



Lecture 6: Pathology of Uterine Cervix

wiseGEEK

▣ Important

▣ Notes

▣ Explanation

CERVICITIS

Noninfectious
(Nonspecific)
Cervicitis

Infectious
cervicitis

Candidiasis
(moniliasis)

Trichomoniasis

Chlamydia
trachomatis
Cervicitis

Herpes simplex
virus (HSV)
Cervicitis

Human
papilloma virus
(HPV) infection

Normal Lining of Cervix and possible changes

Endocervix : Columnar Epithelium

Ectocervix : Squamous Epitheliums

(most cancers arise from junction between them)

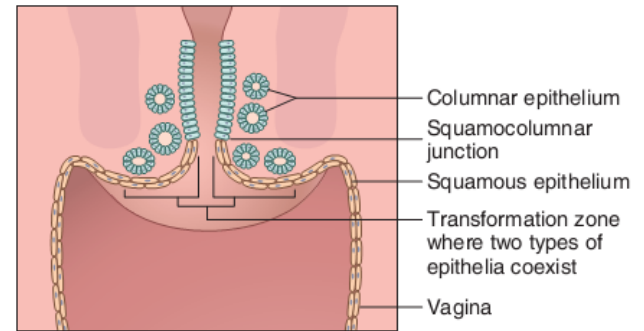


Figure 18-4 Development of the cervical transformation zone.

EROSION/ECTROPION

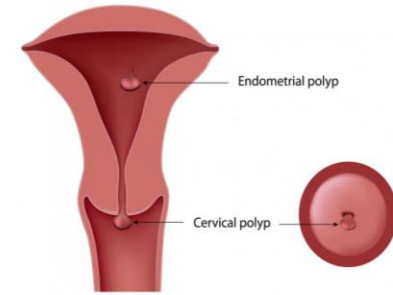
- **Columnar epithelium replacing squamous epithelium**, grossly resulting in **an erythematous area**.
- It is a typical response to a variety of stimuli including hormones, chronic irritation and inflammation (chronic cervicitis).
- It is **benign** and has no malignant potential.

SQUAMOUS METAPLASIA

- **Columnar cells are replaced by squamous cells**. It is seen in cervix at the **squamocolumnar junction**.
- Squamous metaplastic epithelium is the area most affected by **HPV infection** and the area where **dysplasia and malignant transformation starts**.
- Squamous metaplastic epithelium is **benign** and by itself not considered premalignant.

Cervical Polyp

- **Definition** : inflammatory proliferations of cervical mucosa, small, pedunculated mass and are **not true neoplasms (always benign)**.
- **Most** originate from the **endocervix** (endocervical polyps) with a **few** from the **ectocervix** (ectocervical polyps).
- The lesion is characterized by **overgrowth of benign stroma covered by epithelium**.
(The stroma contains **thick-walled blood vessels** and **fibrous** and some **inflammatory cells**)
- Cervical polyps are covered by **columnar epithelium (endocervical)** or **stratified squamous epithelium (ectocervical)** or **partially by both**.

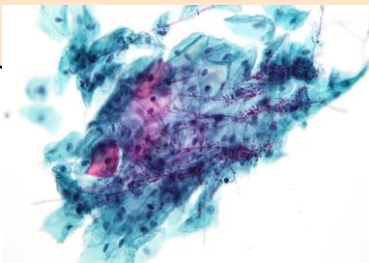


Cervicitis

- **Definition** : Inflammation of cervix. (Can be non-infectious or infectious)

	Noninfectious (Nonspecific) Cervicitis	Infectious cervicitis
Caused by	Chemical (e.g. douche, deodorant) or mechanical (e.g. tampon, diaphragm) irritation. It is often acute inflammation but may be chronic.	Various organisms e.g. staphylococci, enterococci, Gardnerella vaginalis, Trichomonas vaginalis , Candida albicans and Chlamydia trachomatis .
Clinical appearances	Often asymptomatic. The cervix appears red and swollen.	May be asymptomatic May manifest as vaginal discharge or itching
Histology	<ul style="list-style-type: none"> • Inflammatory cells are seen (neutrophils, plasma cells and lymphocytes). • Squamous metaplasia of endocervical glandular epithelium is common in chronic cervicitis. • Often some of the glands are dilate to form mucus-filled cysts called nabothian cysts. 	Most often involves the endocervix. (usually vaginal tract inflammation occur also)

