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Review Article

Virology in Carcinoma of Cervix

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Abstract

Cervical cancer represents a significant public health issue worldwide, particularly prominent among women in low- and middle-income countries. It is the fourth most common malignancy among women globally. It is predominantly caused by a persistent infection with high-risk types of human papillomavirus (HPV). Out of the more than 200 types identified, approximately 14 are considered high-risk for the development of cervical cancer [8]. HPV types 16 and 18 are the most dangerous, responsible for about 70% of all cervical cancer. The virus infects the basal cells of the epithelium, where it usually remains in a non-replicative state. As the infected cells differentiate and move towards the surface, the virus begins to replicate, completing its life cycle without causing cell death [10]. This non-lytic lifecycle allows the virus to persist unnoticed by the host immune system which has an oncogenic potential. In a small fraction of infections, HPV DNA integrates into the host genome. This integration disrupts the usual virus lifecycle and the regulation of viral oncogenes, E6 and E7. These genes are pivotal in the progression to cancer; they encode proteins that can inactivate tumor suppressor pathways involving p53 and retinoblastoma (Rb) proteins, eventually leading to malignant transformation. Understanding the virology of HPV and its interaction with the host factors provides crucial insights into the mechanisms of cervical cancer development. This knowledge is fundamental in guiding the development of preventive strategies, such as vaccines and targeted therapies, and improving screening methods to detect precancerous changes early.

Keywords: *Virology; Carcinoma of Cervix; Human Papillomavirus (HPV); Retinoblastoma (Rb)*

Introduction to Cervical Cancer: Global and Indian Perspectives

Cervical cancer, arising from the cervix, represents a significant public health issue worldwide, particularly prominent among women in low- and middle-income countries. It is predominantly caused by a persistent infection with high-risk types of Human Papillomavirus (HPV). Despite being largely preventable through vaccination and effective screening methods, cervical cancer continues to pose serious challenges due to disparities in access to healthcare services and lack of awareness [1].

Global impact of cervical cancer

Globally, cervical cancer is the fourth most common cancer in women, with approximately 604,000 new cases and 342,000 deaths reported in 2020 [2]. The incidence rates vary significantly across different regions, being highest in Sub-Saharan Africa, Latin America, and parts of Asia. This variation is largely attributed to differences in the availability of HPV vaccination and cervical screening programs

[3]. The World Health Organization (WHO) has launched a global initiative to eliminate cervical cancer as a public health problem, which includes targets for vaccination, screening, and treatment to be met by 2030 [4].

Epidemiology of cervical cancer in India

In India, cervical cancer ranks as the second most frequent cancer among women between 15 and 44 years of age. Annually, there are about 96,922 new cases and 60,078 deaths due to cervical cancer, accounting for nearly a quarter of the world's cervical cancer deaths [5]. The age-standardized incidence rate of cervical cancer in India is about 22 per 100,000 women, which is significantly higher than the rates observed in more developed regions [6].

The high prevalence of cervical cancer in India can be attributed to several factors including limited access to comprehensive HPV vaccination programs and inadequate screening practices across rural and urban divides. Moreover, socio-cultural barriers and low health literacy contribute to the underutilization of preventive services, leading to late-stage diagnoses and lower survival rates [7].

Cause of cervical cancer: Focus on virology

Cervical cancer is primarily caused by persistent infection with certain types of human papillomavirus (HPV), a small DNA virus that infects the epithelial cells. This section outlines the role of HPV in the causation of cervical cancer, detailing the types involved, their pathogenesis, and the interaction with host factors that can lead to cancer progression.

Human papillomavirus (HPV) and its oncogenic types

HPV is a non-enveloped DNA virus that infects the skin and mucous membranes. Out of the more than 200 types identified, approximately 14 are considered high-risk for the development of cervical cancer [8]. HPV types 16 and 18 are responsible for almost 70% of all cervical cancer cases worldwide [9]. Other high-risk types include HPV 31, 33, 45, 52, and 58, which also contribute significantly to cervical carcinogenesis.

Mechanism of HPV-induced carcinogenesis

The lifecycle of HPV is closely integrated with the epithelial differentiation process. The virus infects the basal cells of the epithelium, where it usually remains in a non-replicative state. As the infected cells differentiate and move towards the surface, the virus begins to replicate, completing its life cycle without causing cell death [10]. This non-lytic lifecycle allows the virus to persist unnoticed by the host immune system, which is crucial for its oncogenic potential.

