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

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ABSTRACT
Cervical cancer is a growth of cells that starts in the cervix. The cervix is the lower part of the uterus that connects to the vagina. Various strains of the human papillomavirus, also called HPV, play a role in causing most cervical cancers. HPV is a common infection that's passed through sexual contact.

KEYWORDS: Cervix, vagina, pelvic pain, vaginal discharge, Human Papilloma Virus, carcinoma, CIN, SIL.

INTRODUCTION
Cervical cancer is a type of cancer that develops in the cervix or in any layer of the wall of the cervix. It is due to the abnormal growth of cells that can invade or spread to other parts of the body. Early on, typically no symptoms are seen. Later symptoms may include abnormal vaginal bleeding, pelvic pain or pain during sexual intercourse. While bleeding after sex may not be serious, it may also indicate the presence of cervical cancer. Persistent infection with high-risk types of **Human Papillomavirus (HPV)** is the primary cause. Early detection and treatment can significantly improve prognosis.[1,2]

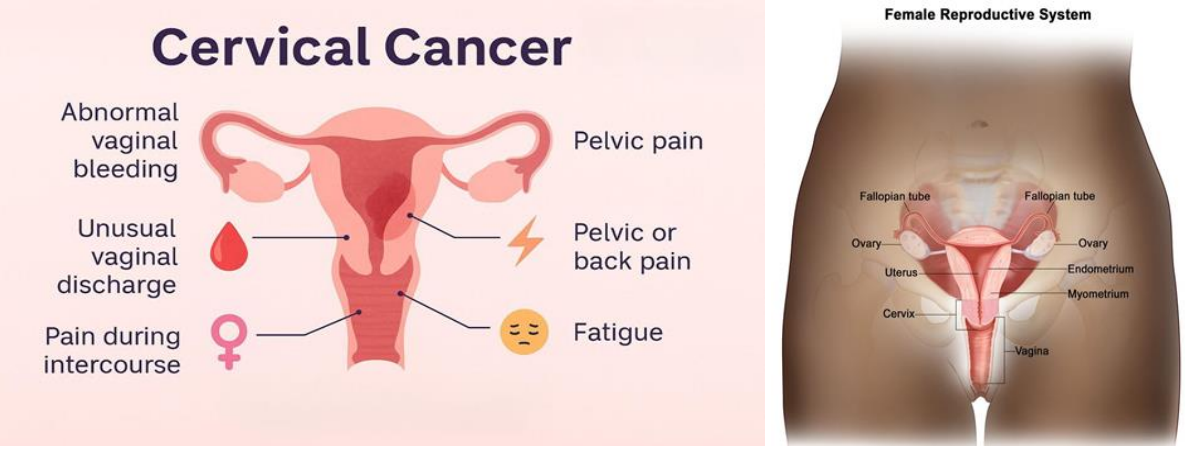

Figure 1: Cervical cancer.

Epidemiology

- Cervical cancer is the **fourth most common cancer** among women globally.
- Majority of cases occur in **low- and middle-income countries** due to poor screening facilities.
- India alone contributes to nearly **one-fifth of global cervical cancer deaths.**
- Peak incidence commonly occurs between **35–55 years** of age.
- The introduction of HPV vaccination has significantly reduced incidence rates in vaccinated populations.

Histological Types

- **Squamous Cell Carcinoma (SCC):** Accounts for about 70-80% of cases, arising from the transformation zone of the ectocervix.
- **Adenocarcinoma:** Accounts for about 15-25% of cases, arising from glandular cells of the endocervix.

Anatomy of the Cervix

The cervix is divided into:

Ectocervix: Outer part lined with squamous epithelium.

Endocervix: Inner canal lined with columnar epithelium.

Transformation zone (TZ): Area where squamous and columnar epithelium meet; most cervical cancers originate from this zone due to higher susceptibility to HPV infection.

Etiology and Risk Factors

The primary cause of cervical cancer is persistent infection with high-risk types of the Human Papillomavirus (HPV).[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.**
- **E7:** Binds to and inactivates the **retinoblastoma protein (pRb)**, leading to uncontrolled cell cycle progression.

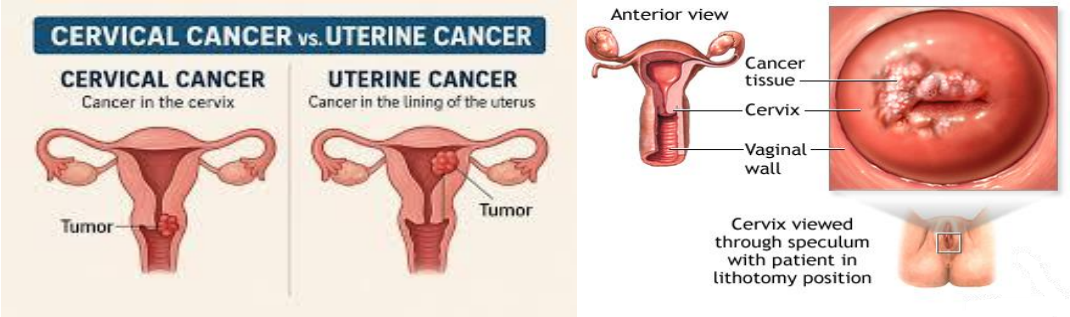

Figure 2: Anatomy of Cervix.

