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Review article

The immune system and human Papillomavirus: Insights into their complex interplay

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ABSTRACT

Background: Human papillomavirus (HPV) is a common sexually transmitted virus strongly linked to cervical and other cancers. The immune system plays a key role in controlling HPV infection, yet the virus has evolved mechanisms to evade immune detection. Understanding these interactions is essential for improving prevention and treatment strategies. This review aimed to elucidate the complex interplay between HPV and the host immune system via the production of both benign and malignant skin lesions. Although the immune system is often capable of clearing HPV infections, a proportion of individuals develop persistent or recurrent infections, which significantly increases the risk of progression to malignancy. The core objective of this study was to analyze the immunological mechanisms involved in the host response to HPV and to identify the key factors that modulate this response. These factors include viral genetic variability for example the E6 and E7 oncoproteins responsible for cellular transformation, host immune competence, and individual immunogenetic profiles. Additionally, this review examined the impact of immunosuppression—whether due to underlying disease or therapeutic interventions—on susceptibility to HPV infection and persistence. Environmental influences on immune function were also discussed in the context of HPV pathogenesis. Collectively, the evidence highlights the pivotal role of the immune system in determining infection outcomes and suggests that a more profound understanding of host-virus interactions could inform the development of targeted immunotherapeutic and preventive strategies. This comprehensive synthesis provides a conceptual framework for future research aimed at optimizing immune-based approaches (Prophylactic Vaccines) to control HPV-associated diseases.

Introduction

Human Papillomavirus (HPV) is a tiny DNA virus from the Papillomaviridae family, it infects skin and mucous membrane cells, with over 200 identified types [1]. These types are categorized as low-risk (causing warts) or high-risk (linked to cancers like cervical cancer). High-risk types, such as HPV-16 and HPV-18, can persist by integrating their DNA into host cells, and the virus often evades the immune system, leading to long-term infections [2]. While the vast majority (90%) of HPV infections are transient, resolving spontaneously within two years [3], a smaller proportion (approximately 10%) become persistent[4]. The persistent infection with high-risk HPV genotypes, particularly types 16 and 18, is a well-recognized etiological factor in the development of several malignancies, most notably cervical cancer [5] and other significant health conditions such as male infertility and prostate disease[6] The asymptomatic nature of most HPV infections can contribute to spreading the virus as individuals remain

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undiagnosed and unknowingly transmit the virus in addition the oncoprotein including E6 and E7 work synergistically to override cell cycle checkpoints, inhibit apoptosis, promote cellular proliferation, and induce genomic instability [7]. Several studies have documented the frequent occurrence of multiple HPV within different strains of infections within a single individual. This phenomenon, known as co-infection, suggests that exposure to various HPV genotypes can occur at age [8], our results suggest that most new detections in middle-aged women reflect the recurrence of previously acquired HPV [9]. Despite the availability of safe and effective HPV vaccines, infection with high-risk HPV genotypes persists as a significant global public health challenge. Cervical cancer, linked to HPV infection, remains the fourth most common cancer among women worldwide [10]. The emerging field of research on the human microbiome and its interaction with the immune system is proving vital for understanding HPV infection. Specifically, the composition of the vaginal microbial community appears to significantly influence the body's immune response to HPV. This means the particular balance of bacteria in the vagina plays a key role in whether someone can clear an HPV infection or if it becomes persistent [11].

This article review aims to explore the complex relationship between HPV and the human immune system, focusing on how this interaction contributes to both benign and cancerous skin lesions. It examines the immune mechanisms involved in combating HPV and highlights key factors influencing this response, such as viral genetics (notably E6 and E7 oncoproteins), immune competence, and genetic predispositions. The review also considers the effects of immunosuppression and environmental factors on HPV persistence and disease progression. Ultimately, it seeks to provide a foundation for future research to enhance immune-based strategies, particularly prophylactic vaccines, for controlling HPV-related diseases.

Cervical Cancer-associated HPV

One of the most prevalent malignancies impacting women globally is cervical cancer. The International Agency for Research on Cancer (IARC) estimates that there were 265,700 fatalities and 527,600 new cases of the disease in 2012. In 2020, approximately 604,000 women were diagnosed, with 342,000 deaths, giving an age-standardized incidence rate of around 13.3 per 100,000 women while in 2022, about 660,000 new cases of cervical cancer were diagnosed worldwide, along with 350,000 deaths. The problem is exacerbated in developing countries, where cervical cancer is the second most frequent cancer in women and was expected to be the cause of 230,200 cervical cancer deaths in 2012. This is primarily because of programs for screening that have not proved extremely effective[12, 13].

