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Human Papillomavirus and Uterine Cervical Carcinoma Risk

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Abstract

Uterine Cervical Carcinoma (UCC) is the most common gynecological malignancy internationally, with a rising incidence in recent years. Accumulating data indicates that specific viral infections, especially that are caused by oncogenic viruses including Epstein-Barr virus (EBV) that may contribute to UCC development in addition to progression. Understanding the complex interplay between EBV infections and UCC risk is crucial for developing novel preventative and therapeutic interventions. Therefore, this review study focuses on the human papillomavirus (HPV) infection and the etiology of Uterine Cervical Carcinoma.

Keywords: Human papillomavirus, HPV16-like, UCC, viral oncoproteins.

Introduction

Uterine cervical carcinoma (UCC) is still a chief global health concern, accounting for significant morbidity and mortality in women worldwide. Despite considerable study efforts and advances in screening and prevention strategies, UCC continues to pose a substantial public health challenge, particularly in low- and middle-income countries (1). A comprehensive understanding of the etiological factors underlying the development of UCC is central to devising enhanced prevention, early detection, and treatment strategies. Although extensive research has been conducted on the etiology and pathogenesis of UCC, the specific mechanisms underlying its development are not yet fully understood. Various factors, including age, obesity, hormonal imbalances, genetic predisposition, and environmental exposures, have been implicated in UCC development. Lately, a growing

body of data has painted viral infections, particularly the Human Papillomavirus (HPV), as a critical factor in UCC pathogenesis (2).

Viruses, as obligate intracellular parasites, are well-recognized for their capacity to influence host cellular processes, potentially leading to malignant transformation. Several viruses, such as HPV, Epstein-Barr virus (EBV), and hepatitis B and C viruses (HBV and HCV), have been identified as oncogenic and play crucial roles in the pathogenesis of various human cancers. However, the association between viral infections, especially HPV infection, and UCC remains an active area of investigation, with inconsistent findings reported in the literature (3).

This study aims to provide a comprehensive overview of the current facts regarding the relationship between HPV infections and UCC risk. We will discuss the evidence supporting the involvement of this virus in the development of UCC, focusing on its potential roles in oncogenesis, molecular mechanisms, and clinical implications. Eventually, elucidating the role of viral infections in UCC may lead to novel preventive and therapeutic strategies for this prevalent and life-threatening disease.

Human papillomavirus (HPV) infection and etiology of UCC

There are over 100 different types of HPV, which are categorized into three risk groups: high-risk, intermediate-risk, and low-risk, based on their association with UCC (4).

High-risk HPV types, which include HPV strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, are powerfully associated with UCC, as they can cause persistent infections and lead to the development of precancerous lesions that may finally progress to cancer. HPV 16 and 18 are the most common high-risk strains, responsible for about 70% of UCC cases worldwide (5). Two species, α9 (HPV16-like) and α7 (HPV18-like), are significant in the context of UCC diagnosis. HPV-16 is a high-risk HPV type belonging to the Alpha-papillomavirus genus. It is responsible for almost 50–60% of all UCC, making it the most prevalent and oncogenic HPV type (6). The carcinogenic potential of HPV-16 is chiefly attributed to the expression of two viral oncoproteins, E6 and E7. These oncoproteins play a crucial role in HPV16-mediated cervical carcinogenesis by disturbing normal cellular regulatory pathways (7, 8). The E6 oncoprotein of HPV16 targets the tumor suppressor protein p53, promoting its ubiquitin-mediated degradation and impairing its ability to regulate cell cycle progression, apoptosis, and DNA repair (9).

The E7 oncoprotein, on the other hand, inactivates the retinoblastoma protein called (pRb), which is a crucial cell cycle regulator, causing uncontrolled cell proliferation and genomic instability. Also, E6 and E7 can cooperate to induce chromosomal aberrations and telomerase activation and immortalize infected cervical epithelial cells, eventually resulting in malignant transformation (10, 11) (Figure 1).

The strong association between HPV-16 and UCC underscores the importance of HPV vaccination and screening programs to put off infection and early detection of cervical precancerous lesions. At present, available prophylactic HPV vaccines, like the bivalent, quadrivalent, as well as nonvalent vaccines, protect against HPV-16 and other high-risk HPV types. These vaccination programs have been shown to appreciably reduce the incidence of HPV-16-associated cervical intraepithelial neoplasia and invasive UCC (12). Besides, persistent HPV-16 infection serves as an expensive biomarker for the early identification of women at high risk for cervical cancer development. Molecular testing for HPV-16 and other high-risk HPV types in cervical cancer screening programs can improve the sensitivity as well as specificity of detecting cervical precancerous lesions, thereby improving the overall effectiveness of cervical cancer prevention strategies (13).

