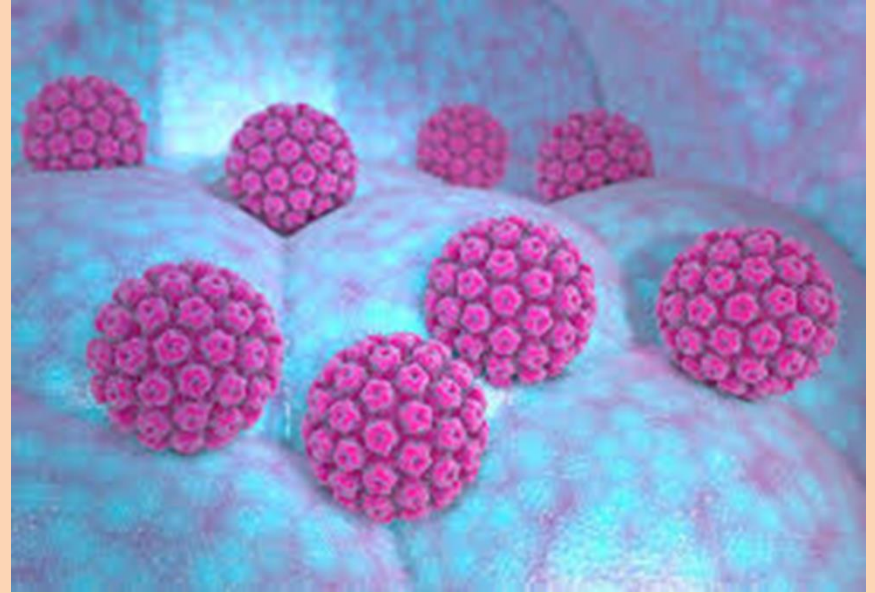


HPV Review

Pathology/laboratory

دکتر رامین آذر هوش
دانشیار آسیب شناسی

- According to the U.S. Centers for Disease Control and Prevention, about 79 million Americans are infected with HPV and over 14 million become newly infected each year.



What is being tested?

- Human papillomavirus (HPV) is a group of more than 150 related viruses.
- Some types of HPV are considered high risk because they can cause cancer.



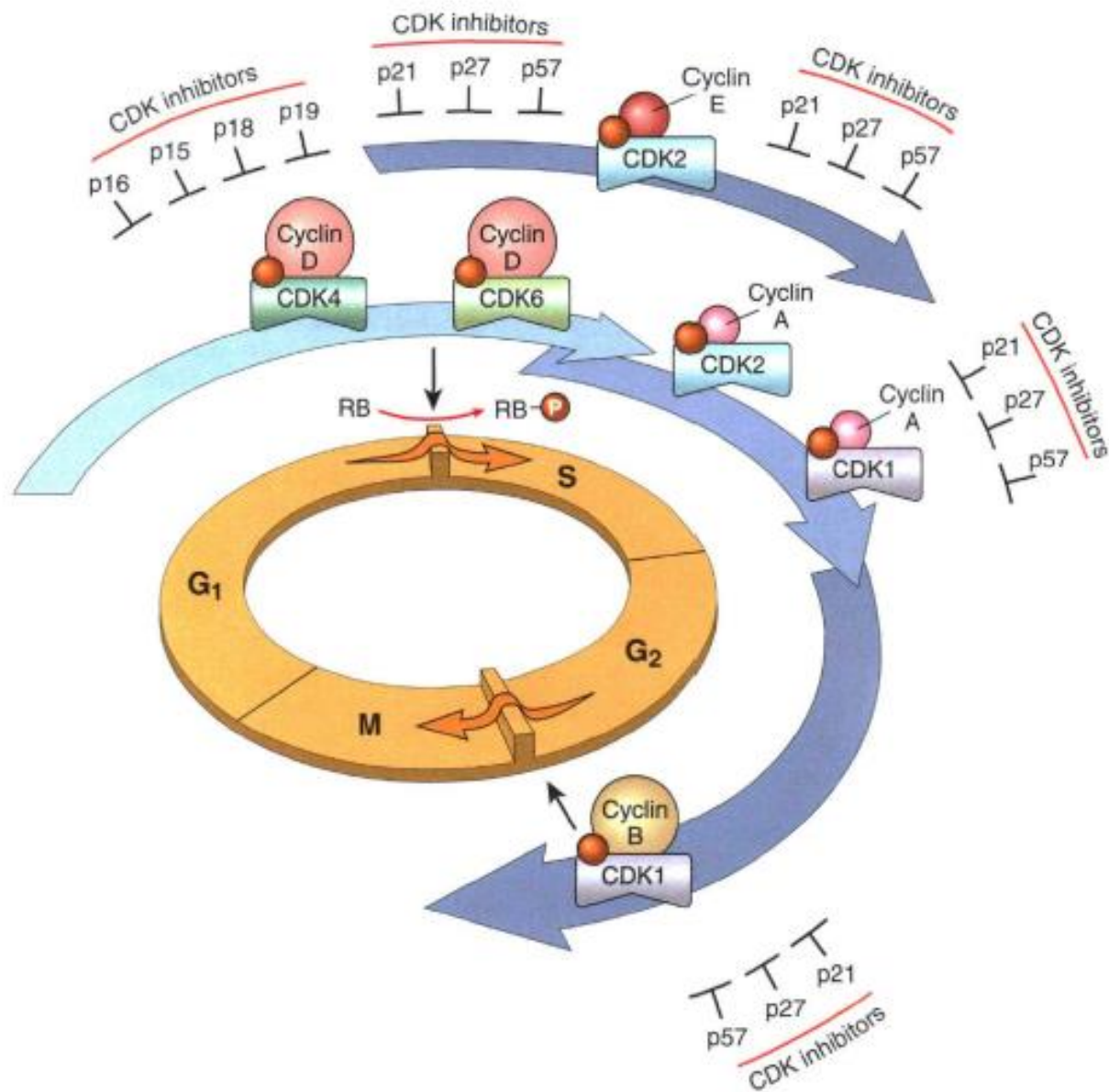
high-risk HPV types

- infection with **high-risk HPV** types, such as types **16, 18, 31**, and **45**, can favor the development of cancer.
- Co-factors such as **cigarette smoke** can also enhance the risk of such HPV-related cancers.

