EJPMR, 2026, 13(4), 383-394 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

CERVICAL CANCER AND HUMAN PAPILLOMAVIRUS (HPV) VACCINATION: PATHOGENESIS, PREVENTION AND CLINICAL EFFICACY

Astitwa Maity*, Rudranil Khanra and Dr. Dhrubo Jyoti Sen

School of Pharmacy, Techno India University, Sector-V, Salt Lake City, EM: 4/1, Kolkata-700091, West Bengal, India.

***Corresponding Author: Astitwa Maity**

School of Pharmacy, Techno India University, Sector-V, Salt Lake City, EM: 4/1, Kolkata-700091, West Bengal, India. **DOI:** https://doi.org/10.5281/zenodo.19482234

How to cite this Article: Astitwa Maity*, Rudranil Khanra and Dr. Dhrubo Jyoti Sen. (2026). Cervical Cancer and Human Papillomavirus (HPV) Vaccination: Pathogenesis, Prevention and Clinical Efficacy. European Journal of Pharmaceutical and Medical Research, 13(4), 383–394.

Article Received on 04/03/2026 **Article Revised on 25/03/2026** **Article Published on 01/04/2026**

ABSTRACT

One of the most important achievements in cancer research has been the establishment of persistent infection with specific human papillomaviruses (HPV) genotypes as the cause of cervical cancer. Since then, various diagnostic and therapeutic approaches have been developed based on this finding. The purpose of this article is to provide an overview of the most recent developments in the biology, prevention, and treatment of HPV-related cervical cancer. The current knowledge status on vaccinations, diagnostic tools, and cervical cancer treatments is discussed. The most recent WHO recommendations on vaccinations are discussed, as well as announcements of future changes. The final section of this article summarizes new promising diagnostic and therapeutic approaches, as well as views and the most recent findings on self-administered diagnostic tests, therapeutic vaccines, and circulating cell-free DNA. Although tremendous progress has been made in the past few years, the strategy of vaccination and testing still remains the cornerstone in the fight against HPV-related cervical cancer.

KEYWORDS: Human papillomavirus (HPV), HPV vaccination, Cervical intraepithelial neoplasia (CIN), Virus-like particles (VLPs), Vaccine efficacy, Immunization, Epidemiology, Cervical cancer.

INTRODUCTION

Cervical cancer is a cause of significant disease burden. Human papillomavirus (HPV) infection is the cause of cervical cancer in almost 100% of the cases. HPV infection can also lead to genital warts, recurrent respiratory papillomatosis, vaginal, vulval, anal and penile cancers. HPV types 16 and 18 are responsible for more than 70% of HPV-related cervical cancers whilst HPV types 6 and 11 cause approximately 90% of the cases of genital warts. Effective interventions to prevent HPV associated diseases can therefore prevent cervical cancers, genital warts and other less common cancers. Primary prevention can be achieved by vaccination and secondary prevention by screening.

A phenomenal breakthrough in preventive oncology has been made by the development and introduction of this prophylactic vaccine against cancer of the cervix- the first of its kind in the world of oncology. It promises to positively impact the personal lives of millions of women and their families' worldwide. Hopefully, it will prove to be a public health marvel, once successfully implemented. Papanicolaou smears achieved a 60-70% reduction in cancer of the cervix within 3 years of implementation as a secondary preventive measure in those developed countries where the program was introduced effectively. Now with the addition of a primary preventive measure in the form of a prophylactic vaccine against cancer, the impact on the incidence rates of cervical cancer should be even more significant. In developing countries like India, wherein lies a quarter of the world's disease burden, screening alone as a national program is unlikely to work. Universal prophylactic vaccination of young adolescent girls will be a more workable and effective option. As a result, the state of many Indian women with advanced cervical cancer may well become history, provided the medical fraternity, in particular the gynecologists, pediatricians, general practitioners and the Ministry of Health support it as a universal immunization program.[1]

Overview of Cervical Cancer: Researchers need to investigate modern cervical cancer prevention methods and HPV vaccine implementation because cervical cancer constitutes the main cancer death cause for women in developing nations. Most women in underdeveloped nations have advanced cervical cancer, which is often incurable and has a very poor prognosis. The survival rates for women with cervical cancer increase when doctors detect their disease during its initial stages. The process that leads to cervical cancer development starts with high-risk human papillomavirus (HPV) strains creating a persistent infection which results in abnormal cervical cell growth. HPV types 16 and 18 account for approximately 70% of all cervical cancer cases which exist among more than 100 different HPV types. The condition arises from several risk factors which include a weakened immune system, smoking, having multiple sexual partners, starting sexual activity at a young age, and long-term use of birth control pills. The symptoms that may develop include abnormal vaginal bleeding which can happen after intercourse or between periods and pelvic pain and unusual vaginal discharge. Advanced disease symptoms will include weight loss and fatigue and painful urination. Doctors use Pap smear tests together with HPV DNA testing and colposcopy to diagnose the condition, while biopsy serves as the confirmatory method. The vaccination and screening programs serve as the central elements of the prevention strategies. The HPV vaccines Gardasil and Cervarix deliver excellent protection against high- risk HPV type infections. The combination of routine Pap smear tests and HPV testing enables doctors to identify and eliminate precancerous lesions at an early stage. People who practice safe sex and stop smoking will experience a reduced risk of developing the condition. The treatment approach depends on the current stage of the disease. Doctors can operate to cure early-stage cervical cancer through surgical procedures which include hysterectomy and conisation.[2]

