What is the significance of the HPV epidemic?

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Human papillomavirus (HPV) is the most common sexually transmitted infection. The incidence of this infection has been on the rise in recent times. It is estimated that approximately 6 million new HPV infections are acquired each year in the United States alone, and prevalence data suggest that as many as 24 million American adults—that is, 1 in 5—may be infected with HPV. Unfortunately, there is little public awareness and knowledge about the infection and its sequelae. It is well known that more than 90% of cases of anogenital warts are caused by HPV. HPV has been implicated in cancers of the cervix, vulva, vagina, penis, anus, and oropharynx. The virus is a necessary cause of cervical cancer. HPV DNA is detected in almost 100% of cases of cervical cancer.

There have been major strides in recent years in the prevention of this infection and consequently, of diseases related to it. Vaccines are available and licensed in some countries. Two HPV vaccines are available: a quadrivalent (HPV types 6, 11, 16, and 18) vaccine and a bivalent (HPV types 16 and 18) vaccine. Both vaccines show a more than 90% protection against persistent HPV infection for up to 5 years after vaccination. The role of the vaccine in males is still controversial.

The vaccination cost, however, is beyond the reach of many individuals in developing countries where 80% of cervical cancer cases of are found. Many countries in Africa are battling with HIV, malaria, tuberculosis, maternal mortality, and childhood illness. Nevertheless, with increased awareness, political will, and engagement by pharmaceutical countries, HPV vaccines may become affordable in these countries.

Key Words: HPV, human papillomavirus, sexually transmitted disease

Introduction

Human papillomaviruses (HPVs), a group of more than 100 viruses, are called papillomaviruses because certain types may cause warts, or papillomas. The "wart virus" has been known since prehistoric times, but it was not until the 1970s and 1980s that it was studied extensively, and this has lead to a tremendous understanding of the etiology of lesions associated with it. HPVs belongs to the family *Papovaviridae*.[1] The viral genome is enclosed in a 72-capsomere capsid.[1,2] HPV is the most common sexually transmitted infection.[3,4] It is estimated that approximately 6 million new HPV infections are acquired each year in the United States alone, and prevalence data suggest that as many as 24 million American adults—that is, 1 in 5—may be infected with

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HPV.[4] The highest rates of new genital HPV infections, approximately 74% of annual infections, occur among young adults between the ages of 15 and 24.[4]

The virus affects mainly the mucocutaneous parts of the anogenital and oropharyngeal regions of the body. More than 100 genotypes of HPV have been isolated and about 40 types are associated with anogenital tumors. The HPVs are divided into two groups based on their association with risk for cancer. The low-risk HPV types 6, 11, 40, 42, 43, 54, 61, 72, and 81 are of low oncogenic potential, while the high-risk HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82 are associated with cancer.[1] About 15 HPV types have been associated with anogenital cancers. High-risk HPV has been implicated in cancers of the cervix, vagina, vulva, anus, penis and oropharynx.[5] Non-melanoma skin cancer and cancer of the conjunctiva have also been causally linked with HPV.[5]

The HPV genome and mechanism of tumorigenesis

HPV is a relatively small virus containing two strands of DNA within a spherical shell (capsid).

The HPV genome is a single stranded DNA that consists of 8000 base pairs and comprises three major regions.[1] The early region (E1-8) consists of genes responsible for transcription, plasmid replication, and transformation. The late region codes for the major (L1) and minor (L2) capsid proteins, and the control region contains the regulatory elements for transcription and replication. E1 and E2 proteins are essential for viral replication and transcription, and E6 and E7 proteins of high-risk HPV are of major significance in the process of carcinogenesis.

The HPV makes use of the normal process of turnover of epithelial cells, which involves upward migration and differentiation of cells from the basal layer to the superficial layer, to complete its life cycle. The basal cell leaves the cell cycle when it moves to the suprabasal layer of the epithelium, undergoes differentiation as it moves up to the superficial layer of the epithelium, gets disintegrated, and is released into the environment. The virus enters the epithelium through micro abrasions and enters the basal cell. It gets integrated into the chromosome of the cell, and the viral genome is replicated to a copy number of about 100 and is maintained for varying for a period of time within the cell.[6] Differentiation is delayed and less complete in the infected cell.[6] The virus continues its replication as the infected cell moves upwards, and when it gets to the superficial layer of the epithelium, the viral capsid proteins are expressed leading to the production of mature virions. The cell disintegrates and virions are released into the environment ready to start another life cycle.

