



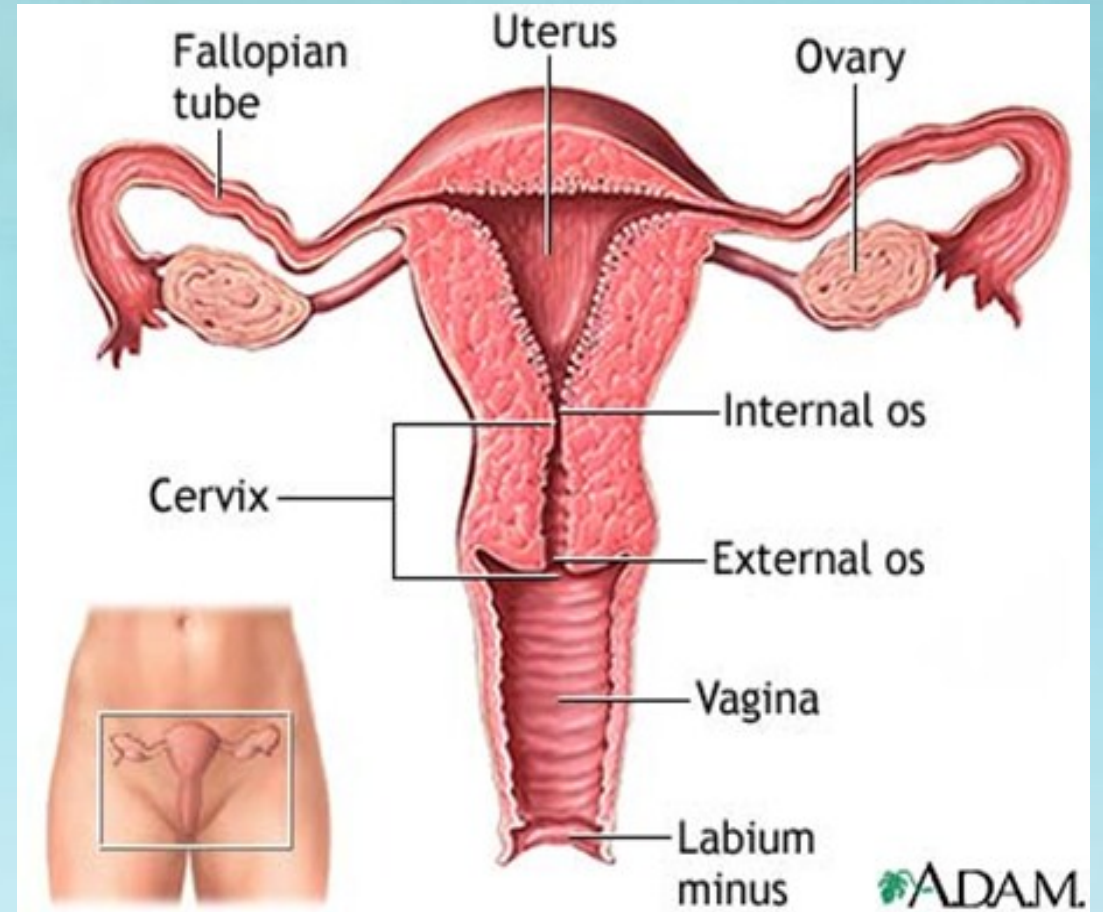
Female Genital Tract Pathology

LEC 1

Dr. Raghad Hanoon

Major Organs of FGT

- Vulva
- Vagina
- Cervix
- Uterus
- Fallopian tubes
- Ovaries



Vulva

- The vulva is the external female genitalia and includes the hair-bearing skin (labia majora) and mucosa (labia minora).
- **Normal histology:** The vulva has **both keratinized and nonkeratinized squamous epithelium with appendageal structures** (hair follicles, sebaceous glands, eccrine and apocrine glands) vary in their localization.
- **Diseases of vulva:**
 1. Vulvitis (more common but not serious).
 2. Non-Neoplastic epithelial disorders.
 3. Tumors; Carcinomas (uncommon but life threatening).

1. Vulvitis

- Inflammation of vulva; It could be **infectious** or **non-infectious**

❖ A. Infectious;

A large variety of organisms can infect the female genital tract, which often are **sexually transmitted**.

- *The most important infectious agents are:*

1. **Human papillomavirus (HPV)**; the causative agent of **condyloma acuminatum**, **vulvar intraepithelial neoplasia (VIN)**, and **vulvar squamous carcinoma**
2. **Herpes simplex virus (HSV-1 or HSV-2)**; the agent of **genital herpes** (vesicular eruption and painful genital ulcerations).

3. *N. gonorrhoeae*; a cause of **suppurative** infection of the vulvovaginal glands.

4. **Syphilis**; (*Treponema pallidum*), which causes **primary chancre** at vulvar sites of inoculation; or **Secondary syphilis (Condyloma lata)**: hyperplasia of epithelium with underlying chronic inflammation rich in plasma cells & endarteritis obliterans.

5. **Candida**; also is a cause of vulvitis, but is **not** sexually transmitted.

- An important complication of vulvitis is obstruction of the excretory ducts of Bartholin glands. This blockage may result in painful dilation of the glands (*Bartholin cyst*) and abscess formation.

❖ B. Non infectious;

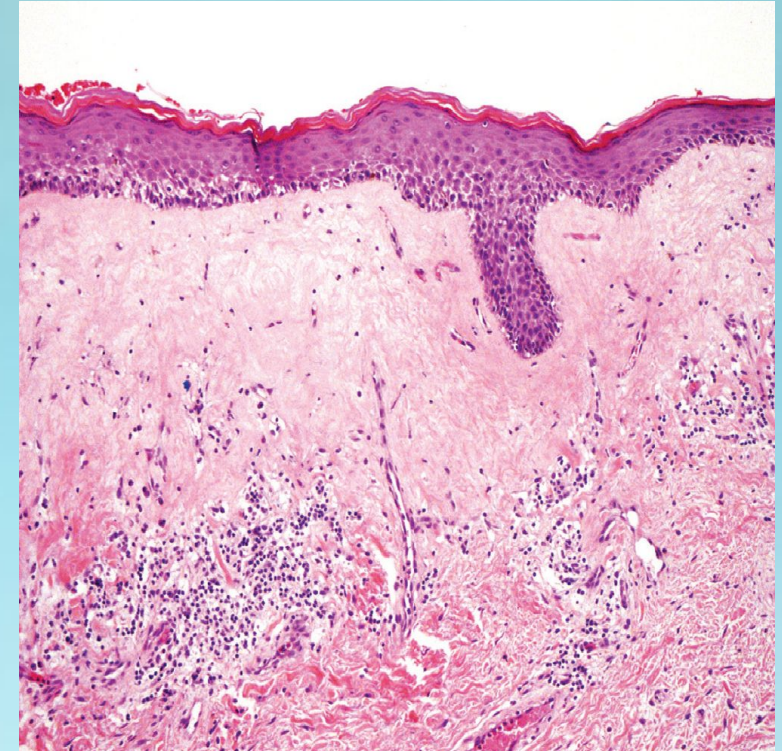
- One of the most common causes of vulvitis is **reactive inflammation** in response to an exogenous stimulus, which may be an irritant (**contact irritant dermatitis**; May be a reaction to urine, soaps, detergents, antiseptics, or alcohol), or an allergen (**contact allergic dermatitis**; may result from allergy to perfumes and other additives in creams, lotions, and soaps, chemical treatments on clothing and other antigens).
- presents as **well- defined erythematous weeping and crusting papules and plaques.**
- Many **inflammatory diseases** that affect skin elsewhere on the body also occur on the vulva, such as **psoriasis, eczema, and others.**

2. Non- Neoplastic epithelial disorders

- There are two forms of non-neoplastic epithelial disorders: **lichen sclerosis** and **lichen simplex chronicus**.
- Both may coexist in **different areas** in the same person, and both may appear macroscopically as **depigmented white lesions**, referred to as **leukoplakia**.
- **Leukoplakia (white patches or plaques)** also are seen in a variety of other benign dermatoses, such as **psoriasis** and **lichen planus** as well as in **malignant lesions** of the vulva, such as squamous cell carcinoma in situ and invasive squamous cell carcinoma. **Thus**, biopsy and microscopic examination are often needed to differentiate these clinically similar-appearing lesions.