To accelerate the complete eradication of cervical cancer via vaccine, the World Health Organization (WHO) 2020 initiated the Global Cervical Cancer Elimination Initiative in 2020. The initiative's goal is to lower the incidence of the disease to less than 4 cases per 100,000 women years in all countries, thereby reducing the imbalances present beyond countries related to it. The project has established a target of 90–70–90, which must be met by 2030. Specifically, 90% of girls must have a vaccination before the age of 15, 70% of women must undergo at least two high-performance test screenings by the age of 45, and 90% of women who are diagnosed with cervical cancer or precancer must receive treatment [12].

The Role of Immune Cells in HPV Infection

The immune system plays a crucial role in defending the body against HPV infection. Immune cells, including Macrophages, dendritic cells, T-cells, and B-cells, are key players in this defense, Table 1 summarize this issue.

Stages of HPV Infection and Immune Response

1. Initial Immune Response

Upon HPV infection, the body initiates an immune response. Antigen-presenting cells recognize viral antigens and activate T and B cells. B cells then produce antibodies to neutralize the virus[22].

2. Chronic Infection and Persistence

If the initial response fails to eliminate the virus, a chronic infection can develop. HPV employs various mechanisms to evade the immune system, allowing it to persist within the host [23].

3. Immune Response During Cancer Development

HPV can induce the transformation of infected cells into cancerous cells. The immune response to these cancerous cells is complex and involves both protective and suppressive

mechanisms. Understanding this interplay is crucial for developing effective immunotherapies[24].

Toll-Like Receptors: Key Players in the Host Response to HPV Infection

To trigger immunological responses, TLR is responsible for recognizing conserved pathogen-associated molecular patterns (PAMPs), controlling endogenous ligands in the body, and encouraging protein cascade events. Furthermore, the ability of TLR to regulate gene expression is essential for establishing a suitable tumor microenvironment, whether it be for immune control or monitoring. Besides from cancer, TLR also plays a role in viral infection, and inflammatory disorders[25]. It has been demonstrated that TLRs are crucial in identifying and activating antiviral immune responses. An increasing quantity of research indicates that HPVs alter TLR expression and disrupt TLR signaling pathways, which results in long-term viral infection and the development of cancer[26].

Toll-like Receptors (TLRs) are innate immune receptors that serve as essential for the initiation of immune responses against viruses. HPV may trigger persistent viral infection and even malignancies by altering the expression level of TLR and interfering with TLR-related signaling pathways[27]. TLR activation and expression alterations may influence HPV infection control and may also accelerate the development of lesions and tumor development primarily associated with eliminating viral infections, blocking pathogen invasion, and averting cancer. It is also essential for triggering and bridging innate and adaptive responses, including cytotoxic cell-mediated subtypes and Th1 responses [28].

The identification of HPV proteins by TLR agonists has consequently emerged as a prospective field of research, and TLR is a major target in immunotherapy research for the prevention or treatment of cancer. They have been incorporated into several cancer-treatment medications, and some remarkable investigations have demonstrated their substantial intrinsic effectiveness in immunotherapy that controls TLR and cytokines. The E6 and E7 proteins of high-risk HPVs disrupt the interferon receptor signaling pathways and the activation of the interferon response genes, actively suppressing the interferon response for HPV infection, a crucial antiviral defense mechanism. By downregulating TLR9, the E7 proteins enable HPV to successfully avoid the innate immune response and postpone the activation of adaptive immunity [27].

The Complex Interplay between HPV and the Immune System: Mechanisms of Persistence and Immune Evasion

The host immunological response adequately eradicates the majority of human papillomavirus infections. On the other hand, human papillomavirus may result in persistent infections in certain individuals, and the persistence of high-risk human papillomavirus infection which is considered one of the main causes of cervical cancer development. The ability of these viruses to escape the human immune system is a crucial step toward their persistence and, eventually, the development of tumors. Viral targeting spans an assortment of different types of cells, receptors, transcription factors, and inflammatory mediators involved in the antiviral immune response, all of which have a role in carcinogenesis. Antigen-presenting cells, macrophages, natural killer cells, Toll-like receptors, nuclear factor kappa B, and several chemokines and cytokines, including interleukins, interferon, and tumor necrosis factor, constitute a few of these targets[29].