- HPV is believed to cause cancer by integrating its genome into nuclear DNA.
- E6 and E7, act as oncogenes that promote tumor growth and malignant transformation.
- HPV genome integration can also cause carcinogenesis by promoting genomic instability associated with alterations in DNA copy number.

- E6 produces a E6 protein that binds to and inactivates P 53 in the host cell .
- Normally, p53 acts to prevent cell growth, and promotes cell death in the presence of DNA damage.

- p53 also upregulates the p21 protein, which blocks the formation of the cyclin D/Cdk4 complex, thereby preventing the phosphorylation of RB, and in turn, halting cell cycle progression by preventing the activation of E2F.



p53

- p53 is a tumor-suppressor protein that arrests the cell cycle and prevents cell growth and survival when DNA damage occurs.
- Thus, inactivation of p53 by E6 can promote unregulated cell division, cell growth, and cell survival, characteristics of cancer.

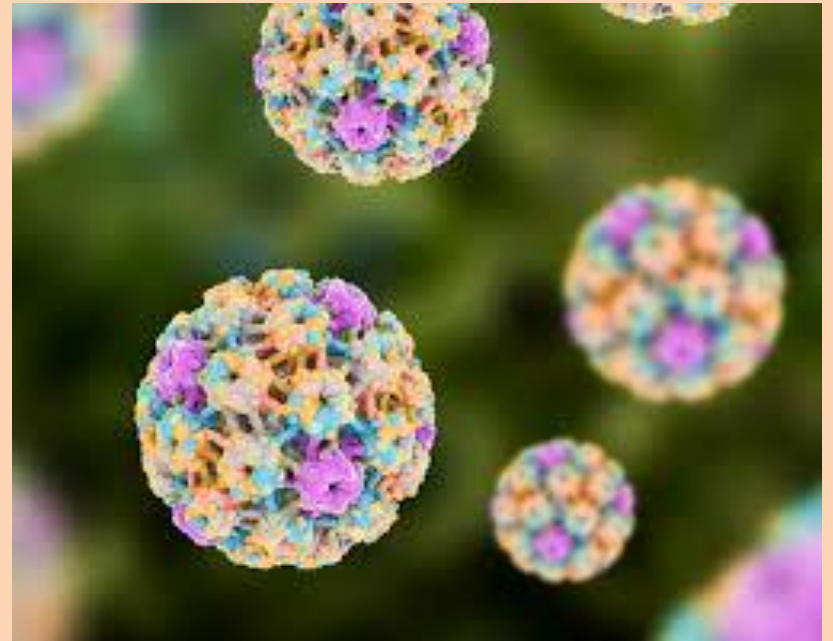
- E6 also has a close relationship with the cellular protein E6-associated protein (E6-AP), which is involved in the ubiquitin ligase pathway, a system that acts to degrade proteins.
- E6-AP binds ubiquitin to the p53 protein, thereby flagging it for proteosomal degradation.

screen for infections with HPV

Why Get Tested?

- To screen for infections with the high-risk types of HPV (hrHPV) that can cause cervical cancer or to follow up on an abnormal Pap smear (Pap test)

HPV testing detects the genetic material (DNA or messenger RNA) of high-risk HPV (hrHPV), primarily to screen for cervical cancer or to determine whether may be at risk of cervical cancer.



When To Get Tested?

- Every 5 years with a Pap smear (preferred) or HPV molecular test alone every 5 years (alternative strategy) when a woman aged 30 to 65 with average risk

- May be screened at a younger age and more frequently if have risk factors, such as a weakened immune system or personal history of precancerous lesions
- If a woman aged 21 to 29 and have an abnormal Pap smear result

Sample Required?

- CERVIX : A sample of cells is taken from the cervical area during a pelvic exam using a swab or small brush.
- The sample is then placed into a bottle containing a preservative.
- The same sample of cells can be used for both the Pap smear and the HPV test.

