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TRANSFORMING CERVICAL CANCER PREVENTION: THE IMPACT OF HPV VACCINES AND MOLECULAR SCREENING

*Preetam Datta [a], Dhrubo Jyoti Sen [b], Beduin Mahanti [c]

[a,b,c]School of Pharmacy, Techno India University, Kolkata-700091, West Bengal, India.

Abstract

Cervical cancer refers to the growth of cells that begin in the cervix. The cervix is the lower part of the uterus that connects to the vagina. Several types of the human papillomavirus, or HPV, cause cervical cancer. The human papillomavirus refers to the common virus that is usually spread through sexual contact.

Keywords:cervix; vagina; pelvic pain; vaginal discharge; Human Papilloma Virus; carcinoma; CIN; SIL

1. Introduction

Cervical cancer is a cancer of the cervix (the lower part of the uterus) caused mainly by persistent Human Papillomavirus (HPV) infection, leading to abnormal cell growth that can become cancerous over time, often with few early symptoms but detectable through screening. Prevention focuses on HPV vaccination and regular Pap/HPV tests, while treatment depends on the stage, involving surgery, radiation, and chemotherapy, with early detection improving outcomes significantly.[1,2]

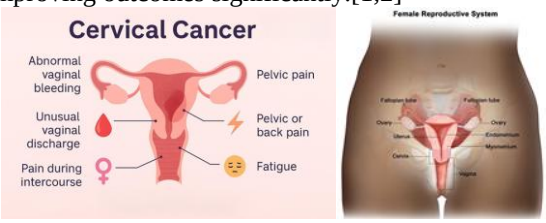

Fig. 1: Cervical cancer

Epidemiology

• Cervical cancer ranks as the **fourth leading malignancy among women worldwide**.
• A disproportionately high burden is observed in **low- and middle-income nations**, largely due to limited access to effective screening and preventive services.
• **India contributes approximately one-fifth of cervical cancer–related mortality globally**, highlighting a significant public health concern.
• The disease most frequently affects women in the **35–55-year age group**.
• Widespread implementation of **HPV vaccination programs** has led to a marked decline in cervical cancer incidence among vaccinated cohorts.

Histological Variants

• **Squamous Cell Carcinoma (SCC):** Represents nearly **70–80% of cervical cancers** and originates from the squamous epithelium of the ectocervical transformation zone.
• **Adenocarcinoma:** Comprises approximately **15–25% of cases**, developing from the glandular epithelium of the endocervical canal.

Cervical Anatomy

The cervix is anatomically classified into the following regions:
• **Ectocervix:** The external portion of the cervix, covered by stratified squamous epithelium.
• **Endocervix:** The inner cervical canal, lined by mucus-secreting columnar epithelium.
• **Transformation Zone (TZ):** The junction between squamous and columnar epithelium; this region is particularly vulnerable to **HPV infection** and serves as the primary site of cervical carcinogenesis.

Etiology and Risk Factors

Persistent infection with **oncogenic (high-risk) Human Papillomavirus (HPV) strains** is the principal etiological factor in the development of cervical cancer. [3,4]

A. **Human Papillomavirus (HPV)**

- **High-Risk Types:** HPV types **16** and **18** are responsible for approximately 70% of cervical cancer cases. Other high-risk types include 31, 33, 45, 52, and 58.
- **Transmission:** HPV is primarily transmitted through sexual contact.
- **Mechanism:** The viral oncoproteins **E6** and **E7** are central to carcinogenesis:
- **E6:** Binds to and degrades the **p53 tumour suppressor protein.**

Table-1: Difference between CIN & SIL

CIN / SIL Category	Histopathological Features	General Management Approach
CIN 1 / LSIL	Low-grade epithelial changes with dysplastic cells confined to the basal one-third of the epithelium; frequently self-limiting.	Conservative management with regular monitoring and repeat screening.
CIN 2 / HSIL	Intermediate-grade dysplasia involving up to two-thirds of the epithelial thickness.	Active intervention using ablative or excisional procedures (e.g., LEEP, cryotherapy).
CIN 3 / HSIL	High-grade lesion showing full-thickness epithelial atypia, including carcinoma in situ.	Definitive excisional treatment such as LEEP or cone biopsy.
Invasive Cervical Cancer	Malignant cells penetrate the basement membrane and extend into the stromal tissue.	Clinical staging followed by appropriate oncologic management (surgery, radiotherapy, chemotherapy, or combinations).

