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Human papillomavirus infection and its role in the pathogenesis of anal cancer

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A B S T R A C T

The incidence of anal cancer has been increasing among both men and women in the general population since the 1970s, and is more common among women than men. Like cervical cancer, anal cancer is associated with human papillomavirus (HPV) infection and is preceded by a precursor lesion, anal high-grade squamous intraepithelial lesions (HSIL) that may take decades to progress to anal cancer. Groups at particularly high risk of anal cancer include immunosuppressed individuals, particularly those with HIV infection, men who have sex with men (MSM), and women with a history of cervical or vulvar HSIL or cancer. HIV-infected MSM constitute the group at highest risk. Once established, HPV may transform the anal epithelium by causing genomic instability, manifest histologically as HSIL. The events associated with progression from HSIL to cancer are poorly understood. Studies are currently in progress to determine whether treatment of anal HSIL reduces the risk of cancer among HIV-infected men and women, and to define the molecular events associated with progression from HSIL to cancer.

Introduction

HPV is the most common sexually transmitted agent, with an estimated 85% of sexually active adults acquiring one or more genital HPV types at some time during their lifetime. HPV only infects epithelial cells, and consequently spread from one epithelial surface to another. Genital HPV types may infect all of the keratinized and mucosal genital epithelia, as well as the oropharyngeal mucosa. They may cause cancer at all of these sites as well, but fortunately only a small fraction of HPV-infected individuals will develop squamous cell cancer due to HPV. HPV is believed to be necessary but insufficient for the development of these cancers, and other factors in addition to HPV play an important role in determining who gets cancer, and these are discussed in the next sections. However, even though only a small proportion of HPV-infected men and women develop HPV-related cancer, the denominator of persons at risk is very large, and the absolute numbers of HPV-related cancers are unacceptably high. Cervical cancer kills more than 250,000 women every year world-wide, and the numbers of other HPV-related cancers such as those of the anus and oropharynx are growing. These data point to the need for more effective implementation of programs to prevent these cancers. In the case of anal cancer, primary prevention through HPV vaccination should lead to nearly complete, if not complete reduction in anal cancer among those not yet exposed to the HPV types covered in the vaccine. Efforts are also underway through the Anal Cancer/HSIL Outcomes Research (ANCHOR) study to determine if secondary prevention for those already exposed to HPV may be useful to reduce the incidence of anal cancer, through identification and removal of the anal cancer precursor lesion, high-grade squamous intraepithelial lesion (HSIL) before it progresses to cancer.

Epidemiology and biology of anal HPV infection

The HPV genome consists of an approximately 8 kb double-stranded circular DNA plasmid. The genome includes an *early* region, which encodes the E1, E2, and E4–E7 proteins, and a *late* region, which encodes two structural capsid proteins, L1, the major capsid protein, and L2, the minor capsid protein.[1] The early and late regions are separated by the non-coding upstream regulatory region (URR) or long control region (LCR). The URR contains four binding sites for E2 and for multiple cellular transcription factors. The HPV E2 protein is expressed when the HPV genome remains in its episomal circular plasmid form, that is, physically separate from the host chromosomal DNA. When all four E2 binding sites in the URR are bound by the HPV E2 protein, expression of the E6 and E7 oncogenes is repressed, and their oncogenic functions are presumably attenuated. One of the steps in malignant transformation

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is integration of the episomal HPV DNA into the host chromosome, which by definition necessitates cleavage of the circular HPV genome to linearize it. Typically the HPV genome is cleaved within the E2 coding region, and when it integrates into host chromosomal DNA, E2 expression is disrupted. The E2 binding sites in the URR are no longer fully occupied, and there is loss of repression of E6 and E7, with potentially higher transforming capability.

There are well over 100 HPV types, with new HPV types defined based on their DNA sequence similarity to previously identified HPV types.[2] These types exhibit a substantial degree of epithelial tissue tropism, with some types preferentially infecting the mucosal and keratinized genital epithelium, and others the keratinized skin of the palms and soles (HPV 1, 2, and 4). Some types exhibit preference for the oral epithelium, such as HPV 13 and 32. There are over 14 oncogenic and multiple non-oncogenic HPV types that preferentially infect the anogenital epithelium. HPVs are divided into clades, with the alpha-9 clade exhibiting the highest level of oncogenicity and these include HPV 16 and 31. The alpha-7 clade also includes oncogenic HPV types, including HPV 18 and 45. HPV 16 is the most common type associated with anal cancer,[3] followed by HPV 18. In the setting of HIV infection, HPV 16 and 18 remain the most important HPV types in anal cancer. However, other oncogenic HPV types may play a larger role proportionally than is seen in the HIV-uninfected population, and more data are needed on the distribution of HPV types in anal cancers found in this population.