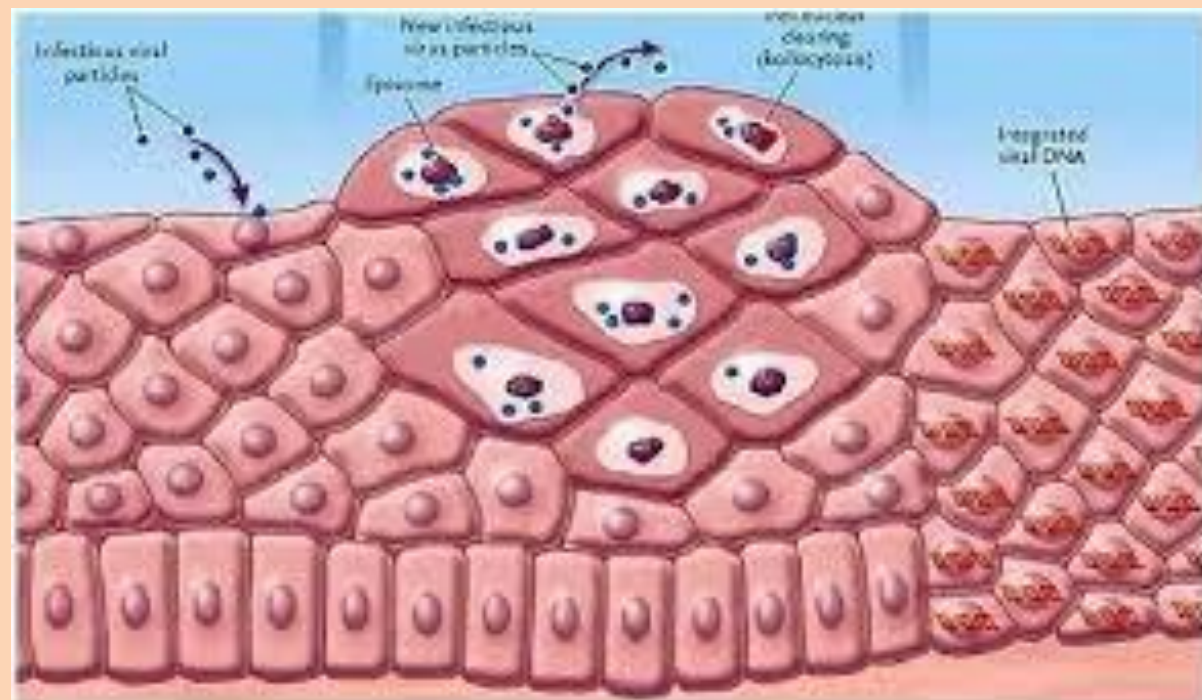


Test Preparation Needed?

- It is typically recommended that refrain from having sex, douching, or using vaginal products such as creams, deodorants, or medications for 24 hours before the test.
- Follow any instructions are given.
- Reschedule the test if having menstruation.
- Empty the bladder before the examination.

Genital HPV infection

- Some types of HPV can cause skin warts, while other types (particularly types 16 and 18)can cause genital warts (condylomata).
- Genital HPV infection is one of the most common sexually transmitted diseases (i.e., spread through oral, anal, or genital sex).



- High-risk HPV—there are 14 high-risk types of HPV that can lead to cancer (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Two HPV types, 16 and 18, cause 80% of all cervical cancers.
- These high-risk types can be detected with an HPV test.

- Low-risk HPV—some HPV strains cause genital warts but rarely cause cancer.
- HPV 6 and HPV 11 cause 90% of all genital warts but are considered "low risk" because they rarely lead to cancer.
- These low-risk types can be diagnosed through visual inspection and, therefore, do not require testing.

- Many HPV infections resolve without treatment—the body is able to clear the infection.
- However, infections with high-risk HPV types that do not go away can lead to cervical cancer.

cervical cancers

- Almost all cervical cancers are caused by persistent infections with high-risk HPV.
- Each year, nearly 12,000 women in the U.S. develop cervical cancer and about 4,000 are expected to die from it.

- Persistent oral infections with high-risk types of HPV are strongly associated with oral SCC, including oropharyngeal cancer.
- Anal SCC has also been linked to HPV types 16 and 18.
- These types are also linked to other cancers, such as those of the vagina and penis.

Purpose of the test

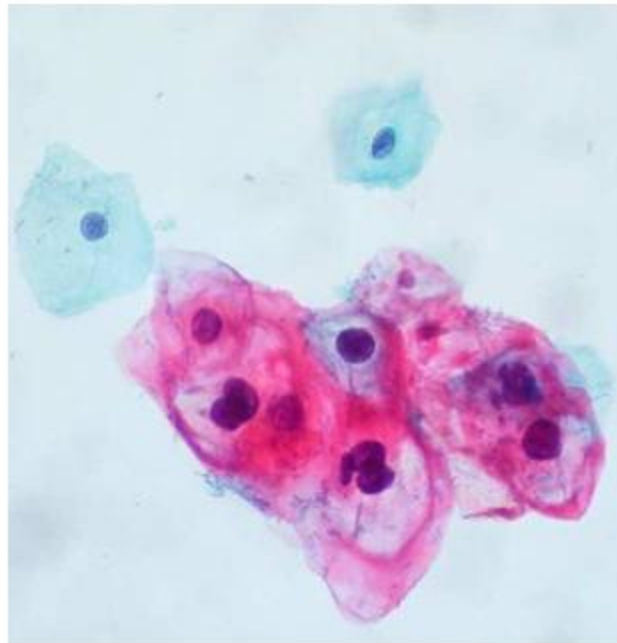
- The purpose of an HPV test is to detect an infection with a high-risk strain of HPV.
- An HPV test may be performed in several situations:



- HPV testing allows patients infected with high-risk HPVs to be monitored effectively and to have any abnormal cervical cells removed before they develop into cancer.

Follow-up

- An HPV test may be used as a follow-up test after an abnormal Pap smear.



Detecting HPV 16 or 18

- If HPV genotyping detects an infection with HPV 16 or 18, may recommend a colposcopy to examine the cervix and a biopsy to look for abnormal cells that require treatment.

Oropharyngeal cancer

- The majority of oropharyngeal carcinoma are caused by HPV.
- HPV-positive oropharyngeal carcinoma may be treated differently than HPV-negative oropharyngeal carcinoma, so HPV testing is an important part of treatment planning.

- Additional considerations after a positive HPV test include:

Detecting HPV 16 or 18

First positive result

- If someone has a positive HPV test after previously testing negative, it usually means a **new HPV infection**.
- While most new HPV infections will be followed up by a negative result in 6 to 12 months, this doesn't always mean that the body has cleared the infection.
- The HPV virus can go dormant and reappear on future tests.

Recurrent positive result:

- A recurrent positive result is a positive HPV test, followed by a negative HPV test, followed by another positive test result.
- Most recurrent positive infections are reactivations of dormant infections that were acquired soon after a person becomes sexually active.
- Recurrent positive results increase the risk for a persistent HPV infection.

