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REVIEW

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Risk factors contributing to the persistent infection of high-risk Human papillomavirus (HPV)

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Abstract

Human papillomavirus (HPV) infection in the reproductive tract is one of the most prevalent sexually transmitted infections worldwide. Persistent infection with high-risk HPV (HR-HPV) types is a major contributor of cervical cancer and its precancerous lesions. The severity and progression of these lesions are closely linked to multiple HPV infections and viral load. Emerging research indicates that the persistence of HR-HPV infection is influenced not only by viral genetic mutations and trait variations but also by host immune response and genetic factors. Investigations into these risk factors are gaining momentum and hold promise for breakthroughs in the diagnosis and identification of prognostic markers for cervical cancer. This review provides a comprehensive overview of recent advancements in this field.

Keywords

Human papillomavirus; Cervical cancer; Persistent infection

1. Introduction

Cervical cancer is a common gynecological tumor that seriously threatens women's lives and health. Epidemiological studies have identified human papillomavirus (HPV) infection as an important environmental factor influencing the occurrence and development of cervical cancer [1, 2]. Majority of women infected with HPV have been shown to resolve spontaneously while, a few may develop persistent infections that progresses to cervical intraepithelial neoplasia (CIN) or even cervical cancer, this indicate that there are other risk factors playing a role in the development of cervical cancer. Recent studies have shown that in addition to external factors such as environment and lifestyle, multiple factors associated with the host and virus itself are likely to possess a certain correlation in the occurrence and development of diseases. A clear understanding of these risk factors will not only aid in identifying women at high risk for persistent HPV infection but also facilitates the development of more precise screening and preventive strategies, potentially improving early intervention and reducing the burden of cervical cancer. This study aims to systematically analyze both viral and host-related factors contributing to the persistence HR-HPV infection, providing insights into their role in cervical cancer progression. By integrating recent findings, we seek to enhance current screening and prevention strategies, ultimately aiding in the early identification of high-risk individuals.

2. Viral factors

2.1 Introduction to HPV

HPV is a small, non-enveloped DNA virus composed of a single copy of double-stranded, closed-loop DNA and associated proteins. A distinctive feature of its genome is that all open reading frames (ORFs) are located on the same DNA strand, with only one DNA strand serving as a template. The coding DNA strand containing ORF can be divided into three regions: early region (E), late region (L), and long control region (LCR). The E-region serves to regulate virus replication, transcription, while also inducing host cell transformation. The L-region plays a role in assembling and stabilizing viral particles. To date, more than 100 types of HPV have been identified worldwide, with more than 40 known to infect reproductive tract. These HPV types are divided into three groups: the low-risk group, moderate-risk group and high-risk group. The low-risk group (HPV 6, 11) are usually associated with genital warts and flat genital warts. Moderate-risk group (HPV 33, 35, 39, 40, 43, 45, 51, 56, 58) are usually associated with low-grade atypical hyperplasia and cancer of the reproductive tract while high-risk group (HPV 16, 18, 31) are associated with malignant tumors of the vulva, vagina and cervix. Notably, the detection rate of HR-HPV in cervical cancer is over 99%, and persistent infection with these HR-HPV types contributes to the progression of invasive cervical cancer.

2.2 Incidence rate and prevalence of HPV infection

HPV infection in the reproductive tract is mainly transmitted through sexual contact, though other modes of transmission have also been reported. Studies indicate that within two years

of initiating sexual activity, up to 50% of women may test positive for HPV in the reproductive tract if closely monitored through HPV testing and cervical cytology [3]. Over a lifetime, approximately 80% of women are estimated to have the probability of HPV infection in the reproductive tract [3]. Among these, 5% develop genital warts, 35% exhibit abnormal cervical scraping, 25% progress to CIN, and less than 1% eventually develop cervical cancer [3]. The prevalence of HPV infection varies significantly by region, influenced by differences in testing methods and tested populations. The subclinical infection and latent infection rates are estimated to be at least three times higher than clinical HPV infection, and if tested for multiple times, the rates may increase up to 3–5 times than a single test.