Anogenital HPV types preferentially infect areas of metaplasia in both the cervix and the anus.[4,5] These areas, referred to as transition zones or transformation zones, are sites where columnar glandular epithelium meets stratified squamous epithelium, and may histologically manifest as squamous metaplasia. To establish infection, HPV binds denuded basement membrane, and after a period of approximately 24 h, enters basal cells of the epithelium. Intact epithelium has several barriers that typically prevent access of HPV to the basement membrane, including layers of surface keratin, tight junctions between epithelial cells and multiple epithelial layers. There are several mechanisms by which the epithelium may be disrupted, including mechanical trauma[6,7] through sexual intercourse, and disruption due to other sexually transmitted infections such as gonorrhea and chlamydia. In people co-infected with HIV, HIV proteins tat and gp120 may also disrupt epithelial tight junctions.[7,8] Each of these may therefore be cofactors increasing the risk of initial HPV infection.

When HPV enters the basal layer of the epithelium, the viral genome is maintained as a relatively quiescent episome. In the basal layer, the HPV E1 protein, with the help of E2, tightly coordinates the division of the viral genome with host cell division, thus maintaining the viral genome at stable, and low viral copy numbers per cell.[6,9] Levels of HPV gene expression remain relatively low until the cells differentiate and begin to move up in the epithelium as part of their normal life cycle. As the cells differentiate, they typically stop dividing. However, the coordination with viral genome replication is lost, and the virus copy number per cell rises, along with level of viral gene expression. Protein expression and active HPV replication increase as infected cells migrate into the suprabasal cell layers and undergo epithelial differentiation, a process that may result in changes that are clinically and histopathologically recognized as squamous intraepithelial lesions (SIL). However, latently infected cells likely also persist within the basal cell epithelium[10,11] with the potential to reactivate at some point in the future and lead to SIL. In the stratum granulosum and spinale the late regions begin to be expressed, including the L1 and L2 proteins. When these are expressed and envelop the HPV genome, they form fully infectious viral particles, which may be released in the most superficial cell layers when the cells slough off and/or die as part of the normal epithelial differentiation and turnover cycle.

HPV infection may persist in the basal cell layer since it is relatively protected from an immunologic standpoint and because levels of viral gene expression are very low, limiting the number of antigens that could trigger an immune response. For this reason, many experts believe that HPV infection is not truly cleared once infection is established, similar to herpes simplex virus. For most people, latent HPV causes no clinically significant disease. However, if an HPV-infected individual becomes immunosuppressed, clinically latent HPV could reactivate, causing SIL and cancer.[12–15]

HPV 16 in particular is much likelier to result in persistent HPV infection, HSIL, and cancer than infection with other high-risk HPV types and low-risk HPV types.[4] Among high-risk HPV types, there are also variants or strains of these types that appear to result in higher risk of malignant transformation through mechanisms that remain poorly understood. Initial exposure of a person to these higher-risk strains of oncogenic HPV types may confer higher risk of progression to cancer.

Overall once HPV enters the basal layers, there may be several different outcomes, depending on a number of factors, including the HPV type (high-risk oncogenic HPV types vs low-risk HPV types), the epithelial site of infection, host immune response and host genetics, and the presence or absence of other factors in the epithelium that may modulate HPV infection, such as HIV and other sexually transmitted infections. One possibility is that the virus begins to express antigens that trigger cellular changes that may be clinically recognizable as a lesion if a biopsy had been taken at that time. However, these antigens may trigger a cell-mediated immune response that leads to the elimination of the abnormal cells, regression of the lesion, and reversion of the HPV infection to latency. A second possibility is that the virus maintains a state of active viral replication that persists despite a host immune response or because of an inadequate host immune response. The changes resulting from active viral replication are typically recognized as low-grade SIL (LSIL). The cells in these lesions do not exhibit signs of transformation and these lesions are not believed to progress to cancer. Instead, they are primarily of clinical importance for their role in HPV transmission and the symptoms that they may cause when manifest as warts. A third possibility is that the virus undergoes an abortive infection, primarily expresses oncogenic early region genes, rather than late region proteins, and this persists due to an absent or inadequate immune response. These lesions are clinically manifest as high-grade SIL (HSIL) and these have the potential to progress to cancer.

The three main HPV proteins involved in the process of malignant transformation are E6, E7, and E5[9] (Table 1). The HPV E6 protein binds and inactivates the tumor suppressor protein p53 through formation of a protein complex that ultimately leads to its physical destruction. Epithelial cells infected with an oncogenic HPV type and expressing the HPV E6 protein have undetectable levels of p53, and functionally this may have the same effect as having a p53 mutation. Known as the “guardian of the genome,” p53 induces DNA repair enzymes and cellular apoptosis when DNA damage cannot be repaired. Cells without functional p53 exhibit chromosomal instability since the repair of DNA damage that may normally occur during the life cycle of a cell is attenuated. Accumulation of genetic mutations as a result of impaired DNA repair mechanisms may be the driving force behind development of HSIL and its progression to cancer. HPV is believed to be necessary but insufficient for this process. This may explain why only a small proportion of people infected with HPV develop HPV-associate cancer, and highlights the importance of cofactors with HPV in development of anal cancer and other HPV-associated cancers.