



Pathology of Uterine Cervix

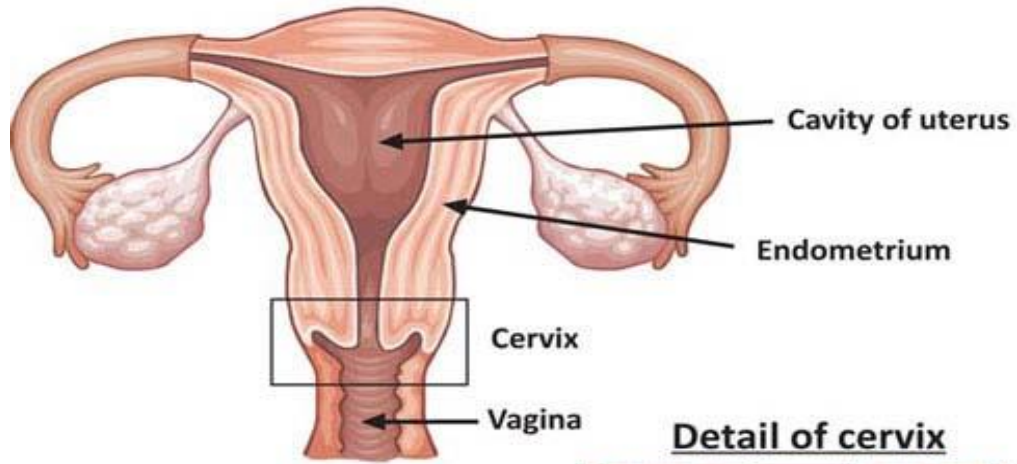
**SUFIA HUSAIN
PATHOLOGY
KSU, RIYADH
APRIL 2017**

REFERENCE: ROBBINS & COTRAN PATHOLOGY AND RUBIN'S PATHOLOGY

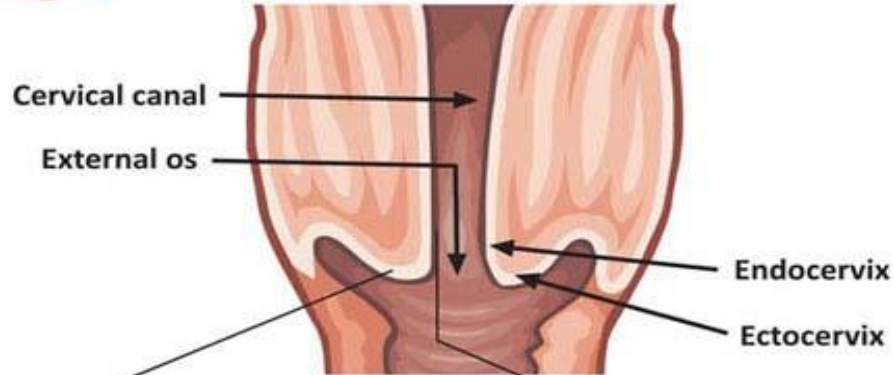
Lecture Outline: Pathology of the uterine cervix.

- A] Some common benign conditions and infections
- B] Understand the concepts of dysplasia and intraepithelial neoplasia in the female genital tract and the role of a cervical screening programme.
- C] Know the incidence, risk factors, clinical presentation, pathological features and prognosis of cervical squamous cell carcinoma.

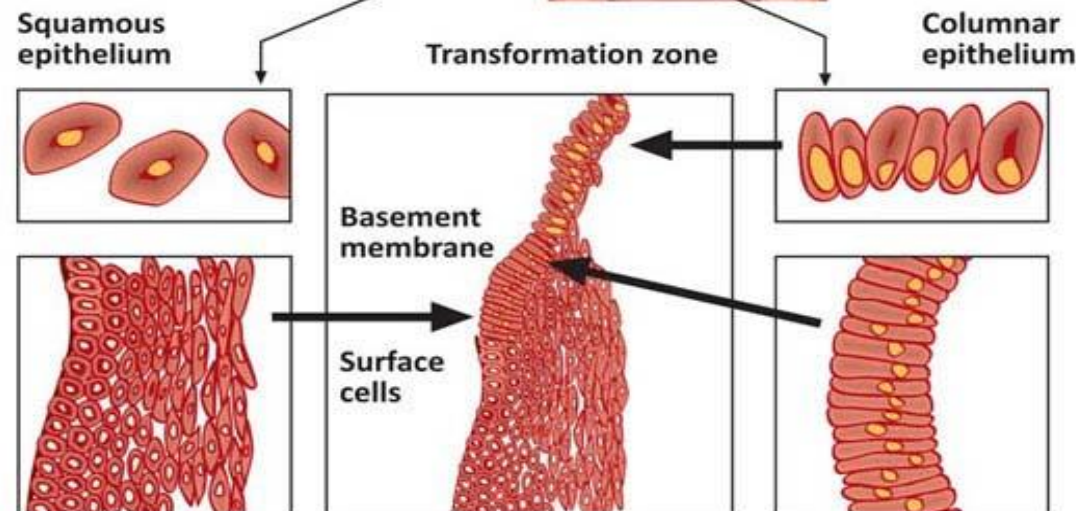
**Uterus and cervix
in cross section (front view)**



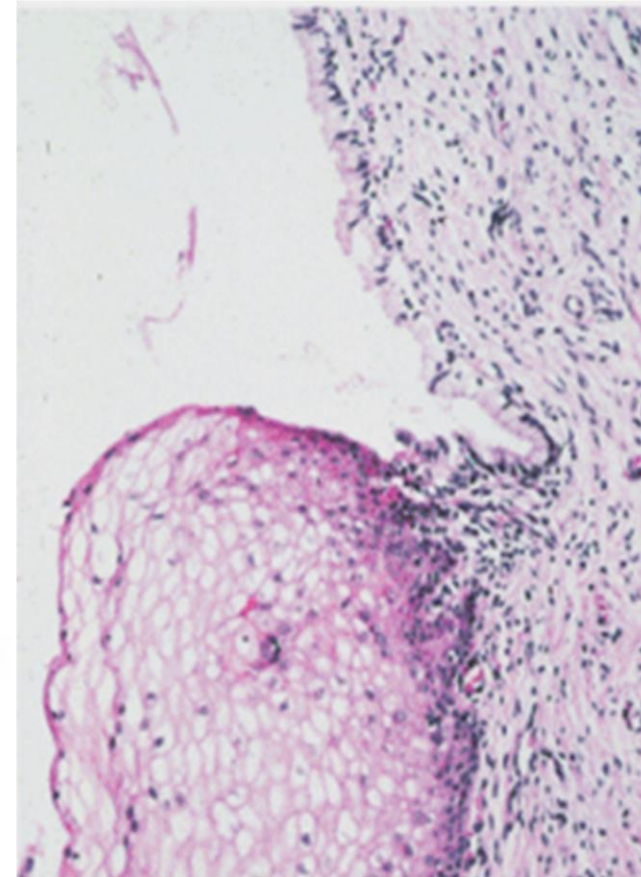
Detail of cervix



Cell types



SQUAMO-COLUMNAR JUNCTION



From: Rubin's Pathology : Clinicopathologic Foundations of Medicine, 5th Edition
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- **EROSION/ECTROPION**

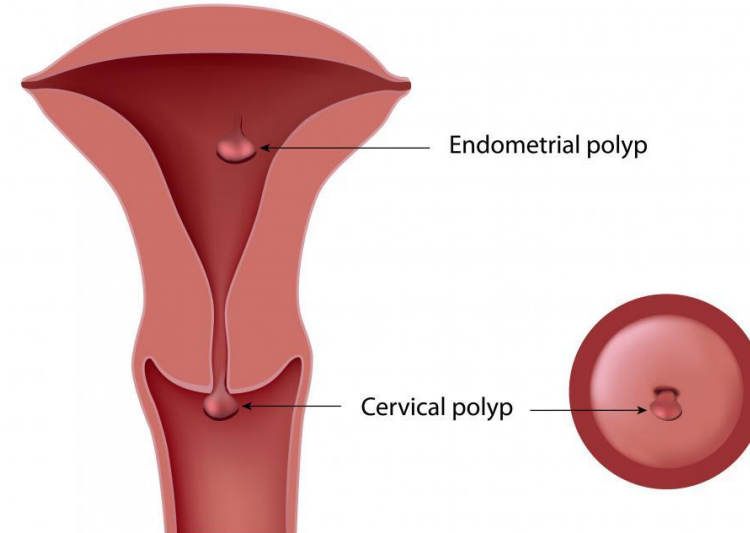
- When squamous epithelium is replaced by columnar epithelium, grossly resulting in an erythematous area.
- It is a typical response to a variety of stimuli including hormones, chronic irritation and inflammation (chronic cervicitis).
- It is benign and has no malignant potential.

SQUAMOUS METAPLASIA

- In it the columnar cells are replaced by squamous cells. It is seen in cervix at the squamo-columnar junction. Squamous metaplastic epithelium is the area most affected by HPV infection and the area where dysplasia and malignant transformation starts. (note: squamous metaplastic epithelium is benign and by itself not considered premalignant)

Cervical polyp

- ▶ This is a small, pedunculated mass.
- ▶ Most originate from the endocervix (endocervical polyps) with a few from the ectocervix (ectocervical polyps).
- ▶ They are inflammatory proliferations of cervical mucosa and are not true neoplasms.
- ▶ The lesion is characterized by overgrowth of benign stroma covered by epithelium.
 - The epithelium covering the polyp is either columnar epithelium or stratified squamous epithelium or sometimes partly by both.
 - The stroma is made up of fibrous tissue with thick-walled blood vessels and inflammatory cells.