The known high-risk factors for HPV infection and HPV related tumors include high-risk sexual behavior, immune suppression and age. Besides sexual behavior, age is supposed to be an important influencing factor. Shi *et al*. [4] found that the cervical HPV infection rate has two peaks (56.1%; 44.4%) in the women with age groups 18–24 and 45–49 years, showing a U-shaped curve. The peak in the age group 18–24 years may be due to the current openness of sexual activity and the lack of a mature immune barrier in the body's reproductive tract. Similarly, the peak in the later age group, especially among postmenopausal women over 50 years may be due to the gradual decline of the body's immune function with age, preventing timely clearance of HPV infections from the body. Additionally, decreased ovarian function and reduced estrogen secretion in women with later age group may lead to a decrease in the number of lactobacilli in the reproductive tract causing an imbalance in the vaginal microbiota. This may further increase the chance and persistence of HPV infection.

2.3 The relationship between HPV infection and cervical intratumoral lesions and cervical cancer

The relationship between HPV and cervical lesions, and the relationship between genital HPV infection and cervical cancer was first proposed by German virologist Zur Hausen [2]. Through epidemiological and biological studies, HPV infection has been identified as a necessary prerequisite for the development of cervical precancerous lesions and invasive cervical cancer [4, 5]. Several epidemiological evidences support this statement: ① HPV DNA can be found in almost all CIN, cervical squamous cell carcinoma and cervical adenocarcinoma, especially associated with high-risk genotypes such as, 16, 18, 31 and 45; ② The degree of correlation between HR-HPV infection and precancerous lesions is relatively high compared to low-risk HPV; ③ The presence of anti HPV 16 antibodies in cervical squamous cell carcinoma; ④ The relative risk (RR) of developing precancerous lesions or cervical cancer in HPV infection ranges from 20–70 in most studies, making this association even stronger than the relationship between smoking and lung cancer; ⑤ Continuous exposure to HPV-16 can lead to the development of cervical cancer in situ. However, if exposure stops, the risk of cancer development disappears; ⑥ HPV infection occurs before cervical cancer.

A prospective study involving 1417 women with normal cervical cytology found that those who tested positive for HPV DNA had a 3.8-times higher risk of developing CIN and 12.7-times higher risk of developing high-grade squamous intraepithelial lesions (HSIL) compared to HPV DNA negative women. When the analysis focused specifically on HPV 16, this risk increased to 5.8 and 63.9 times [6]. Another prospective study showed that 15–28% of HPV DNA positive women developed CIN within 2 years, while only 1–3% of HPV DNA negative women developed squamous intraepithelial lesions (SIL) within 2 years [7].

2.4 Persistence and clearance of HPV infection

As a common sexually transmitted disease, HPV infection is mostly transient. Most studies have reported that the cervical HPV infection naturally clear within 7–12 months, with only a small portion having persistent infection [2, 8–10]. The studies have also shown that the persistent infection with HR-HPV is a necessary condition for cervical lesions [2, 10–13]. Reports indicate that the persistent infection with HR-HPV increases the risk of CINIII by 100–300 times. In contrast, the likelihood of CIN occurring in HR-HPV negative individuals within the following 2 years period are very low. The cytological results of such individuals during the follow-up period also transitions from mild or borderline abnormalities to normal [10].

A prospective study by Dalstein *et al*. [10] comprising of 781 women with normal/ASCUS (Atypicai Squamous Cells of Nnknown Significance)/CIN cervical cytology used the second-generation hybrid capture method (HC II) to detect HR-HPV, and followed up every 6 months, with an average follow-up of 22 months. The results showed the average infection time of HR-HPV positive patients to be 7.5 months (3–42 months), with more than 50% of patients clearing infection within 7.5 months. HPV virus clearance was also related to viral load, and those with a viral load of $\geq$10 pg/mL were less likely to clear infection than those with a viral load of $<$10 pg/mL. Additionally, compared to HR-HPV negative individuals, those with transient and persistent HPV infection were more likely to develop cervical cytological ASCUS and SIL, with relative risk (RR) of 2.38 and 9.13, respectively. Notably, all patients progressing to CIN positive had persistent infection with HR-HPV. The author also found that compared to the HR-HPV negative individuals, HR-HPV low to moderate viral load individuals, and high viral load individuals were more prone to cervical cytological abnormalities, with relative risk (RR) of 1.65 and 8.66, respectively. The study concluded that persistent infection with HR-HPV is an important risk factor for the occurrence of CIN, while a high viral load serves as a predictor for the onset of HSIL [10, 14].