Persistent positive results:

- While most people clear the HPV virus within one to two years without complication, approximately 10% of patients with HPV infections on the cervix develop **persistent infections**.
- A persistent HPV infection is defined as **two consecutive positive HPV tests at least 12 months apart**.

- Patients with persistent HPV infections are at the highest risk of developing dysplasia in the cervix
- so it's important for these patients to work to plan for appropriate follow-up.

GENERAL ASPECTS OF HPV TESTS

- Understanding the technical and operational aspects of available HPV tests is an important part of planning an HPV test-based screening program.
- There are numerous HPV tests available commercially, although only those that have been clinically validated should be used for cervical cancer screening programs.

- HPV can be detected through tests that identify high-risk HPV types, either by amplification of a viral DNA fragment (with or without genotyping), or through mRNA detection

- HPV DNA tests identify the DNA of one or more oncogenic HPV types² without prior DNA amplification.
- Other detection tests amplify a viral DNA fragment using polymerase chain reaction (PCR) to obtain copies, both conventionally and in real-time.

- HPV genotyping identifies specific viral types (usually HPV 16 and 18).
- The mRNA tests identify expression of HPV E6 and E7 oncoproteins

Types of HPV tests generally fall into three categories:

- HPV DNA testing
- HPV ribonucleic acid (RNA) testing
- Detection of cellular markers

HPV DNA testing

- In HPV DNA testing, a patient's cells are examined in laboratory for the genetic material (DNA) of HPV.
- If evidence of HPV is detected, HPV genotyping may be performed to determine the specific strain of HPV causing infection.

HPV ribonucleic acid (RNA) testing

- In HPV RNA testing, a sample of cells is examined in laboratory for RNA.
- This test offers improved specificity compared to HPV DNA testing, reducing the amount of false positives and unnecessary follow-up.
- HPV RNA testing may also include HPV genotyping.

Detection of cellular markers

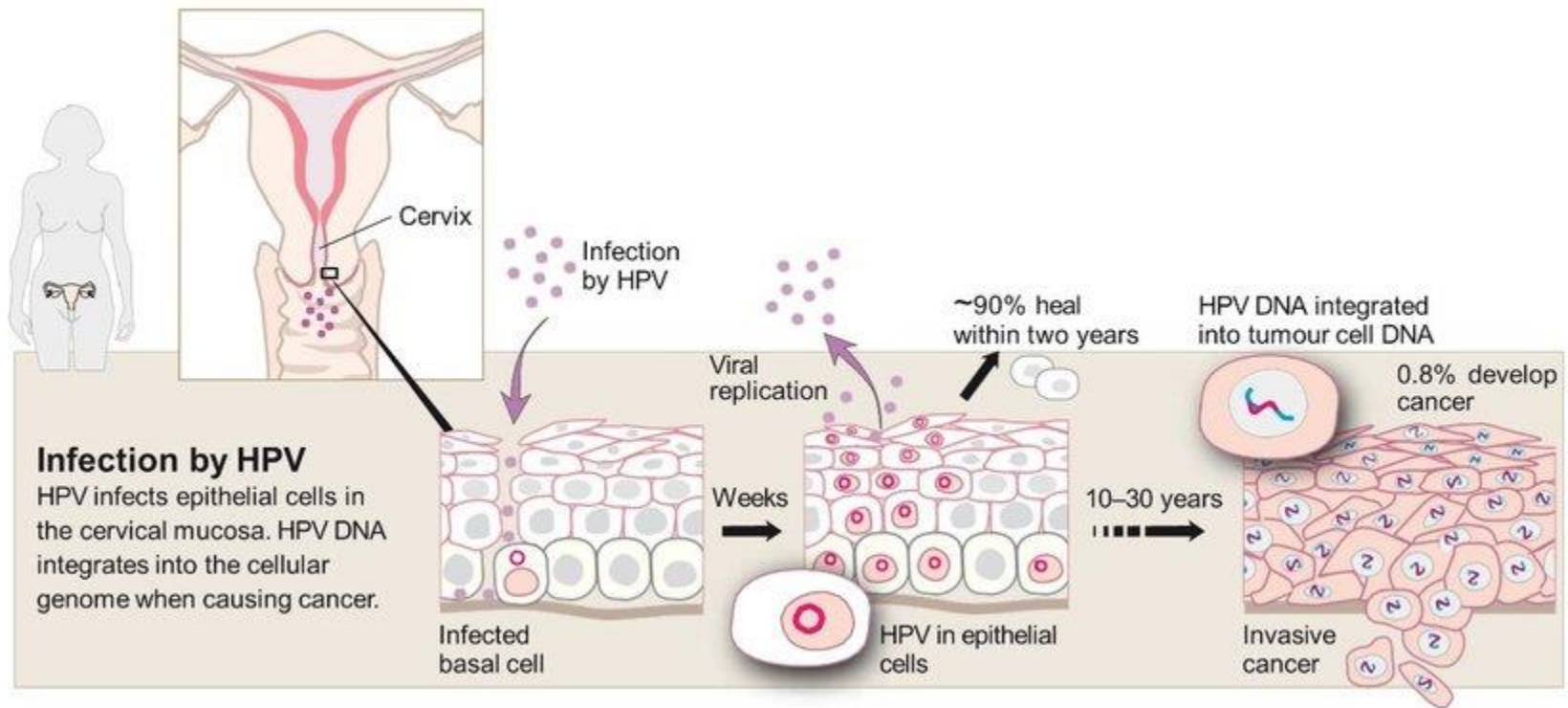
- Unlike other types of HPV testing, cellular marker detection doesn't look for the genetic material of the HPV virus.
- this type of testing looks for evidence of two proteins called p16 and Ki-67.
- The amount of these proteins are elevated in cell samples that are infected with the HPV virus.