In a small fraction of infections, HPV DNA integrates into the host genome. This integration disrupts the usual virus lifecycle and the regulation of viral oncogenes, E6 and E7. These genes are pivotal in the progression to cancer; they encode proteins that can inactivate tumor suppressor pathways involving p53 and retinoblastoma (Rb) proteins. The inactivation of these pathways prevents apoptosis and promotes uncontrolled cell division, leading to the accumulation of genetic damage and eventually, malignant transformation [11].

Host factors and co-factors in HPV-induced carcinogenesis

Various host factors and external co-factors influence the progression from HPV infection to cervical cancer. Genetic predispositions, such as variations in the genes involved in the immune response, can affect an individual's susceptibility to HPV and progression to cancer. External co-factors include smoking, long-term use of oral contraceptives, high parity (number of births), and co-infection with other sexually transmitted infections (STIs) such as *Chlamydia trachomatis* and HIV. These factors may act synergistically with HPV infection to increase the risk of developing cervical cancer [12].

Conclusion of the virology section

Understanding the virology of HPV and its interaction with host factors provides crucial insights into the mechanisms of cervical cancer development. This knowledge is fundamental in guiding the development of preventive strategies, such as vaccines and targeted therapies, and improving screening methods to detect precancerous changes early. The persistence of HPV as the central cause underscores the importance of vaccination programs in the fight against cervical cancer.

Pathophysiology of cervical cancer: Virology and molecular biology of HPV

Cervical cancer's pathophysiology is intimately connected to the virology of the human papillomavirus (HPV), particularly its molecular biology and the mechanisms through which its viral proteins induce oncogenesis. This section provides a detailed analysis of HPV's structure, genetic makeup, and the specific roles of its oncogenic proteins, E6 and E7, in the progression to cervical cancer.

HPV: Structure and genetic makeup

HPV is a non-enveloped virus with an icosahedral capsid approximately 55 nm in diameter. The capsid is composed of 72 capsomers, each made up of five molecules of the L1 protein, the major capsid protein, which is highly immunogenic and the basis for HPV vaccines. The viral genome is a circular double-stranded DNA approximately 8,000 base pairs in length, enclosed within the capsid. The genome is organized into early (E) and late (L) regions based on their expression during the viral lifecycle. The early region contains genes associated with viral replication and cell transformation, including E1, E2, E6, and E7, while the late region encodes structural proteins L1 and L2 [13].

Molecular biology of HPV and viral oncoproteins

The E6 and E7 proteins of high-risk HPV types are the primary molecular agents responsible for the oncogenic transformation of host cells. These proteins interfere with critical cellular regulatory proteins, mainly through the following mechanisms:

- **E6 protein**: The E6 protein of high-risk HPV types promotes the degradation of the tumor suppressor protein p53. Under normal circumstances, p53 regulates the cell cycle and initiates apoptosis in the presence of DNA damage. E6 facilitates the ubiquitination and subsequent proteasomal degradation of p53, impairing the cell's ability to undergo apoptosis in response to genetic damage, thus allowing the accumulation of mutations [14].
- **E7 protein**: Similarly, the E7 protein targets the retinoblastoma (Rb) tumor suppressor protein. Rb controls the cell cycle progression at the G1 phase by preventing the activation of E2F family transcription factors, which are necessary for the transition to the S phase. E7 binds to Rb, releasing E2F and allowing the cell to enter the S phase prematurely, which contributes to uncontrolled cell proliferation and increases the likelihood of genetic errors during DNA replication [15].

HPV-induced carcinogenesis

The carcinogenic process begins when HPV infects the basal cells of the cervical epithelium, usually through micro-abrasions. The virus maintains its genome in an episomal state, replicating alongside host DNA and evading immune detection. Oncogenic risk increases when the viral DNA integrates into the host genome, a process facilitated by disruptions in E2, the viral gene that normally regulates E6 and E7 expression. This integration results in the overexpression of E6 and E7, leading to sustained inhibition of p53 and Rb [16].

The loss of control over cell cycle checkpoints and apoptosis leads to genomic instability, accumulation of mutations, and eventually, the malignant transformation of infected cells. The progression from pre-cancerous lesions to invasive cervical cancer can take years, often providing a window for detection and intervention through screening methods like Pap smears and HPV testing [17].