	Candidiasis (moniliasis)	Trichomoniasis	Chlamydia trachomatis Cervicitis
Site	Involves cervix and vagina	Involves cervix and vagina (sexually transmitted disease)	frequent cause of pelvic inflammatory disease. (most common sexually transmitted disease in the developed countries)
Caused by	Candida albicans , a normal component of the vaginal flora .	Trichomonas vaginalis a unicellular flagellated protozoan .	Chlamydia trachomatis is an obligate, gram-negative intracellular pathogen .
Associated with	Cases of low pH: Diabetes mellitus, pregnancy, antibiotic therapy, oral contraceptive use and immunosuppression	_____	It may coexist with: 1. Neisseria gonorrhoeae 2. lymphogranuloma venereum (painful inguinal and/or femoral lymphadenopathy)
Clinical Presentation	<ul style="list-style-type: none"> white patchy mucosal lesions with thick curdy white discharge vulvovaginal pruritis. Ulcers may develop. 	<ul style="list-style-type: none"> Greenish-yellow frothy and foul smelling vaginal discharge Painful urination vulvovaginal itching or irritation dyspareunia 	<ul style="list-style-type: none"> most often asymptomatic. In symptomatic cases there is a mucopurulent cervical discharge with a reddened, congested and edematous cervix. It may be associated with urethritis
Cytology smear	<ul style="list-style-type: none"> Fungal colonies in the form of spores and branching pseudohyphae on the cervical epithelium. Chronic inflammatory cells are present 	The organism can be found in Pap-stained vaginal smears in a background of inflammatory cells . Diagnosis can also be made by examination of a saline wet preparation in which the motile trophozoites are seen .	



Herpes simplex virus (HSV) Cervicitis

- **HSV Type 2 infection** accounts for **majority** of **genital herpes cases** and is spread by sexual contact.
- It produces **vesicles and painful ulcers** that can involve the cervix, vagina, vulva, urethra and perianal skin.

Human papilloma virus (HPV) infection

- HPV infection of the cervix is **very common**.
- Over 20 serotypes infect the female genital areas.

Clinical behavior :

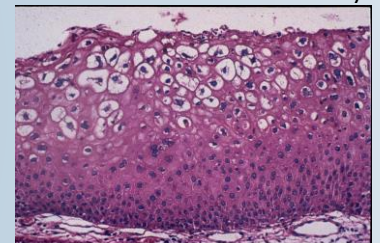
- HPV infection is associated with **increased risk of subsequent cervical cancer** and so long-term follow-up with attention to the cervix, vagina and vulva is necessary.
- HPV infection causes **koilocytic atypia** in the cervical squamous epithelium

HPV infection may cause any of the following depending on the serotype:

1. **Condyloma**: This develops in the squamous epithelium of the cervix. The lesions may be **flat or exophytic condylomma acuminatum**. Usually caused by **HPV serotypes 6 and 11**.
2. **Mild dysplasia**: is usually caused by **"low risk" HPV serotypes, 6 and 11**.
3. **High- grade dysplasia**: is caused by **"high risk" HPV (types 16 and 18)** and **moderate risk HPV(types 31, 33 and 35)**.

- **KOILOCYTES**: are squamous epithelial cells that has undergone structural change due to infection of the cell by **HPV**. They show **koilocytosis** or **koilocytic atypia** which is the following cellular changes:

- Nuclear enlargement
- Irregular nuclear membrane
- Nuclear hyperchromasia
- Perinuclear halo (**clear area around the nucleus**).

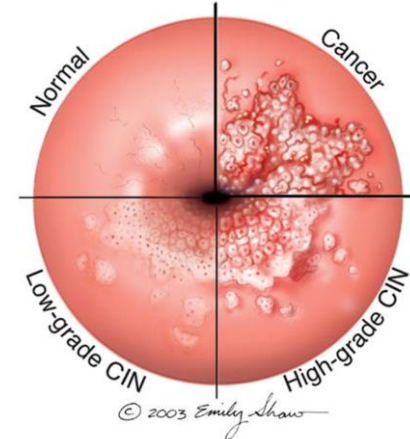


Cervix Carcinoma

- **Cervical carcinoma** is one of the major causes of **cancer-related death in women**.
- Most common cervical cancer is **squamous cell carcinoma**. Other types are adenocarcinoma, neuroendocrine carcinoma etc.
- Nowadays there is dramatic improvement in management of this disease because of **early diagnosis and treatment** and therefore the deaths associated to cervical cancer are **decreasing**.
- This is due to the use of a screening method called **PAP screening test**.
- The wide use of PAP screening has lowered the incidence of invasive cancer and deaths by it.