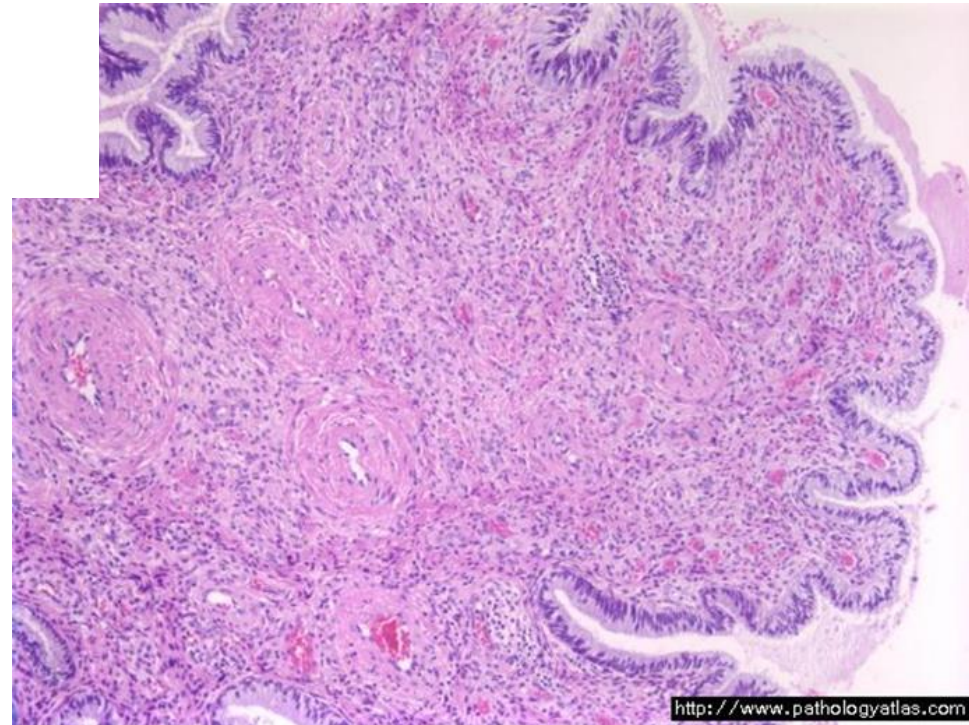
wiseGEEK

<http://images.wisegeek.com/diagram-of-vaginal-polyps.jpg>

Cervical polyp



http://sunnybrook.ca/uploads/cx_polyp_vd_1.jpg



<http://www.pathologyatlas.com>



CERVICITIS

INFLAMMATION OF CERVIX.
CAN BE NON-INFECTIOUS OR INFECTIOUS.

Noninfectious (Nonspecific) Cervicitis

- ▶ Is inflammation of the cervix caused by chemical (e.g. douche) or mechanical (e.g. tampon, diaphragm) irritation. It is often acute but may be chronic.

Clinical appearances

- ▶ Often asymptomatic.
- ▶ The cervix appears red and swollen

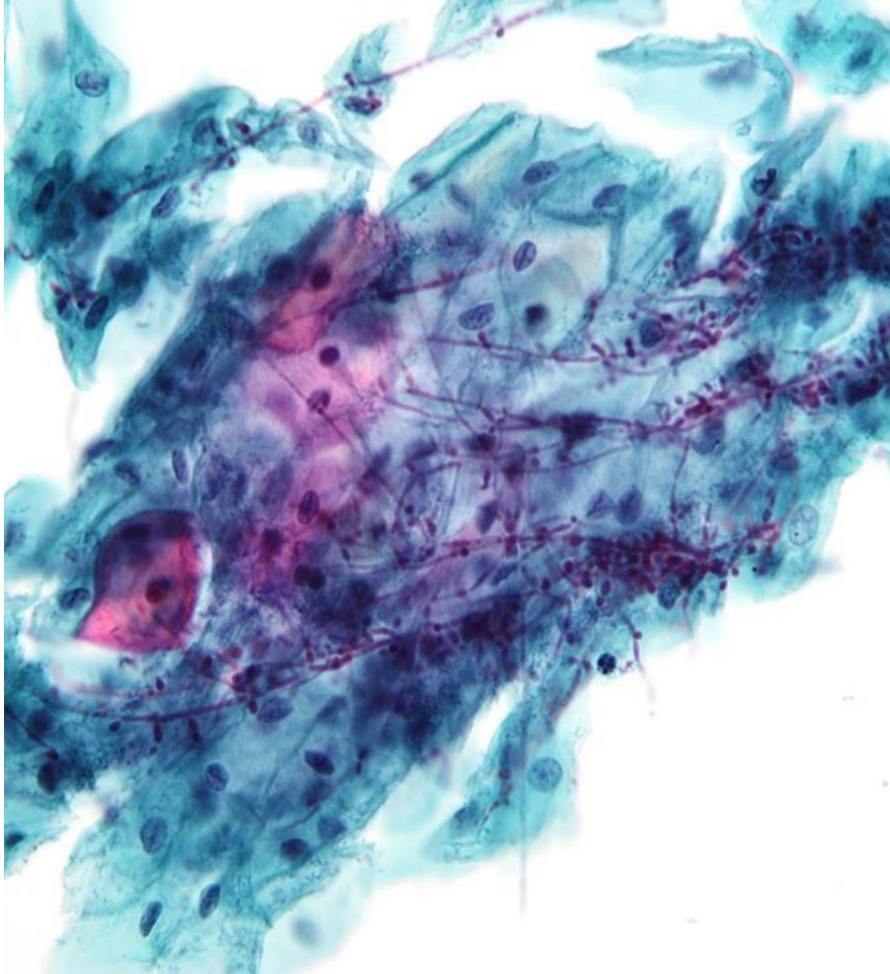
Histology

- ▶ The inflammatory cells are seen (neutrophils, plasma cells and lymphocytes).
- ▶ Squamous metaplasia is common in chronic cervicitis.

Infectious cervicitis

- Can be caused by various organisms e.g. staphylococci, enterococci, Gardnerella vaginalis, Trichomonas vaginalis, Candida albicans and Chlamydia trachomatis.
- Most often involves the endocervix.
- May be asymptomatic
- May manifest as vaginal discharge or itching

Candidiasis (moniliasis)



- Common
- Involves cervix and vagina
- Caused by *Candida albicans*, a normal component of the vaginal flora.
- Associated with diabetes mellitus, pregnancy, antibiotic therapy, oral contraceptive use and immunosuppression.
- Characterized by white patchy mucosal lesions with thick curdy white discharge and vulvovaginal pruritis. Ulcers may develop.
- Cytology smears show: Fungal colonies in the form of spores and branching pseudohyphae on the cervical epithelium. Chronic inflammatory cells are present.

Trichomoniasis

- It is caused by a unicellular flagellated protozoan called *Trichomonas vaginalis*.
- It is sexually transmitted disease
- Involves the vagina and cervix.

Clinical presentation

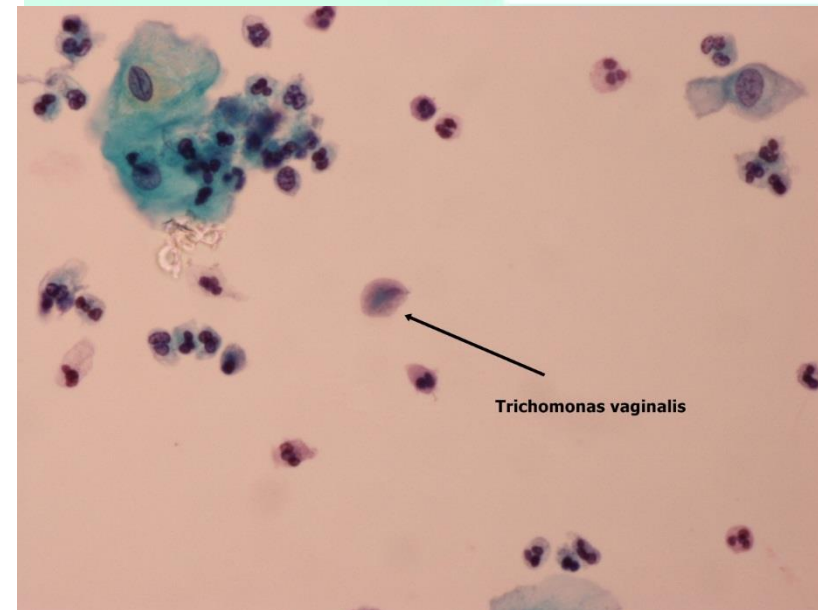
- Greenish-yellow frothy and foul smelling vaginal discharge
- Painful urination
- vulvovaginal itching or irritation
- dyspareunia

Cytology smears show:

- 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.