Hajia M *et al*. [13] conducted a longitudinal study following up 100 women, with one follow-up every 6 weeks for the first 3 months and the next follow-up every 3 months for a total of 15 months. Two consecutive HPV positive cases were defined as persistent infection. The result showed that the persistent HPV infection was associated with the persistence of SIL, with an OR (Odds Ratio) value of 3.91 (95% CI (Confidence Interval): 1.58–9.65). Additionally, persistent high viral load was linked to an even greater risk, with OR value of 4.97 (95% CI: 1.45–

17.02). Based on this, the author concluded that persistent infection of type specific HPV, especially with high viral load, is an important factor in the formation of chronic cervical lesions.

A study [15] reported the results of a prospective study on persistent HPV infection in 2001 that followed 1611 women four times a year from 1993 to 2000, defining the initial two consecutive HPV DNA positive cases as persistent infection. The results showed that compared to HPV negative patients, the relative risk of SIL in patients with HR-HPV persistent infection was 10.19 (95% CI: 5.9–17.6), and the relative risk of SIL in HPV 16 or 18 persistent infection patients was even higher, reaching 11.6 (95% CI: 4.1–33.3). In contrast, the patients with non-persistent infection had a relative risk of 8.68 (95% CI: 2.3–15.1) for SIL.

2.5 HPV load and cervical lesions

Swan *et al*. [16] used f-specific PCR (Polymerase Chain Reaction) fluorescence assay in 1999 to detect HPV (16, 18, 31, 45) DNA in 149 women with CIN II–III, 176 women with CINI, and 270 women with normal cervical provide full name of the cytology. The results showed significantly elevated levels of HPV DNA in cells with the severity of cervical lesions (p = 0.0004). Further analysis of HPV types indicated that, only the number of HPV 16 DNA was highly correlated with the severity of cervical lesions (normal cytology 2.2 $\times$ 10^2, CIN I 4.1 $\times$ 10^7, CIN II–III 13 $\times$ 10^9 pieces). However, the underlying reasons why HPV DNA levels correlate with disease severity and why HPV 16 differs significantly from other HR-HPV in terms of viral expression remains unclear.

Similarly, Sun *et al*. [17] tested the HPV positivity rate and HPV viral load through HC II in 30 patients with cervical SIL or cervical cancer in Taiwan, China. The positivity rate of HPV DNA was 70% in cervical cancer patients and, 21% in the control group, with OR of 6.6 (95% CI: 2.6–17.0). The risk of developing SIL and cervical cancer in patients with high viral load was also found significantly higher than those with low viral load, with OR of 18.0 (95% CI: 3.0–108.5). Based on these findings, the authors concluded that high viral load of HR-HPV is a major risk factor contributing to the development of SIL and cervical cancer.

Josefsson *et al*. [18] reported the results of using PCR technology to determine the HPV 16 virus load in 478 cases of cervical carcinoma in situ and 608 normal controls. The study divided patients into 5 groups based on the viral load from low to high. The result showed that in comparison to HPV 16 negative individuals, the risk for cervical in situ cancer among HPV 16 positive individuals gradually increased from the low to high viral load group, with OR of 2.0, 4.4, 8.1, 18.7 and 68.8, respectively. A study by Ylitalo *et al*. [19] from the same research center also demonstrated the relationship between persistent high levels of HPV 16 virus and the occurrence of cervical cancer *in situ* at the same time, which was published in Lancet. They conducted HPV 16 DNA quantitative PCR detection on cervical *in situ* carcinoma and the control group, and analyzed the relationship between HPV virus levels and cervical *in situ* carcinoma in the years prior to diagnosis. Research indicated that the risk for developing cervical cancer *in situ* increases with increasing virus load over the years. To illustrate this, patients were divided into three groups based on their HPV virus levels in the year before diagnosis. Compared to HPV negative individuals the OR values for cervical cancer *in situ* was 3.1, 10.3 and 43.1. Additionally, they pointed out that the level of HPV 16 virus can continue to increase 13 years or even longer before diagnosis, even in patients who initially had normal cytological results. Among patients diagnosed with cervical cancer, those who exhibited a high HPV 16 viral load 10 years ago had a 30-fold higher relative risk of developing cervical cancer in situ compared to those who were negative for HPV 16. Therefore, the author concluded that sustained high HPV l6 viral levels can increase the risk of developing cervical cancer *in situ*.