WHO recommendations

- For the general population of women, HPV-DNA detection is recommended as the primary screening method – starting at the age of 30 years, with regular testing every 5–10 years.
- For women living with HIV, HPV-DNA detection starting at the age of 25 years, with regular screening every 3–5 years.

HPV

PATHOLOGY



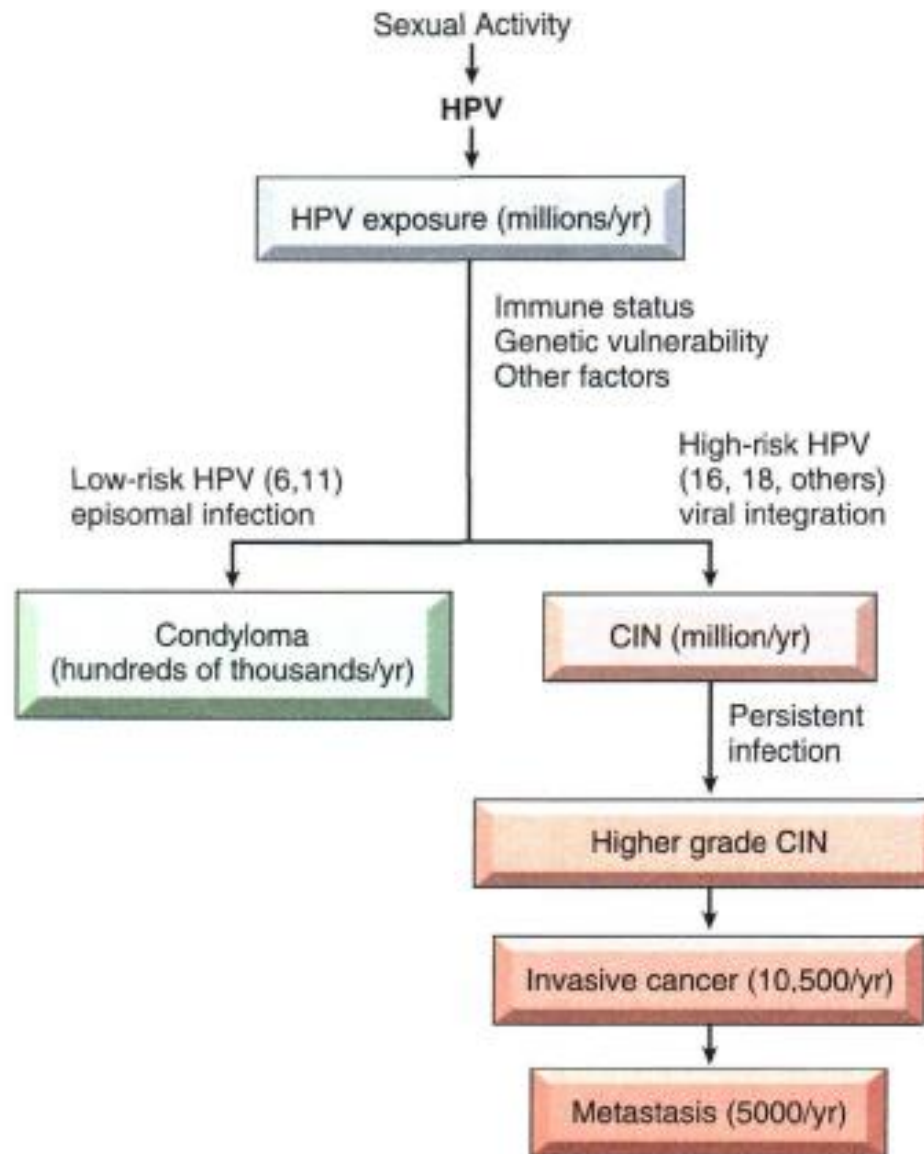
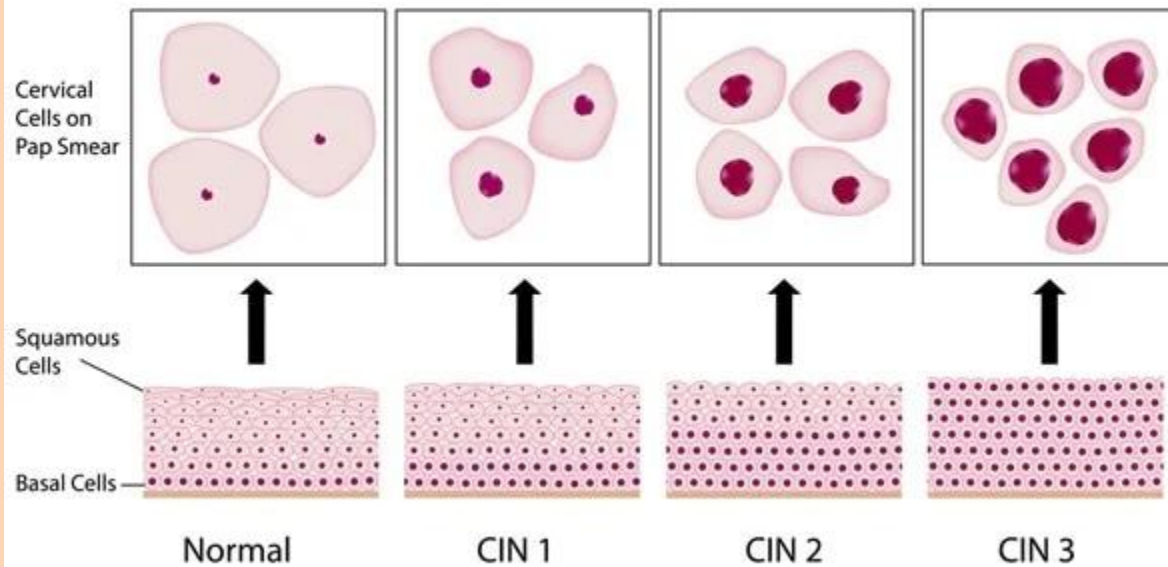


Figure 19-6

An attempt to depict the sequence of events that may follow human papillomavirus (HPV) infection. CIN, cervical intraepithelial neoplasia.