<http://www.medthical.com/trichomoniasis.html> *Trichomonas vaginalis*



<http://137.189.150.85/cytopathology/Slide/31-7G3.jpg> *Trichomonas vaginalis*

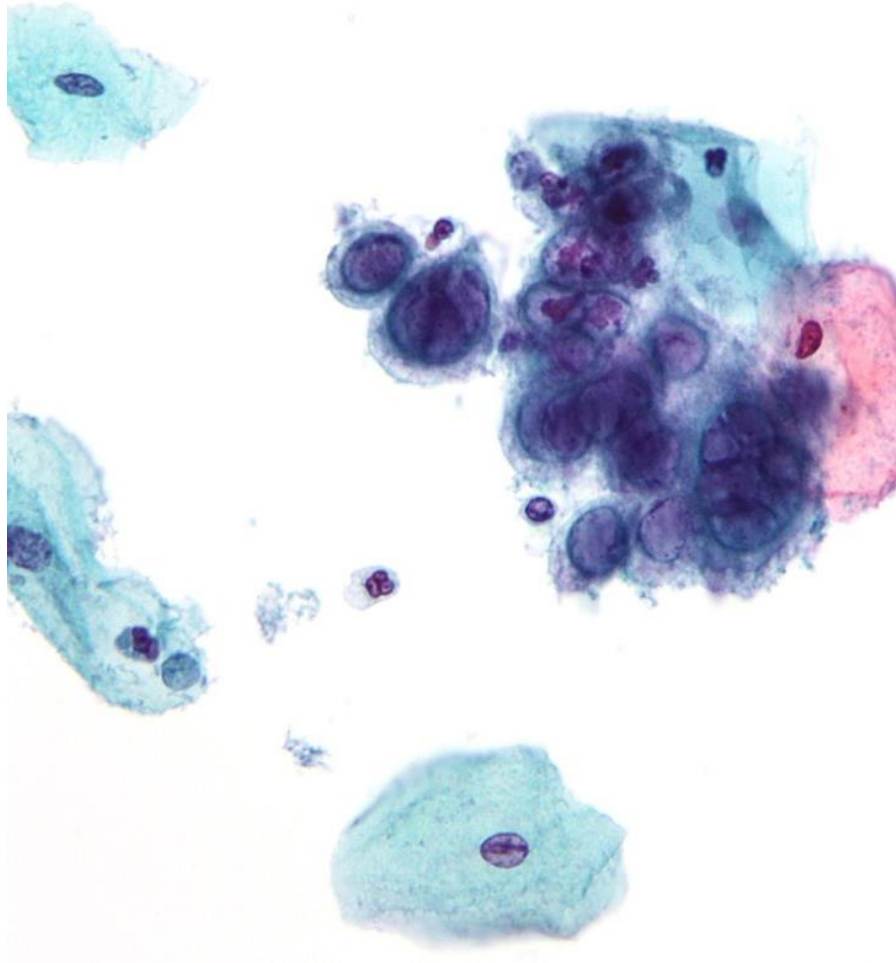
Chlamydia trachomatis Cervicitis

- ▶ Chlamydia trachomatis is an obligate, gram-negative intracellular pathogen.
- ▶ Chlamydial cervicitis is the most common sexually transmitted disease in the developed countries. It may coexist with Neisseria gonorrhoeae infection.
- ▶ It is a frequent cause of pelvic inflammatory disease.
- ▶ Chlamydial infection can also cause a condition known as lymphogranuloma venereum

Clinical appearances

- ▶ Is 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.

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 ulcers that can involve the cervix, vagina, vulva, urethra and perianal skin.

"Herpes simplex virus pap test" by Nephron - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Herpes_simplex_virus_pap_test.jpg#/media/File:Herpes_simplex_virus_pap_test.jpg

Human papilloma virus(HPV) infection

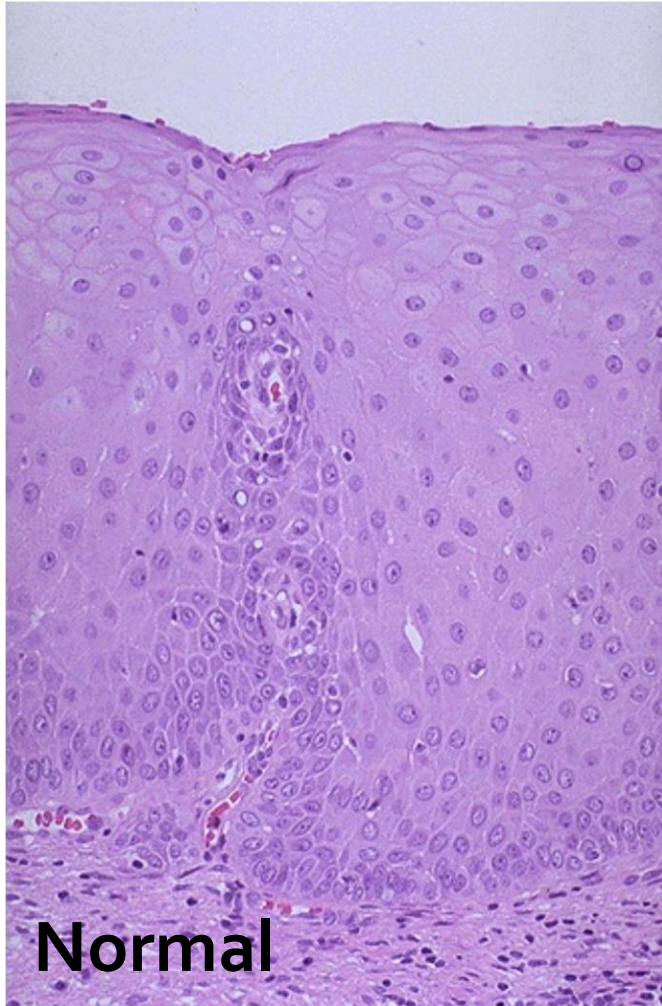
- ▶ HPV infection of the cervix is common.
- ▶ Over 20 serotypes of HPV infect the female genital areas and cause a variety of different lesions depending on the serotypes.

Clinical behavior

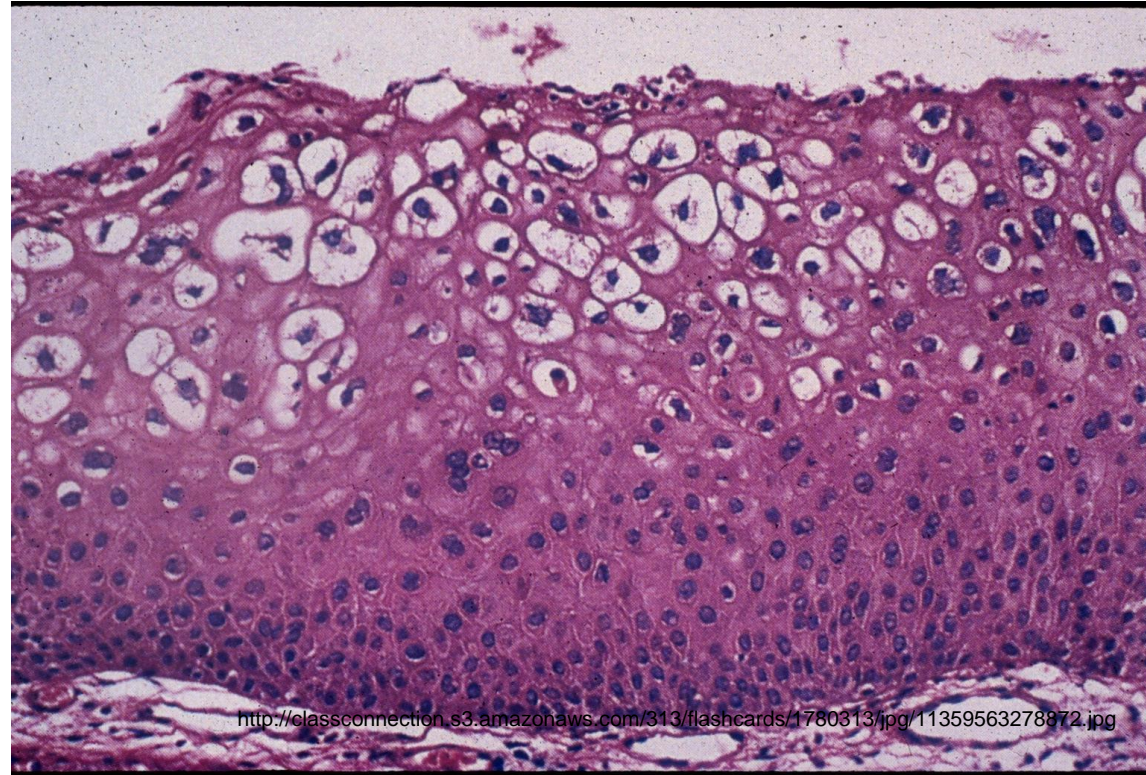
- ▶ HPV infection is associated with increased risk of subsequent cervical cancer.
- ▶ HPV infection causes **koilocytic atypia** in the cervical squamous epithelium

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

- 1) Condyloma:** This develops in the squamous epithelium of the ectocervix. 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).



Normal



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).



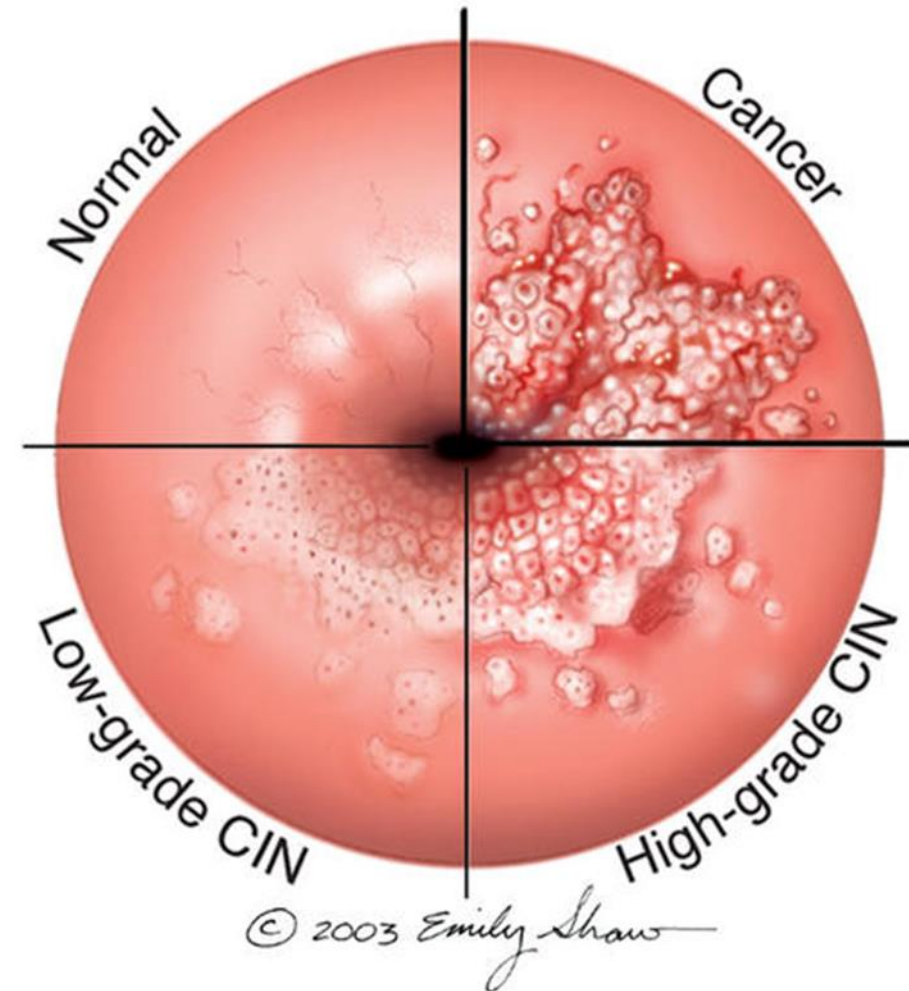
CERVICAL INTRAEPITHELIAL NEOPLASIA(CIN)
OR
SQUAMOUS INTRAEPITHELIAL LESIONS (SIL)
AND
CERVICAL CARCINOMA

Cervix Carcinoma

- ▶ Most common cervical cancer is **squamous cell carcinoma**. Other types are adenocarcinoma, neuroendocrine carcinoma etc.
- ▶ Cervical carcinoma used to be a major causes of cancer-related death in women.
- ▶ 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 program 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).