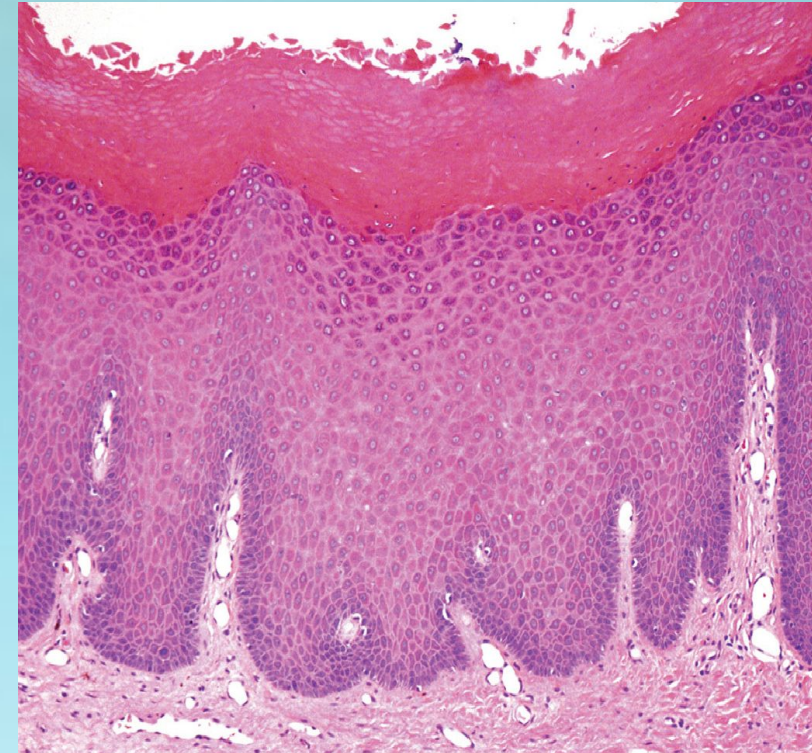
A. Lichen Sclerosus:

- **Clinical presentation:** smooth, white plaques or macules that in time may enlarge and coalesce.
- **Mic.:** the lesion is characterized by:
 1. Thinning of the epidermis,
 2. Disappearance of rete ridges,
 3. A zone of acellular, homogenized, dermal fibrosis,
 4. A band like mononuclear inflammatory cell infiltrate
- **Age:** It is most common in postmenopausal women but it can occur in any age.
- **Cause:** the exact cause is unknown , An autoimmune reaction in a genetically susceptible patient due to previous skin damage or irritations probably involved in its pathogenesis.
- **Risk:** there is an 1% to 5% increased risk of vulvar squamous cell carcinoma.



B. Lichen Simplex Chronicus

- **Clinically:** it presents as leukoplakia
- **Mic.:**
 - 1-Hyperkeratosis .
 - 2- Epithelial thickening (particularly of the stratum granulosum) ,
 - 3-Increased mitotic activity in the basal and suprabasal layers; but **no epithelial Atypia**
 - 4-Lymphocytic infiltration of the dermis is sometimes present.
- **Cause:** Nonspecific condition resulting from rubbing or scratching of the skin to relieve pruritus. is the end stage of many inflammatory dermatoses
- **Risk:** Generally, there is **no increased predisposition to cancer.**



3. Tumors

❖ Benign tumors

□ Condylomas

- Any raised (exophytic) or wartlike lesions.
- There are **two main types**:

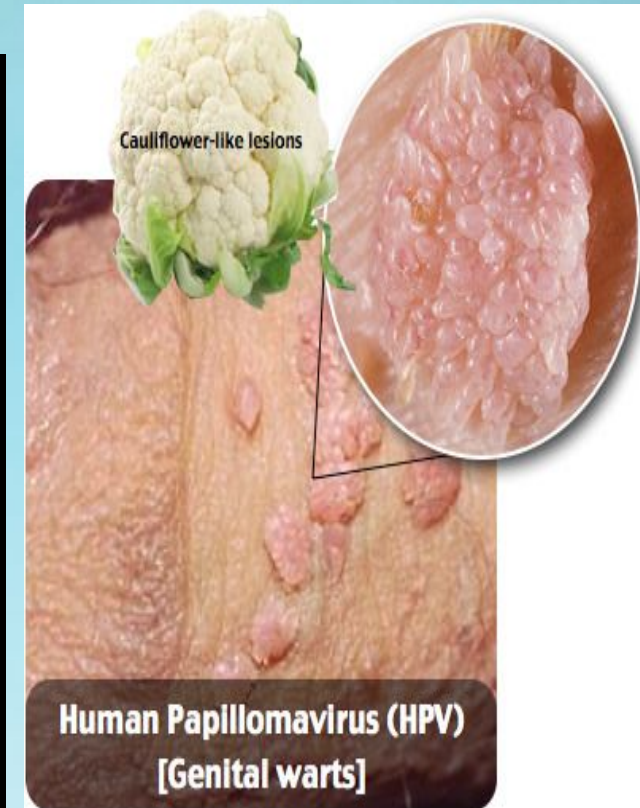
1. Condyloma acuminatum:

- The most common type.
- **Location:** They may occur anywhere on the **anogenital surface** (vulva, perineum, and perianal regions, vagina and, less commonly the cervix).
- **Cause:** HPV subtypes 6 and 11. (HPV is **sexually transmitted**, and identical lesions occur in men on the penis and around the anus in men and women; HPV 6 and 11 are low-risk viral types, and hence, **vulvar condylomas do not commonly progress to cancer**. However, women with condyloma acuminatum are at risk of having other HPV-related lesions in the vagina and cervix.
- **HPV vaccines** provide excellent protection against infection by low-risk HPV and genital warts.

2. Condyloma lata: seen in **secondary syphilis**.

❑ Gross of Condyloma acuminatum:

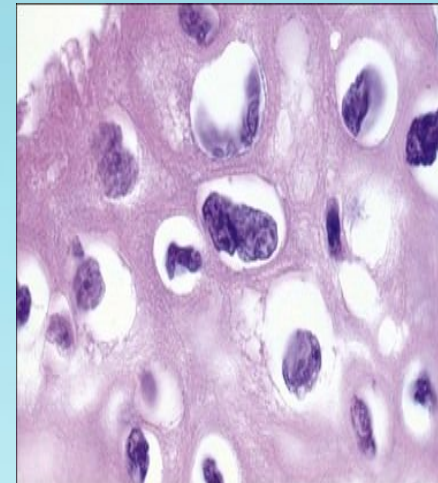
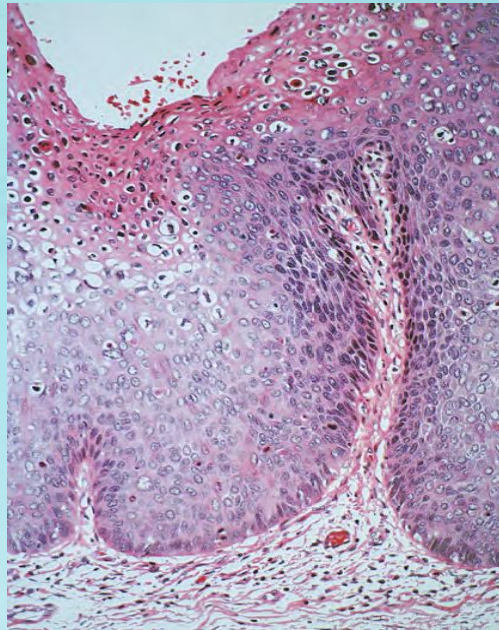
- Papillary and distinctly elevated, they are often **multiple**, are **red-pink to pink-brown** lesions that measure range from **a few millimeters** up to **several centimeters** in diameter.