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]

Table 1: Difference between CIN & SIL.

CIN/SIL Grade	Description	Management Principle
CIN 1 / LSIL (Low-Grade SIL)	Mild dysplasia, abnormal cells in the lower third of the epithelium. Often resolves spontaneously.	Observation/Follow-up (often watch and wait).
CIN 2 / HSIL (High-Grade SIL)	Moderate dysplasia, abnormal cells in the lower two-thirds.	Treatment (e.g., LEEP, cryotherapy).
CIN 3 / HSIL	Severe dysplasia or Carcinoma in situ (CIS), abnormal cells filling the full thickness of the epithelium.	Treatment (e.g., LEEP, cone biopsy).
Invasive Cancer	Abnormal cells breach the epithelial basement membrane and invade the underlying stroma.	Staging and definitive treatment (surgery, radiation, chemotherapy).

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

CLINICAL FEATURES

Early-Stage (Often Asymptomatic)

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.
- **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]

Table 2: FIGO stage.

FIGO Stage	Description
Stage I	Confined to the cervix.
Stage II	Extends beyond the uterus but not to the lower third of the vagina or the pelvic sidewall.
Stage III	Extends to the pelvic sidewall and/or involves the lower third of the vagina and/or causes hydronephrosis/non-functioning kidney.
Stage IV	Extends beyond the true pelvis or involves the bladder/rectal mucosa (IVA), or distant metastasis (IVB).

Diagnostic Tools

Colposcopy
Biopsy (gold standard)
Endocervical curettage
Imaging for staging: Ultrasound, MRI, CT, PET-CT

Pharmacological and Non-Pharmacological Management

Figure 3: Monoclonal antibody.

Management depends heavily on the stage of the cancer

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. Surgery

- **Early Stage (IA2, IB1, IIA1): Radical Hysterectomy** (removal of the uterus, cervix, part of the vagina, and parametrium) plus pelvic lymphadenectomy.
- **Fertility-Sparing Surgery: Radical Trachelectomy** (removal of the cervix and parametrium) for very early-stage disease in women who wish to preserve fertility.

2. Chemotherapy and Radiotherapy (Chemoradiation)

Chemoradiation is the standard for locally advanced cervical cancer (Stages IB3, II, III, IVA).

- **Primary Treatment: External Beam Radiation Therapy (EBRT)** combined with **Brachytherapy** (internal radiation) is the primary non-surgical treatment.
- **Radiosensitizer Chemotherapy: Cisplatin** is the most commonly used chemotherapy drug, given concurrently with radiation to enhance the radiation's cytotoxic effect.

3. Targeted Therapy and Immunotherapy

- **Targeted Therapy (Advanced/Recurrent Cancer):**
- **Bevacizumab:** A monoclonal antibody that inhibits **Vascular Endothelial Growth Factor (VEGF)**, an angiogenesis promoter. It is often combined with chemotherapy (e.g., Paclitaxel + Topotecan).
- **Immunotherapy (Advanced/Recurrent Cancer):**
- **Pembrolizumab:** A **PD-1 inhibitor** (checkpoint inhibitor) used for patients with recurrent or metastatic cervical cancer that progresses after standard chemotherapy. It blocks the interaction between PD-1 and its ligands, allowing the immune system to recognize and attack cancer cells.[9,10]

HPV Vaccination

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.

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.

Figure 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

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[11,12]

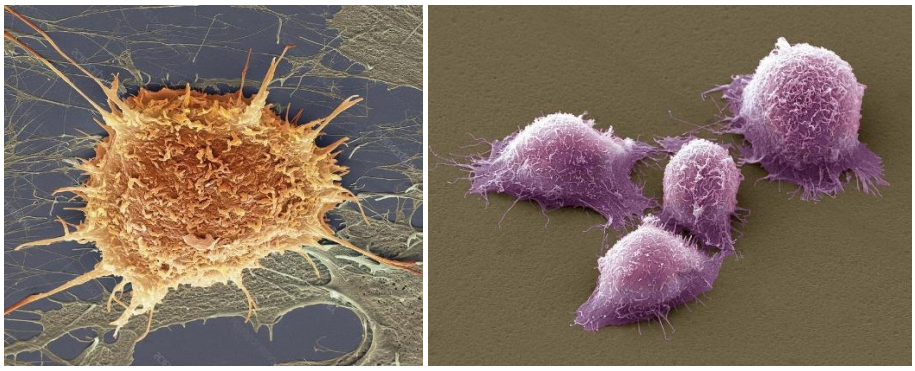

Figure 5: Scanning Electron Micrograph of Cervical Cancer Cells.

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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