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HUMAN PAPILLOMA VIRUS INFECTION AND CERVICAL CANCER: A REVIEW

***Dr. Anusha T. Solanki (BDS)**

Gujarat India.

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***Corresponding author: Dr. Anusha T. Solanki (BDS)**
Gujarat India.

ABSTRACT

Among many types of HPV, around 15 which are linked to cancer. In addition, the age-specific HPV prevalence varies across different populations and showed two peaks of HPV positivity in younger and older women. However, there are still many countries where the population-based prevalence has not yet been identified. Moreover, cervical cancer screening strategies are different between countries. Organized cervical screening programs are potentially more effective than opportunistic screening programs. In spite of the successful implementation of the HPV vaccination program in many countries all over the world, problems related to HPV prevention and treatment of the related diseases will continue to persist in developing and underdeveloped countries. Viral infections contribute as a cause of 15–20% of all human cancers. Infection by oncogenic viruses can promote different stages of carcinogenesis.

KEYWORDS: HPV, cancer, carcinogenesis.

INTRODUCTION

HPV is a double-stranded DNA virus belonging to the Papovaviridae family. Almost 200 HPV types have been identified with more than 40 types colonizing the genital tract. All HPV infection types are divided into two groups based on their carcinogenic properties; these are high risk and low risk. High-risk types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, and 59 Others are classified as potential high-risk (which are 53, 66, 70, 73, and 82). Currently, it is well known and proven that HPV16and 18 are the most virulent high-risk genotypes, causing about 70% of all invasive cervical cancer in the world.[1,4]

Papillomavirus genome is comprised of a small double-stranded and highly conserved DNA with an approximate size of 8000 base pairs and consists of three regions. The molecular biology of this small DNA molecule is complex. There are six early proteins, three regulatory proteins (E1, E2, and E4) and three oncoproteins (E5, E6, and E7) encoded in 4000 base pairs (bp) that participate in viral replication and transformation of cell. Another 3000 bp region of DNA molecule encodes two structural proteins L1 and L2 that compose the capsid of virus. The viral DNA replication and transcriptional regulatory elements are controlled by a long control region (LCR) that is encoded in a 1000 bp region.[2,5,18]

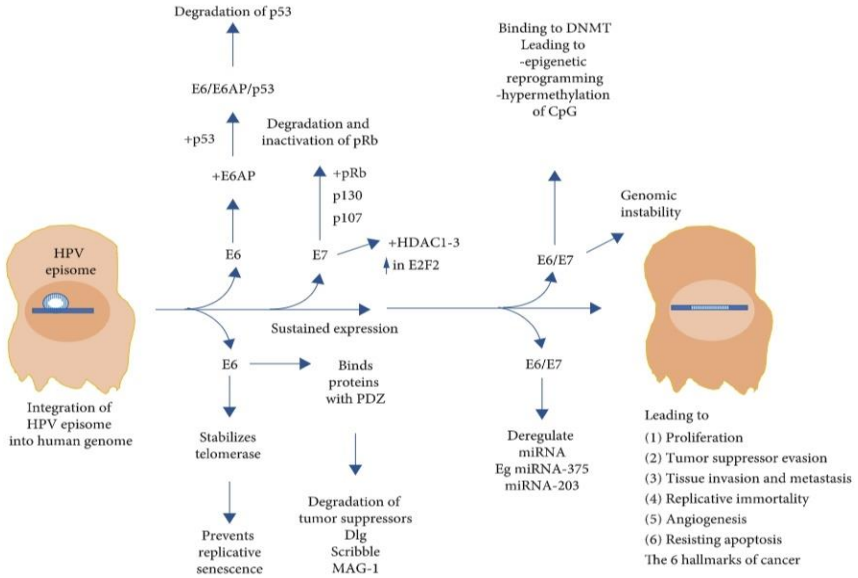
According to the World Health Organization's (WHO) statistics, common cancers are one of the most prevalent causes of mortality worldwide with 8.2 million deaths in 2012, and this trend has not changed in recent years. Viral infections contribute to 15–20% of all human cancers, whereby several viruses play considerable roles in the multistage development of malignant cancers. Over the past two decades, it has become obvious that several viruses play an important role in the development of human cancers. Around 15% to 20% of cancer cases are associated with viral infections. Oncogenic viruses can facilitate various stages of carcinogenesis.[1,3,11]