Other cancers caused by human papillomavirus (HPV)

While HPV is most widely known for its role in causing cervical cancer, it is also implicated in the development of several other types of cancers. These include cancers of the anus, oropharynx (which includes parts of the throat, tongue, soft palate, and tonsils), penis, vulva, and vagina. This section explores the association between HPV and these cancers, detailing the types of HPV involved and the mechanisms of carcinogenesis.

Anogenital cancers

- **Anal cancer**: HPV is found in about 90% of anal cancers. HPV type 16 is the most common type associated with anal cancer, similar to cervical cancer. The mechanism of carcinogenesis is also similar, involving the E6 and E7 proteins and their interaction with cellular tumor suppressor proteins [18].
- **Vulvar and vaginal cancers**: HPV types 16 and 18 are responsible for approximately 40% of vulvar cancers and 70% of vaginal cancers. These cancers develop through mechanisms akin to those seen in cervical cancer, involving the disruption of cell cycle control and inhibition of apoptosis [19].

Oropharyngeal cancer

This is the most common non-anogenital cancer caused by HPV. In recent decades, there has been a significant increase in the incidence of oropharyngeal cancer attributed to HPV, particularly in developed countries. HPV type 16 is again the most implicated type. It affects the basal epithelial cells of the oropharynx, leading to cancer through molecular pathways involving the E6 and E7 proteins [20].

Penile cancer

HPV DNA is found in approximately 40 - 50% of penile cancer cases. The carcinogenic process is similar, with HPV 16 being the predominant type involved. The cancer often develops in areas of epithelial transformation, where mucous membranes meet skin, and follows a pathogenesis pathway involving the deregulation of the cell cycle and apoptosis [21].

Mechanisms of HPV-induced carcinogenesis in non-cervical cancers

The molecular mechanisms of carcinogenesis in HPV-related cancers outside the cervix are broadly similar to those in cervical cancer. The virus infects epithelial cells at various sites, with the high-risk types expressing the E6 and E7 oncoproteins, which interfere with the tumor suppressors p53 and Rb, respectively. This interference results in the prevention of programmed cell death and uncontrolled cellular proliferation, leading to cancer. Furthermore, factors such as immune response, genetic susceptibility, and exposure to other environmental co-carcinogens play critical roles in the progression from infection to cancer.

Prevention and screening

The prevention strategies effective against HPV-related cervical cancer, primarily HPV vaccination and screening, are also applicable to other HPV-associated cancers. Vaccination against HPV can significantly reduce the incidence of these cancers, and raising awareness about the broader oncogenic potential of HPV is crucial for public health strategies aiming to reduce the burden of HPV-related cancers globally [22].

Clinical features of cervical cancer

Cervical cancer often presents without symptoms in its early stages, which is why screening is crucial. As the disease progresses, the following clinical features may become evident:

- **Abnormal vaginal bleeding**: This includes bleeding between regular menstrual periods, after sexual intercourse, or after menopause.
- **Vaginal discharge**: Increased vaginal discharge that may be watery, foul-smelling, or tinged with blood is common.
- **Pelvic pain**: Pain during intercourse or at other times can be a sign of advanced cervical cancer.
- **Other symptoms**: These may include weight loss, fatigue, back pain, leg pain, swollen legs, and leakage of urine or feces from the vagina, indicating more advanced disease [23].

Staging of CA cervix [24]

Stages	Clinical findings
I	Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
IA	Invasive carcinoma that can be diagnosed only with microscopy with maximum depth of invasion < 5 mm.
IA1	Stromal invasion < 3 mm in depth.
IA2	Stromal invasion >/= 3 mm and < 5 mm in depth.
IB	Invasive carcinoma confined to the uterine cervix, with measured deepest invasion >/= 5 mm.
IB1	Tumour measures < 2 cm in greatest dimension.
IB2	Tumour measures >/= 2 cm and < 4 cm in greatest dimension.
IB3	Tumour measures >/= 4 cm in greatest dimension.
II	Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall.
IIA	Limited to the upper thirds of the vagina without parametrial involvement.
IIA1	Tumour measures <4 cm in greatest dimension.
IIA2	Tumour measures >/= 4 cm in greatest dimension.
IIB	With parametrial involvement but not up to the pelvic wall.
III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes.
IIIA	Involves the lower third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney from tumour.
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent.
IIIC1	Pelvic lymph node metastasis only.
IIIC2	Para-aortic lymph node metastasis.
IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.
IVA	Spread to adjacent pelvic organs.
IVB	Spread to distant organs.