Several reports have indicated that the load of HR-HPV virus is related to the degree and scope of cervical lesions [20, 21]. The HPV DNA load shows an upward trend with the severity and scope of the lesion. Patients with high viral load have an increased risk of developing lesions above high SIL (OR = 35.0, 95% CI: 4.2–294.5) and large-scale lesions (OR = 5.3, 95% CI: 1.1–24.9). However, no significant correlation has been observed between low levels of HPV DNA, low SIL and smaller lesion size [20].

On the contrary, a study by Lorincz *et al*. [22] in 2002 showed that HR-HPV infection significantly increases the risk of cervical lesions above CIN III, while high viral loads cannot further predict the risk of cervical lesions above CIN II. Most studies have shown that an increase in HPV 16 viral load is associated with the occurrence or progression of CIN III or cervical cancer, but this phenomenon does not appear to be present in other HR-HPV. This suggest that only specific type of HPV DNA load is associated with tumor progression [2, 16, 18, 19, 23, 24]. The quantitative PCR method has been identified to provide reliable and repeatable HPV virus load detection [2]. However, the current scale standards and detection methods for viral load need to be further clarified, and further studies with sufficient sample size are needed to establish clinically relevant guidelines [2].

2.6 HPV gene variation and their role in carcinogenesis

A large number of studies have confirmed that different HPV types have different pathogenic abilities, so it is reasonable to believe that intra type variations of specific HR-HPV types may also have different carcinogenic abilities. Although more than 100 HPV species have been identified, research on viral gene mutations is currently mainly focused on HPV 16. According to the phylogenetics classification method, HPV 16 can be divided into six types; European type (E), Asian type (As), Asian American type (AA), African type 1 (Afl) and African type 11 (Af2) based on their source of origin and nucleic acid sequence of the upstream regulatory region (URR) of the virus. Current studies [25, 26] have shown that the HPV 16 gene variant has different carcinogenic abilities, with the European type being considered as a low-risk type. Berumen *et al.* [27] found that the infection frequency of HPV 16 AA in cervical cancer among Mexican women was 21 times higher than that of normal controls, while the infection frequency of

HPV 16 E in cervical cancer was only 2.7 times higher than that of normal controls. The relative risk of HPV 16 AA suffering from cervical cancer (OR = 27.0) was significantly higher than that of HPV 16 E (OR = 3.4). Therefore, it was speculated that the high distribution of HPV 16 AA in Mexican population might be an important reason for the high incidence rate of cervical cancer. In addition, a small number of studies have suggested that gene mutations in other HR-HPV types (such as HPV 18, 31, 58, *etc.*) are also high-risk factors for inducing cervical cancer [26, 28]. However, due to lack of sufficient data on gene variations in other HPV types, further multicenter studies are needed to confirm their statistical significance.

Besides the upstream regulatory region and E6 gene, there are currently limited research on the variation patterns of other regions of the HPV genome (such as, LI, LZ, E7, *etc.*). Therefore, it is imperative to focus on whole genome sequencing of HPV positive specimens in order to better define the HPV genome mutation sites precisely related to the onset of cervical cancer. This will help target the viral genome mutation regions for *in-vitro* functional research and further elucidate their epidemiological mechanism.