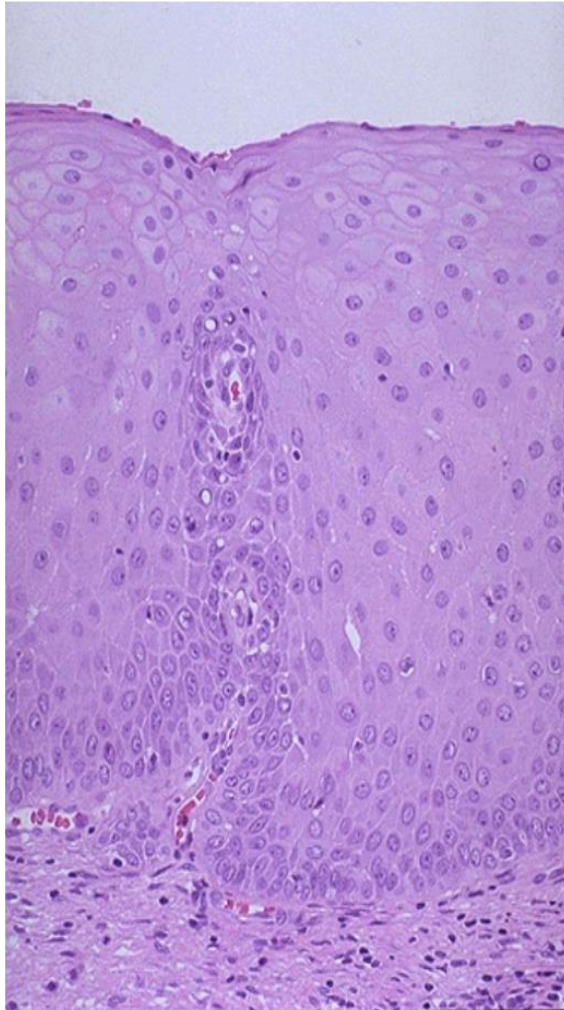
- ▶ All invasive squamous cell carcinomas arise from non invasive pre-cancer epithelial lesions called **cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL)**.
- ▶ Timely detection and diagnosis of CIN/SIL is essential in preventing the development of carcinoma (invasive lesion) and therefore providing curative treatment.
- ▶ **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)

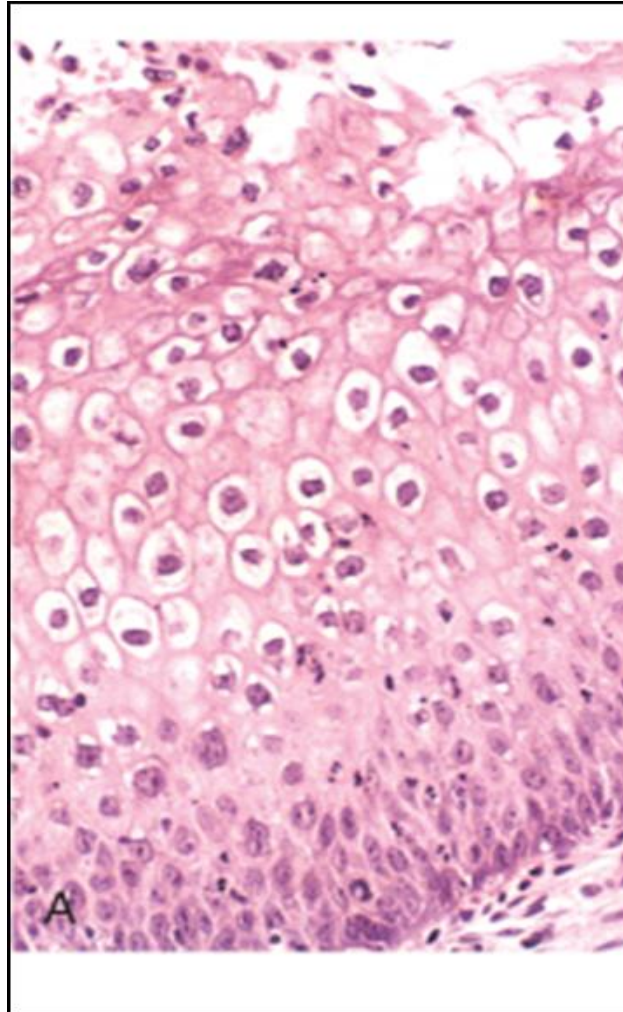
- ▶ CIN are precancerous lesions of the cervix.
- ▶ Pre-cancer changes can precede the development of an overt cancer by many years.
- ▶ **CIN lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start straight off as High Grade CIN.**
- ▶ On the basis of histology, pre-cancer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

Cervical biopsy



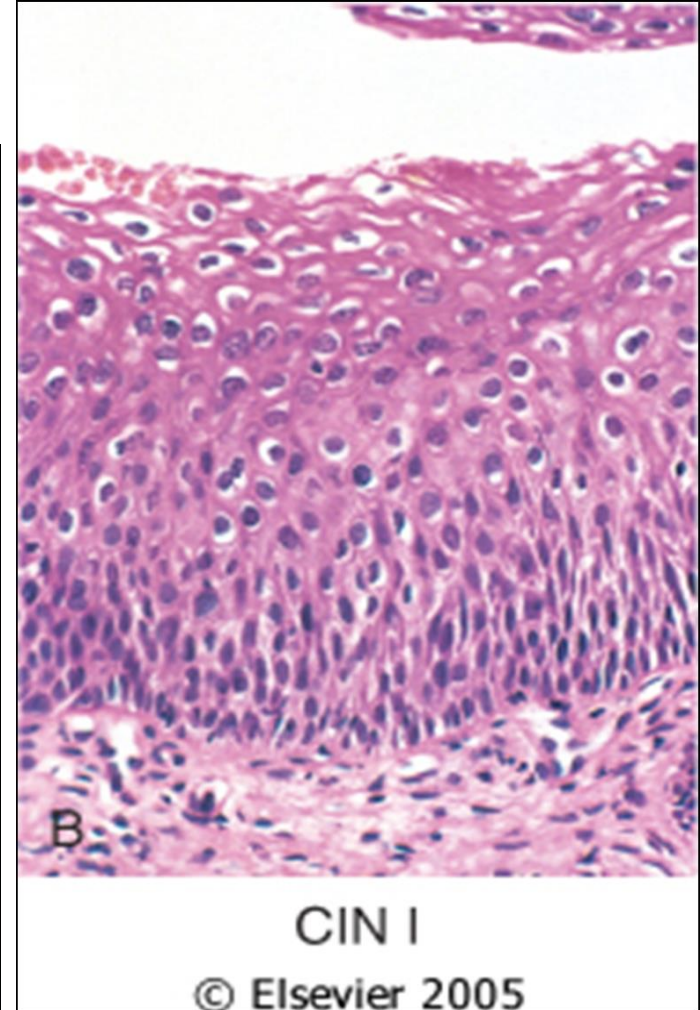
<http://www.microcorre.com/GYN/FEM003.jpg>

Normal



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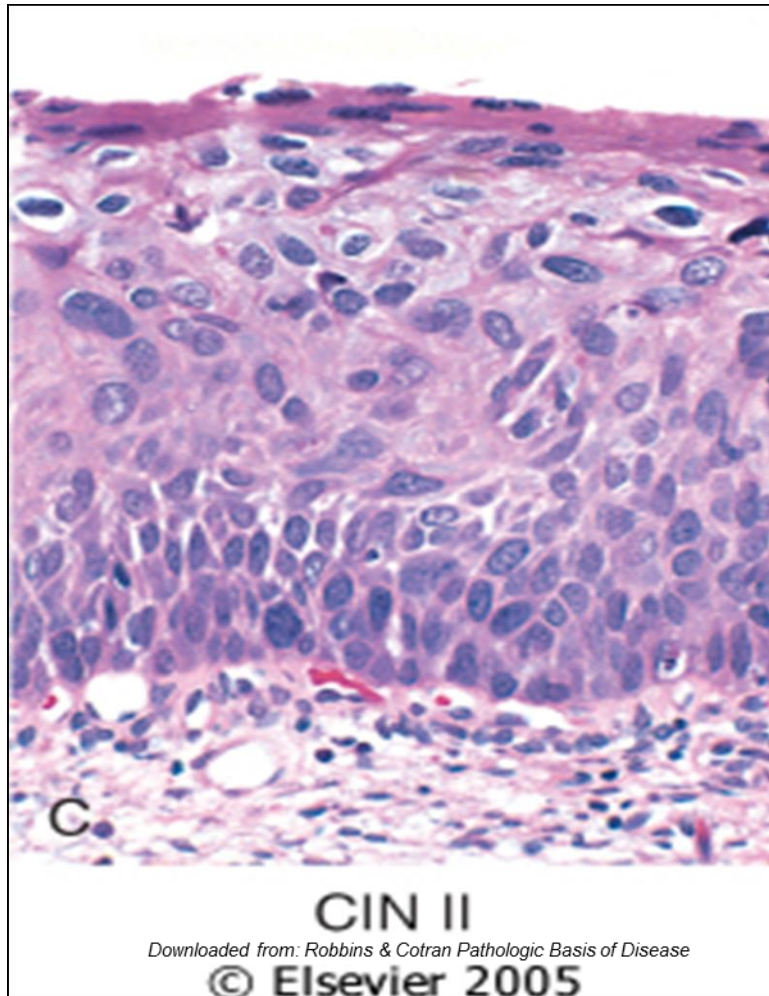
Koilocytotic atypia of HPV