Cervical Intraepithelial Neoplasia (CIN)



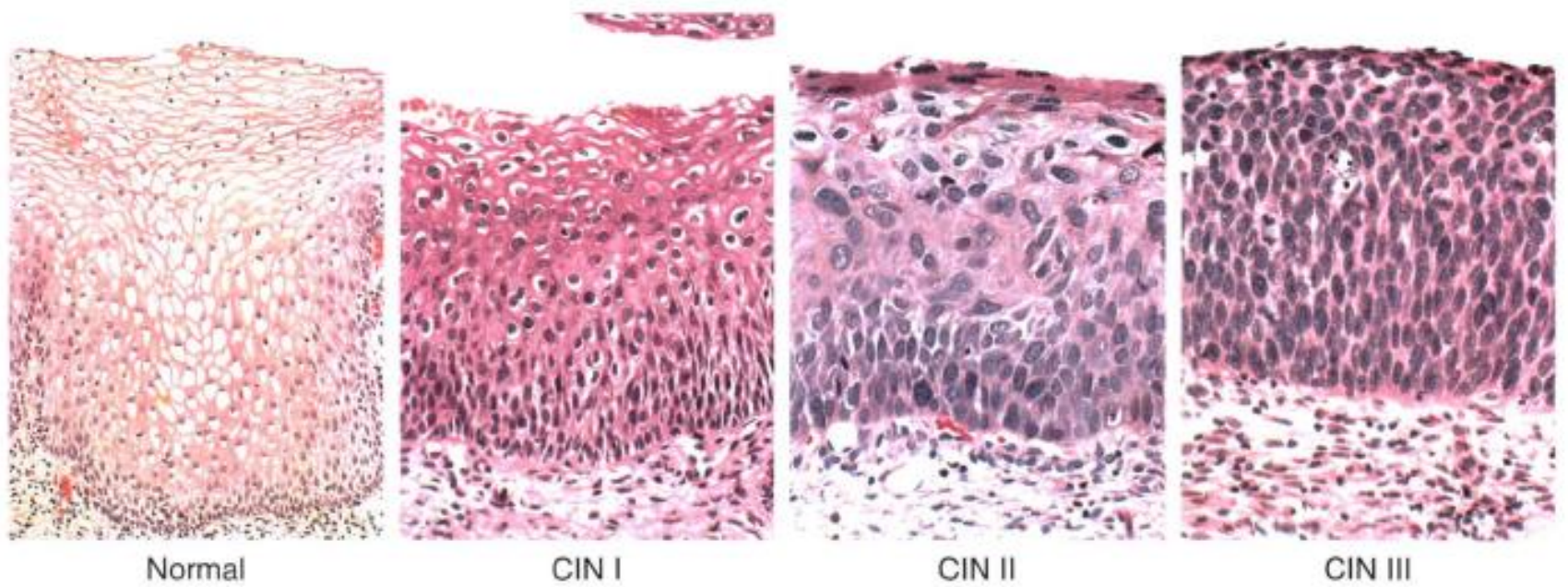


Figure 19-7

Spectrum of CIN: normal squamous epithelium for comparison; CIN I with koilocytotic atypia; CIN II with progressive atypia in all layers of the epithelium; CIN III (carcinoma in situ) with diffuse atypia and loss of maturation.