Precancerous lesion of cervical carcinoma: cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL).

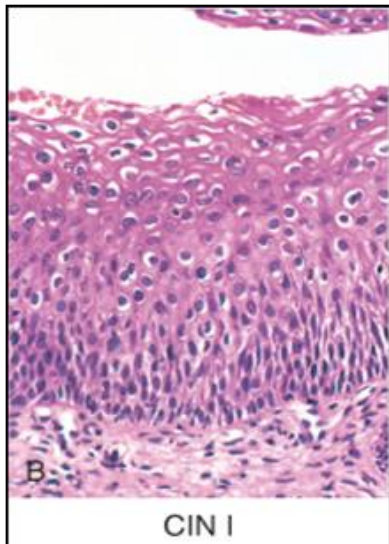
- All invasive squamous cell carcinomas arise from **non invasive pre-cancer epithelial lesions** called **cervical intraepithelial neoplasia (CIN)** or **squamous intraepithelial lesions (SIL)**.
- **SIL** is the terminology used in **cytology (pap smears)**
- **CIN** is the terminology used in **histology (biopsies)**
- Timely detection and diagnosis of CIN/SIL is essential in **preventing the development of carcinoma (invasive lesion)** and therefore providing curative treatment possible.
- **Not all cases of CIN/SIL progress to invasive cancer** and some cases of CIN/SIL may spontaneously regress.
- **The risk of progression to cancer is more in the high grade CIN/SIL** and they are associated the high-risk HPV serotypes.



Cervical intraepithelial neoplasia (CIN)

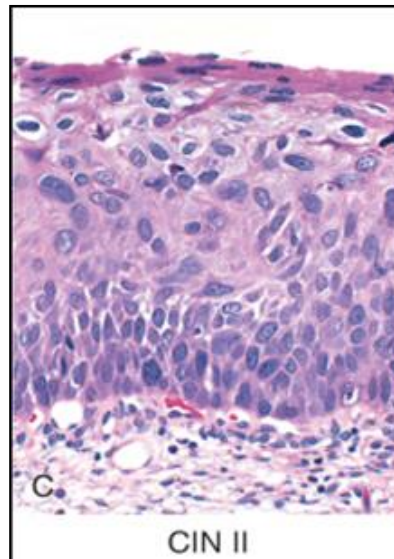
- CIN are precancerous lesions of the cervix.
- Pre-cancer changes can precede the development of an overt cancer by many years.
- CIN lesions may begin as Low Grade CIN and **progress** to High Grade CIN, or they **might start straight off** as High Grade CIN.
- On the basis of histology, pre-cancer lesions are graded as follows:
 - CIN I : Mild Dysplasia
 - CIN II : Moderate Dysplasia
 - CIN III : Severe Dysplasia and Carcinoma in situ.

Cervical biopsy (Histology CIN)



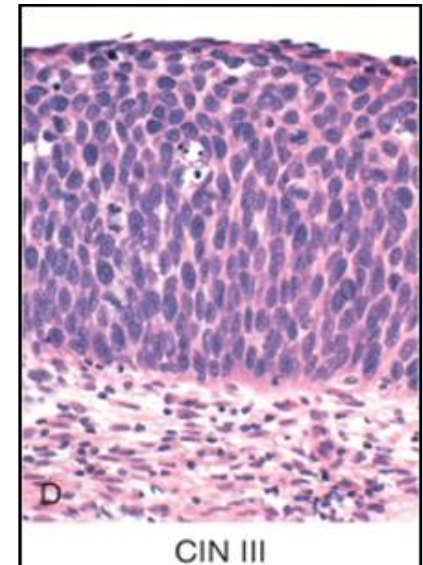
Mild dysplasia = CIN I

with HPV associated koilocytotic atypia. **Lower 1/3rd** of the epithelium is replaced by pleomorphic cells.



Moderate dysplasia = CIN II.

There is progressive atypia in the layers of the epithelium; **lower 2/3rd** of the epithelium is replaced by pleomorphic cells.