The majority of individuals with HPV infections resolve HPV-associated lesions within 1-2 years, suggesting that the host immune system is generally effective in combating HPV infection[30]. However, despite mounting an immune response, HPV-associated lesions can persist for extended periods, often months or even years, before regressing. Additionally, there is a significant delay of 6-12 months before the detection of anti-HPV antibodies in infected individuals. These observations suggest that HPV viruses have evolved mechanisms to evade host immune surveillance, potentially increasing the risk of persistent HPV infection in individuals exposed to additional risk factors[24].

To evade immune recognition, HPV-driven tumors establish an immunosuppressive microenvironment, similar to various other tumor types. This immunosuppressive environment is characterized by the infiltration of immunosuppressive cell types, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Tregs) [31]. Table 2 illustrates the HPV mechanisms to evasion the immune system.

The HPV Vaccine: A Comprehensive Guide

The HPV vaccine provides substantial protection against a range of HPV-related diseases. It is highly effective in preventing the majority of cervical cancers and can also lower the risk of other HPV-associated malignancies. Moreover, the vaccine prevents genital warts caused by specific HPV types and may offer additional protection against certain sexually transmitted infections. Extensive research has validated the safety and efficacy of HPV vaccines [37]. The HPV vaccine is built on Virus-Like Particles (VLPs), which are non-infectious shells mimicking the outer structure of the actual virus. These VLPs are made from the L1 major capsid protein of HPV and are produced using recombinant DNA technology. They do not contain viral DNA, so they cannot cause infection or cancer [38].To enhance the immune response, the vaccine includes an aluminum-based adjuvant. Once administered, the immune system recognizes the VLPs and produces protective antibodies. If the vaccinated individual is later exposed to HPV, these antibodies help neutralize the virus and prevent infection [39].

Current HPV vaccines demonstrate high, but not absolute, efficacy in preventing human papillomavirus (HPV) infection. While no vaccine offers complete protection (100%), HPV vaccines significantly reduce the risk of HPV-associated diseases[40]. Depending on the specific vaccine and age of the recipient, the HPV vaccination series consists of either two or three doses administered intramuscularly over 6 months. Completion of the entire series is essential for optimal protection**.** Extensive clinical trials involving millions of participants have established the HPV vaccine as a safe and well-tolerated intervention. Serious side effects are exceedingly rare[41]. Routine HPV vaccination is recommended for all pre-adolescents (typically 11-12 years old) regardless of gender. Catch-up vaccination for individuals up to the age of 26 is also recommended for those who were not previously vaccinated. There are several types of HPV vaccines available, differing in the number of HPV types they cover:

1. Bivalent vaccine: Protects against two types of HPV (types 16 and 18), which cause most cases of cervical cancer.

2. Quadrivalent vaccine: Protects against four types of HPV (types 16 and 18, in addition to types 6 and 11), which cause most cases of genital warts.

3. Nine-valent vaccine: Protects against nine types of HPV, including those that cause most cases of cervical cancer and genital warts[42]. Table 3 summarizes the role of some vaccines in HPV.

Beyond the Vaccine: Factors Influencing HPV Immunity

Several factors influence the immune response to HPV according to a previous study by Hewavisenti et al.,[23], including age, sex, overall health, and nutrition. Younger individuals have a stronger immune response due to heightened sensitivity, increased immune cell production, and stronger inflammatory and adaptive reactions. In contrast, aging leads to immunosenescence, reducing recovery speed, vaccine effectiveness, and resistance to infections[43].

HPV can affect both men and women, with women at higher risk for cervical cancer. Men may also develop genital warts and certain cancers, making HPV a significant health concern for all genders [44]. Individuals with chronic illnesses or weakened immune systems may have a reduced response to the HPV vaccine, as conditions like HIV/AIDS, autoimmune diseases, or immunosuppressive treatments can weaken the body's ability to develop strong immunity [23]. A balanced diet supports immune function through essential nutrients, while malnutrition weakens immunity, increasing infection risk and reducing vaccine effectiveness[45]. Furthermore, Smoking and chronic stress weaken the immune system by increasing inflammation, disrupting immune responses, and reducing vaccine effectiveness [46].