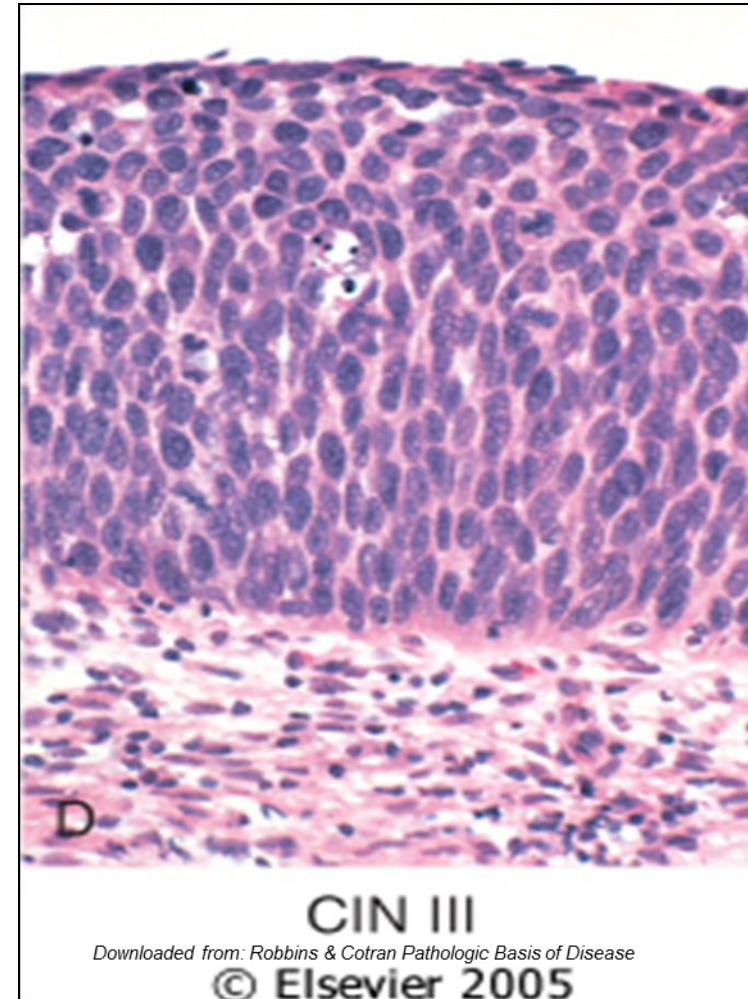
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**Mild dysplasia = CIN I
with HPV associated koilocytotic
atypia. Lower 1/3rd of the
epithelium is replaced by
pleomorphic cells.**

Cervical biopsy



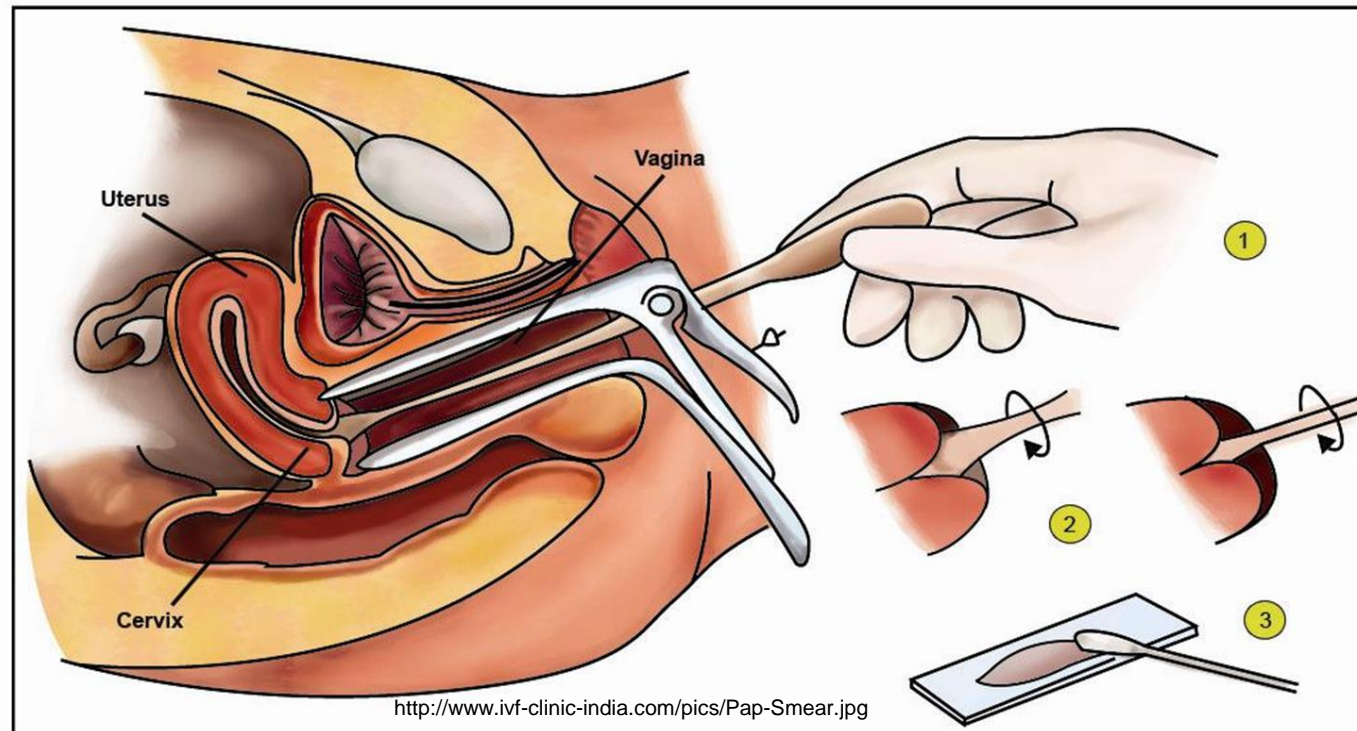
Moderate dysplasia = CIN II. There is progressive atypia in the layers of the epithelium; lower 2/3rd of the epithelium is replaced by pleomorphic cells



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

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. PAP test is the cytologic examination of the cells of cervix. In it the cervix is examined and the cells lining the cervical wall at the transformation zone are scrapped/ sampled with a spatula and then transferred onto a slide, processed, stained (Papanicolaou stain) and examined under a light microscope to look for squamous intraepithelial lesions and a diagnosis is made.
- This screening for precancer should be done on all women usually from age of 21 years and onwards.



Cytology Pap Smear/Screening

The terminology used in Pap smears is squamous intraepithelial lesions (SIL).

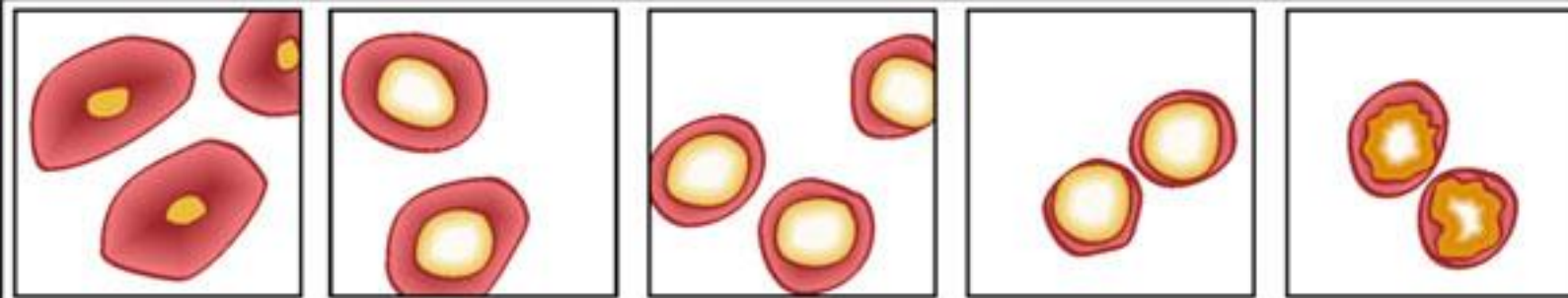
SILs are divided into low grade and high grade SIL.