- **Microscopical features of Condyloma acuminatum:**

- **Papillary (papillomatosis), exophytic, treelike cores of stroma covered by thickened squamous epithelium .**

The surface epithelium shows characteristic viral cytopathic changes referred to as *koilocytic atypia* (nuclear enlargement, hyperchromasia, and a wrinkled nuclear contour (raisinoid nuclei) and a cytoplasmic perinuclear halo).



❖ Malignant tumors

□ Carcinoma of the Vulva

- Represents about **3%** of all female genital tract cancers, occurring mostly in women older than age 60.
- Approximately **90%** of carcinomas are squamous cell carcinomas; most of the other tumors are adenocarcinomas or basal cell carcinomas.
- There are **two distinct forms** of vulvar squamous cell carcinomas that differ in pathogenesis and course

1. HPV-negative carcinoma

2. HPV-positive carcinoma

- Both forms of vulvar carcinoma tend to remain confined to their site of origin for a few years but ultimately invade and spread, usually first to regional lymph nodes. The risk of metastasis correlates with the depth of invasion. As with most carcinomas, prognosis is dependent on tumor stage.

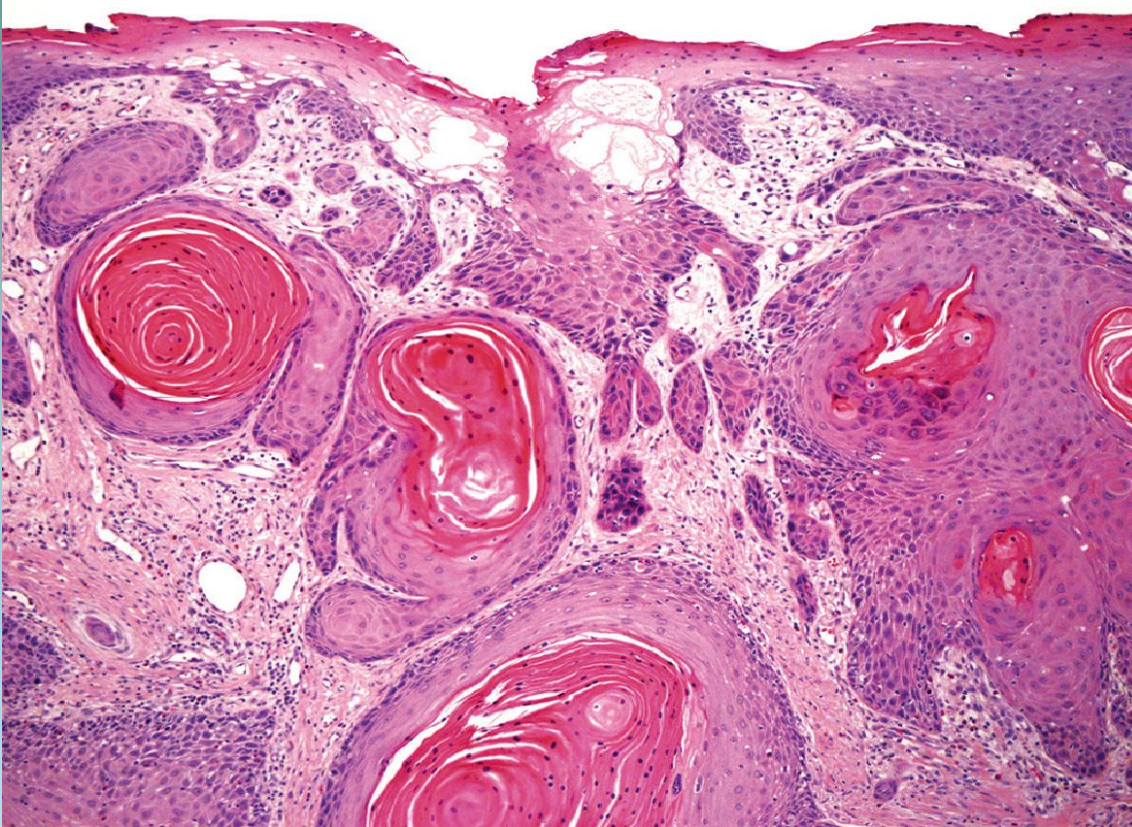
HPV-negative carcinoma	HPV-positive carcinoma
Occur in older women (average 75 years of age).	Occur in younger women (average 60 years of age).
Unrelated to HPV infection	Related to infection with high-risk HPVs, most commonly HPV-16.
Sometimes following a long history of reactive epithelial changes (lichen sclerosus).	Is often preceded by precancerous changes in the epithelium termed vulvar intraepithelial neoplasia (VIN).
Unifocal and typically are well-differentiated keratinizing squamous cell carcinomas	Often multifocal and warty and tend to be poorly differentiated squamous cell carcinomas

□ Gross:

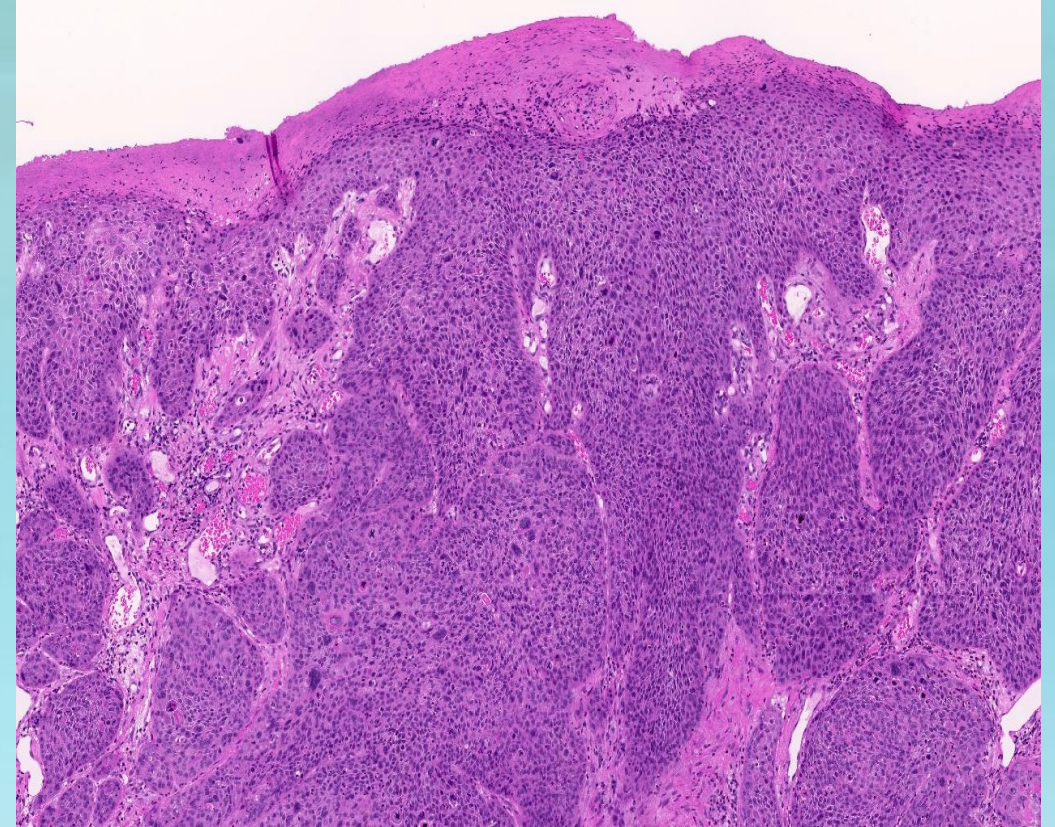
- Early vulvar carcinomas commonly manifest as areas of **leukoplakia**. In about one-fourth of the cases, the lesions are pigmented owing to the presence of melanin. **With time**, these areas are transformed into **overt exophytic or ulcerative endophytic tumors**.