Severe dysplasia = CIN III (carcinoma in situ). There is diffuse atypia and loss of maturation. All levels of the epithelium are replaced by pleomorphic cells, **(full**

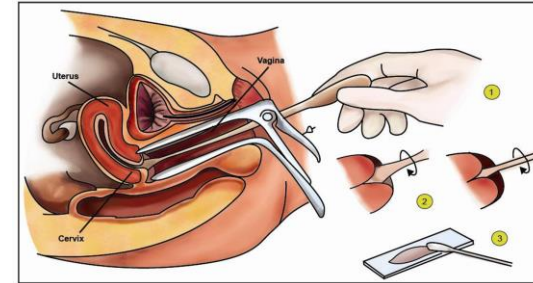
PAP SCREENING TEST: Cytology screening for precancerous lesions

- Cytologic examination can detect precancerous squamous intraepithelial lesions **long before any abnormality can be seen grossly, using the PAP test.**
- This screening for precancer should be done on all young and old women (usually from age of 21 onwards).

the cells lining the cervical wall at the transformation zone are scrapped/sampled with a spatula

transferred onto a slide, processed, stained
(Papanicolaou stain)

examined under a light microscope to look for squamous intraepithelial lesions and a diagnosis is made.



Cytology Pap Smear/Screening

SILs are divided into low grade and high grade SIL:

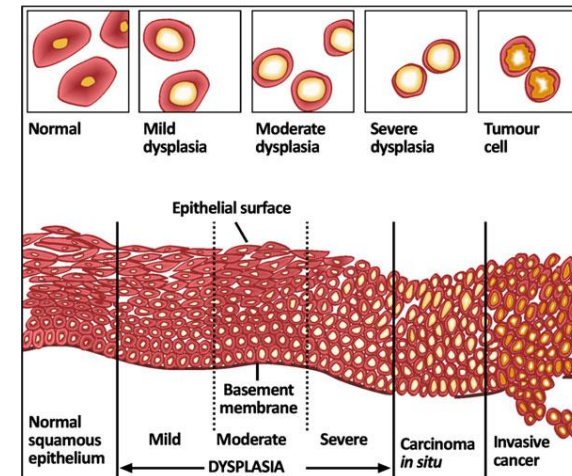
In cytology smear report these are few of the possible diagnoses:

1. Normal cells
2. Low Grade SIL (= CIN1/mild dysplasia)
3. High Grade SIL (= CIN2 and 3/moderate to severe dysplasia)

(the reduction in cytoplasm and the increase in the nucleus to cytoplasm ratio, which occurs as the grade of the lesion increases. This reflects the progressive loss of cellular differentiation on the surface of the lesions from which these cells are exfoliated)

About 1 to 5% of low Grade SIL become invasive squamous cell carcinomas.

About 6 to 74% of high Grade SIL become invasive squamous cell carcinomas.



CIN/SIL & RULES OF PAP TEST

Signs of CIN/ SIL :

- There are **no visible symptoms** of dysplasia of the cervix, and it is **difficult to diagnose without a Pap smear or Pap exam**. Therefore regular pap exams should be done to detect any abnormal cells.

General rules of Pap Screening for CIN/SIL and carcinoma cervix via pap smear are:

- The common testing procedure for HPV infection is a cytology pap smear screening test/exam.
- The Pap smear detects HPV infection early.
- **Should start at the age 21.**
- **For women between age 21 to 29:** cytological screening pap test should be done **every 3 years**
- **For women between age 30-64 :** there are 2 possibilities:
 1. Either only cytology screening pap test is done **every 3 years**
 2. Or there is co-testing in which **cytology screening pap test is done along with DNA in-situ hybridization HPV testing, every 5 years.**
- **NOTE:** This HPV DNA in-situ hybridization (ISH) test, is called the **Diegene Hybrid Capture test to identify the serotype of the viral strain**. This test will determine whether you carry **high or low risk strains of the virus**. DNA screening test **should not be used before age 30.**

Risk Factors and causes for CIN/ SIL and cervical carcinoma

Risk Factors :

- Early age at first intercourse
- Multiple sexual partners
- A male partner with multiple previous sexual partners
- Persistent infection by high risk papillomaviruses
- Other risk factors; **low socioeconomic groups**
- rare among virgins and multiple pregnancies.

Causes :

HPV virus (The HPV is the number one reason for abnormal cells of the cervix).