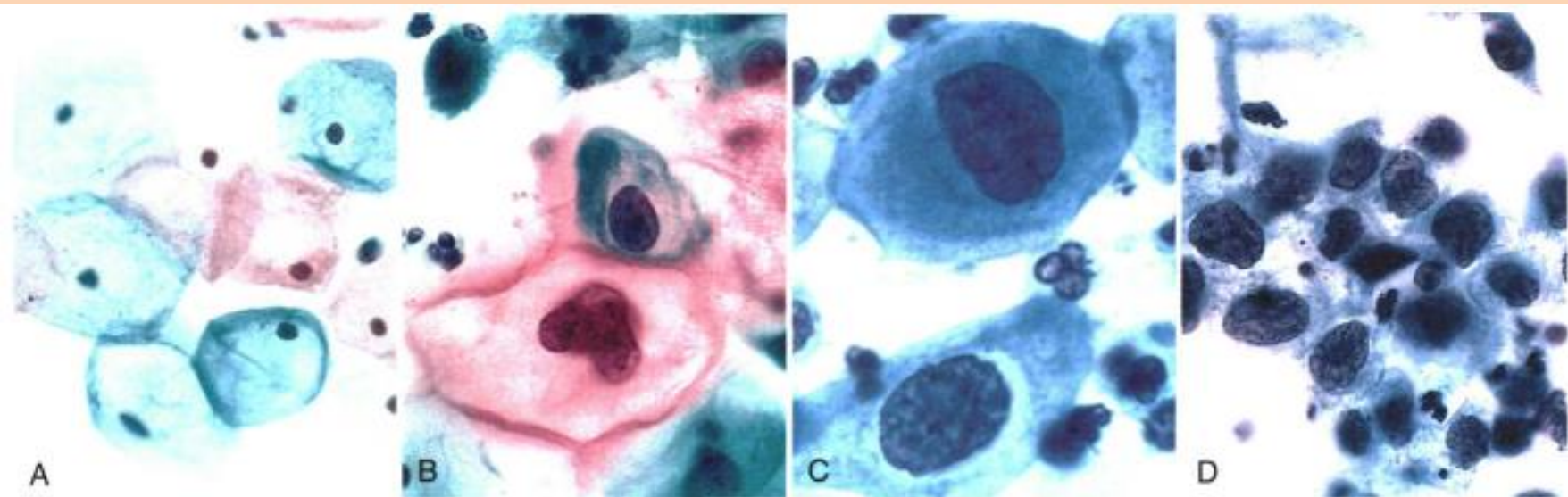
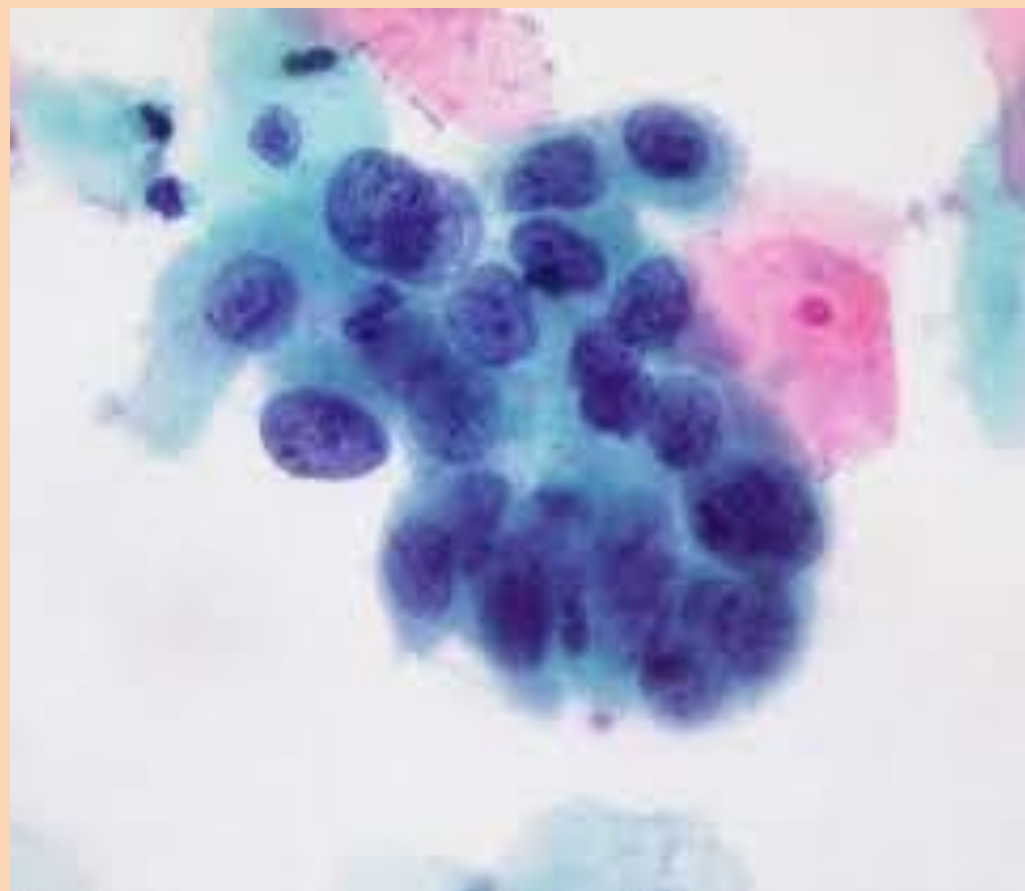


Figure 19-8

The cytology of CIN as seen on the Papanicolaou smear. A–B, Cytoplasmic staining in superficial cells may be either red or blue. A, Normal exfoliated superficial squamous epithelial cells. B, CIN I. C, CIN II. D, CIN III. Note the reduction in cytoplasm and the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. This reflects the progressive loss of cellular differentiation on the surface of the cervical lesions from which these cells are exfoliated (see Figure 19-7). (Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston, Massachusetts.)



