinicopathological features of postoperative tissue. They found that HPV DNA existed in 7.4% of the tissue, indicating that HPV may be related to the occurrence of ovarian cancer. In addition, the rate of HPV16 infection in ovarian cancer tissue was significantly higher than that in normal ovarian tissue. These results implicate HPV as the cause of ovarian cancer.

Vulvar and vaginal cancer

Domestic and foreign studies have shown that HPV DNA is present in the majority of vulvar and vaginal cancer patients. In 2008, Sutton *et al.* [3] studied paraffin-embedded tissue sections from 116 cases of vulvar squamous cell carcinoma and found 81 HPV-positive cases, among which HPV16 was the most common type of infection. DeVuyst *et al.* [4] detected HPV DNA in 40.4% and 69.9% of 1873 cases of vulvar cancer and 136 cases of vaginal cancer, respectively. HPV16 accounted for 75.0% of the detected cases, and its

detection rate was 5% more than that of cervical cancer. Therefore, HPV infection likely plays an important role in the development of vulvar and vaginal cancers. In addition, infection with high-risk HPV types may be a risk factor for these two kinds of cancers.

Penile cancer

HPV is closely related to penile cancer. Infection with HPV16 is the most common type of HPV infection among penile cancer cases and might also be a cause of penile cancer. In 2009, Miralles-Guri *et al.* [5] provided a systematic and comprehensive review of 1466 penile cancer cases from 1986 to 2008. They found that 46.9% of cases were infected with HPV. Among these cases, infection with HPV16 was the most common (60.2%), followed by HPV18 (13.3%). Calmon *et al.* [6] detected HPV DNA in 48.9% of 47 specimens of penile squamous cell carcinoma. Most detected HPV types were high-risk HPV (42.5%). Therefore, high-risk HPV plays an important role in the development and progression of penile cancer.

Breast cancer

HPV16 and HPV18 can promote the immortalization of normal human breast epithelial cells. Possible infection pathways of HPV in the breast include: 1) Transfer of HPV from the genital tract to the blood and (or) lymphatic metastasis. 2) Invasion of HPV through sexual activity. 3) Invasion of HPV along mammary ducts, thus inducing the carcinogenesis of terminal lobular units or ductal epithelial basal stem cells. Researchers have extensively studied the presence of HPV in breast cancer tissue but reported significantly different results and correlations. However, with the development of various detection technology, many reports have implied that HPV exists in breast cancer tissue. Pereira *et al.* [7] analyzed 61 cases of fresh frozen breast cancer specimens and reported that 16, or 26%, of these case were HPV positive

Bladder cancer

The relationship between HPV and bladder cancer has drawn increased attention along with the development of PCR technology, which has enabled the growth of relevant research on HPV. A meta-analysis by Chinese scholars of literature on HPV and bladder cancer from the past 10

years reported that 35.60% of Asian patients with bladder cancer were infected with HPV; 34.29% of these cases were infected with high-risk HPV types. Moreover, 47.20% of Chinese mainland patients with bladder cancer were infected with HPV [8]. Zhu Weizhi *et al.* [9] used second-generation hybrid capture technology to test 65 cases of bladder transitional cell carcinoma and 30 cases of normal bladder tissue. They found that high-risk HPV16/18 was present in 42 cases of bladder cancer tissue at a positive rate of 64.60%. High-risk HPV16/18 was also found in two cases of normal bladder tissue with a positive rate of 6.70%. This result indicated that the detection rate of high-risk HPV16/18 in bladder cancer tissue was significantly higher than that in normal bladder tissue. Therefore, HPV16/18 infection may be involved in the incidence of bladder transitional cell carcinoma and likely affects the malignancy grade and progression of bladder cancer.

HPV and gastrointestinal malignant tumors

Oral cancer

The occurrence of oral cancer is a multi-step, multi-factorial complex process. In recent years, studies have found that the occurrence of oral squamous cell carcinoma is closely related with high-risk HPV16 and HPV18 infection [10]; that the number of vaginal intercourse and oral sex partners has increased among oral cancer patients; that marijuana users are mostly HPV-positive; and that HPV-positive patients have better prognosis. Babiker *et al.* [11] screened 200 cases of oral disease patients for HPV and reported that high-risk HPV infection accounted for 6%, or 12, cases. Among these 12 cases, eight were oral cancer cases and four were non-neoplastic lesion cases, in which HPV16 accounted for 50%. These results suggested that high-risk HPV is a risk factor for oral cancer.

Esophageal cancer

Esophageal cancer is one of the ten most common malignant tumors in China. Many scholars have begun to study the effect of HPV infection on esophageal epithelial cell carcinoma. Their results showed that in different regions, the positive HPV rate ranged between 0% and 67%. Dabrowski *et al.* [12] performed quantitative DNA analysis

in 56 cases of esophageal cancer and 56 cases of normal mucosal tissue from patients in southeastern Poland. Their results showed that 50%, or 28 cases, of esophageal cancer patients were positive for HPV DNA. Among these cases, five were positive for HPV16 and HPV18, accounting for 8.9% of cases. Only four cases in the normal mucosa group were positive for HPV DNA. No high-risk types were detected. The incidence of HPV in esophageal cancer was significantly higher than that in the control group.

Gastric cancer

Gastric cancer originates in gastric mucosa epithelial cells and is related with HPV infection. Chinese scholars used in situ PCR and immunohistochemistry to detect E6, the HPV16 cancer gene, in tissue samples from gastric cancer patients in Shaanxi Province. They detected HPV16 E6 in 25% (11/40) of 40 cases of gastric cancer but not in 40 cases of corresponding non-tumor healthy tissue. In addition, the infection rate of HPV16 in cardiac carcinoma was significantly higher than that in non-cardiac cancer [13].