Human Papillomavirus (HPV) & its type: Over 200 types of HPV have been identified. Types of HPV are usually grouped according to their oncogenic potential as low-risk and high-risk types. Human Papillomavirus (HPV) is a small, double-stranded DNA virus that primarily infects epithelial cells of the skin and mucous membranes. It is one of the most common viral infections worldwide and is usually transmitted through sexual activity. While most cases of HPV are transient and disappear on their own within a short time without treatment, persistent infection with certain types of HPV can cause serious health problems, including cancer.[3]

Types

Low-Risk HPV types: Low-risk HPVs are not associated with cancer development. Instead, they typically cause benign growths such as genital warts. The most common low-risk types are HPV 6 and HPV 11. These types are responsible for the majority of genital wart cases and may also contribute to conditions like recurrent respiratory papillomatosis.

High-Risk HPV types: High-risk HPVs have a strong association with the development of cancer. Among these, the two most important types of high-risk HPVs are type 16 and type 18, as these types of viruses account for the majority of cervical cancer worldwide. Other types of high-risk HPVs include types 31, 33, 45, 52, and 58.

These types of viruses, if associated with the host cells, can cause cancer by progressing from a pre-cancerous stage to a cancerous stage. Other types of cancer that have a high association with high-risk HPVs include anal, vaginal, vulvar, penile, and oropharyngeal cancer.

Need & Significance of the study: Cervical cancer is still a problem for women especially in countries that are not as developed. Even though we can prevent it for the part it is still very common because many women do not know about it and there are not enough programs to check for it and not enough women getting vaccinated. The main reason women get cancer is because of a bad infection with certain types of Human Papillomavirus, which is why getting vaccinated and checking for it early can really help. In places like India a lot of women find out they have cancer when it is already very advanced because they do not have access to regular check-ups and good healthcare. Women are also embarrassed to talk about it they do not know much about it they cannot afford to get help and the programs that are supposed to prevent it are not working well. So it is really important that we teach women about Human Papillomavirus, how it spreads and what they can do to prevent it like getting vaccinated and getting checked regularly.[4]

This study is important because it looks at how Human Papillomavirus causes cancer and what we can do to prevent it like getting vaccinated. By learning more about how cancer spreads what puts women at risk and what Human Papillomavirus does to the body we hope to make healthcare better. If women know more about it and we have public health programs we can reduce the number of women who get cervical cancer make healthcare less expensive and help women live better lives. Cervical cancer and Human Papillomavirus are still problems, which is why this study says we need to make sure all women can get vaccinated and get checked for Human Papillomavirus as part of our national health plan. This will help reduce the number of women who get cancer and make our public health better in the long run. Human Papillomavirus vaccination and screening programs are really important, for women's health.

Ultimately, this study emphasizes the importance of integrating HPV vaccination and screening programs into national health policies to reduce the burden of cervical cancer and promote long-term public health improvement.

AIM

To study the role of Human Papillomavirus (HPV) in the development of cervical cancer and to evaluate the importance of preventive strategies, particularly HPV vaccination and screening, in reducing disease burden.

OBJECTIVE

- To study the structure, classification, and types of Human Papillomavirus (HPV).
- To explain the molecular mechanism by which high-risk HPV types cause cervical cancer.
- To analyse the risk factors associated with HPV infection and cervical carcinogenesis.
- To evaluate the role of HPV vaccines in primary prevention.
- To assess the importance of screening methods such as Pap smear and HPV DNA testing in secondary prevention.
- To highlight the public health significance of implementing vaccination and screening programs, especially in developing countries.
- To understand the epidemiology and global burden of cervical cancer.

Anatomy and Histology of the cervix

Female Reproductive System

Introduction: The female reproductive system consists of internal and external organs responsible for reproduction, menstruation, and hormone production. In the context of cervical cancer, understanding the anatomical structure of the cervix and its surrounding tissues is essential, as cervical malignancy originates from specific epithelial cells within this region.[5]

Components of the Female Reproductive System

1. **Ovaries**
- Paired glands located on either side of the uterus
- Produce female hormones: estrogen and progesterone
- Release ova (eggs) during ovulation

2. **Fallopian Tubes**
- Muscular tubes connecting ovaries to uterus
- Site of fertilization

3. **Uterus**
- Hollow, muscular organ where foetal development occurs
- Divided into fundus, body, and cervix

4. **Cervix:** The cervix is the lower, narrow part of the uterus that opens into the vagina. It plays a crucial role in cervical cancer development.

The cervix has two main types of epithelium

- **Squamous epithelium** (outer part – ectocervix)
- **Columnar epithelium** (inner canal – endocervix)

The area where these two meet is called the transformation zone, which is the most common site for HPV infection and cervical cancer development.[6]

Parts of Female Reproductive System

Transformation Zone: The region where the squamous epithelium of the ectocervix meets the columnar epithelium of the endocervix is known as the squamocolumnar junction. The area surrounding this junction is called the transformation zone. This region undergoes continuous cellular changes and is highly susceptible to infection by high-risk HPV types. Most precancerous lesions and cervical cancers develop in this zone.