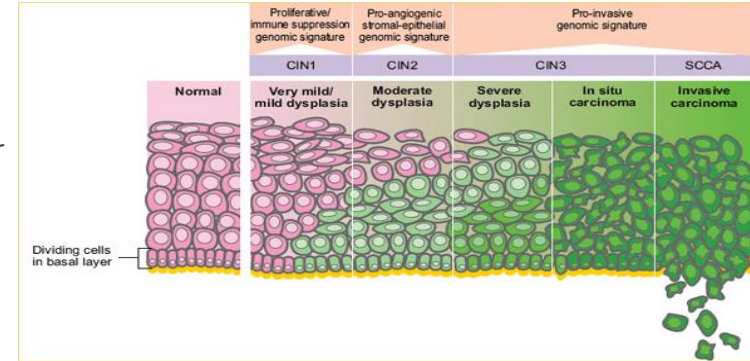
- HPV is a skin virus, which results in warts, common warts ,flat warts, genital warts (condylomas), planter warts, and precancerous lesions.
- HPV can be detected in 85 -90 % of pre-cancer lesions.
- **High risk types HPV : 16, 18, 31, 33, 35**, 39, 45, 52, 56, 58, and 59.
- **Low risk types HPV: 6, 11**, 42, 44 . These types result in condylomas.

Treatment :

laser or cone biopsy is the most effective method of managing patients with High grade SIL in cancer prevention

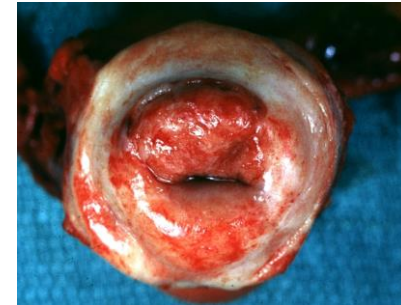
Cervical Carcinoma, Invasive

- **About 75 -90%** of invasive cancers **are Squamous cell carcinomas** ,which generally evolve from pre-cancer CIN/SIL lesions.
- The remainder are **Adenocarcinoma**.
- **Both are caused by HPV virus**
- Squamous cell cancers are appearing in increasingly younger women, now with a peak incidence at about 45 years, about 10-15 years after detection of their precursors.



Morphology :

- Mainly in the region of the **transformation zone**, and range from microscopic **foci of early stromal invasion to grossly frank tumors encircling the cervical Os.**
- The tumors may be **invisible** or **exophytic**.
- Cervical carcinomas are **graded from 1 to 3** (i.e. well, moderately and poorly differentiated) based on cellular differentiation and **staged from 1 to 4** depending on clinical spread.



Staging :

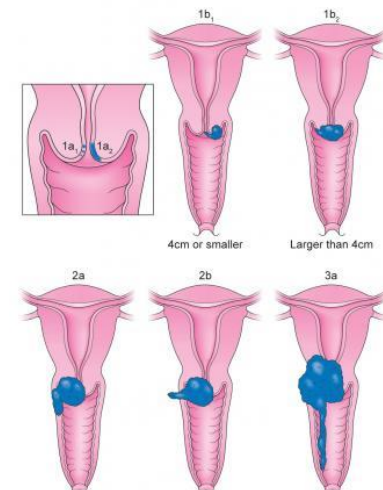
0 = Carcinoma in Situ

1 = Confined to the cervix

2 = Extension beyond the cervix **without extension to the lower third of Vagina or Pelvic Wall**

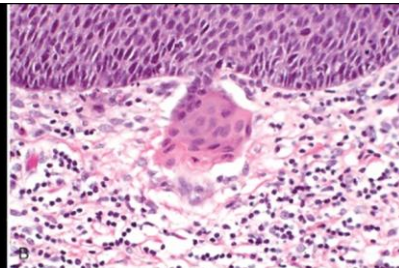
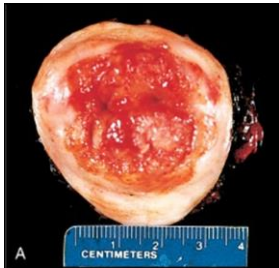
3 = Extension to the pelvic wall and/or lower third of the vagina

4 = Extends to adjacent organs



Clinical Presentation :

- Many of cervical cancers are diagnosed in early stages, and the vast majority are diagnosed in the pre-invasive phase.
- More advanced cases are seen in women who either **have never had a Pap smear or have waited many years since the prior smear.**
- The early stages of cervical cancer may be completely **asymptomatic.**
- In late stage, Vaginal bleeding, contact bleeding, cervical mass, dyspareunia. (**feeling pain during intercourse**)
- In advanced disease, metastases may be present in the abdomen, lungs or elsewhere.
- Symptoms of advanced cervical cancer may include: loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, swollen legs, heavy bleeding from the vagina, bone fractures, and/or (rarely) leakage of urine or faeces from the vagina.