Mic.:



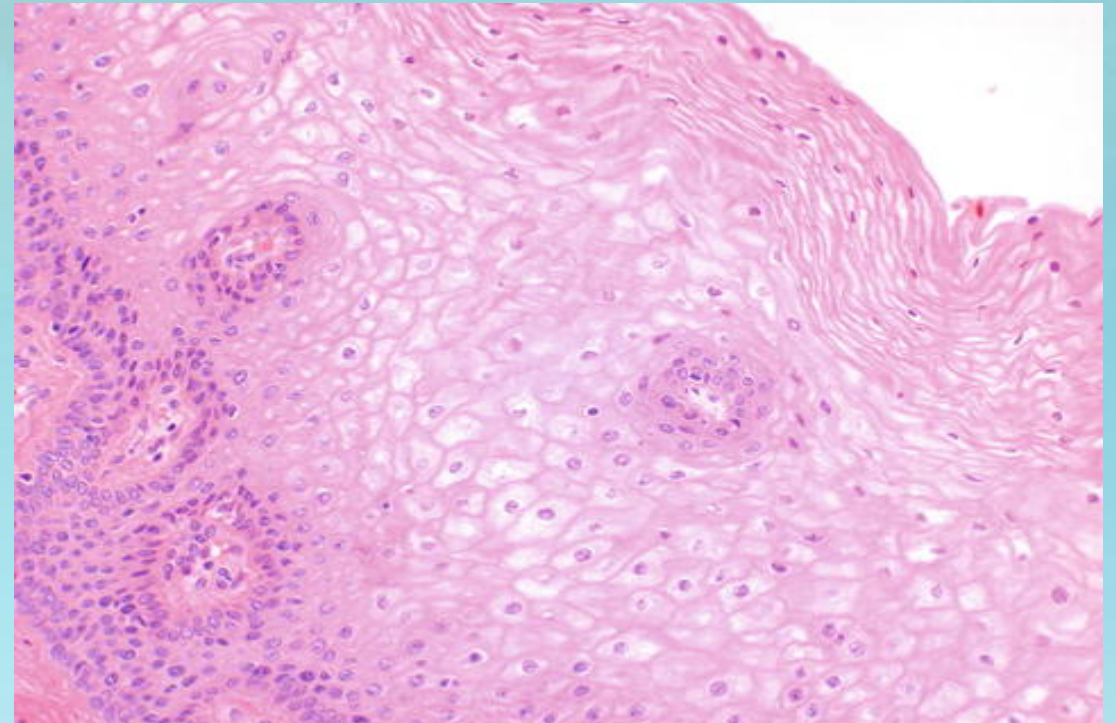
- **Well-differentiated, keratinizing squamous cell carcinoma of the vulva (HPV negative)** composed of invasive nests of malignant squamous cells with central keratin pearls.



- **Poorly differentiated (Nonkeratinizing) squamous cell carcinoma (HPV-positive)**

Vagina

- The vagina is seldom the site of primary disease; **more often it is secondarily involved** in the spread of cancer or infection arising in cervix, vulva, bladder, or rectum.
- The only primary disorders discussed here are **vaginitis, and primary tumors.**



- **Normal histology of the vagina:** is lined by **non-keratinized stratified squamous epithelium.** During reproductive life, the epithelium is highly glycogenated due to the effect of estrogen

❖ Vaginitis

- Is a common condition that is usually **transient** and of **no clinical consequence**.
- It is associated with the production of a vaginal discharge (**leukorrhea**).
- Usually caused by normal commensals that become pathogenic in **predisposed individuals** e.g.

- Diabetes
- Systemic antibiotic therapy
- After abortion or pregnancy
- elderly with compromise immune response & AIDS.

- The frequent organisms are **Candida Albicans** and **Trichomonas vaginalis**.

❖ **Candida vaginitis:**

- Cause vulvovaginal pruritus, erythema, swelling, and **curdlike vaginal discharge**.
- Severe infection may result in mucosal ulcerations.

❖ **Trichomonas vaginalis:**

- Produces a watery, copious **green discharge**, in which parasite can be identified microscopically.

However, T. vaginalis can also be identified in 10% of asymptomatic women.

❖ Malignant Tumors of the vagina

1. Squamous cell carcinoma

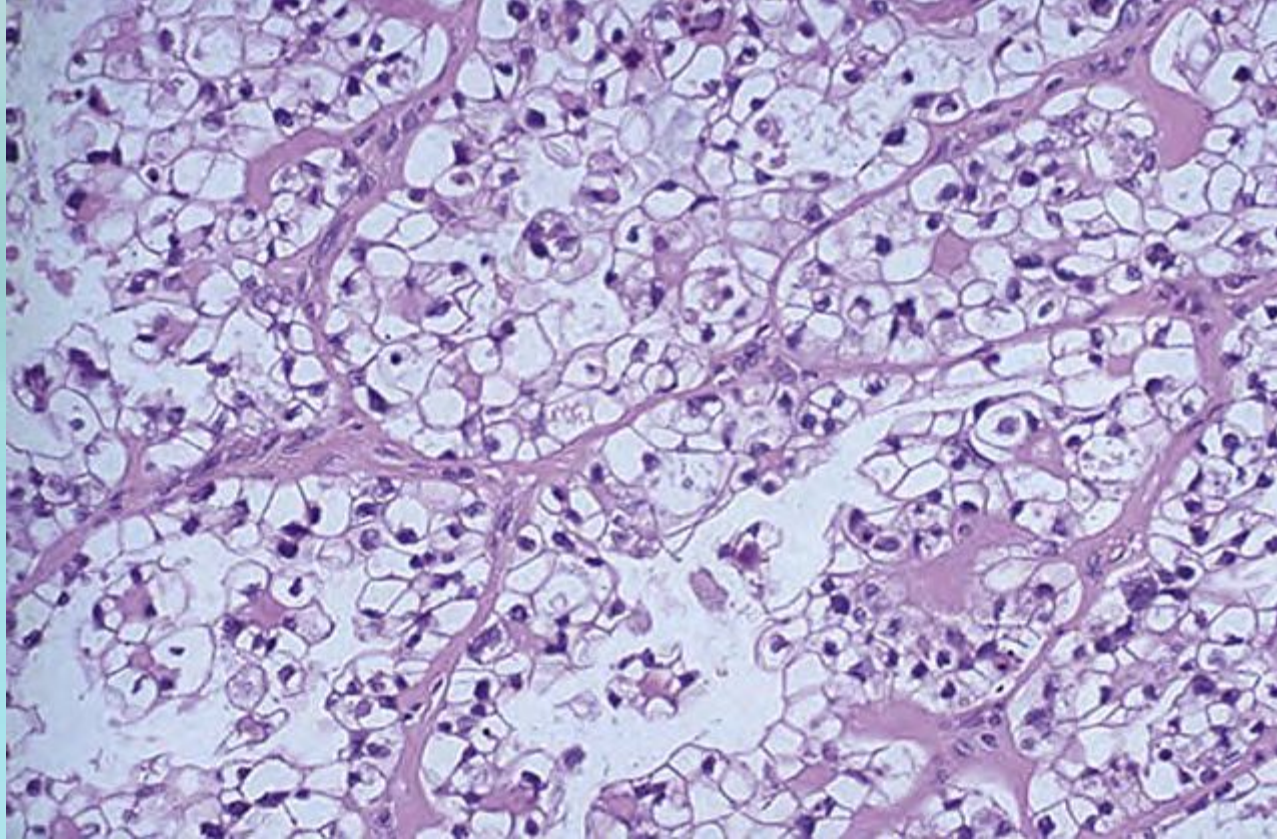
- Is very rare (it accounts for about 1% of malignant neoplasms in the female genital tract).
- Usually occurs in **elderly women**.
- Vaginal intraepithelial neoplasia (VIN) is a precursor lesion associated with HPV infection.