The key action of the E6 protein of high-risk HPV is to cause immortalization of the infected cell, a process that may eventually lead to malignant transformation. It does this by enhancing the degradation of p53 protein, a protein that promotes apoptosis. The E6 protein also activates the enzyme telomerase, which counteracts the shortening the chromosome telomeres — a cell-aging process. The high-risk E7 protein is the major transforming protein of the HPVs. It acts by binding pRb, a protein that binds and inhibits transcription factors of the E2F family. Binding of pRb by E7 will therefore lead to the release of E2F transcription factors that stimulate entry into the S-phase and lead to cell replication.1,6,7 This process is normally checked by p53 protein, which causes apoptosis, but in HPV-infected cells, p53 protein is not available, as it is constantly being degraded by E6 protein. The continued actions of E6 and E7 proteins in a cell persistently infected with HPV leads to increasing genomic instability, accumulation of oncogene mutations, further loss of cell-growth control, and ultimately, cancer.[5,7]

The E6 protein of low-risk HPV does not bind p53 protein, and this may be the reason for the benign nature of the tumors that they cause.[1]

Genital warts

Genital warts (condylomata acuminata) are the most common clinical, visible manifestation of genital HPV infection. They are highly infectious with a transmission rate of 65%, and the interval between exposure and infection is 3 weeks to 8 months.[8,9] It is well known that more than 90% of cases of genital warts are caused by low-risk HPV types 6 and 11.[10,11] Recent studies have shown that 20%-50% of lesions also contain coinfection with high-risk HPV types.[9,12]

It is estimated that 1% of the American population has genital warts, and women and men have similar rates of infection, with a female to male ratio of 1.4:1.[11] Between half a million to one million cases are diagnosed annually.[11] Cases of anogenital warts have been on the increase worldwide. Available data suggest that genital warts occur worldwide at similar rates to those observed in the United Kingdom and the United States.

Epidemiological studies have shown that the risk of acquiring an anogenital wart infection increases with cigarette smoking, oral contraceptive use, and increased sexual activity with multiple sexual

partners. Anogenital warts are also increased in situations where there is a deficiency of cell-mediated immunity, as occurs with HIV, diabetes, and the use of immunosuppressant drugs.

In males, the effects of genital warts are found on the glans penis, penile shaft, prepuce, and anal area. In about 5% of cases, the urethral meatus and urethra are involved; bladder involvement is rare.[13,14] In females, genital warts affect the vulva, vagina, cervix, groin, and anal area. Rarely, genital warts can also develop in the mouth or throat of individuals who engage in oral sex. Genital warts can have a negative psychological impact on an individual. It affects sexual activity. Very large warts may complicate vaginal delivery. Vertical transmission can occur at the time of delivery, and this could lead to juvenile-onset recurrent respiratory papillomatosis, a highly debilitating and potentially life-threatening condition.[15]

HPV-related cancers

Cervical cancer

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 493000 new cases of this cancer and 274000 deaths due to this cancer worldwide in 2002.[16] It is projected that in the absence of any intervention, by 2020, 0.7 million cases will occur—about a 40% increase from 2002.[17]