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

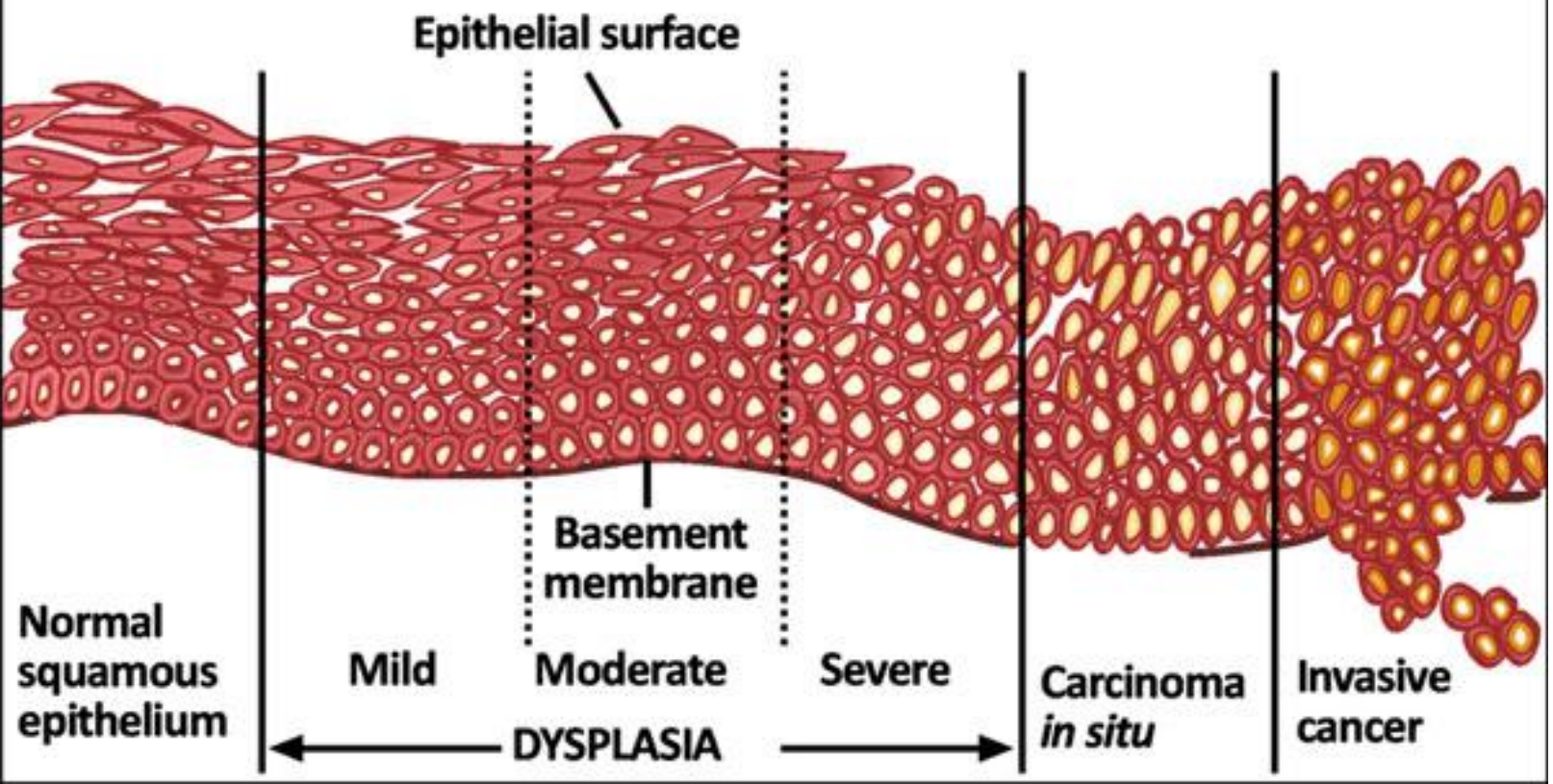
- a) Normal cells/ Negative for squamous intraepithelial lesion
- b) Low Grade SIL (= CIN1/mild dysplasia) (LSIL)
- c) High Grade SIL (= CIN2 and 3/moderate to severe dysplasia) (HSIL)

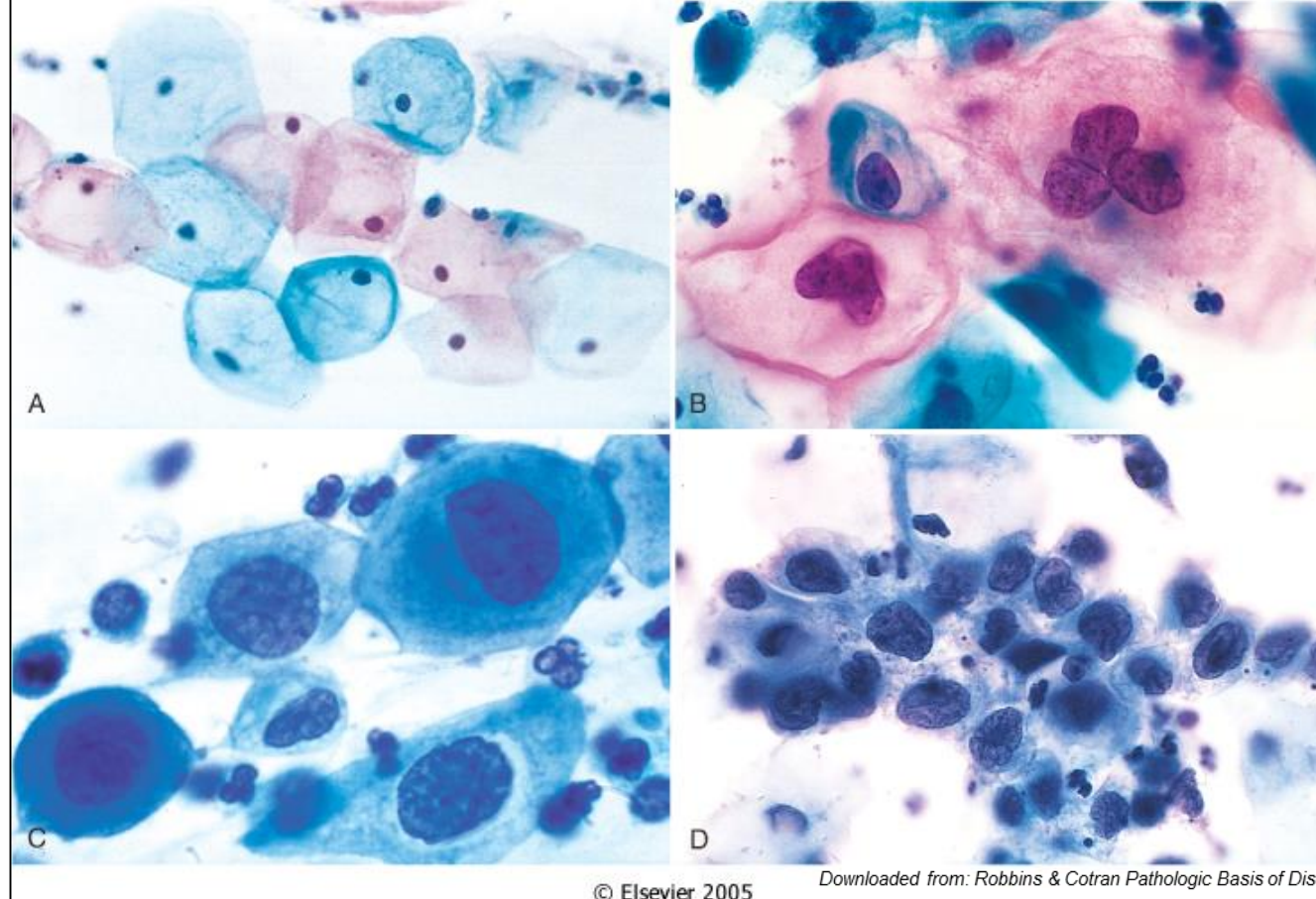
❖ About 1 to 5% of low Grade SIL become invasive squamous cell carcinomas

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



Normal **Mild dysplasia** **Moderate dysplasia** **Severe dysplasia** **Tumour cell**





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The cytology of cervical intraepithelial neoplasia as seen on the Papanicolaou smear.

Cytoplasmic staining in superficial cells (A&B) may be either red or blue.

A, Normal exfoliated superficial squamous epithelial cells.

B, CIN I/ low grade SIL

C, CIN II/ high grade SIL.

D, CIN III/ high grade SIL.

Note 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.

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

- ▶ The cause: 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

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/exam .
- ▶ Therefore regular pap exams should be done to detect any abnormal cells.

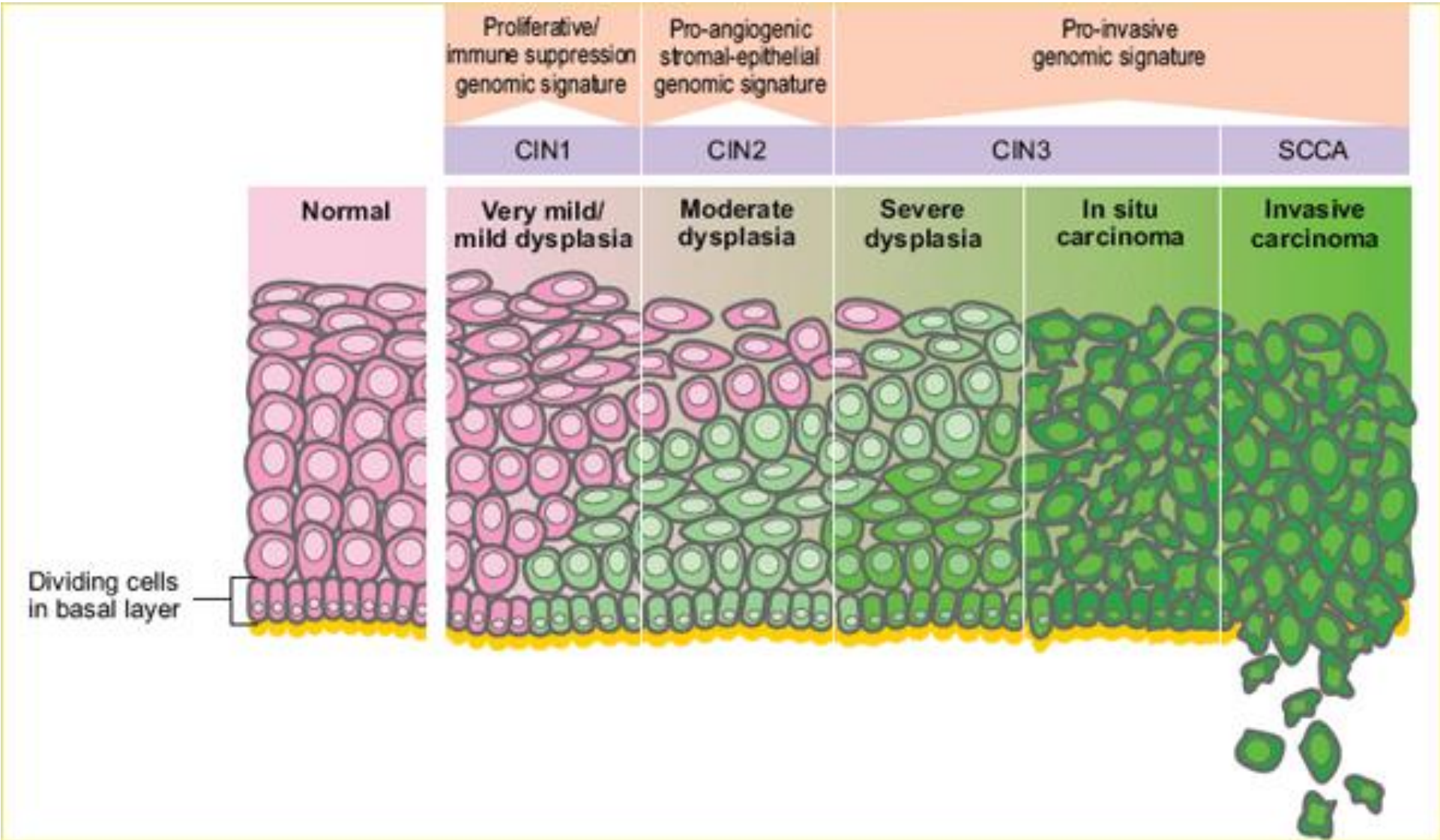
General rules of Pap Screening for CIN/SIL and carcinoma cervix using the PAP smear test are:

- It is a common testing procedure for HPV infection.
- The Pap smear detects HPV infection early.
- Should start pap test by the age of 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**
 - a) Either **only cytology** screening pap test is done every **3 years**
 - b) 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 Digene 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. HPV DNA screening test should not be used before age 30.