Treatment :

Depending on the stage the treatment options are:

1. **If you still want to be able to have children**, the cancer is removed with a **laser or cone biopsy (cervical conization)**, and then you are watched closely to see if the cancer comes back.
2. **Simple hysterectomy** (removal of the whole uterus including part of the vagina).
3. **Radical hysterectomy** (removal of the whole uterus including part of the vagina along **with the removal of lymph nodes in the pelvis**).
4. Adjunct chemotherapy and radiotherapy.

Summary (from Robbin's basic pathology)

SUMMARY

Cervical Neoplasia

- Risk factors for cervical carcinoma are related to HPV exposure, such as early age at first intercourse, multiple sexual partners, and other factors including cigarette smoking and immunodeficiency.
- Nearly all cervical carcinomas are caused by HPV infections, particularly high-risk HPV types 16, 18, 31, and 33; the HPV vaccine is effective in preventing infection due to HPV types 16 and 18.
- HPV expresses E6 and E7 proteins that inactivate the p53 and Rb tumor suppressors, respectively, resulting in increased cell proliferation and suppression of DNA damage-induced apoptosis. Loss of *LKB1* gene is also involved.
- In high-grade cervical dysplasias (CIN II and III), HPV is incorporated into the genome of the host cell.
- Not all HPV infections progress to CIN III or to invasive carcinoma. The time course from infection to invasive disease is usually 10 years or more. In general, the risk of progression is proportional to the degree of dysplasia.
- The Pap smear is a highly effective screening tool for the detection of cervical dysplasia and carcinoma and has significantly reduced the incidence of cervical carcinoma.

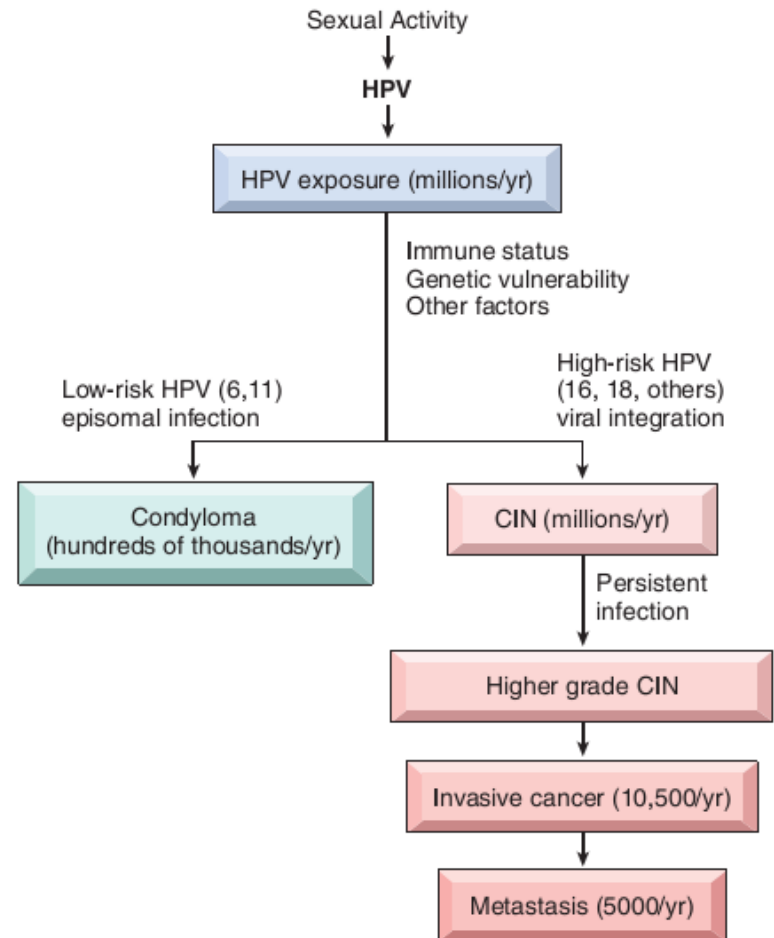


Figure 18-5 Possible consequences of human papillomavirus (HPV) infection. Progression is associated with integration of virus and acquisition of additional mutations as discussed in the text. CIN, cervical intraepithelial neoplasia.

Thank You!

We hope you found this helpful and informative.

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