HPV infection is now widely recognized as the principal etiologic agent in the development of cervical dysplasia and cervical cancer. The magnitude of this risk association is even greater than that between smoking and lung cancer.[18,19] HPV-DNA is found in 99.7% of cases of cervical cancer, which makes HPV a necessary cause of virtually all cervical cancer.[20,21] The most common HPV types identified are, in order of decreasing prevalence, HPV types 16, 18, 33, 45, 31, 58, 52, 35, 59, 56, 51, 39, 6, 68, 73, 66, and 70.[21] HPV types 16 and 18 are responsible for about 70% of all carcinomas of the cervix worldwide. Although HPV is a necessary cause of cervical cancer, it is not a sufficient cause. Cofactors are necessary for the progression from cervical HPV infection to cancer. The established cofactors include long-term use of hormonal contraceptives, high parity, tobacco smoking, and coinfection with HIV.[5] Coinfection with *Chlamydia trachomatis* (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression, and certain dietary deficiencies are other probable cofactors.[5] Genetic and immunological host factors and other viral factors such as variants of type, viral load, and viral integration, are likely to be important, but these cofactors have not been clearly identified.[5]

Cancer of the vulva

The majority (60%-90%) of vulva cancers and their precursor lesions found in young individuals are also strongly associated with HPV.[5] The HPV-related cancers of the vulva are of the basaloid or warty histological subtypes. Hording et al[22] found HPV types 16 and 33 in 12 of 17 (71%) invasive warty carcinomas and in 10 of 10 (100%) invasive basaloid carcinomas. The tumors diagnosed in young individuals are usually of the basaloid or warty histological subtypes. Less than 10% of vulva cancers in older individuals are associated with HPV.[5,23]

Cancer of the vagina

Cancers of the vagina are less frequent than vulvar cancers: the age-standardized incidence rate (ASR) is 0.3 to 0.7 per 100000 individuals in most countries.[17] Many squamous cell carcinomas of the vagina are preceded by vaginal intraepithelial neoplasia (VAIN). HPV plays a similar role in cancer of the vagina as in cancer of the cervix. Between 64% and 91% of vaginal cancers and 82% and 100% of VAIN-3 lesions are HPV-DNA positive. [5]

Cancer of the penis

Cancer of the penis is a rare malignancy, and it accounts for less than 0.5% of cancers in men.[17,23] In Western countries, the ASR is less than 1 per 100000 men.[17] HPV has been implicated in the development of dysplastic, precancerous, and cancerous lesions of the male genitalia, including squamous cell cancer of the penis, verrucous carcinoma of the penis, and penile squamous intraepithelial neoplasias (ie, squamous cell carcinoma in situ, bowenoid papulosis, erythroplasia of Queyrat, or Bowen's disease of the genitalia).\l "B1" [24-26] A history of anogenital warts is associated with a 5- to 6-fold increase in risk of penile squamous carcinoma.[27] Studies using polymerase chain reaction (PCR) technology have reported a detection of HPV types 16, 18, 31, and 33 in up to 82% of invasive and in-situ penile carcinoma.[27,28] Preliminary reports have also linked HPV transmission with the subsequent development of bladder and prostate cancers.[25,26]

Anal cancer

Anal cancer is a rare disease and accounts for up to 4% of all cancers of the lower gastrointestinal tract.[29] The annual incidence is about 1 in 1000000 in a heterosexual population. Each year there are about 500 new cases in the United Kingdom and 3500 new cases in the United States. The incidence amongst

males who have anal-receptive sexual intercourse with males was estimated to be as high as 37 per 100000 person years.[30] It is also twice as common in HIV-positive than in HIV-negative individuals.[29,30]

Anal HPV infection is the most significant risk factor for the development of anal intraepithelial neoplasia (AIN), the precursor lesion to anal cancer. HPV DNA has been reported to be found in 88% of cases of squamous cell carcinoma of the anus.[31] HPV type 16 has been shown to be particularly associated with anal cancers.

Oral cavity and oropharyngeal cancer

It has long been established that tobacco and alcohol are significant risk factors for cancers of the mouth and oropharynx. However, many studies in the last 20 years or so have demonstrated the role of HPV in the pathogenesis of cancers of the oral cavity and the oropharynx.[32-34] The prevalence of HPV DNA is higher in oropharyngeal cancers than in oral cancer.[5] A recent meta-analysis by Kramier et al[35] found that the prevalence of HPV-DNA was 35.6% (range, 11%-100%) in oropharyngeal squamous cell carcinomas (SCCs), 23.5% (range, 4%-80%) in oral SCCs, and 24.0% (range, 0%-100%) in laryngeal SCCs. HPV-DNA positivity is highest in tonsillar cancers: the prevalence is more than 50%. HPV type 16 is the predominant type and is found in 87% of HPV-infected oropharyngeal cancers and 68% of HPV-infected oral cavity cancers.[36]

Some studies have reported that individuals with HPV-positive oral and oropharyngeal cancers tend to be younger than those who are HPV-negative.