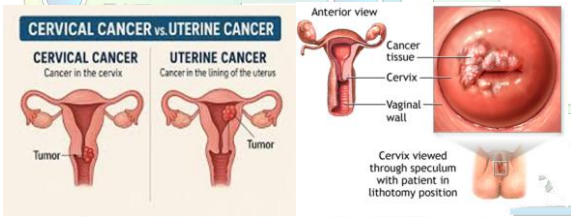

Fig. 2: Anatomy of Cervix

B. **Other Risk Factors**

- **Immunosuppression:** Conditions like HIV infection (AIDS) or organ transplantation significantly increase risk.
- **Smoking:** Tobacco by-products are found in cervical mucus and act as co-carcinogens.
- **Chlamydia Infection:** Co-infection may increase the risk.
- **Long-term use of Oral Contraceptives (OCs).**
- **Multiple full-term pregnancies.**

Pathogenesis: From Infection to Invasion:

Cervical cancer develops slowly, typically over years, through a series of precancerous changes known as **Cervical Intraepithelial Neoplasia (CIN) or Squamous Intraepithelial Lesion (SIL).**[5,6]

The persistent integration of high-risk HPV DNA into the host genome leads to the sustained expression of E6 and E7, driving the cell from normal to CIN and eventually to invasive carcinoma.

Types of Cervical Cancer:

1. Squamous Cell Carcinoma (SCC)

Most common form (about 70–80% of cases).
Arises from ectocervical squamous epithelium.

2. Adenocarcinoma

Originates from glandular epithelium of endocervix.
Increasing incidence in recent years.

3. Others (Rare)

Adenosquamous carcinoma
Neuroendocrine tumours
Small cell carcinoma
Post-coital bleeding
Intermenstrual bleeding
Vaginal discharge

Advanced Stage

Pelvic pain
Dyspareunia
Foul-smelling discharge
Post-menopausal bleeding
Urinary or bowel symptoms due to tumour compression
Leg oedema (advanced disease)

Diagnosis and Staging:

A. Screening and Initial Diagnosis

- **Papanicolaou (Pap) Smear:** A cytological test to detect precancerous or cancerous cells.
- **HPV DNA Testing:** Highly sensitive test to detect the presence of high-risk HPV types. **Co-testing** (Pap smear + HPV test) is the current standard for women over 30.

Diagnostic Tools[9]:
Colposcopy
Biopsy (gold standard)
Endocervical curettage
Imaging for staging: Ultrasound, MRI, CT, PET-CT
Pharmacological and Non-Pharmacological Management:

- **Colposcopy and Biopsy:** If screening is abnormal, a colposcopy (magnified visualization of the cervix) is performed, followed by a directed biopsy to confirm the diagnosis and grade the lesion.

B. Staging (FIGO System)

The **International Federation of Gynaecology and Obstetrics (FIGO)** staging system is used to classify the extent of the cancer, which guides treatment.[7,8]

Management depends heavily on the stage of the cancer.

Table-2: FIGO stage

FIGO Stage	Description
Stage I	Malignancy limited entirely to the cervical tissue.
Stage II	Tumor spreads outside the cervix and uterus but does not reach the pelvic wall or the lower one-third of the vagina.
Stage III	Disease involvement reaches the pelvic sidewall and/or the distal one-third of the vagina, and may be associated with ureteric obstruction leading to hydronephrosis or renal dysfunction.
Stage IV	Cancer extends outside the true pelvis or directly infiltrates the bladder or rectal mucosa (Stage IVA), or presents with distant metastatic spread (Stage IVB).

A. Treatment for Precancerous Lesions (CIN 2/3)

- **Excision Procedures:**
- **Loop Electrosurgical Excision Procedure (LEEP):** A heated wire loop removes the abnormal tissue.
- **Cold Knife Cone Biopsy:** A scalpel is used to remove a cone-shaped piece of tissue.

- **Ablative Procedures:**
- **Cryotherapy:** Freezing the abnormal cells.
- **Laser Ablation:** Using a laser to destroy the abnormal cells.