Human papillomavirus α9 species include HPV types 16, 31, 33, 35, 52, and 58. HPV α7 species include HPV types 18, 39, 45, 59, and 68. These species comprise numerous high-risk HPV types that are powerfully associated with the development of UCC (14).
Low-risk HPV types are not characteristically associated with UCC but can cause benign lesions like genital warts or mild dysplasia. These include HPV strains 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108 (4).

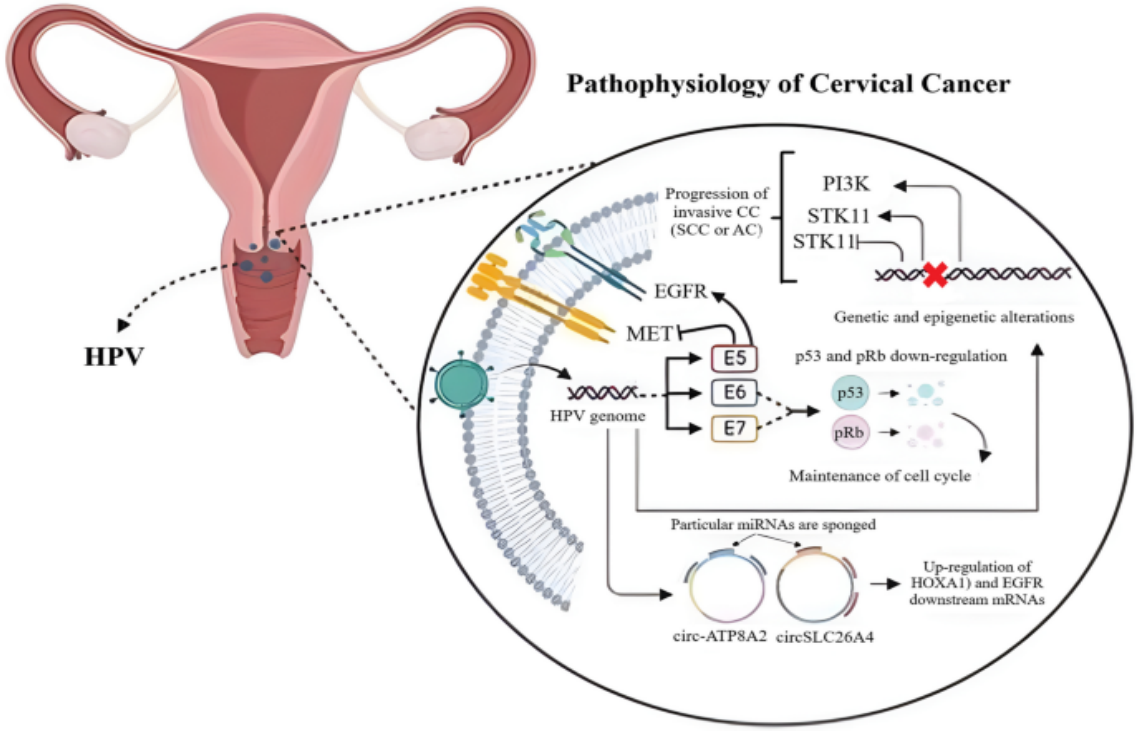

Figure. 1: Viral pathogenesis of cervical cancer (Heydarnia *et al.,* 2024) (11)

Although low-risk types do generally not lead to cancer, it is still necessary to monitor in addition to treating any HPV infection to maintain overall health. The relation between UCC and HPV types is usually based on the risk categories. High-risk types are the primary cause of UCC, while intermediate-risk types have a weaker association, and low-risk types are commonly not linked to the development of UCC. After a while, the accumulation of genetic mutations and chromosomal abnormalities in infected cells contributes to the progression from low-grade to high-grade precancerous lesions (cervical intraepithelial neoplasia, CIN) and, eventually, to invasive UCC (15).
There are more than a few proposed mechanisms by which HPV might pay for the development of UCC, such as promoting genomic instability, deregulating cell cycle control, and inhibiting apoptosis (16). HPV might down-regulate the expression of major histocompatibility complex (MHC) molecules, hindering antigen presentation and recognition by cytotoxic T cells (17).
Oncogenic viral infections can induce a persistent inflammatory response characterized by infiltrating immune cells and letting go of pro-inflammatory cytokines, chemokines, and reactive oxygen species. This chronic inflammation may cause the formation of a tumor-promoting microenvironment. HPV infection may cause epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA regulation. This

can cause the unusual expression of genes involved in cell cycle regulation, apoptosis, and DNA repair, thereby facilitating carcinogenesis (18).