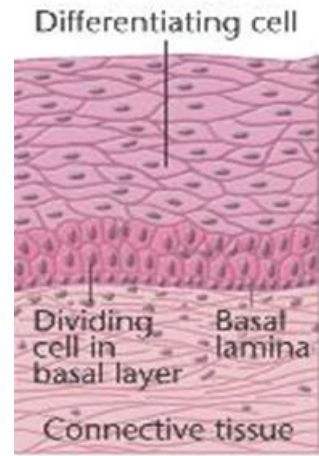
Cervical Carcinoma, Invasive

- About 75-90% of invasive cancers are Squamous cell carcinomas, which generally evolve from pre-cancer CIN/SIL lesions.
- The remainder are Adenocarcinoma.
- 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.

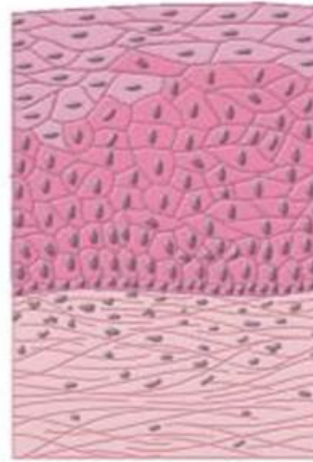


http://home.ccr.cancer.gov/inthejournals/archives/images/guis_img.png Reference
 Gius D, Funk MC, Chuang EY, Feng S, Huettner PC, Nguyen L, Bradbury CM, Mishra M, Gao S, Buttin BM, Cohn DE, Powell MA, Horowitz NS, Whitcomb BP, Rader JS.
 Profiling microdissected epithelium and stroma to model genomic signatures for cervical carcinogenesis accommodating for covariates. *Cancer Res* 67: 7113–23, 2007