2. Clear cell adenocarcinoma

- Usually affects **adolescent and young females** whose mothers took diethylstilbestrol during pregnancy. (This medication used widely in the past(1940-1970) to prevent miscarriage).
- The tumor may arise from the cervix rather than the vagina in a third of the cases.
- It is preceded by increase in gland number (adenosis)

3. Embryonal rhabdomyosarcoma (Sarcoma botryoides)

- Produces soft polypoid masses (grape like) and is usually seen in **infants and children** younger than 5 years of age.

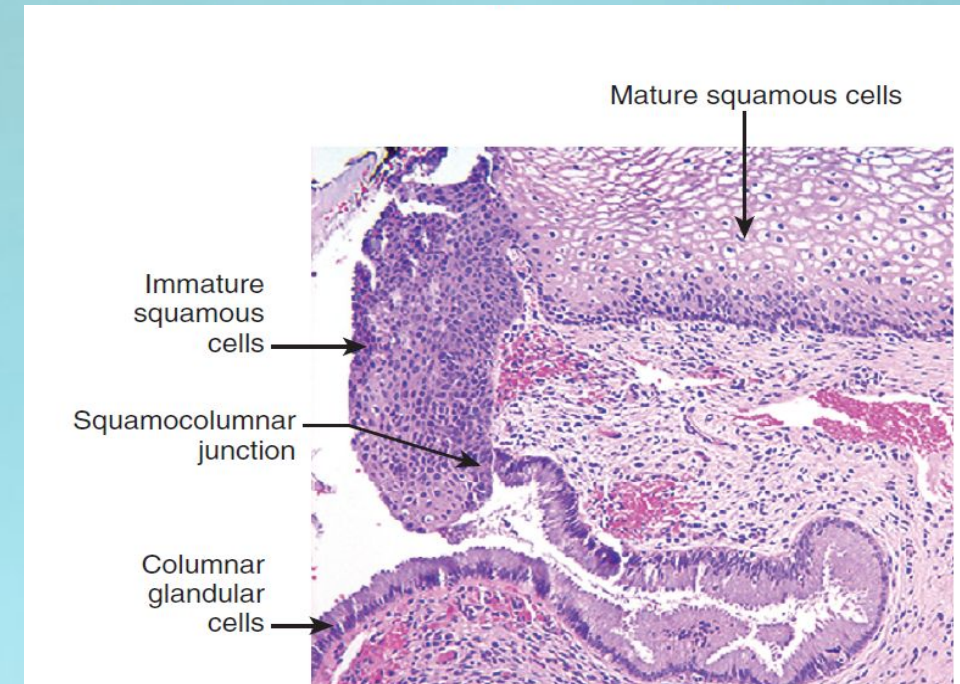


- **Clear cell adenocarcinoma of vagina:**

Vacuolated cells forming irregular clusters with ill-defined glandular lumens.

Cervix

- Consists of **ectocervix** (covered by squamous epithelium that is continuous with vaginal wall) and **endocervical canal** (lined by columnar mucinous epithelium). The position of the squamocolumnar junction (**transformation zone [TZ]**) is variable and changes with age and hormonal influence.
- **TZ** are most susceptible to HPV infection, and hence this is where cervical precursor lesions and cancers develop.
- Most cervical lesions are relatively banal inflammations (**cervicitis**), but the cervix also is the site of one of the most common **cancers** in women worldwide.



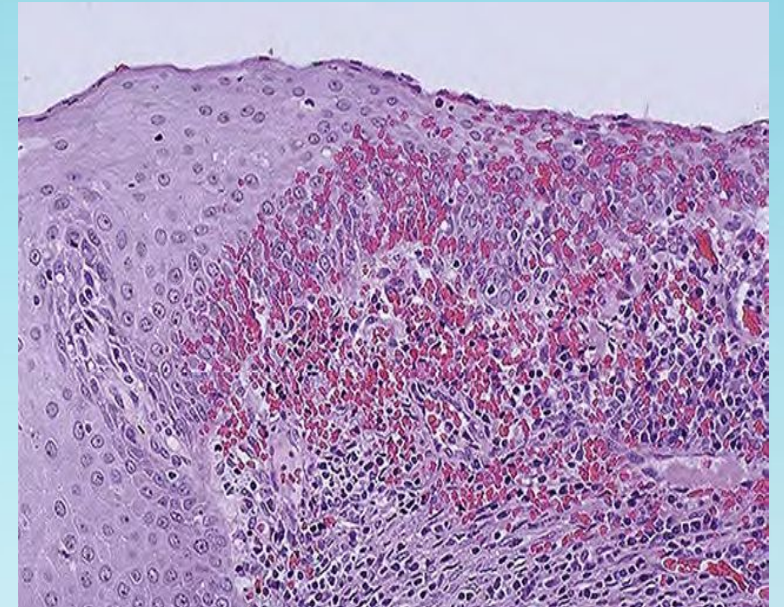
Cervical **transformation zone** showing the transition from mature glycogenated squamous epithelium, to immature metaplastic squamous cells, to columnar endocervical glandular epithelium.

❖ Cervicitis:

- Inflammation of the cervix are **extremely common**, and are associated with **purulent vaginal discharge**.
- These inflammation can be infectious or noninfectious cervicitis.
- **Microorganisms** often present are indigenous, incidental vaginal aerobes and anaerobes, streptococci, staphylococci, enterococci, Escherichia coli, **Chlamydia trachomatis**, Ureplasma urelyticum, T. vaginlais, Candida spp., Neisseria gonorrhoeae, herpes simplex genitalis, and HPV.
- Many of these organisms **are transmitted sexually**, so cervicitis may represent sexually transmitted disease.
- Among these organisms, **C. trachomatis** represent **40 % of cases** of cervicitis encountered in sexually transmitted disease clinics.