Functions of the Cervix

The cervix performs several important functions

- Acts as a passage for menstrual blood from the uterus to the vagina
- Produces cervical mucus that regulates sperm entry into the uterus
- Serves as a protective barrier against infections
- Dilates during childbirth to allow delivery of the baby

Relevance to Cervical Cancer: The epithelial cells in the transformation zone are particularly vulnerable to HPV infection. Persistent infection with high-risk HPV types can cause abnormal cellular changes that may progress to cervical intraepithelial neoplasia and eventually cervical cancer. For this reason, cervical screening methods such as the Pap smear primarily collect cells from the transformation zone.

Histopathology of Cervical Tissue

Introduction: The study of the histopathologic-feature of the cervix is the microscopic view of the cervical tissue's normal structure and recognition of abnormal changes in the cervical tissue caused by precancer (cervical cancer). The cervix is made up of several different types of epithelial tissues and can undergo cellular changes (abnormal or normal) especially with persistent high-risk HPV infectious agents. Evaluation of these tissues under the microscope can help identify such microscopic changes for early detection, diagnosis, and management of cervical cancer.

Normal Histology of Cervical Tissue

The cervix contains two main types of epithelial lining

1. Stratified Squamous Epithelium (Ectocervix)

o Covers the outer portion of the cervix that faces the vagina.
o Consists of multiple layers of flattened epithelial cells.
o These cells provide protection against mechanical and microbial injury.

2. Simple Columnar Epithelium (Endocervix)

o Lines the cervical canal.
o Composed of mucus-secreting columnar cells arranged in a single layer.
o Cervical glands within this region produce mucus that helps regulate sperm entry and protects the uterus from infections.

The junction where these two epithelial types meet is called the squamocolumnar junction, and the surrounding area is known as the transformation zone. This zone is particularly susceptible to HPV infection and is the most common site for the development of cervical precancerous lesions.[7]

Cervical Intraepithelial Neoplasia (CIN):- Abnormal cell changes in the epithelial cells are called cervical intraepithelial neoplasia (CIN). It is a condition that can sometimes be caused by infection with high-risk HPV strains.

CIN does not mean cancer is present; it is cell growth on the cervix that could turn into cancer if not treated. Cervical intraepithelial neoplasia or CIN is a condition where abnormal cell growth on the cervix can occur. The abnormal cell growth, on the cervix can be caused by HPV strains. CIN is not cancer. It can lead to cancer if left untreated.

Pathogenesis: CIN usually starts in the transformation zone of the cervix. This is where the squamous epithelium of the ectocervix meets the epithelium of the endocervix. The transformation zone is very prone to HPV infection. When high-risk HPV types infect cells the viral proteins mess up the normal cell cycle. As a result the infected cells start to grow leading to dysplasia which is abnormal cell growth. CIN is often linked to HPV infection and abnormal cell growth in the cervix. The transformation zone of the cervix is at risk, for CIN. HPV infection can cause CIN and CIN can lead to cell growth.

Classification of CIN: CIN is classified according to the extent of abnormal cell growth within the epithelial layer:

CIN I (Mild Dysplasia)
- Abnormal cells are confined to the lower one-third of the epithelial layer.
- Often associated with early HPV infection.
- Many cases regress spontaneously without treatment.

CIN II (Moderate Dysplasia)
- Abnormal cells extend into the lower two-thirds of the epithelium.
- The risk of progression to cancer is higher compared to CIN I.
- Medical monitoring or treatment is usually required.

CIN III (Severe Dysplasia / Carcinoma in-situ)
- Abnormal cells occupy nearly the entire thickness of the epithelial layer.
- Although the basement membrane remains intact, the lesion has a high potential to progress to invasive cervical cancer if untreated.

Clinical Detection: Cervical Intraepithelial Neoplasia is usually found out by doing cervical screening tests, like the Pap smear or the Human Papillomavirus DNA testing. When the doctors find cells they do more tests. They use something called colposcopy. Biopsy to see if the person really has Cervical Intraepithelial Neoplasia and to figure out how bad the Cervical Intraepithelial Neoplasia.[8]

Human Papilloma Virus [HPV]

Introduction to HPV: HPV is a collective time period used to describe a own family of small viruses that haven't any outer membrane and are made of strands of DNA. The majority of the time HPV infects the epithelial cells that are located for your pores and skin and to your mucous membranes (the membranes that line your nose, mouth & throat). HPV is one of the most regularly said sicknesses across the globe; it's miles one of the maximum standard sexually transmitted diseases (STDs) amongst adults. Normally, most HPV infections are asymptomatic and remedy on their personal. However, there are numerous traces of HPV which are related to extreme medical situations which include cervical most cancers.

General Characteristics: There are over 200 different HPV types, all in the same large family of viruses. HPV viruses are species specific and generally will only infect epithelial tissues. An HPV virion itself is made up of a protein capsid (made primarily of L1 and L2 proteins) enclosing a circular piece of DNA, called the viral genome. HPV viruses have no lipid envelope, which gives them a good deal of stability when they are in the environment.

Clinical Significance: The majority of HPV infections will go away on their own (after a period of time) through your body's immune system. High-Risk (HR) types of HPV are more prone to cause abnormal cell changes and may eventually lead to cancers (mainly cervical cancer). However, many HR-HPV infections will resolve before causing any disease. The HPV virus can also cause other types of benign (non-cancerous) skin growths (for example, warts) from infection with Low-Risk (LR) HPV types.