B. Treatment for Invasive Cancer (FIGO Stage I-IV)

1. Surgical Management[10]

• **Early-stage disease (IA2, IB1, IIA1):** Managed primarily by **radical hysterectomy**, which involves excision of the uterus, cervix, upper vaginal segment, and parametrial tissues, along with **pelvic lymph node dissection**.
• **Fertility-preserving option:** In selected women with very early-stage cervical cancer who desire future fertility, **radical trachelectomy**—removal of the cervix and parametrium while retaining the uterus—may be performed.

2. Chemotherapy and Radiotherapy (Concurrent Chemoradiation)[11]

Concurrent chemoradiation represents the **standard of care for locally advanced cervical cancer** (Stages IB3, II, III, and IVA).
• **Definitive non-surgical therapy:** A combination of **external beam radiation therapy (EBRT)** and **brachytherapy** (intracavitary radiation) constitutes the main treatment approach.
• **Concurrent chemotherapy: Cisplatin** is commonly administered alongside radiation as a radiosensitizing agent to increase tumor cell sensitivity to radiation.

3. Targeted Therapy and Immunotherapy

• **Targeted therapy (advanced or recurrent disease):**
• **Bevacizumab:** A monoclonal antibody targeting **vascular endothelial growth factor (VEGF)**, thereby inhibiting tumor angiogenesis. It is typically used in combination with chemotherapeutic agents such as **paclitaxel and topotecan**.

• **Immunotherapy (advanced or recurrent disease):**
• **Pembrolizumab:** A **programmed death-1 (PD-1)**

checkpoint inhibitor indicated for patients with recurrent or metastatic cervical cancer showing progression after conventional chemotherapy. It enhances anti-tumor immune responses by blocking PD-1–ligand interactions, enabling immune-mediated cancer cell destruction. [11,12]

a. HPV Vaccination[13]:

Types of Vaccines

Bivalent (Cervarix) – HPV 16, 18

Quadrivalent (Gardasil) – HPV 6, 11, 16, 18

Nonavalent (Gardasil 9) – broader coverage

Recommended Age:

Girls: **9–14 years** (most effective before sexual activity)

Catch-up vaccination up to **26 years**

Vaccination significantly reduces risk of high-grade CIN and cervical cancer.

Fig. 3: Monoclonal antibody

Prevention:

Prevention is the most effective strategy against cervical cancer.

A. **Primary Prevention: HPV Vaccination**

- **Vaccines:** Quadrivalent (HPV 6, 11, 16, 18), Nonavalent (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58).
- **Mechanism:** The vaccines contain virus-like particles (VLPs) of the L1 major capsid protein, which elicit a strong immune response and high titers of neutralizing antibodies. These antibodies prevent initial infection upon exposure.
- **Recommendation:** Recommended for both boys and girls, optimally starting at age 11 or 12.

Fig. 4: Recombinant vaccine

B. **Secondary Prevention: Screening**

- **Regular Pap Smear/Co-testing:** Crucial for detecting precancerous lesions (CIN) before they progress to invasive cancer.

Complications:

- Infertility (post surgery or radiation)
- Fistula formation (vesicovaginal or rectovaginal)
- Hydronephrosis
- Metastasis (lungs, liver, bones)
- Psychological stress and reduced quality of life

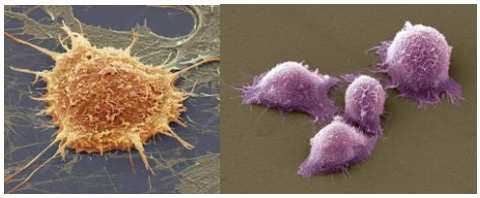

Fig. 5: Scanning Electron Micrograph of Cervical Cancer Cells

Recent Advances:

Liquid-based cytology improving screening accuracy

Self-sampling HPV test kits for remote areas

Artificial intelligence (AI)-assisted colposcopy

Checkpoint inhibitors in immunotherapy

Personalized medicine approaches under research[14,15, 16]

Conclusion: Cervical cancer is largely preventable through the widespread use of the **HPV vaccine** (primary prevention) and **cervical screening** (secondary prevention). The pathogenesis is well-understood, centering on the oncogenic activity of HPV's E6 and E7 proteins. Management for invasive disease involves a multidisciplinary approach, with **surgery, chemoradiation (Cisplatin)**, and increasingly, **targeted therapy (Bevacizumab)** and **immunotherapy (Pembrolizumab)** forming the backbone of treatment.

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