(a) Normal cervical cells



(b) Dysplasia



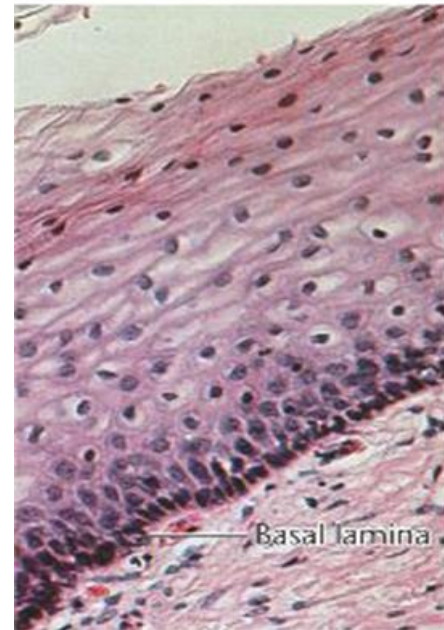
(c) Carcinoma *in situ*



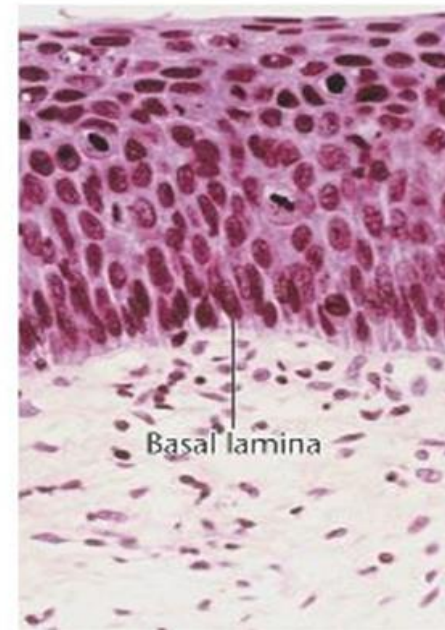
(d) Malignant carcinoma



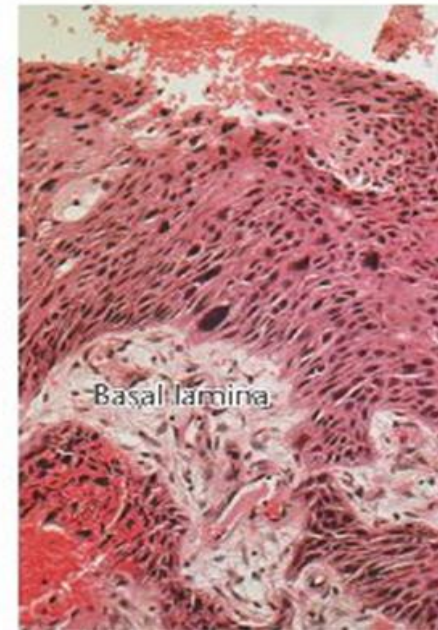
(e) Normal cervical epithelium



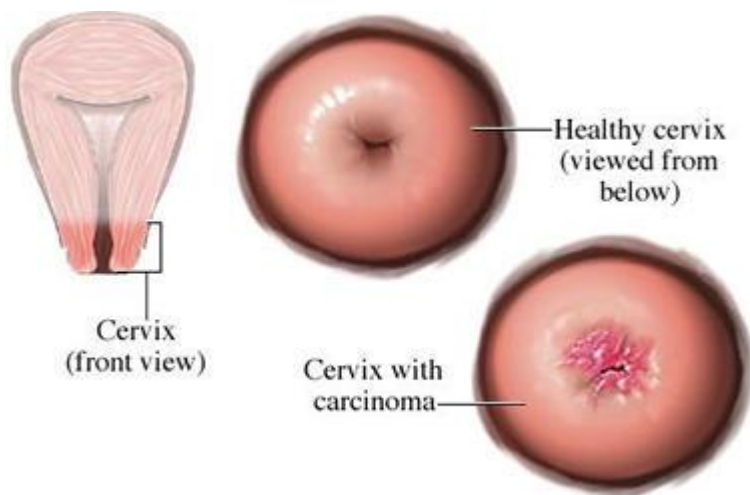
(f) Dysplastic epithelium



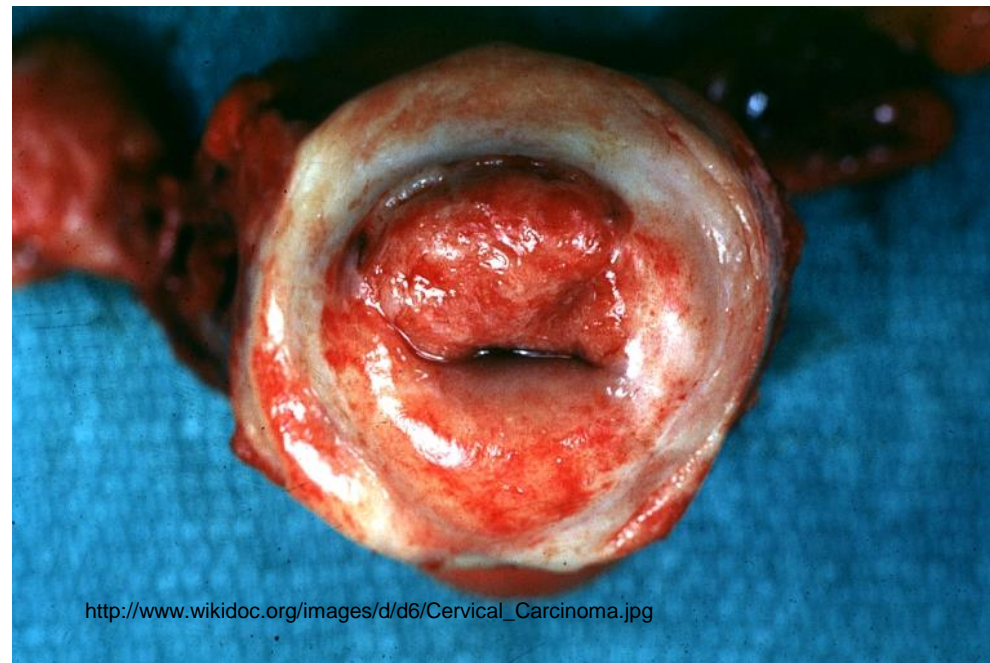
(g) Malignant carcinoma



Cervical cancer



<http://ehealthmd.com/content/what-cervical-cancer>



http://www.wikidoc.org/images/d/d6/Cervical_Carcinoma.jpg



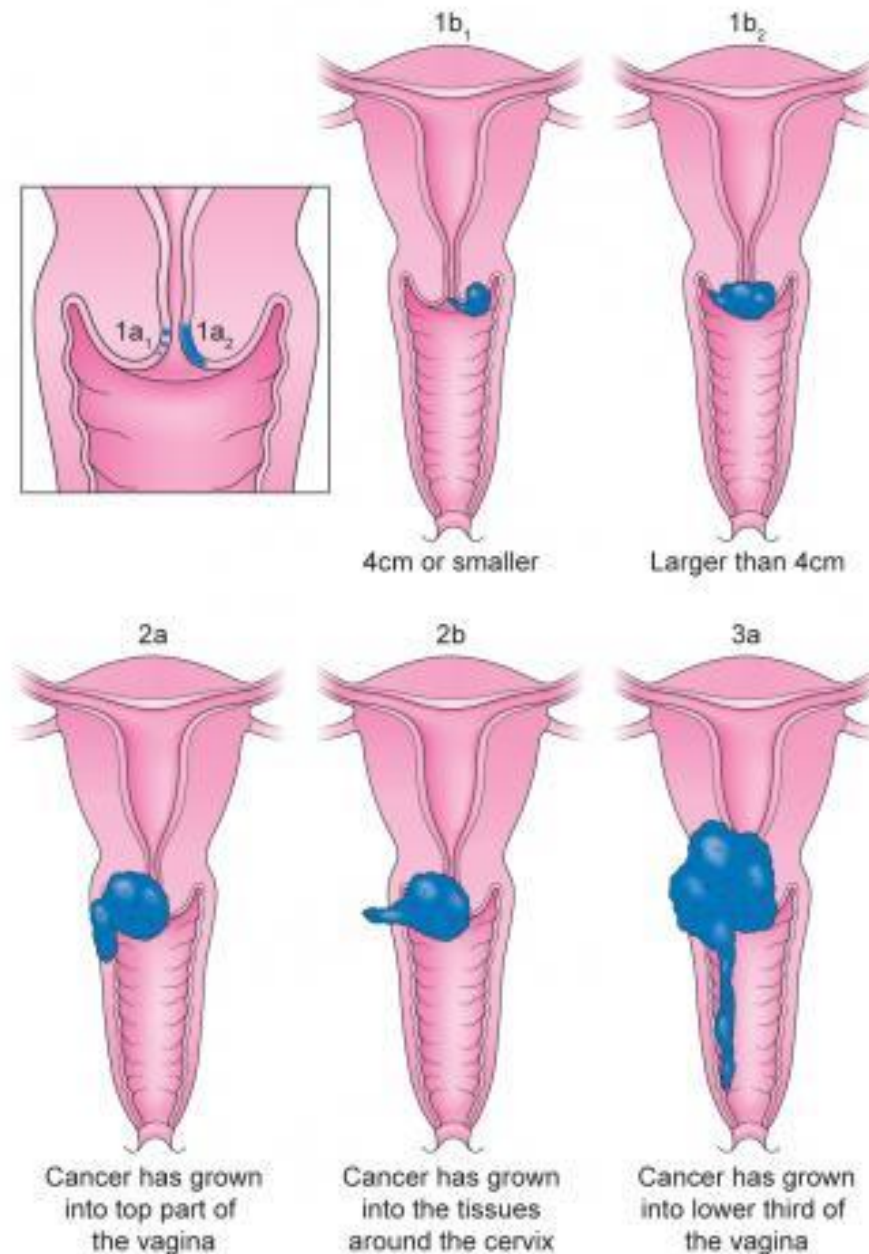
http://www.wikidoc.org/images/d/d6/Cervical_Carcinoma.jpg

CERVICAL CARCINOMA (INVASIVE CARCINOMA), 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.

For additional information: Cervical Carcinoma, 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



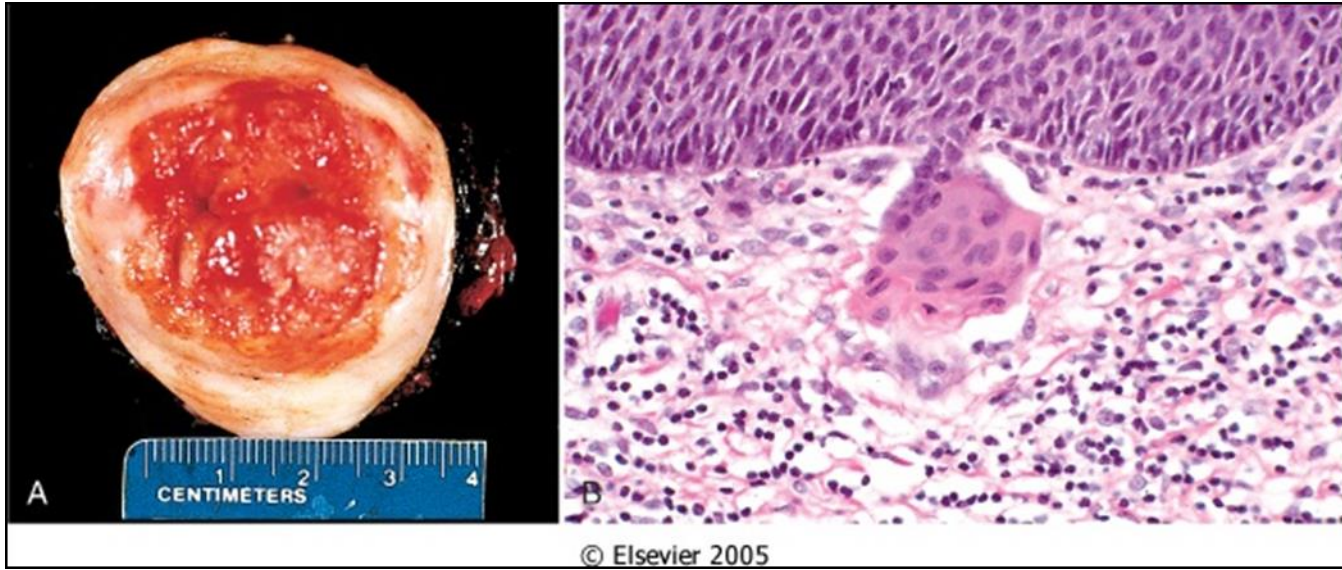
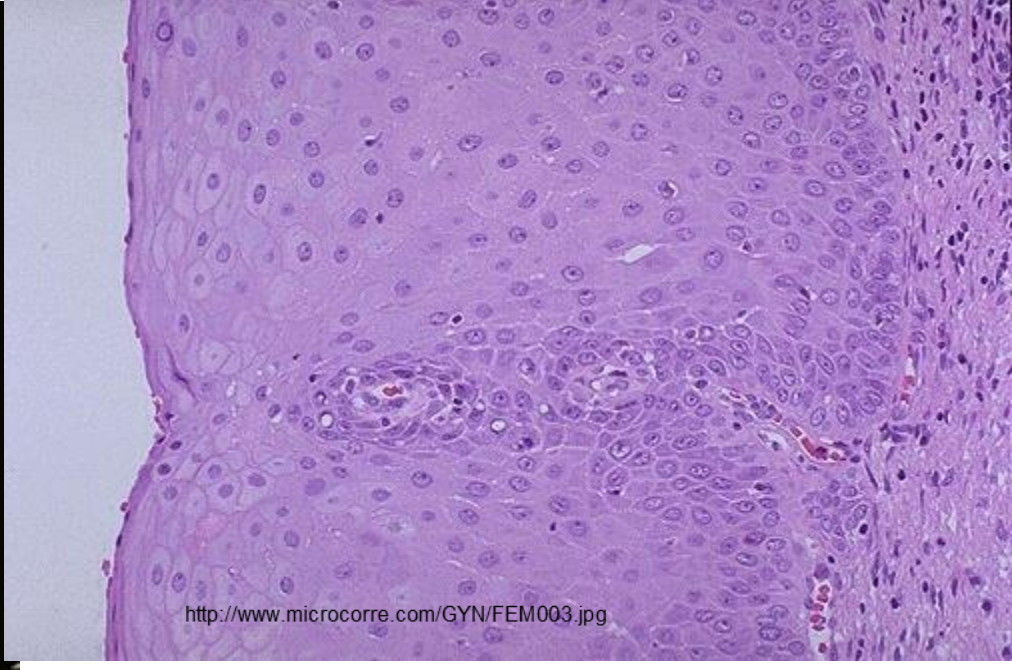
Cervical Carcinoma, Clinical Course

- Nowadays, due to the pap screening test, 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 last prior pap smear.
- The early stages of cervical cancer may be completely asymptomatic.
- Vaginal bleeding, contact bleeding, or cervical mass
- Dyspareunia.
- 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

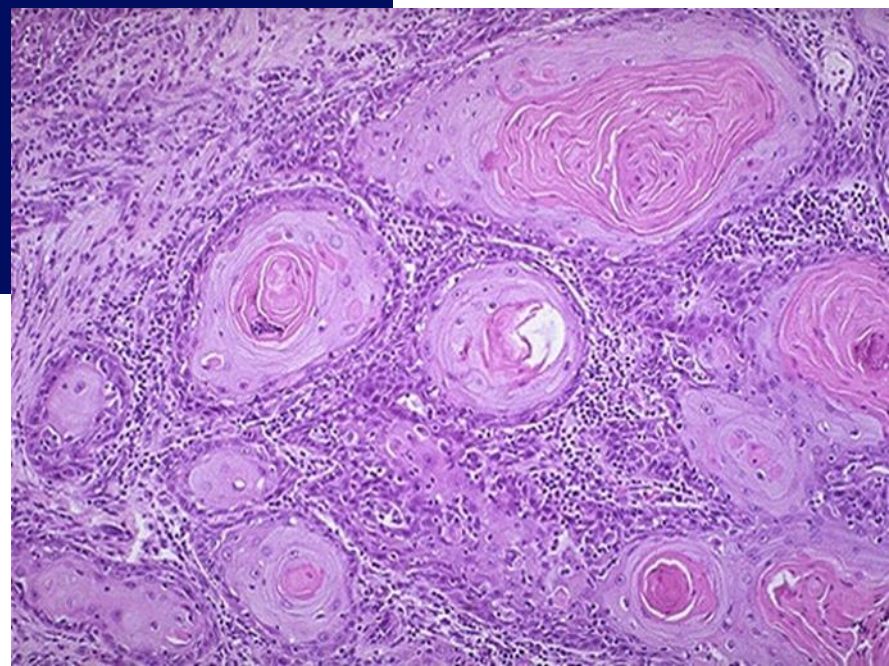
Cervical Carcinoma: Treatment

Depending on the stage there are different treatment options:

1. If patient wants to be able to have children, the cancer is removed with a cone biopsy (*cervical conization*), and then followed up regularly.
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.



A, Carcinoma of the cervix, well advanced. B, Early stromal invasion occurring in a cervical intraepithelial neoplasm





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http://o.quizlet.com/i/3xE_77-MhwN_qHE5saVMMQ_m.jpg