Virology and Classification: Human Papillomavirus (HPV) consists of double stranded circular DNA and has a size of 8,000 base pairs. HPV is a small virus that doesn't have a viral envelope and is part of the family of viruses called Papillomaviridae. The target cells for the virus are the epithelial cells found in the skin and mucous membranes.

HPV has a spherical protein coat called an icosahedral capsid containing mostly the structural proteins known as L1 and L2. The L1 and L2 proteins play essential roles in the assembly and infection of the HPV virus.

The HPV genome can be divided into three domains which correspond to three functional regions:

The Early (E) Region: The early region contains genes that code for the proteins (E1 to E7) involved in HPV viral replication and regulation of the viral lifecycle. Some of these proteins are important for oncogenesis (E6 and E7) because they interfere with normal host cell (tumour suppressor) protein function.

The Late (L) Region: The late region contains genes that code for the proteins (L1 and L2) used to form the protein shell (capsid) of the virus.

Long Control Region (LCR): This region is a long, non-coding, regulatory region of the genome that has a role in controlling viral replication and gene expression. HPV can enter the basal layer of epithelial cells through minor injuries (abrasions). The virus can replicate in the host cell and ultimately propagate the infection within the host cell through differentiation of the infected host cell, which causes the infected host cell to migrate towards the epithelial surface. As opposed to most other viruses, HPV does not result in host cell death (lysis), but can persist.[9]

Classification of HPV: HPV types are classified based on their genetic structure and disease-causing potential. Broadly, they are divided into the following categories:

1. Based on Oncogenic Potential

Low-Risk (Non-Oncogenic) Types

- Cause benign lesions such as genital warts
- Common types: HPV 6 and HPV 11
- Rarely associated with cancer High-Risk (Oncogenic) Types
- Associated with cervical cancer and other malignancies
- Major types: HPV 16 and HPV 18
- Other important types: HPV 31, 33, 45, 52, 58
- Responsible for the majority of HPV-related cancers

2. Based on Tissue Tropism

- **Cutaneous HPV types**

Infect the skin and cause common warts

- Mucosal HPV types: Infect mucosal surfaces (genital, anal, oral regions) and are associated with both benign and malignant conditions.

3. Based on Phylogenetic Classification:

HPV is further grouped into different genera based on genetic similarity

- **Alpha-papillomavirus:** Infect mucosal epithelium; includes most high-risk types (e.g., HPV 16, 18)
- **Beta-papillomavirus:** Infect skin; associated with cutaneous lesions.
- **Gamma-papillomavirus:** Also infect skin; generally less pathogenic

Modes of Transmission: Human Papillomavirus (HPV) is primarily transmitted through direct contact with infected skin or mucosal surfaces. It is one of the most common sexually transmitted infections worldwide. Transmission does not require penetration and can occur through close physical contact involving infected epithelial tissue.[11]

Sexual Transmission

- The principal mode of HPV transmission is through sexual contact, including vaginal, anal, and oral intercourse.
- Infection occurs when the virus enters the body through micro- abrasions in the skin or mucous membranes.
- Both symptomatic and asymptomatic individuals can transmit the virus.
- Early onset of sexual activity and multiple partners increase the risk of transmission.

Skin To Skin Contact

- HPV can spread through direct skin-to-skin contact in the genital area, even without penetrative intercourse.
- This explains why barrier methods such as condoms reduce but do not completely eliminate the risk of transmission.

Vertical Transmission (Mother to Child)

- Transmission can occur from an infected mother to her child during vaginal delivery.
- This may lead to conditions such as recurrent respiratory papillomatosis in infants, although it is relatively rare.

Oral Transmission

- HPV may be transmitted through oral-genital contact, leading to infection of the oropharyngeal region.
- High-risk HPV types are associated with cancers of the throat and oral cavity.

Indirect Transmission

- Transmission through contaminated objects (fomites) such as medical instruments or surfaces is considered rare.
- Proper sterilization and hygiene practices significantly reduce this risk.

HPV Life Cycle and Infection Mechanism:- HPV infects basal keratinocytes through microwounds in the epithelium, strictly linking its life cycle to cellular differentiation. The virus establishes a low-copy infection, replicates its genome alongside the host cell, and matures in upper layers, releasing progeny through shedding without immediate cell death. High-risk HPV E6/E7 proteins can cause persistent infection and cancer.

High-risk vs Low-risk HPV

Features	High Risk	Low Risk
Cancer Potential	High	None
Common types	16, 18, 31, 33, 45, 52, 58	6, 11
Disease Outcome	Cancer precancerous lesions	Genital warts
Mechanism	Disrupt p53 & Rb	Minimal cellular disruption
Persistence	Long-term	Usually transient

Infection Mechanism

Entry into Host Tissue: The Human Papillomavirus gets into our body through cuts in the skin or the mucous membrane and this usually happens when we have sex. The Human Papillomavirus goes after the basal cells, in the skin. These cells can keep dividing over and over again.

Attachment and Internalization: The viral capsid proteins, which are the L1 and L2 proteins, stick to things on the outside of the host cell. When the viral capsid proteins have attached to the host cell the virus goes into the cell. Then the virus releases its DNA into the part of the cell and the DNA is moved to the nucleus of the host cell, where the viral capsid proteins and the virus do their thing with the DNA of the virus.[12]

HPV Life Cycle Stages

Establishment Phase: Inside the nucleus of basal cells the Human Papillomavirus DNA is found as an episome, which's basically a circular piece of DNA that exists on its own. The Human Papillomavirus replicates itself at a low rate using the enzymes of the host cell and this allows the infected basal cells to keep dividing while still keeping the Human

Papillomavirus genome inside them.