Prevention of HPV infection

Sex education

The best protection against HPV is to avoid sexual contact with any person who might be carrying this virus. It has also been reported that the risk of contracting HPV is directly proportional to the number of sexual partners an individual keeps.[24] Several studies have shown that there is generally a lack of awareness of HPV among different populations surveyed worldwide. There is also very poor knowledge of the economic and societal burden of HPV. There is therefore a great need for public enlightenment about this virus. Education messages about HPV should include information about the route of transmission of HPV, the risk factors for viral transmission (such as multiple sexual partners, smoking, and alcohol), and the sequelae of infection by this virus.

Condoms

Anogenital HPV infections are transmitted by skin-to-skin or mucosa-to-mucosa contact and are not dependent upon exposure to semen or vaginal secretions.[37] The use of condoms during intercourse might reduce, but will not totally eliminate, transmission of HPV. Penetrative sexual intercourse is not strictly necessary for a person to become infected.[37] Many studies[38-40] have demonstrated the uncertainty of the protective nature of the condom in the acquisition of this infection. Educational messages must emphasize this finding.

Circumcision

Many studies have reported the preventive role of circumcision in penile cancer and more recently, in HIV transmission.[41-44] A recent large study involving 1913 couples concluded that male circumcision is associated with a reduced risk of penile HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners.[45]

HPV vaccines

The development of vaccines against HPV is a major stride in the prevention of HPV infection and consequently reducing the societal and economic burden of HPV-related diseases such as cervical cancer. HPV vaccines contain the major capsid L1 proteins, which self-assemble into virus-like particles (VLP) resembling HPV.[46,47] These particles do not contain viral genetic material and thus are unable to multiply, and therefore are not infectious. Two HPV vaccines are now available, a quadrivalent (HPV types 6, 11, 16 and 18) vaccine and a bivalent (HPV types 16 and 18) vaccine. Both vaccines show greater than 90% protection against persistent HPV infection for up to 5 years after vaccination. They are given to girls between the ages of 9 and 13 years old.

There have been many arguments for and against vaccination in men. The morbidity and mortality rates from HPV type 16- and type 18-related anal, penile, and oropharyngeal cancers among men are lower than the morbidity and mortality rates from cervical cancer among women.[48] Also, the efficacy of the HPV vaccine in preventing these diseases has not yet been established. HPV vaccines will, however, provide protection against genital warts in men. The strongest argument for immunizing men is that with high immunization coverage of both men and women, transmission of the virus may be significantly reduced or even eliminated, and, as a result, eventually women who have not been immunized will get protection.[49]

The cost of the vaccination—three doses cost about US $400—is beyond the reach of many individuals in developing countries where 80% of cervical cancer cases are found. Many countries in Africa are seriously battling with the burden of high rates of HIV, malaria, tuberculosis, maternal mortality, and childhood illness. Cancer is generally not yet given the same priority as these other conditions. Nevertheless, with increased awareness of HPV and HPV-related diseases, greater political will, and engagement in this issue by pharmaceutical companies who make the vaccines, HPV vaccines may become affordable in these countries.

Conclusion

HPV infection is a major sexually transmitted disease worldwide. In addition to causing condyloma accuminata in infected men and women, oncogenic subtypes have been associated with a large variety of cancers effecting both sexes. Among the most important, cervical cancer is a global disease of epidemic proportions, with 80% of cases diagnosed in women from Africa and other developing countries. Awareness and education are the key components of prevention, however vaccination has been recently made available. Healthcare providers involved with sexual and reproductive health, child and adolescent medicine, immunization, and cancer control must be aware of the key issues surrounding the introduction of HPV vaccines. □

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