3. Host factors

A follow-up study conducted by Muñoz *et al*. [29] on more than 1000 women showed increased risk for HR-HPV infection. However, the risk for HR-HPV infection did not differ significantly based on HPV type but was instead closely related to the patient's own condition. This proves that some host factors, including immune response and genetic background, play a decisive role in the outcome of HPV infection and the occurrence and development of cervical cancer.

3.1 Immune response

Most HPV infections are naturally cleared, indicating that the virus can stimulate the host to produce sufficient immune defense mechanisms to combat infection. The host's immune response plays an important role in the outcome of HPV infection, influencing whether the HPV infection is cleared or progresses to persistent infection.

Unlike systemic infection, HPV infection is limited to the initial site of infection and therefore surface of the cervical mucosa serves as the first line of defense. Cervical lesions associated with HPV infection are often characterized by reduced infiltration of inflammatory cells and decreased levels of cytokines, suggesting that HR-HPV infected sites exist in an immune-privileged state. Natural killer cell (NK cells) function by killing target cells infected by the virus at the early stage of infection, and their killing activity is not limited by MHC (Major Histocompatibility Complex). In precancerous and malignant lesions caused by HPV 16 infection, the killing activity of NK cells is suppressed against keratinocytes infected with HPV decreases, while it is normal in patients spontaneously clearing HPV infection. Sherif *et al.* [30] used RT (Reverse transcription)-PCR technology to detect the expression levels of IFN (Interferon)-γ and IL (Interleukin)-10 mRNA in the epidermis and subepidermis of 11 normal cervical tissues and 25 HPV 16 positive CIN samples. They found significantly lower expression of IFN-γ mRNA and significantly higher expression of IL-10 mRNA in CIN compared to that in normal cervical tissues. This suggest that HPV 16 infection may shift local immune responses away from Thl response mode, potentially contributing to the occurrence and development of cervical cancer. Additionally, IL-18, an important cytokine primarily produced by macrophages, has been shown to induce the production of IFN-γ stimulate Thl cell responses, and promote the production of virus specific CTL. IL-18 also promotes TNF expression, which enhances antiviral immune responses. However, studies have shown that the E6 and E7 proteins of HPV 16 can inhibit IL-18 receptor binding through competitive inhibition mechanisms and thus inhibits the induction of IFN-γ by IL-18 in monocytes and NK cells. This may be immune evasion strategy that serve to evade immune surveillance [31, 32].

Langerhans cells (LC) are antigen-presenting cells located in the epidermis, which can mediate local CD (Cluster of Differentiation) 4 T cell responses. Cervical cancer and precancerous lesions often occur in the cervical transitional zone. Recent studies have found that the density of immature LC in the transitional zone is significantly reduced compared to the cervical outer opening. LC from the transitional zone and CIN region, when subjected to the same stimulation, induces lower cell proliferation and IL-2 levels compared to LC from the cervical outer opening. In contrast, the immunosuppressive factor IL-10 is produced at high levels in these regions. This indicates that a decrease in LC density and changes in cytokine and chemokine expression in the cervical transitional zone causes a decrease in immune surveillance in the transitional zone [33].

3.2 Genetic susceptibility

The *HLA* (Human Leukocyte Antigen) gene family was among the first genetic factors identified in relation to cervical cancer susceptibility. HLA molecules are key molecules involved in antigen processing and presentation, thereby participating in the immune response and regulation of the body. The HLA gene group is located in the short arm of human chromosome 6 (6P21.31), and have a total length of 3.6 Mb, accounting for approximately 1/3000 of the entire human genome. The HLA gene complex is highly polygenic and polymorphic. It can be divided into three gene types: I, II and III based on the distribution of gene loci on chromosomes and the functional differences of the molecules encoded in HLA complexes. Research on the correlation between HLA and cervical cancer has mostly focused on HLA class II genes, with particular attention to three groups of HLA class II alleles: the first group of *HLA-DR Beta 1 (DRBI) * 13* (containing *DRBI * 1301-1305* alleles) and *HLA-DQ Beta 1* (*DQBI) * 0603*; Group 2: *DRBI * 1501* and *DQBI * 0602*; Group 3: *DQBI * 03* (including *DQBI * 0301-0303*). Studies have found that the latter two sets of alleles can increase the risk of cervical cancer [34], and multiple studies on women from different regions have consistently found a protective effect of *DRBI * 13* and/or *DQBI * 0603* on cervical cancer. Although these findings provide strong evidence of HLA's role in cervical cancer susceptibility, the individual contributions of these alleles remain unclear. Further large-

scale investigations are necessary to better understand their specific impact on disease development and progression.