Table 1

Diagnosis of cervical cancer

The following steps are typically involved in the diagnosis of cervical cancer:

- **Screening tests**: Pap smear tests and high-risk HPV DNA tests are the primary screening tools used to identify precancerous conditions or early-stage cervical cancer.

- **Colposcopy**: If abnormal cells are found during screening, a colposcopy can be conducted to examine the cervix more closely and take biopsies. Colposcopic evaluation usually depends upon the recognition of four different features:

1. Intensity of acetowhitening.
2. Margins and surface contour of acetowhite areas.
3. Vascular features.
4. Colour changes after iodine application.

Low grade CIN (Cervical intraepithelial neoplasia) is seen as thin, smooth acetowhite lesions with well demarcated but irregular, feathery or angular margins.

High grade CIN with thick, dense, greyish acetowhite areas with well demarcated, regular margins which may occasionally be raised or everted.

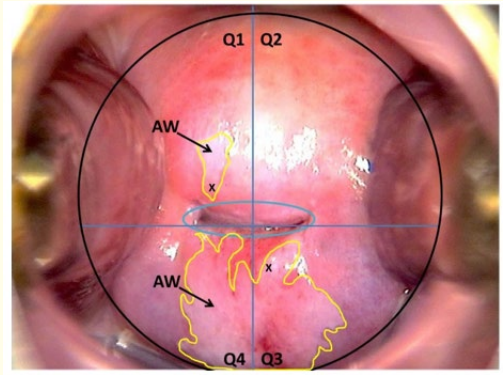

Figure 1: *Colposcopic findings in abnormal lesions of the cervix.*

- **Biopsy**: A biopsy, where a small section of tissue is removed from the cervix for analysis, is the definitive method for diagnosing cervical cancer.
- **Imaging tests**: Ultrasound, CT scans, MRI, and PET scans may be used to determine the extent (stage) of cancer [24].

Treatment, prophylaxis, and vaccination

Treatment options

The treatment of cervical cancer depends on the stage of the disease, the size of the tumor, the patient's age, and whether she wants to have children in the future. Common treatments include:

- **Surgery**: Surgical options range from simple procedures to remove abnormal cells to more extensive procedures like hysterectomy.
- **Radiation therapy**: This may be used alone or in combination with surgery and often involves external beam radiation and brachytherapy.
- **Chemotherapy**: Often used alongside radiation therapy, especially for more advanced stages of the disease [25].

Stage	Treatment modality
IA	Conization, modified radical trachelectomy (fertility sparing) Modified radical hysterectomy + sentinel lymph node (SLN)
IB	Modified radical hysterectomy + pelvic lymph node dissection or SLN
II A	Radical hysterectomy + pelvic lymph node dissection OR, chemoradiation
II B	Chemoradiation to pelvic field
III A	Chemoradiation to pelvic field
III B	Chemoradiation to pelvic field + extended field
III C	Chemoradiation to pelvic field + extended field + systemic chemotherapy
IV A	Chemoradiation to pelvic + extended fields OR, pelvic exenteration
IV B	Systemic chemotherapy + radiation, pelvic or modified field. Palliative treatment.

Table 2

Prophylaxis and vaccination

HPV vaccines are the primary prophylactic approach to reduce the risk of cervical cancer. Vaccines like Gardasil and Cervarix are effective against the major cancer-causing strains of HPV, notably HPV types 16 and 18. It is recommended that both girls and boys receive the vaccine at ages 11 - 12, though it can be administered as early as age 9 up to age 26 [26].

Screening

Regular screening through Pap tests or HPV tests is crucial for the early detection of precancerous changes and cervical cancer. It is recommended for women to start screening at age 21 and continue until at least age 65, following more specific guidelines based on age and health history [27].

Conclusion

The global and national statistics highlight the pressing need to enhance preventive measures, specifically through increased coverage of HPV vaccination and improved screening practices. The success of these interventions is crucial for reducing the incidence and mortality rates associated with cervical cancer, particularly in resource-limited settings like India. Ongoing research and policy efforts must focus on overcoming barriers to these services to make strides towards the elimination of cervical cancer as a significant public health concern.

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