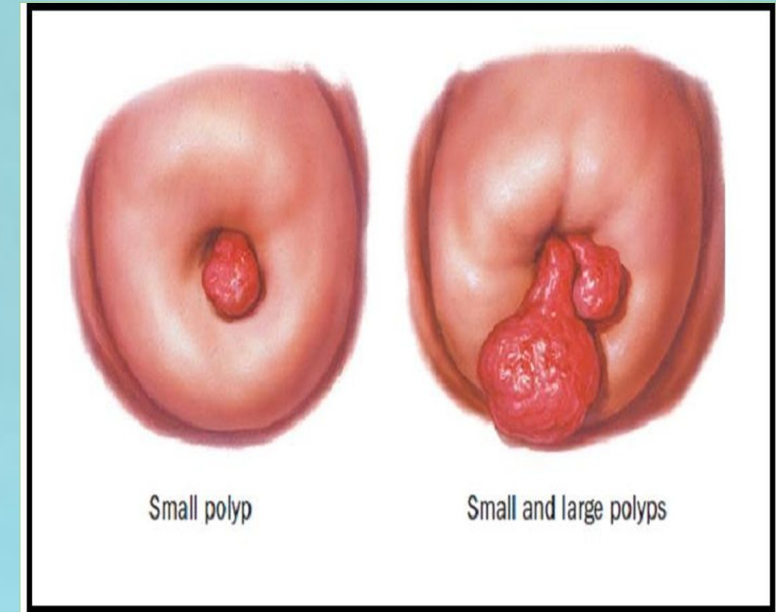
□ Morphology:

- **Gross:** Hyperemia, edema around margin of external os., **Nabothian cyst** may be grossly visible (translucent, filled with a clear fluid) caused by obstruction of submucosal cervical glands so that glandular cystic dilation occurs.
- **Microscopically:** chronic inflammatory cell infiltrate (lymphocytes) in the submucosa; there is also hemorrhage.



❖ Endocervical Polyp

- **Benign exophytic growth** that arise within the endocervical canal .
- **Pathogenesis** may be **inflammatory in origin**.
- **Gross:** range up to few cm in diameter, **soft, covered by smooth glistening surface**
- **Mic.:**
- Polypoid lesion composed of a **fibrous stroma covered by mucus-secreting endocervical columnar epithelium**, often accompanied by **inflammation and cystically dilated endocervical glands filled with mucin secretion**
- **Clinical significance:** they may be the source of **irregular vaginal “spotting” or bleeding**, but have **No malignant potential**
- **Treatment:** surgical excision is curative.



NEOPLASIA OF THE CERVIX

❖ Premalignant and malignant neoplasm of the Cervix

□ Pathogenesis:

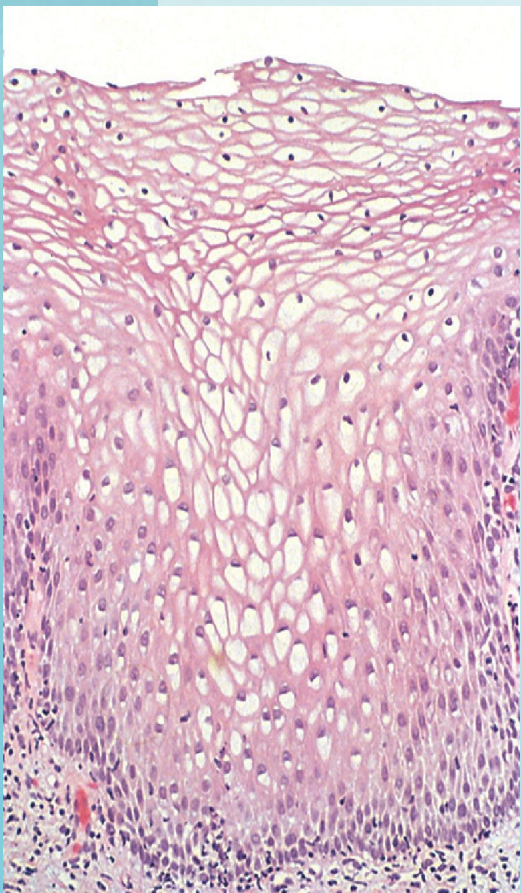
- High-risk HPV(16 and 18) is the causative agent of cervical neoplasia, it has a tropism for the immature squamous cells of the transformation zone.
- Most HPV infections are transient and are eliminated within months by the host immune response.
- A subset of infections persists, however, and some cause cervical intraepithelial neoplasia (CIN), which are precursors from which most invasive cervical carcinomas develop.
- Important risk factors for the development of CIN and invasive carcinoma thus are directly related to HPV exposure and include:
 - Early age at first intercourse
 - Multiple sexual partners
 - Male partner with multiple previous sexual partners
 - Persistent infection by high-risk strains of papillomavirus.
- HPV alone is insufficient to cause cancer; other factors e.g. exposure to co-carcinogens (cigarette smoking) and host immune status determine whether an HPV infection regresses or persists and eventually progresses to cancer.

■ Human papilloma virus (HPV):

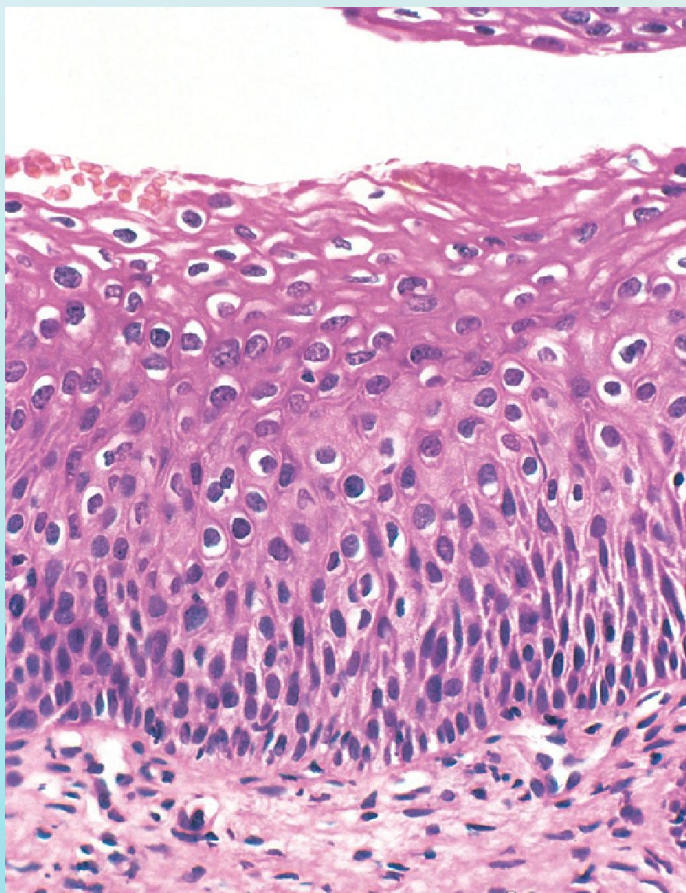
- DNA viruses more than 100 type HPV types have been identified that are grouped into those of **high** and **low oncogenic risk** based on their genotypes.
- **Low risk HPVs (6 and 11)** are the cause of sexually transmitted vulvar, perineal, and perianal **warts (condyloma acuminatum)**. In which the **viral DNA does not integrate into the host genome**.
- **High-risk HPVs (16 and 18):** implicated in **squamous cell carcinomas** arising at many sites, including the cervix, vagina, vulva, penis, anus, tonsil, and other oropharyngeal locations.
- **HPV types 16 & 18** usually **integrate** into the host genome...they start to **produce** the **viral E6 and E7 proteins**, which **interfere** with the activity of the **tumor suppressor proteins, p53 and RB, respectively**. The result is a **transformed cell**, capable of **autonomous growth** and susceptible to the acquisition of further mutations (cancer progression).
- The recently introduced HPV vaccine is very effective in preventing HPV infections and hence cervical cancers.