Maintenance Phase: As infected basal cells divide the viral DNA goes to the cells. Early proteins like E1 and E2 help control the virus replication. At the time E6 and E7 change how the host cell cycle works to keep the virus going. The viral DNA is, in the cells and E1, E2, E6 and E7 help the virus. E1 and E2 are important for the virus to make copies of itself. The host cell cycle is changed by E6 and E7 to support the virus.

Productive (Replication) Phase: When the infected cells move up and change the virus starts to make copies of itself much faster. The late genes, which are L1 and L2 get turned on. This helps make the proteins that the new viruses need to form. The infected cells moving upward and differentiating causes the viral replication to increase significantly. The L1 and L2 late genes are expressed during this process. They help create the proteins that are required for new virus formation.

Assembly and Release: New viral particles are assembled in the upper layers of the epithelium. These virions are released as mature epithelial cells are naturally shed. HPV does not destroy host cells (non-lytic release), which helps it evade immune responses.[13]

Pathogenesis of Cervical Cancer

Entry of HPV: Entry of HPV is the initial step in infection, where the virus gains access to epithelial cells of the cervix. This step is essential for establishing infection and subsequent disease development.

Mechanism of Entry

- **Through Micro-abrasions:** HPV enters via small epithelial injuries, commonly during sexual contact. Intact epithelium resists infection.
- **Targeting Basal Cells:** The virus infects basal layer cells of the epithelium, as these cells actively divide and support viral replication.
- **Attachment to Cell Surface:** Viral capsid protein L1 binds to receptors (such as heparan sulfate proteoglycans) on host cells.
- **Internalization:** The virus enters the cell via endocytosis, and viral DNA is transported to the nucleus.

Site of Entry

- Predominantly occurs in the transformation zone of the cervix
- This region is highly vulnerable due to continuous epithelial turnover

Persistent infection: Persistent HPV infection means the virus stays in the cells for a long time usually, over 1-2 years. Most HPV infections go away on their own because the immune system fights them off. When high-risk HPV types stick around they can cause cervical cancer. HPV infection is a deal and persistent HPV infection is what we need to worry about. The immune system usually clears HPV. Sometimes it doesn't. That's when problems can start, with high-risk HPV types and cervical cancer.

Mechanism of Persistence

- **Failure of Immune Clearance:** In some individuals, the immune system is unable to eliminate the virus effectively.
- **Episomal Maintenance:** HPV DNA remains in the nucleus as an episome and replicates along with host cells.
- **Low-Level Replication:** The virus maintains a steady presence without causing immediate cell death.

Role of High-Risk HPV Types

- High-risk types such as HPV 16 and 18 are more likely to persist.

- These types interfere with normal cell cycle regulation.
- Long-term infection increases the risk of malignant transformation.

Cellular Changes
- Continuous viral activity leads to abnormal cell proliferation
- Early stages show mild dysplasia
- May progress to CIN (Cervical Intraepithelial Neoplasia)

Development of CIN: Cervical Intraepithelial Neoplasia (CIN) represents precancerous changes in the cervical epithelium caused mainly by persistent high-risk HPV infection. These changes occur gradually and are confined above the basement membrane.[14]

Development of CIN
- **Initiation:** Persistent infection with high-risk HPV (especially 16, 18)
- **Cellular Dysplasia:** Abnormal cell growth and loss of normal maturation
- **Grading of CIN**
  - **CIN I: Mild dysplasia (lower one-third)**
  - **CIN II: Moderate dysplasia (two-thirds)**
  - **CIN III: Severe dysplasia (full thickness, pre-cancer)**
- **Basement Membrane**

Remains intact in all CIN stages
Progression to Cervical Cancer
Mechanism of Progression
- **Persistent HPV Infection**

Long-term viral presence is essential
- **Genetic Changes:** Activation of oncogenes and inactivation of tumor suppressor genes
- **Basement Membrane Invasion:**

Abnormal cells break the membrane → invasive cancer
Stages of Progression:- HPV Infection → CIN I → CIN II → CIN III → Invasive Cancer

Time Course
- Slow progression (10–20 years)
- Provides opportunity for early detection

Clinical Features
Signs and symptoms: Early Stage (Often Asymptomatic):-
- No obvious symptoms
- Detected mainly through screening (Pap smear)

Common Symptoms
- **Abnormal vaginal bleeding**
  - Between menstrual cycles
  - After sexual intercourse (post-coital bleeding)
  - After menopause
- **Unusual vaginal discharge**
  - Watery, foul-smelling, or blood-tinged
- **Pelvic pain**
  - Persistent or intermittent pain in lower abdomen

Advanced Stage Symptoms
- Pain during intercourse
- Difficulty in urination or bowel movements
- Lower back or leg pain
- Swelling of legs (lymphedema)
- Fatigue and weight loss