Immunotherapy for HPV-Associated Diseases: Current Progress and Future Directions

Ongoing research is centered on the development of innovative immunotherapy techniques to address HPV infection. Several promising approaches are currently under investigation. Understanding the cells and metabolites involved in the post-HPV and tumor microenvironment enables its immunomodulation as a therapeutic approach, as well as the development of drugs aimed at this purpose. A more profound understanding of the intricate relationship between the immune system and various cancers, particularly those etiologically linked to HPV, has significantly advanced the investigation and

development of therapeutic vaccines targeting these specific malignancies [47]. This therapeutic modality seeks to stimulate the immune system to recognize and eradicate HPV-infected cells. Prominent immunotherapy strategies include:

1. **Immune Checkpoint Inhibitors:** Research on immune checkpoint inhibitors focuses on developing antibodies to neutralize T lymphocyte receptors like PD-1, PDL-1, and CTLA-4, which are upregulated in tumor cells to prevent apoptosis and promote tumor growth. Monoclonal antibodies are also being explored to block receptors, such as EGFR, that contribute to tumor progression. Current strategies targeting EGFR, NKG2D, and other key receptors for HPV-related cancers are being clinically evaluated [48].

2. Therapeutic Vaccines: vaccines can stimulate the immune system to generate specific antibodies capable of combating the HPV virus.

3. **T-Cell Modification:** McCormack *et al.* explored the use of naïve T cells to generate HPV-specific T cells as a potential treatment for immunocompromised patients. Their study demonstrated that naïve T cells could be isolated and modified ex vivo to specifically recognize HPV antigens, thereby enhancing their cytotoxic activity against HPV-infected cells. The successful expansion and strong antiviral response of these modified T cells highlighted their potential as an immunotherapeutic intervention. This approach is particularly relevant for individuals with weakened immune systems, who may struggle to mount an effective immune response against HPV. By leveraging antigen-specific T-cell therapy, this strategy offers a promising avenue to enhance immune control over HPV-related diseases, including cancers [49].

4. Gene Therapy: A previous study by Graham provided a comprehensive analysis of HPV gene expression, its regulatory mechanisms, and potential strategies for developing novel antiviral therapies and diagnostics. The research examined how both viral and host factors tightly regulate HPV gene expression, impacting viral replication and pathogenesis. It also explored key regulatory components, such as host cell interactions, splicing mechanisms, and viral promoters, concerning disease progression. Furthermore, the study discussed potential antiviral strategies designed to interfere with viral transcription and replication, as well as emerging diagnostic methods targeting HPV gene expression. These findings have contributed to the development of more effective diagnostic tools and treatment approaches for HPV-related diseases [50].

The Role of the Vaginal Microbiome in Shaping the Immune Response to HPV

The intricate interplay between the human microbiome and the immune system is a burgeoning field of research. In the context of HPV infection, this interaction is particularly significant, as evidence suggests that the composition of the vaginal microbial community can substantially influence the host's immune response to the virus [11]. The vaginal microbiome is a complex ecosystem of microorganisms, primarily bacteria that colonize the female genital tract. The composition of this microbial community is influenced by various factors, including age, sex, sexual activity, and antibiotic use[51].

The vaginal microbiome can modulate the immune response to HPV in several ways including Altering Inflammatory Responses: The vaginal microbiome can influence the intensity of the host's inflammatory response to HPV infection. Certain bacterial species may exacerbate inflammation, while others may mitigate it[52]. Modulating Immune Cell Function: The microbiome can influence the function of various immune cells, such as T cells, B cells, and antigen-presenting cells[53]. Interacting with the Virus: The microbiome can directly interact with the virus, affecting its ability to replicate and spread.Impacting Vaccine Efficacy: The composition of the vaginal microbiome may influence the efficacy of HPV vaccines[54].

Numerous studies have demonstrated a correlation between alterations in the vaginal microbiome and the risk of HPV-associated cervical cancer. These studies suggest that certain bacterial species may increase cancer risk, while others may decrease it.

Proposed mechanisms linking the vaginal microbiome to HPV-associated diseases include the Production of Antimicrobial Compounds: Some bacteria produce antimicrobial compounds that can inhibit viral growth. Modulating Innate Immunity: The microbiome can influence pattern recognition receptors (PRRs), which play a crucial role in initiating the innate immune response. Interacting with Viral Antigens: The microbiome can interact with viral antigens, affecting how they are recognized by the immune system[55]. Figure 1 explains How the Vaginal Microbiome Affects the Immune Response to HPV.