Within 12 to 24 months of exposure to the virus, 90% of HPV infections are cleared or become inactive. However, infections by the high-risk HPV types persist which then increase the risk of progression to cervical cancer. At the present time, we have a relatively clear picture of HPV infection's natural history, oncogenic properties, screening, and prevention algorithms.[16,24]

However, HPV infection rates continue to persist, especially in developing countries, where cervical cancer incidence and prevalence are still high. This is due to different reasons, which include low socioeconomic status, lack of population awareness, and inadequately implemented screening and vaccination programs.Thus, it is necessary to continue this discussion and to refocus attention of specialists and population worldwide to HPV infection and related diseases.[8,17,20]

Figure 1

Progression of cervical cancerogenesis which involves HPV gene integration, leading to sustained expression of E6 and E7, impacting and dysregulating the various pathways including the inactivation and degradation of p53 and pRB that lead to uncontrolled cellular division, proliferation, tumor suppressor evasion, and other features of tumorigenicity.



Cervical cancerogenesis can be defined as the complex mechanism of uncontrolled cellular division that can involve HPV gene integration together with other cellular changes and epigenetic factors. As the HPV infection occurs, the DNA can undergo mutations under the cellular and other environmental conditions leading to viral DNA integration and operation with the host DNA synthesis machinery. As a result, virus can escape cellular and immune defense mechanisms while promoting cell proliferation and inhibiting cellular apoptotic mechanisms.[12,25]

Oncogenic potential of HPV16 depends on the regulation of viral transcriptional factors. At the initiation of viral infection, the HPV 16 genome can be presented as unintegrated small DNA molecule also called episome and results in benign and precancerous lesions of the cervix. However, HPV 16 can integrate its genome into the host genome, which in turn can lead to the development of cervical carcinoma and cervical intraepithelial neoplasia grade III.[10] Viral genome integration in combination with dysregulation of the E2 protein, which is a repressor of the oncoprotein, contributes towards the carcinogenic process. These events cause overexpression of E6 and E7 proteins that eventually contribute to viral carcinogenesis by altering cellular apoptotic mechanism.[5,9,10]

There are many types of HPV, which are found to be associated with cancerous diseases—16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 types.[6,13,14] The most carcinogenic HPV type is HPV16, and 50% of all

cervical cancers are associated with HPV16.[7,15] In HPV16-positive cells, it is found that E6 and E7 viral genes are retained integrated into the host genome and are expressed, although in some HPV16-infected cells E6/E7 overexpression can be absent. Moreover, E6/E7 overexpression is also found in cells infected by other HPV types.[21,22]

This binding leads to the degradation of p53 and thus leads to cell proliferation. E7, on the other hand, binds pRb causing its inactivation and degradation. Both the low-risk and high-risk E7 protein has been shown to target the pRB family members including p107 (RBL1) and p130 (RBL2) for degradation.[19,23] pRb downregulates E2F a transcription factor. As pRb is deactivated by E7, E2F is upregulated and cell proliferation genes are activated. Furthermore, E6 and E7 have been shown to form complexes with hundreds of other proteins in the host cell.[26,27,28]

CONCLUSION

Cervical cancer is associated with considerable morbidity and mortality all over the world. It is well known that one of the main causative agents for cervical cancer is high-risk HPV strains, and this type of malignancy is preventable. High incidence of cervical cancer with considerable mortality is an evidence of HPV infection abundance with the absence of the HPV screening and low public awareness of the problem. Substantial incidence and mortality from cervical cancer make the screening program very important. Enhancing public awareness of underlying causal factors is a priority that should be emphasized for prevention programs. Incorporation of HPV testing into screening strategies has a high potential to decrease morbidity and mortality from cervical make the screening program very important.

Enhancing public awareness of underlying causal factors is a priority that should be emphasized for prevention programs. Incorporation of HPV testing into screening strategies has a high potential to decrease morbidity and mortality from cervical cancer. The knowledge of HPV prevalence and type distribution could contribute to the successful vaccination program implementation. The educational health promotion projects for the population should be provided to reinforce the knowledge and conversance of this public health problem. From the review given here, it is clear that the HPV screening along with the vaccination program should be implemented and supported at a governmental level in developing countries with high incidence and mortality of cervical cancer.

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