Epidemiology

1. **Global Burden:** Cervical cancer remains a major public health problem worldwide. It is the fourth most common cancer among women, with approximately 660,000 new cases and 350,000 deaths annually. A significant proportion (around 90%) of deaths occur in low- and middle-income countries due to limited access to screening and treatment facilities.
2. **Worldwide Cases:-** The incidence of cervical cancer varies widely across regions. The highest burden is observed in Sub-Saharan Africa, Southeast Asia, and parts of Latin America, where healthcare infrastructure is limited. In contrast, North America and Western Europe show lower incidence due to well-established screening and vaccination programs.
3. **Trends (Increase/Decrease):** Over the past few decades, cervical cancer incidence has shown declining trends in developed countries, mainly due to organized screening programs and HPV vaccination. However, in many developing countries, the incidence remains stable or increasing, particularly in rural and underserved populations.
4. **Reasons for Trends**

Factors responsible for decrease
- Widespread HPV vaccination programs targeting adolescents
- Regular screening methods such as Pap smear and HPV DNA testing
- Increased public awareness and better healthcare access

Factors responsible for increase
- Lack of organized screening programs
- Poor awareness and late diagnosis
- Early age of marriage and multiple pregnancies
- Limited vaccination coverage
- Socioeconomic and hygiene-related factors

5. **India Burden:** India contributes a substantial share of the global cervical cancer burden, with approximately 1.2 lakh new cases and 75,000 deaths each year. It is one of the leading cancers affecting Indian women, particularly in rural areas where awareness and healthcare services are limited.[15]

6. **State-wise Distribution (India):** The burden of cervical cancer varies across different states:
- High incidence states: Bihar, Uttar Pradesh, West Bengal, Assam
- Moderate incidence: Madhya Pradesh, Odisha, Rajasthan
- Low incidence states: Kerala, Tamil Nadu

States with lower incidence generally have better literacy rates, healthcare access, and screening coverage.

7. **Trends in India:** India has shown a gradual decline in cervical cancer incidence, especially in urban areas, due to improved awareness and opportunistic screening. However, the disease remains highly prevalent in rural populations due to limited access to healthcare, low screening rates, and poor vaccination coverage. Efforts by government and health organizations are slowly improving the situation, but significant gaps still remain.

Screening and Diagnosis

Pap Smear (Papanicolaou Test): Pap smear is a screening test used to detect abnormal, precancerous, or cancerous cells from the cervix.

Procedure
- A speculum is inserted to visualize the cervix
- Cells are collected from the transformation zone using a spatula or brush
- The sample is spread on a slide or preserved in liquid medium
- Examined under a microscope

Purpose
- Early detection of Cervical Intraepithelial Neoplasia (CIN)
- Identification of early-stage cervical cancer
- Helps in reducing incidence and mortality

Advantages
- Simple and non-invasive
- Cost-effective
- Widely used for mass screening

Limitations
- May give false-negative results
- Requires repeated testing
- Depends on sample quality

HPV DNA testing: HPV DNA testing is a molecular diagnostic test used to detect the presence of high-risk Human Papillomavirus (HPV) DNA in cervical cells.

Principle
- Based on detection of viral genetic material using techniques like PCR (Polymerase Chain Reaction)
- Identifies oncogenic HPV types (e.g., 16, 18)

Procedure
- Cervical cell sample collected (similar to Pap smear)
- Sample preserved in liquid medium
- DNA is extracted and analysed in the laboratory
- Results indicate presence or absence of high-risk HPV

Purpose
- Early identification of women at risk of cervical cancer
- Detects infection before cellular abnormalities develop
- Used in combination with Pap smear (co-testing)

Advantages
- High sensitivity
- Detects infection at early stage
- Helps in better risk assessment

Limitations
- Cannot differentiate transient vs persistent infection
- More expensive than Pap smear
- May cause anxiety if positive without disease

Clinical Use
- Primary screening method in some settings
- Follow-up test after abnormal Pap smear
- Co-testing with Pap smear for better accuracy

Prevention

Primary prevention (vaccination)

Definition: Primary prevention of cervical cancer is achieved through HPV vaccination, which prevents infection by high-risk HPV types responsible for most cervical cancers.[16]

Principle
- Vaccines contain Virus-Like Particles (VLPs)
- These mimic HPV structure but contain no viral DNA
- Stimulate the immune system to produce protective antibodies

Types of HPV Vaccines
- Bivalent: Protects against HPV 16, 18
- Quadrivalent: Protects against HPV 6, 11, 16, 18
- Nonavalent**:** Covers 9 HPV types (broader protection)

Vaccination Schedule
- 9–14 years: 2 doses (0, 6 months)
- 15–26 years: 3 doses (0, 2, 6 months)

Target Population
- Adolescent girls (before sexual exposure)
- Boys may also be vaccinated for broader protection

Benefits
- Prevents majority of cervical cancer cases
- Reduces incidence of genital warts
- Provides long-term immunity

Limitations
- Does not treat existing infection
- Screening still required after vaccination

Secondary prevention (screening)
Definition: Secondary prevention refers to the early detection of precancerous lesions (CIN) and early-stage cervical cancer through regular screening.