Table 1. The role of different immune cells in HPV infection, persistence, and clearance.

Immune cells	Subtype	Function	Ref.
Macrophages	M1	Phagocytosis, Ag presentation, and Cytokine production	[14]
	M2	Suppress anti-tumor immune response.	
Natural Killer cell		They play an important role in the early stages of infection. Direct kill virus-infected cells and cancer cells and have an indirect role in T-cell activation. These cells kill virus-infected cells and	[15]
Dendritic cell		Ag presents to CD+8 T-cell, viral clearance via regulatory function, and may have a role in inducing cervical cancer.	[16]
B-cell		B cells produce antibodies or plasma cells produce antibodies that bind to the virus, marking it for destruction by other components of the immune system, such as phagocytes or the complement system. Antibodies also help prevent the virus from infecting new cells.	[17]
T-cell	CD+4	These cells play a central role in coordinating the immune response. When they detect the virus, they activate other immune cells to attack the virus. Interact with Ag on MHC II molecules, Cytokine production, and subsequent CD+8 T-cell activation.	[18]
	CD+8	These cells directly kill virus-infected cells. They recognize HPV-infected cells and eliminate them. Act as a major cell in defense mechanisms for intracellular pathogen (viral infection) and tumor cells, can recognize Ag on MHC I molecules thus inducing IFN-α and IFN-γ production.	[19]
	Regulatory T cells	Suppress the activity of other immune cells, such as T cells and B cells, to prevent autoimmune reactions and maintain immune tolerance. They play a crucial role in preventing excessive inflammation and tissue damage.	[20]
	NKT	While the specific role of NKT cells in HPV infection is still under investigation, there is growing evidence to suggest that they may play a significant role in both the early stages of infection and the subsequent development of HPV-associated diseases.	[21]

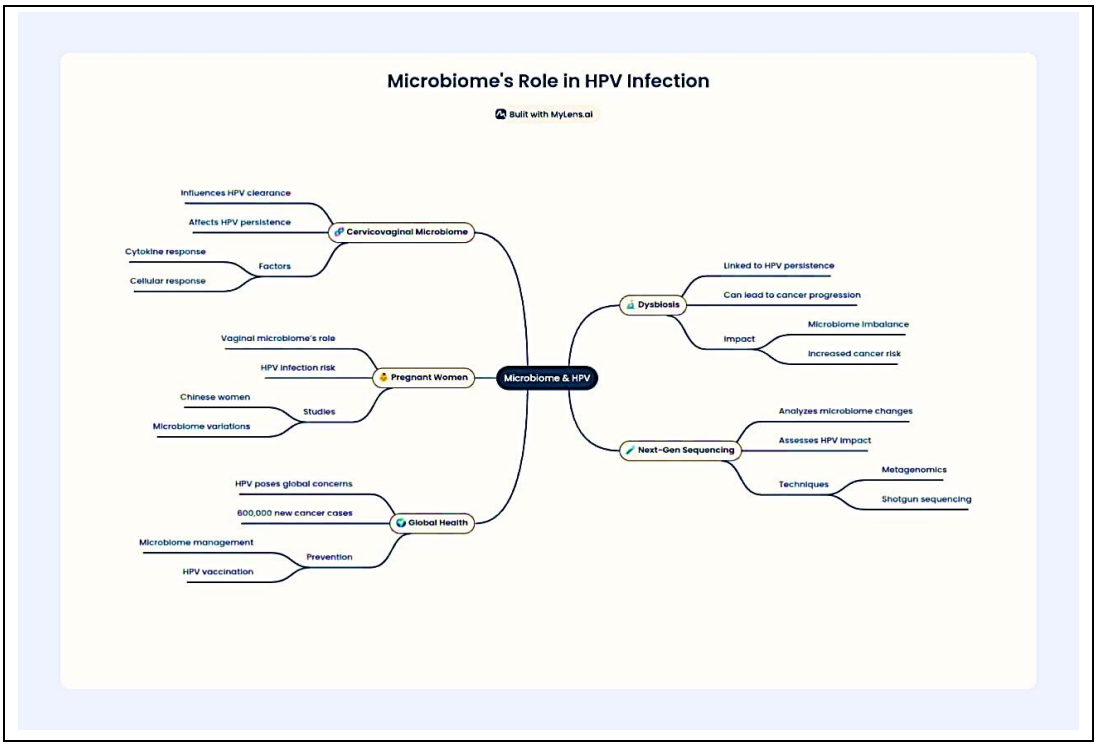
Table 2. HPV immune evasion strategies.