□ Premalignant: Cervical Intraepithelial Neoplasia (CIN):

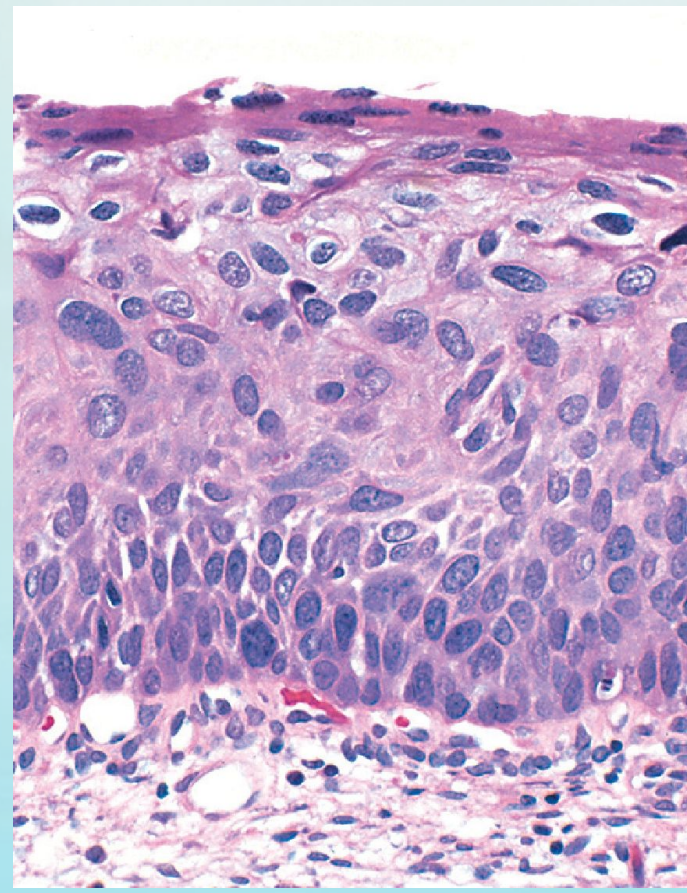
- Precancerous cervical epithelial changes are the precursor lesion for squamous cell carcinoma of the cervix.
- Nearly all invasive cervical squamous cell carcinomas arise from cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL).
- Detection of CIN by the Pap smear at an early stage permits curative treatment.
- Cytological examination can detect CIN long before any abnormality can be seen grossly.
- Precancerous changes usually take many years to evolve into overt carcinomas.
- The peak age of CIN incidence is about 30 years, whereas that of invasive carcinoma is about 45 years .
- Microscopic features of CIN and carcinoma in situ:
 - Based on histology, precancerous changes are graded as-
 - CIN I: Mild dysplasia
 - CIN II: Moderate dysplasia
 - CIN III: Severe dysplasia/carcinoma in situ



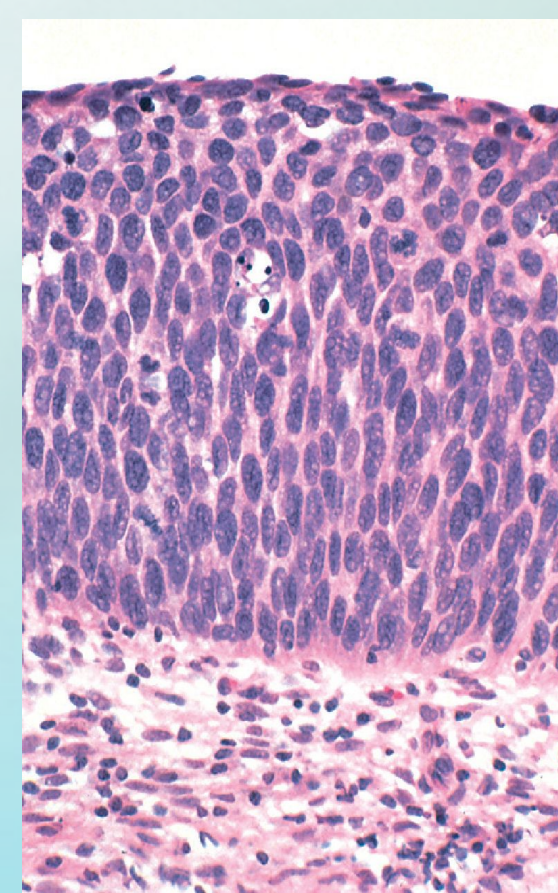
Normal



(CIN I)



(CIN II)



(CIN III)

□ **Spectrum of CIN:** normal squamous epithelium for comparison; (CIN I); dysplastic changes (nuclear atypia characterized by nuclear enlargement, hyperchromasia, coarse chromatin granules, and variation in nuclear size and shape) **in the lower third** of the squamous epithelium and koilocytotic change in the superficial layers of the epithelium); (CIN II); dysplastic changes **extends to the middle third** of the epithelium, The superficial layer in some cases shows the koilocytotic changes. (CIN III); dysplastic changes **affect all layers of the epithelium**. Koilocytotic change usually is absent.

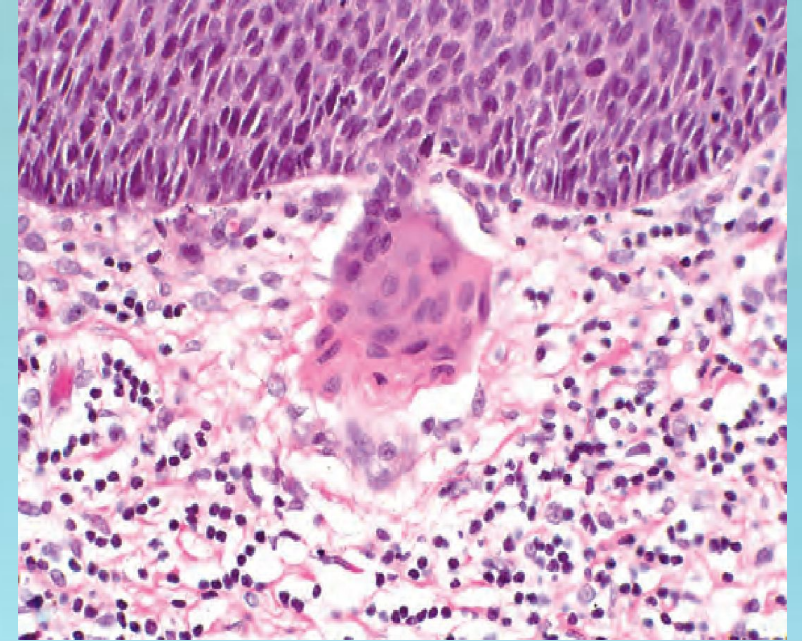
□ The current *Bethesda system* divides the precancerous lesions into only two groups:

- Low-grade SIL (LSIL): equivalent (CIN I)
- High-grade SIL (HSIL): equivalent (CIN II) or (CIN III)

◆ Natural history of squamous intraepithelial lesions

Lesion	Regress	Persist	Progress in 10 years
LSIL (CIN I)	60%	30%	10% to HSIL
HSIL (CIN II, III)	30%	60%	10% to carcinoma

- With time, dysplastic changes become more atypical, but the alterations are confined to the epithelial layer. These changes constitute *carcinoma in situ*.
- The next stage is *invasive carcinoma* (the basement membrane is no longer intact and atypical/malignant epithelial cells *invade deeply into the stroma*)
- **Note:**
 - The above progression sequences do not occur in all the cases.
 - **Cervical cytology** and **cervical colposcopy** remain the basis of cervical cancer prevention.