Methods of Screening
- Pap smear: Detects abnormal cervical cells
- HPV DNA testing: Identifies high-risk HPV infection
- Visual **inspection (VIA):** Uses acetic acid to detect lesions (low-resource settings)

Purpose
- Detect disease at an early, treatable stage
- Prevent progression from CIN to invasive cancer
- Reduce mortality and complications

Screening Recommendations (General)
- Women aged 21–65 years
- Regular screening at defined intervals
- Combination of Pap smear and HPV testing improves accuracy

Advantages
- Early diagnosis and timely treatment
- Cost-effective in long-term prevention
- Significantly reduces incidence of cervical cancer

Limitations
- Requires repeated testing
- Limited access in rural areas
- Depends on awareness and healthcare facilities

Lifestyle modifications
Safe Sexual Practices
- Use of protection (condoms)
- Avoid multiple sexual partners
- Delayed initiation of sexual activity

Regular Screening
- Periodic Pap smear and HPV testing
- Early detection of abnormalities

Personal Hygiene
- Maintain genital hygiene
- Use clean menstrual products

Avoid Smoking
- Smoking weakens local immunity
- Increases risk of cervical cancer

Healthy Diet
- Intake of fruits and vegetables
- Rich in antioxidants and vitamins (A, C, E)

Boost Immunity
- Regular physical activity
- Adequate sleep and stress management

HPV Vaccines
Types of vaccines
1. **Bivalent Vaccine**
- Protects against HPV 16 and 18
- Targets high-risk oncogenic types
- Mainly prevents cervical cancer

2. **Quadrivalent Vaccine**
- Protects against HPV 6, 11, 16, 18
- Covers both cancer-causing and wart-causing types
- Prevents cervical cancer and genital warts

3. **Nonavalent Vaccine**
- Protects against 9 HPV types: (6, 11, 16, 18, 31, 33, 45, 52, 58)
- Provides broadest protection
- Covers majority of cervical cancer cases

Vaccination schedule
1. **Age 9–14 Years (Preferred Age Group):**
- 2-dose schedule
  - 1st dose: Day 0
  - 2nd dose: After 6 months
- Provides strong and long-lasting immunity

2. **Age 15 Years and Above:**
- 3-dose schedule
  - 1st dose: Day 0
  - 2nd dose: After 2 months
  - 3rd dose: After 6 months

3. **Special Situations**
- Immunocompromised individuals:
  - Always require 3 doses regardless of age

Mechanism of Action: HPV vaccines work by stimulating the immune system to produce protective antibodies against HPV without causing infection.

Mechanism
- Virus-Like Particles (VLPs): The vaccine contains VLPs made from HPV L1 capsid protein. These resemble the virus but lack viral DNA, so they are non-infectious.
- Immune **Activation:** After injection, VLPs are recognized as foreign antigens, activating the immune system.
- Antibody Production: The body produces neutralizing antibodies against HPV.
- Prevention **of Viral Entry:** These antibodies bind to HPV and block its attachment and entry into cervical epithelial cells.
- Immunological **Memory:** Memory B cells are formed, providing long-term protection against future infections.

Safety and Efficacy

Contraindications: Contraindications are conditions in which HPV vaccination should be avoided or postponed to prevent adverse outcomes.

Major Contraindications

- **Severe Allergic Reaction (Anaphylaxis)**
  - History of hypersensitivity to any vaccine component
  - Previous severe reaction to a prior HPV vaccine dose

Precautions / Temporary Contraindications

- **Pregnancy**
  - HPV vaccine is not recommended during pregnancy
  - Can be given after pregnancy
- **Acute Illness**
  - Moderate or severe illness with fever
  - Vaccination should be postponed until recovery

Conditions NOT Contraindicated

- Mild illness (e.g., cold, mild fever)
- Lactation (breastfeeding)
- Use of antibiotics

Adverse Effects: HPV vaccines are generally safe and well tolerated. Most adverse effects are mild and temporary.

Common Adverse Effects

- Injection site reactions: pain, redness, swelling
- Fever (mild)
- Headache
- Fatigue Moderate Effects:
- Nausea
- Dizziness
- Muscle or joint pain

Rare Adverse Effects

- Allergic reactions (anaphylaxis)
- Fainting (especially in adolescents after injection)

Vaccine Efficacy: HPV vaccines are highly effective in preventing infections caused by high-risk HPV types and significantly reduce the incidence of cervical cancer and related diseases.

Efficacy against HPV Types

- HPV 16 & 18: ~90–95% protection (major cause of cervical cancer)
- Quadrivalent vaccine: Also protects against HPV 6 & 11 (genital warts)
- Nonavalent **vaccine:** Covers ~90% of cervical cancer-causing types

Effect on Disease Prevention

- Significant reduction in CIN (precancerous lesions)
- Decrease in cervical cancer incidence
- Reduction in genital warts cases Duration of Protection:
- Long-lasting immunity (10+ years)
- No booster required currently (as per available data)

Factors Affecting Efficacy

- Highest when given before HPV exposure
- Reduced effectiveness if already infected
- Better response in younger age groups

Real-World Impact

- Countries with high vaccination coverage show:
  - Reduced HPV infection rates
  - Decline in cervical cancer cases
  - Lower prevalence of genital warts

Discussion: Cervical cancer is a major public health problem, particularly in developing countries, and is strongly associated with persistent infection by high-risk HPV types.[17]

Key Findings

- HPV infection is the primary cause of cervical cancer
- High-risk types (16 and 18) contribute to the majority of cases
- Disease progression is slow, allowing early detection

Role of Prevention

- Primary prevention: HPV vaccination significantly reduces infection risk
- Secondary prevention: Screening (Pap smear, HPV testing) enables early detection of precancerous lesions

Public Health Perspective

- Developed countries show declining trends due to effective screening and vaccination
- Developing countries like India still have high burden due to lack of awareness and limited healthcare access

Challenges

- Low vaccination coverage
- Limited screening programs in rural areas
- Social stigma and lack of awareness