HPV can disrupt the apoptotic machinery, thus promoting the survival and proliferation of UCC. HPV can cause genome instability by integrating its viral DNA into the host genome. This integration disrupts the normal function of cellular genes and regulatory elements, causing the dysregulation of cell cycle control and DNA repair mechanisms (19).

Accepting the molecular biology of HPV infection and UCC development has been essential in developing prevention and screening strategies, including HPV vaccines and HPV-based UCC screening tests, to reduce the incidence and mortality of UCC worldwide (20)

HPV vaccines, such as Gardasil and Cervarix, defend against the most common high-risk HPV types, particularly HPV 16 and 18. By preventing infection with these types, the vaccines can effectively reduce the likelihood of developing precancerous cervical lesions and, eventually, UCC. Extensive vaccination has the potential to decrease the overall incidence of UCC significantly. Studies have already shown a decline in the occurrence of high-risk HPV infections as well as precancerous cervical lesions in vaccinated populations. When an essential portion of a population is vaccinated against HPV, it can create herd immunity, which means that even unvaccinated individuals will be indirectly protected due to reduced virus circulation in the population (21).

Herd immunity, also known as community immunity, occurs when a substantial proportion of a population is immunized against a contagious disease. Subsequently, herd immunity reduces the overall circulation of the pathogen and indirectly protects unvaccinated individuals. The impact of herd immunity in UCC prevention is mainly relevant given the etiological role of HPV in the development of this malignancy (22).

Persistent high-risk HPV infection is responsible for almost all cases of UCC. Consequently, achieving herd immunity through widespread HPV vaccination can decrease the incidence of UCC significantly. More than a few factors contribute to the development of herd immunity in the context of HPV vaccination. At first, the widespread vaccination of adolescents, both male and female, can considerably reduce the prevalence of high-risk HPV strains in the population. This reduced prevalence can cause a decline in the transmission of HPV to unvaccinated individuals, thereby lowering their risk of developing UCC (23).

Secondly, herd immunity can assist specific population groups that may be at higher risk for HPV infection or cervical cancer but have lower vaccination rates. For instance, particular minority or socioeconomically underprivileged populations might face barriers to accessing HPV vaccination. Moreover, herd immunity can protect these groups by reducing the overall circulation of high-risk HPV strains (24).

Self-sampling for HPV testing has emerged as a valuable instrument in UCC prevention, contributing quite a few benefits that can help improve the overall effectiveness of screening programs and facilitate early detection of HPV infections, particularly among high-risk groups (25). Some key benefits of self-sampling for HPV testing during UCC prevention include the following: Self-sampling allows women to collect their samples in the privacy of their homes without the need for a clinical appointment. This can increase participation, more than ever, among women who may be reluctant or unable to attend traditional clinic-based screenings because of cultural, logistical, or financial barriers (26).

Self-sampling provides a more at-ease and less invasive alternative to clinician-collected samples. Many women find self-sampling less intimidating and more acceptable, which

can encourage them to undergo regular HPV testing as part of their UCC prevention routine (27). Self-sampling can help reduce costs associated with clinic visits, clinician time, and resources. By facilitating increased participation in HPV testing, self-sampling can contribute to more cost-effective UCC screening programs (28).
Self-sampling can get better access to UCC screening among hard-to-reach populations, such as women living in remote areas or those with limited access to healthcare services (29). Self-sampling can help reduce health disparities and improve UCC prevention efforts in underserved communities by making HPV testing easier. With increased participation in HPV testing through self-sampling, more women can be screened for high-risk HPV infections. Early discovery of these infections allows for timely intervention, such as close monitoring or treatment, to prevent precancerous lesions and UCC (30).
It is significant to note that self-sampling accuracy depends on the quality of the sample collected and the type of HPV test used. High-quality self-sampling kits and perceptive HPV tests are essential for reliable results. In conclusion, self-sampling for HPV testing is a vital device in UCC prevention, as it can increase participation rates, improve access to screening, and facilitate early detection and intervention, ultimately contributing to a reduction in the incidence of UCC (31). It is significant to consider other risk factors for UCC, such as obesity, smoking, hormone replacement therapy, tamoxifen use, and a family history of Lynch syndrome, as these factors have more consistent associations with UCC risk (32).

Conclusion

Recognizing the implications of HPV infection in UCC etiology and pathogenesis is vital for addressing the escalating burden of UCC. Developing innovative preventative and therapeutic interventions requires thoroughly understanding the intricate relationship between viral infections and UCC risk.

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Ethics statement

No ethical approval needed for this review article. The author approved that this research follows the journal's ethical guidelines as appeared on the journal's author guidelines page.

Author contributions

Qasim A.J: Conceptualization, writing—original draft, and editing; Zeadan A. M & Sura M. Abbas : revised the final draft and agreed to the published.

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