Single nucleotide polymorphism (SNP) is a new generation of molecular genetic marker. At present, it is believed that the combination between SNPs play an important role in determining the risk of complex polygenic genetic diseases [35–37]. However, the research on related SNP loci and genetic susceptibility to cervical cancer is still in the ascendant [38]. P53, an earliest studied tumor suppressor gene associated with the genetic background of cervical cancer, has been shown to exhibit polymorphism at codon 72 and also found to associate with cervical cancer susceptibility [39–41]. However, the relationship between P53 gene polymorphism and the risk of HPV related cervical cancer has not been consistently confirmed across diverse ethnic populations, including those from Europe, America, Asia, Africa and Latin America [42, 43]. Recent research has expanded to include metabolic detoxification genes and other immune related genes in SNP locus research. Some scholars believe that the homozygous *GSTM1* (Glutathione S-transferase M1) blank genotype has a 3.3-fold higher risk of cervical cancer compared to women with *GSTM1* positive heterozygous genotype [44–46]. Studies [47] among women in the United States and Venezuela found that the *GSTM1* ineffective genotype increased the risk of cervical cancer in American women, while it did not increase the risk for Venezuelan women. This indicates that the same susceptibility factor may have different effects on different races and populations. Ongoing research continues to explore the relationship between other SNP loci and the incidence of cervical cancer.

While a high HPV viral load has been associated with an increased risk of cervical lesion progression, some studies have reported cases where viral persistence does not directly correlate with lesion severity, suggesting the involvement of additional co-factors such as host immune response and genetic predisposition [48–50]. Moreover, variations in detection techniques and viral quantification methods across studies may contribute to inconsistencies in reported , highlighting the need for standardized protocols to improve clinical ap associations plicability [51].

Recent studies have demonstrated that different HPV variants, even within the same high-risk type, can exhibit varying oncogenic potential due to genetic mutations affecting viral oncogene expression and immune evasion mechanisms [52, 53]. Additionally, regional differences in HPV subtype prevalence may contribute to variations in cervical cancer risk, highlighting the need for further epidemiological studies to assess the true impact of specific variants on disease progression [54].

Although HR-HPV viral load has been considered a key factor in the progression of cervical lesions, some studies have shown that viral load alone does not always correlate with the severity of disease progression [55]. Other factors, such as host immune response, genetic susceptibility, and HPV genotype variations, may play a significant role in determining whether HPV infection persists and leads to malignancy [56–58].

Despite providing a comprehensive review of factors influencing persistent HPV infection, this study has several limitations. First, variations in study design and sample populations among the referenced literature may introduce heterogeneity, affecting the generalizability of findings. Second, differences in sample selection criteria, including age distribution, HPV subtype prevalence, and geographic variations, may impact the interpretation of risk factors [59]. Additionally, while viral load is recognized as a key factor in HPV persistence, its clinical significance remains debated, as variations in measurement techniques and detection thresholds may lead to inconsistent conclusions [60].

In summary, persistent HR-HPV infection is a critical factor in the development of cervical cancer, influenced by viral characteristics, host immune response, and genetic susceptibility. Identifying these risk factors is essential for early screening and intervention. Future research should focus on refining HPV genetic screening methods to improve risk stratification and enhance cervical cancer prevention strategies. The integration of HPV genotyping into routine screening programs may enable more precise identification of high-risk individuals and facilitate personalized clinical management. Additionally, further investigations into host-virus interactions and the role of co-factors influencing HPV persistence could provide valuable insights for targeted prevention and therapeutic approaches.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

TF—designed the study and carried them out. TF, YHY—supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. Both authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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