Future Scope

- Expansion of vaccination programs
- Increased awareness campaigns
- Improved access to screening and healthcare services

CONCLUSION

Cervical cancer remains a major global health burden, especially in low- and middle-income countries, despite being preventable and treatable when detected early. Conventional treatments such as surgery, chemotherapy, and radiotherapy provide significant clinical benefits but are often limited by toxicity and lack of tumour specificity. With advancements in pharmaceutics, innovative drug delivery systems—including nanoparticles, controlled release implants,

immunotherapeutics, and gene-based strategies—have opened new avenues for improving the precision and safety of cervical cancer treatment. These modern approaches enhance drug targeting, reduce systemic side effects, and hold the potential to overcome limitations associated with traditional therapies. Overall, pharmaceutics plays a critical role in shaping the future of cervical cancer management by contributing to more effective, patient-oriented, and technologically advanced treatment strategies. Cervical cancer is a preventable and treatable disease, especially when detected early through vaccination against the human papillomavirus (HPV) and regular screening. While a significant global health issue, particularly in low-resource countries, early detection and intervention dramatically improve survival rates. Continued efforts to improve screening access and "see and treat" strategies are key to reducing the burden of the disease worldwide.

- Primary prevention: HPV vaccination is highly effective for preventing the types of HPV that most commonly cause cervical cancer.
- Secondary prevention: Regular screening is crucial for early detection. Recommended screening methods include Pap smears, HPV tests, or co-testing, depending on age.
- "See and treat" approach: In resource-poor settings, simple screening methods like Visual Inspection with Acetic Acid (VIA) allow for immediate treatment of precancerous lesions, which is vital in areas with poor follow-up rates.
- Community and healthcare system involvement: Successful screening programs require high coverage rates and the ability to provide treatment to those who test positive, highlighting the need for strong health services and community engagement.

Impact and outlook

- Global health burden: Cervical cancer remains a major cause of death for women globally, especially in countries with limited access to vaccination and screening programs.
- Survival rates: Survival is significantly higher with early detection. The 5-year relative survival rate is about 91% if diagnosed in an early stage, but drops to around 60% if the cancer has spread to nearby tissues or organs.
- Future directions: Ongoing research focuses on improving screening tests (like point-of-care HPV tests), developing more accessible vaccines for different regions, and exploring new therapies such as targeted therapies and immunotherapies.

REFERENCE

1. Bosch FX, de Sanjosé S. "The epidemiology of human papillomavirus infection and cervical cancer". Disease Markers, 2007; 23(4): 213–227.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries". CA: A Cancer Journal for Clinicians, 2021; 71(3): 209–249.
3. Singh A., & Gupta R. Advances in nanotechnology-based cervical cancer therapy. Journal of Pharmaceutical Sciences, 2021; 110(4): 1450–1462.
4. Coleman RL., et al. Pembrolizumab in advanced cervical cancer. New England Journal of Medicine, 2019; 382(20): 1923–1934.
5. Dunne EF, Park IU. "HPV and HPV-associated diseases". Infectious Disease Clinics of North America, 2013; 27(4): 765–778.
6. Tewari KS. "Cervical Cancer". New England Journal of Medicine, 2025; 392(1): 56–71.
7. Canavan TP, Doshi NR. "Cervical cancer". American Family Physician, 2000; 61(5): 1369–1376.
8. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. "Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries". Lancet, 2020; 395(10224): 591–603.
9. Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A. "Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature". Gynecological Endocrinology, 2011; 27(8): 597–604.
10. Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. "HPV-mediated cervical carcinogenesis: concepts and clinical implications". The Journal of Pathology, 2006; 208(2): 152–164.
11. Marrazzo JM, Koutsky LA, Kiviat NB, Kuypers JM, Stine K. "Papanicolaou test screening and prevalence of genital human papillomavirus among women who have sex with women". American Journal of Public Health, 2001; 91(6): 947–952.
12. Kufe D. Holland-Frei cancer medicine (8th ed.). New York: McGraw-Hill Medical, 2009; 1299. ISBN 978-1-60795-014-1. Archived from the original on 1 December 2015.
13. Bosch FX, de Sanjosé S. "The epidemiology of human papillomavirus infection and cervical cancer". Disease Markers, 2007; 23(4): 213–227.
14. van Nagell JR, Greenwell N, Powell DF, Donaldson ES, Hanson MB, Gay EC. "Microinvasive carcinoma of the cervix". American Journal of Obstetrics and Gynecology, 1983; 145(8): 981–991.
15. Preetam Datta, Dr. Dhrubo Jyoti Sen, Dr. Pruthviraj K. Chaudhary, Shloka V. Chaudhari and Honey Riteshkumar Parmar; Focus on prevention & HPV and cervical cancer: progress in prevention, vaccination and early detection: European Journal of Biomedical and Pharmaceutical Sciences, 2025; 12(11): 311-316.
16. Lin Y, Zhou J, Dai L, Cheng Y, Wang J. "Vaginectomy and vaginoplasty for isolated vaginal recurrence 8 years after cervical cancer radical hysterectomy: A case report and literature review".

The Journal of Obstetrics and Gynaecology Research, 2017; 43(9): 1493–1497.
17. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. "Epidemiologic classification of human papillomavirus types associated with cervical cancer". The New England Journal of Medicine, 2003; 348(6): 518–527.