Condyloma Acuminatum

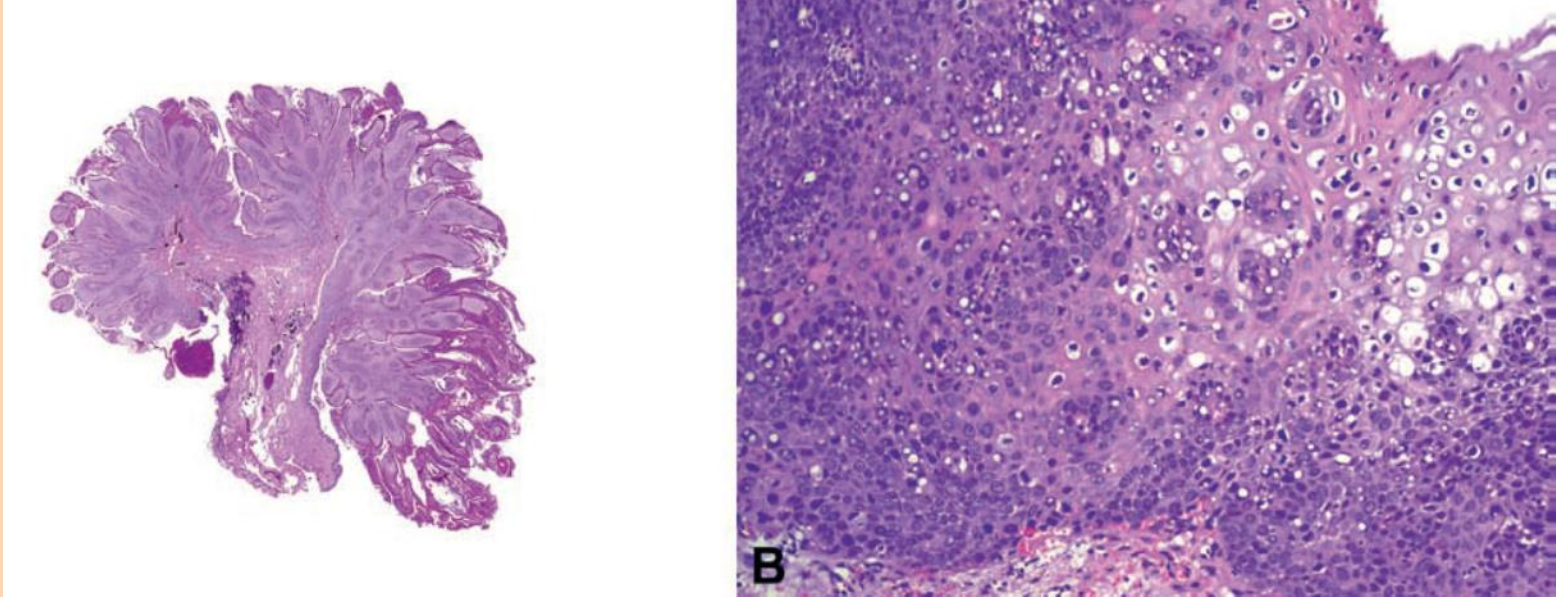
- HPV causes substantial disease in men/women, including benign and malignant lesions of the external genitalia.

Condyloma(genital wart)

- is a common clinical manifestation of nononcogenic genital HPV infection.
- These benign epithelial lesions are highly infectious and occur most frequently among 25 to 29 years of age.



Condyloma



- proliferation of squamous epithelium with an acanthotic and papillomatous architecture, showing orderly epithelial maturation
- Hyperkeratosis, parakeratosis, and koilocytic atypia are common

Condyloma

- nononcogenic mucosal HPV types 6/11 are detected in 75% to 100% of condylomas
- one-half are coinfecting with oncogenic mucosal HPV types, particularly HPV16.

Condyloma

- Most condylomas are transmitted sexually.
- Whose sexual partners have HPV-related cervical lesions have an increased (50% to 85%) incidence of penile condyloma.

children

- When genital condyloma occurs in children, sexual abuse should be suspected.

- After the initial infection, autoinfection is common.
- The incubation period for penile condyloma varies from several weeks to months or even years.



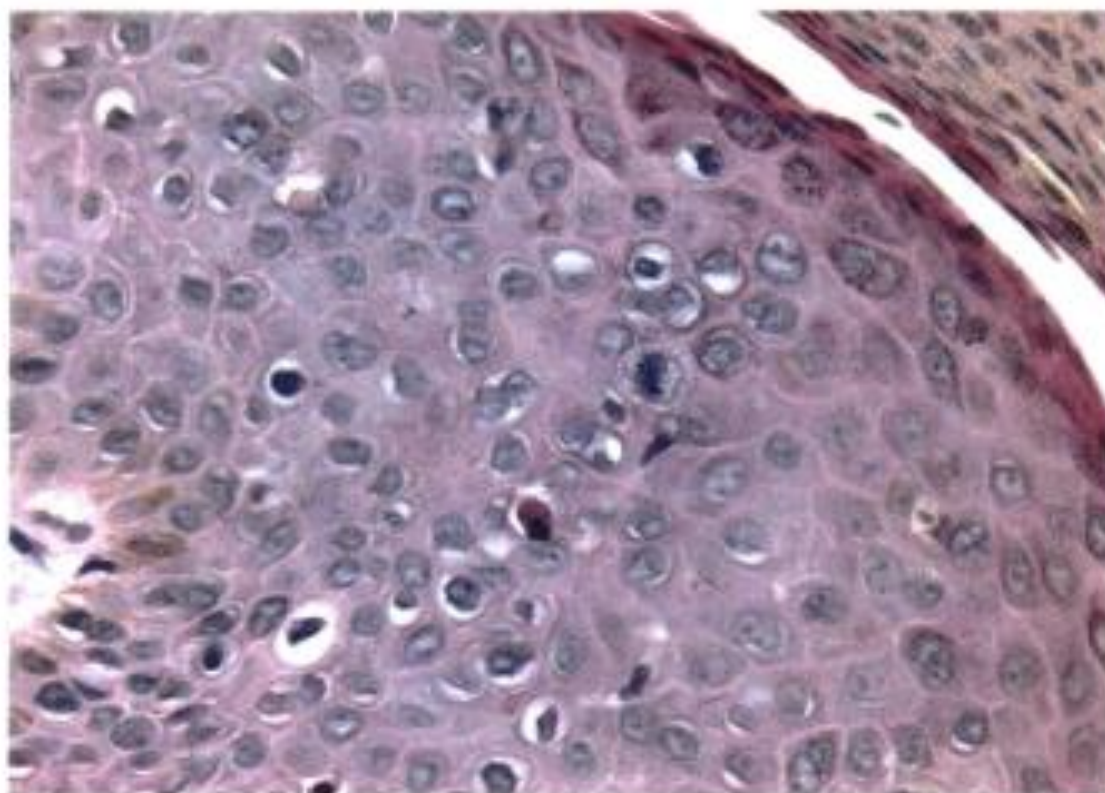


Figure 18-1

Bowen disease (carcinoma in situ) of the penis. The epithelium above the intact basement membrane (not seen in this picture) shows hyperchromatic, dysplastic, dyskeratotic epithelial cells with scattered mitoses above the basal layer.