The strategies	Action	Ref.
Down-regulation of MHC I	Prevent T-cell activation	[32]
Inhibit Apoptosis	Targeting p53 via HPV's E6 oncoprotein interfering with p53-regulated genes	[33]
Suppress immune-related protein produced by HPV.	Reduce activation of immune cells and prevent cytokine production.	[34]
Latency	Downregulation of Viral Proteins, Integration into the Host Genome, and Immunosuppression HPV may induce the production of immunosuppressive molecules that can dampen the immune response. Finally, HPV can infect cells located in immune-privileged sites, such as the cervix and skin. These areas have limited immune surveillance, making it more difficult for the immune system to detect and eliminate the virus.	[35]
Molecular stage	Integrate viral genome into the host cell genome.	[36]

Table 3: Overview of HPV vaccines: types, components, mechanisms, targets, importance, and challenges.

Vaccine Type	Component of Vaccine	Mechanisms of action	Target	Importance	Challenge
Prophylactic Vaccines	Virus-like particles (VLPs) derived from LI protein	Induces neutralizing antibodies to prevent HPV Infection	HPV types 16, 18, and others	Prevents cervical cancer and genital warts	Limited therapeutic effect on existing Infections
Therapeutic Vaccines	E6/67 oncoproteins as antigens	Stimulates cytotoxic T-cell response to eliminate infected cells	HPV-infected cells expressing E6/E7	Potential to treat HPV-related cancers	Immune evasion by HPV and delivery challenges
DNA Vaccines	Plasmid DNA encoding E6/E7 antigens	Promotes antigen expression and T-cell activation	HPV-Infected cells	Safe and stable with potential for mass production	Low Immunogenicity in humans
Peptide Vaccines	Synthetic peptides from E6/E7 proteins	Activates T-cell response against HPV-Infected cells	HPV-specific epitopes	Customizable and specific Immune targeting	Short half-life and weak Immune response
Dendritic Cell Vaccines	Dendritic cells loaded with HPV antigens	Enhances antigen presentation to T-cells	HPV-Infected cells	Highly specific immune activation	Complex preparation and high-cost

Figure 1. Influence of the vaginal microbiome on immune response to HPV (Design according to current study using https://mylens.ai/).



Conclusion

This study investigated the complex interaction between HPV and the host immune system, emphasizing the pivotal role of immune responses in determining the course of infection. The findings demonstrate that effective immune surveillance is crucial for viral clearance, while persistent infections significantly increase the risk of cervical cancer and other HPV-associated diseases. The research examined the mechanisms by which HPV evades immune detection, the influence of the vaginal microbiome on infection dynamics, and the potential of immunotherapeutic strategies as promising avenues for treatment.

Recommendations

Based on the findings of this study, several key recommendations can be proposed to advance HPV research and improve clinical outcomes. First, an in-depth exploration of the mechanisms by which HPV evades immune detection is essential for the development of targeted and effective therapeutic strategies. Second, given the significant role of the vaginal microbiome in modulating HPV infection, comprehensive studies are needed to identify specific microbial species and elucidate their functional impact on viral persistence and clearance. To improve the effectiveness of HPV prevention and treatment, further investment in the development and optimization of immunotherapeutic approaches is critical. Strengthening awareness, screening, and vaccination programs—especially in developing countries where HPV-related cancers are prevalent—remains critical to reducing disease burden globally. Moreover, the potential of personalized medicine—tailored to individual variations in immune response and microbiome composition—should be actively investigated. Finally, reinforcing public health initiatives, including HPV vaccination programs, early detection through screening, and widespread educational campaigns, remains vital for reducing the global burden of HPV-related diseases.

Conflict of interest

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Data available on request

Authors' contribution

Maryam Qasim Mohammed: Conception and design of the review, comprehensive literature search, synthesis of findings, and drafting of the original manuscript**.** Maha H. Salman: Contribution to study design, literature acquisition, and critical input during manuscript preparation.Mohanad K. Aneed Al-Saedi: Supervision, critical review of the manuscript, and substantial editing for intellectual content. All authors read and approved the final version of the manuscript to be submitted.

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