Colorectal cancer

HPV infection was firstly assumed to be associated with squamous cell carcinoma. However, later studies reported that adenocarcinoma might also be associated with HPV infection because HPV DNA was first detected in tissue from cecal adenocarcinoma cases. Using PCR analysis to analyze the relationship between HPV infection and colorectal cancer, Ma Heng *et al.* [14] detected HPV in 135 cases of colorectal cancer and in 25 cases of normal colorectal mucosa. Their results showed that the overall HPV positive rate of colorectal cancer was 32.59%, which was significantly higher than that in normal mucosa tissue. Most cases were infected with HPV16, followed by HPV18. At the same time, they confirmed that HPV infection was unrelated with the location of colorectal cancer, pathological grade, clinical stage, and lymph node metastasis.

Anal cancer

The incidence of anal cancer is low compared with those of other cancers but has increased in recent years. Most cases of anal cancer are associated with HPV, especially HPV16 [15]. Varnai *et al.* [16] detected HPV DNA by using PCR and found that 80.9% of anal cancer cases were positive for HPV.

This result indicated that high-risk HPV infection could increase the risk of anal cancer.

HPV and respiratory tract malignant tumors

Nasopharyngeal carcinoma

Via fluorescence quantitative PCR detection, Huang Zhongqiang *et al.* [17] found that out of 150 cases of nasopharyngeal carcinoma, 55 cases (36.7%) were positive for HPV16 and HPV18. Out of 50 cases of normal healthy people, three cases (6%) were positive for HPV16 and HPV18. The detection rate of HPV in the case group was significantly different from that in the control group, indicating that HPV16 and HPV18 are closely related with the incidence and development of nasopharyngeal cancer and may even cause this type of cancer.

Tonsil cancer

Maier *et al.* [18] studied specimens from 223 cases of head and neck tumors. The HPV detection rate in tonsil cancer cases was 37.5%, ranking the first. These cases were mainly infected with HPV16, thus implicating HPV infection in tonsil cancer. Studies have also shown that patients with HPV-positive tonsil cancer and tongue cancer have better prognosis [19].

Laryngeal cancer

By using in situ hybridization, Jiangyin Rong *et al.* [20] detected HPV16 and HPV18 mRNA in laryngeal mucosa from 123 cases of laryngeal squamous cell carcinoma and 123 cases of healthy individuals. The HPV16 E6 and HPV18 E6 positive rates were 46.34% and 35.77%, respectively. The high-risk HPV positive rate was considerably higher than that in the normal group, indicating that HPV infection is an important risk factor for laryngeal cancer. The retention and sustained expression of the E6 fragment is closely related with the carcinogenesis of laryngeal tissue.

Lung cancer

Lung cancer is one of the most serious malignant tumors that endanger human health. Many scholars believe that HPV is a risk factor for lung cancer [21]. Kong Linghui *et al.* [22] used specific PCR detection to detect HPV16 and

HPV18 DNA in 47 cases of non-small cell lung cancer and in 13 cases of benign lung lesions. They detected HPV16 and HPV18 DNA in 42.55% (20/47) of the non-small cell lung cancer group. This detection rate was significantly higher than the detection rate of 7.69% (1/13) in the benign lung lesions group. Thus, HPV infection exists in lung cancer tissue.

HPV and ophthalmic malignant tumors

Conjunctival cancer

HPV is implicated in the development of conjunctival cancer via interaction with UV or other factors. Payayed *et al.* [23] detected HPV DNA in 92.9% of conjunctival tissue from conjunctival cancer cases. Most scholars believe that HPV may be associated with conjunctival cancer but that HPV alone is not carcinogenic and must work with other factors to cause conjunctival cancer.

Retinoblastoma

Retinoblastoma is a malignant tumor produced by the loss of function of the tumor suppressor gene; this loss-of-function is caused by a mutation in the Rb gene. HPV infection is a risk factor for retinoblastoma. Animal experiments showed that transgenic mice expressing HPV16 E6 and E7 can develop neuroblastoma. Montoya *et al.* [24] detected HPV DNA in 82.3% of five cases of hereditary binocular retinoblastoma. By contrast, 7 out of 10 randomly selected cases were negative for HPV.

HPV and skin cancer

Skin cancer is divided into two categories: melanoma and non-melanoma. The most common categories of melanoma are malignant melanoma, squamous cell carcinoma, and basal cell carcinoma. Karagas *et al.* [25] detected HPV DNA in 252 cases of squamous cell carcinoma, 525 cases of basal cell carcinoma, and 461 control cases. They found that DNA levels in the squamous cell carcinoma group were significantly higher than those in the control group were not significantly different between the basal cell carcinoma and control groups. The HPV positive rate was 19% to 58%, with high-risk HPV types being dominant. These results

indicated that malignant skin tumors might be associated with HPV infection.

Summary

Tumorigenesis is a multi-step process that is caused by the interaction of multiple factors. Persistent HPV infection is a direct cause of cervical cancer, and is correlated with tumorigenesis in other organ systems. Although relevant studies were conducted in different geographical locations and reported different specimen sources and detection methods, research results had shown that HPV-related tumors are mainly caused by high-risk HPV types, especially HPV16. However, the close relationship between HPV infection and tumorigenesis needs further study. The correlation of HPV with tumor development in other organ systems will clarify tumorigenesis and broaden research ideas for tumor treatment.

Declarations

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No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

J Zhang made the literature analysis and wrote, discussed and revised the manuscript of this review.

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