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Keywords: human papilloma virus, cancer epidemic, HPV vaccine, treatment of HPV infection.

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Human Papilloma Virus: An Oncogene

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I. Introduction

90% of HPV infections are symptomless, and resolve within a span of two years approximately[1]. If HPV infection still persists, it results in either warts or precancerous lesions. These lesions, depending on the site affected, increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, or throat. Majorly cervical cancer is due to HPV; mainly two types, HPV16 and HPV18 (most common oncogenic virus) [1]. HPV6 and HPV11 leads to genital warts and laryngeal papillomatosis[1].Uterine cervical cancer, being the third most common cancer in women all around the world and the second most common cancer in Indian women, is caused by infection via these oncogenes[2]. HPV is associated with more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 70% of oropharyngeal cancers and more than 60% of penile cancers[2].

HPV has an infectious intra-epithelial cycle and infecting, both cutaneous and mucosal squamous epithelium[2]. The HPVs belongs to the family Papillomaviridae that consists of small, non-enveloped deoxyribonucleic acid (DNA) viruses. The genome of HPV consists of double-stranded cDNA and encodes DNA sequences for six early (E1, E2, E4, E5, E6, and E7) and two late proteins (L1 and L2).[2] The E1 and E2 proteins are the early viral proteins required for replication and translation of virus, E2 also regulates the expression of E6 and E7, E4, and E5 helps in viral assembly and growth stimulation, whereas late proteins L1 and L2 forms minor and major capsid proteins.[2]These viruses can be classified into high risk and low-risk HPV types depending on their oncogenic potential. HPV 16 has the highest ability to cause cancer.

The HPV infects squamous epithelial cells, which has proliferating capacity, and get to the basal cell during trauma. In these cells, HPV causes the expression of viral genes that helps in the viral replication. The interaction of HPV with the host cells occurs via surface receptors such as heparin sulphate proteoglycans and alpha 6 integrin. The early proteins E1 and E2 are required for the initiation of replication. The protein E2, being the transcriptional repressor of E6 and E7, controls the expression of E6 and E7. The mode of replication is the rolling circle mechanism during which the virus gets integrated into the human genome. The integration disturbs the E2 gene thereby resulting in a higher expression of E6 and E7 oncoproteins and leading to cell transformation. After the viral replication, the L1 and L2 gene products form the virus capsid and the mature virus is produced. Finally, the virus is released with the help of E4 protein.

II. Associated Cancer with HPV

1. Cervical cancer

Main type of cancer caused by HPV infection. But, cervical cancer is quite uncommon. In 2018, approximately 311 000 women died from cervical cancer; more than 85% of these deaths occurring in low- and middle-income countries.[3]Although most HPV infections clear up on their own and most pre-cancerous lesions resolve spontaneously, there is a risk for all women that HPV infection may become chronic and pre-cancerous lesions leading to cervical cancer in certain years.HPV infection can spread from a mother to baby during pregnancy.

It takes period of 15 - 20 years for cervical cancer to develop in a healthy women. It can take only 5 to 10 years in women with weakened immune systems (such as those with untreated HIV). Women with HIV/AIDS, are at a 22-fold increased risk of cervical cancer. Because the transformation of normal cervical cells into cancerous ones is slow, cancer occurs in people having been infected with HPV for a long time, usually over a decade or more (persistent infection).

2. Anal cancer

Sexually transmitted HPVs are the reason for anal cancers. The risk for anal cancer is 17 to 31 times higher in HIV-positive individuals which also had HPV infection.

3. Penile cancer

Approximately 50% of penile cancers are associated with HPV. HPV16 being the most common type. The risk of penile cancer increases 2- to 3-fold for patients infected with HIV and HPV.

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4. Head & neck cancer

Oral infection with high-risk carcinogenic HPV (most commonly HPV 16) is associated with head and neck cancers. This association has no relation with tobacco and alcohol use. Sexually transmitted HPV is the reason for 25% of cancers of the mouth and upper throat (the oropharynx) universally.

This type of cancer is more commonly seen in men than in women.

5. Lung cancer

Certain studies links HPV to benign and malignant tumours of the respiratory tract. People with lung cancer were more likely to have several high-risk forms of HPV antibodies compared to those who did not have lung cancer.

6. Skin cancer

In very rare cases, HPV may cause epidermodysplasia verruciformis (EV) in individuals with a weakened immune system. The virus, unchecked by the immune system, causes the overproduction of keratin by skin cells, resulting in lesions resembling warts or cutaneous horns which could transform into skin cancer. The types of HPV is associated with it are HPV5, HPV8, and HPV14.

7. Head and neck cancer

Due to a remarkable shift in the epidemiology of head and neck cancer in this country there has been drastic increase in its cases. While exposure to mutagens like tobacco and alcohol remains the most common risk factor for squamous cell cancers, a rapidly expanding subset of head and neck cancers are acquired through human papillomavirus (HPV) infection. Most head and neck cancers caused by HPV form in the part of the throat that includes the base of the tongue and the tonsils. Symptoms of oropharyngeal cancer includes a long-lasting sore throat, earaches, hoarseness, swollen lymph nodes, pain when swallowing, and unexplained weight loss. Some people have no symptoms.

The vaccine protects against the types of HPV that can cause oropharyngeal cancers, so it may also prevent oropharyngeal cancers.

Other infections caused by HPV[4]

Genital warts: These ate flat lesions, small cauliflower-like bumps or tiny stem like protrusions. In women, genital warts appear mostly on the vulva but can also occur near the anus, on the cervix or in the vagina. In men, genital warts appear on the penis and scrotum or around the anus. Genital warts rarely cause discomfort or pain, though they may itch or feel tender.

Common warts: Common warts appear as rough, raised bumps and usually occur on the hands and fingers. They can be painful.

Plantar warts: Plantar warts are hard grainy growths appearing on the heels or balls of your feet. They may cause discomfort.

Flat warts: Flat warts are flat-topped, slightly raised lesions. They can appear anywhere, but children usually get them on the face and men tend to get them in the beard area. Women tend to get them on the legs.

III. HPV Vaccine[3]

At present, there are 3 vaccines that protect against both HPV 16 and 18, which are the reason for 70% of cervical cancers. The third vaccine protects against other three HPV types, which are responsible for 20% of cervical cancers. Given that the vaccines which are only protecting against HPV 16 and 18 also have some cross-protection against other less common HPV types which cause cervical cancer, WHO considers the three vaccines equally protective against cervical cancer. Two of the vaccines also protect against HPV types 6 and 11, which cause anogenital warts.HPV vaccines work best if administered prior to exposure to HPV.

IV. Treatment Protocol[5]

There is no cure for HPV, but doctors can often treat the warts and precancerous lesions caused by the infection through:

- A loop electrosurgical excision procedure(electric current to remove abnormal tissue)
- Freezing techniques
- Surgery
- Medicated creams for direct application to the skin for genital warts.

Treatment depends on the stage of the disease and options include surgery, radiotherapy and chemotherapy. Palliative care is also an essential for cancer management to relive pain and suffering.

Diagnosis of cervical cancer must be made by histopathologic examination. Staging is done based on tumour size and spread of the disease to distant organs.

V. Conclusion

With the increasing cases of cancer, especially in women, awareness should be created worldwide focussing on prevention rather than cure. The discovery of HPV vaccine prevents infection by certain strains of HPV. But for the vaccine to be effective, it should be given before the activation of the respective virus. Hence, prevention is better than cure. Measures should be taken to lower the chances of being getting infected. An HPV test combined with PAP test can be used as preventive measure by women older than 30 years.

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