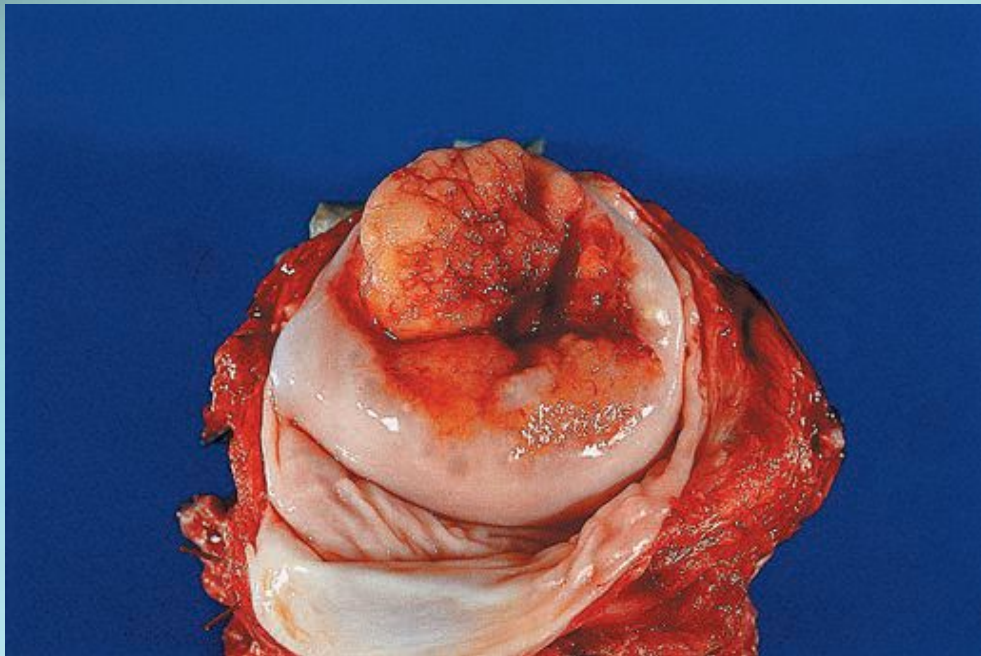
Early invasion in squamous cell carcinoma showing an invasive nest breaking through the basement membrane of a high-grade squamous intraepithelial lesion.

❑ Malignant: Invasive Carcinoma of the Cervix

- Worldwide , cervical cancer is the **fourth cancer** in female after breast, colorectal and lung. It is one of the **major** causes of cancer-related deaths in women in the **developing world**. While, **in developed countries** HPV incidence and prevalence is decreasing due to **screening programs** and **vaccination** leading to dramatic **improvement** in patient survival due to early diagnosis , detection of precancerous conditions by using **Pap smear** and **treatment** confirming that the cervical carcinoma is a preventable disease.
- **The most common cervical carcinomas are:**
 1. **Squamous cell carcinomas (75%)**, followed by
 2. **Adenocarcinomas and mixed adenosquamous carcinomas (20%)** and
 3. **Small cell neuroendocrine carcinomas (<5%)**.
- All of these types of carcinomas are **associated with high-risk HPV**.
- **Age:** Squamous cell carcinoma has a peak incidence at the age of **about 45 years**, some 10 to 15 years after detection of precursor SIL.

Gross:

Invasive carcinomas of the cervix develop in the region of the **transformation zone** and range from **invisible** microscopic foci of early stromal invasion to grossly visible **exophytic** ulcerating masses or **deeply infiltrative** cancer that **encircle the external os**.



The tumor is a **red to tan to yellow mass** that is **exophytic** (growing outward and extending above the surrounding normal smooth epithelium).

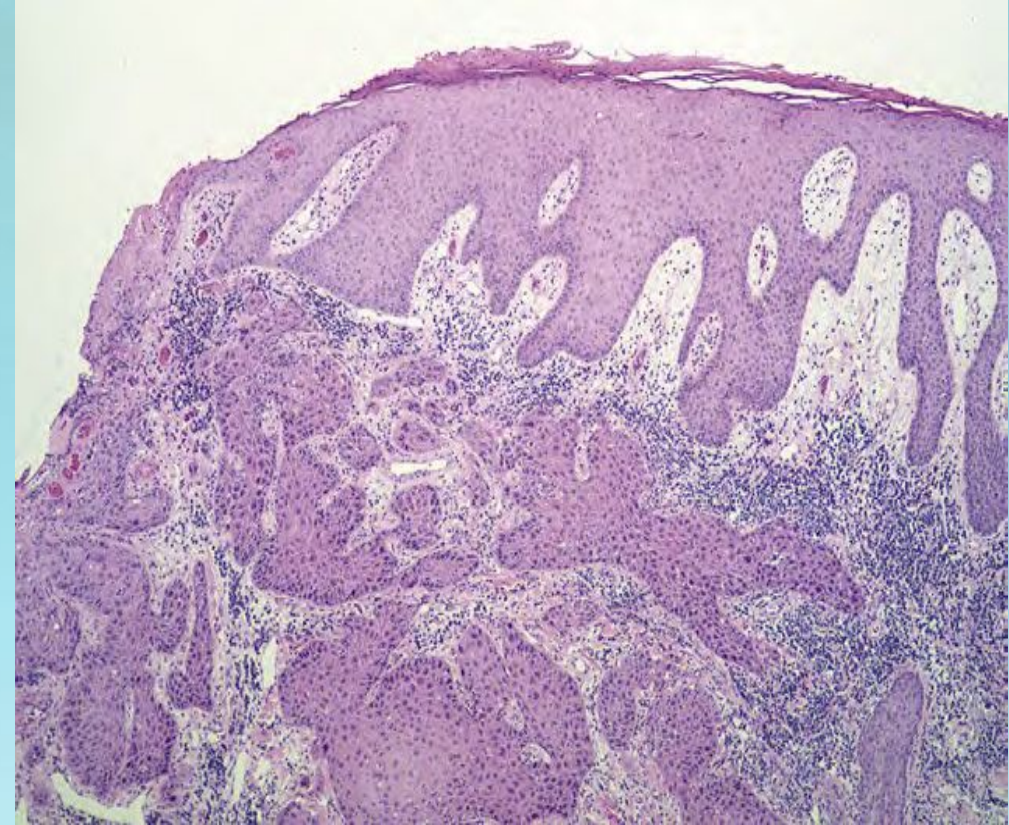


This total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) on sectioning in half shows an **advanced cervical squamous cell carcinoma**

Mic.:

Squamous cell carcinoma is composed of **nests of malignant squamous epithelium, either keratinizing or nonkeratinizing, which invade the underlying cervical stroma**

- **Grading:** cervical carcinomas are **graded from 1 to 3** based on the degree of cellular differentiation
- **Staging:** from 1 to 4 depending on the extent of clinical spread.



□ Clinically:

- Vaginal bleeding, leukorrhea (whitish vaginal discharge), painful coitus (dyspareunia), postcoital bleeding or dysuria.

□ Treatment:

- Early invasive carcinomas (microinvasive carcinomas) can be treated by **cervical cone excision**; most other invasive carcinomas require **hysterectomy with LN dissection +/- radiation and chemotherapy**

□ Prognosis:

- Depends on stage of cancer at diagnosis, and to some degree, histologic subtype (small cell neuroendocrine carcinoma have a very poor prognosis).
- Advanced cervical carcinoma **spreads by** (i) **direct extension** to contiguous tissues, including paracervical soft tissue, bladder, ureters, rectum and vagina (ii) **lymphovascular invasion** to lymph nodes and (iii) **distant metastases**.

