Pathology of Lower Female Genital Tract

Nisreen Abu Shahin, MD

Professor of pathology

University of Jordan, School of Medicine

Vulvar Diseases- Topics

NON-NEOPLASTIC (MORE COMMON):

LICHEN SCLEROSUS
LICHEN SIMPLEX CHRONICUS
CONDYLOMA ACCUMINATUM

NEOPLASTIC (LESS COMMON):

DYSPLASIA (VIN)
VULVAR CANCER

Pathology of Lower Female Genital Tract

- **Vulvar Diseases:**

- Include non-neoplastic and neoplastic diseases.
- The neoplastic diseases are much less common.
- Of the neoplastic disorders, **squamous cell carcinoma is the most common.**

Non-neoplastic Vulvar Diseases

- **Lichen sclerosus**
- **Lichen Simplex Chronicus**
- **Condyloma accuminatum**

Skin condition that affects the vulva, mainly in post menopausal women.

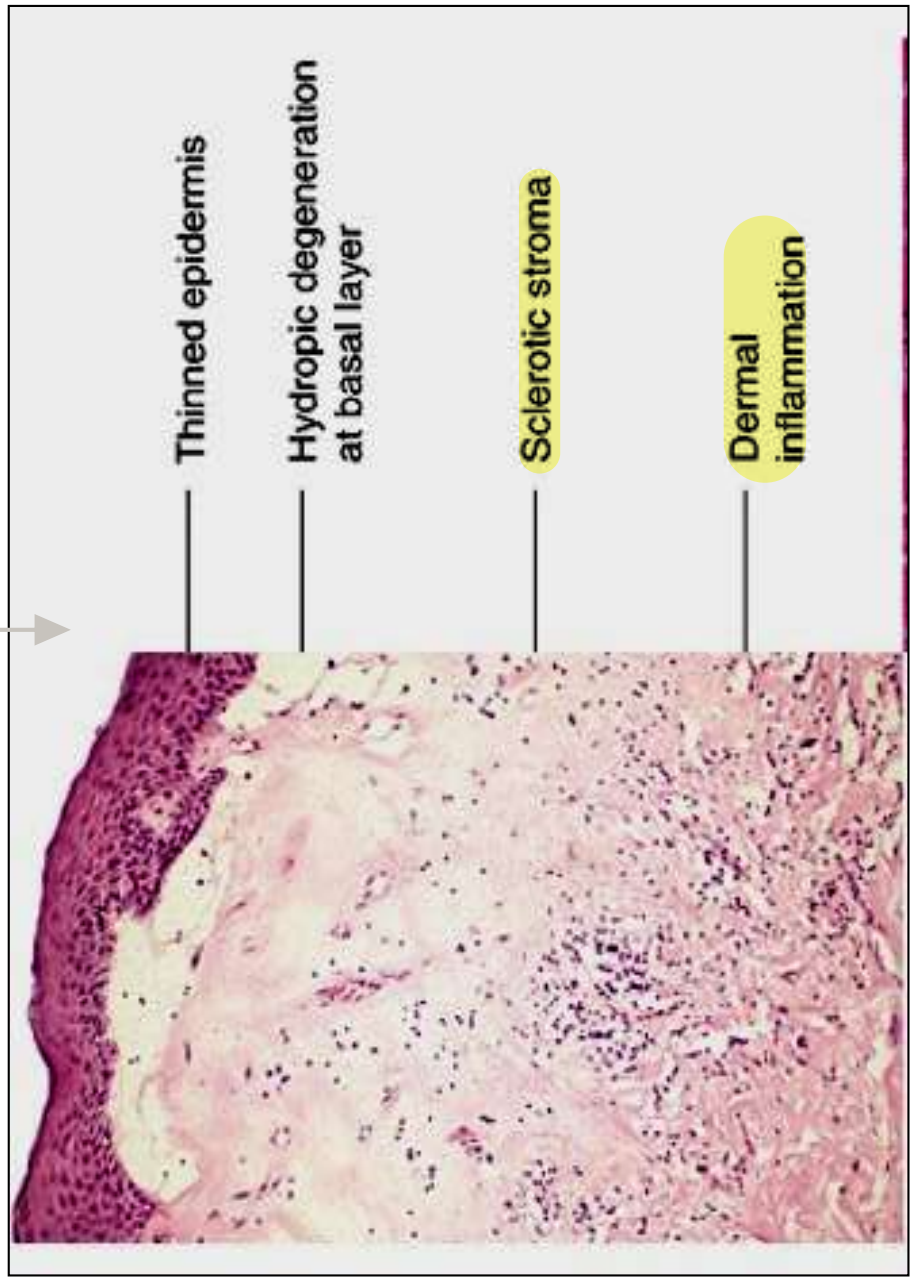
Lichen sclerosus

- **postmenopausal** women.
- white plaques; thinned out skin

- Microscopically: thinning of epidermis, disappearance of rete pegs, hydropic degeneration of basal cells

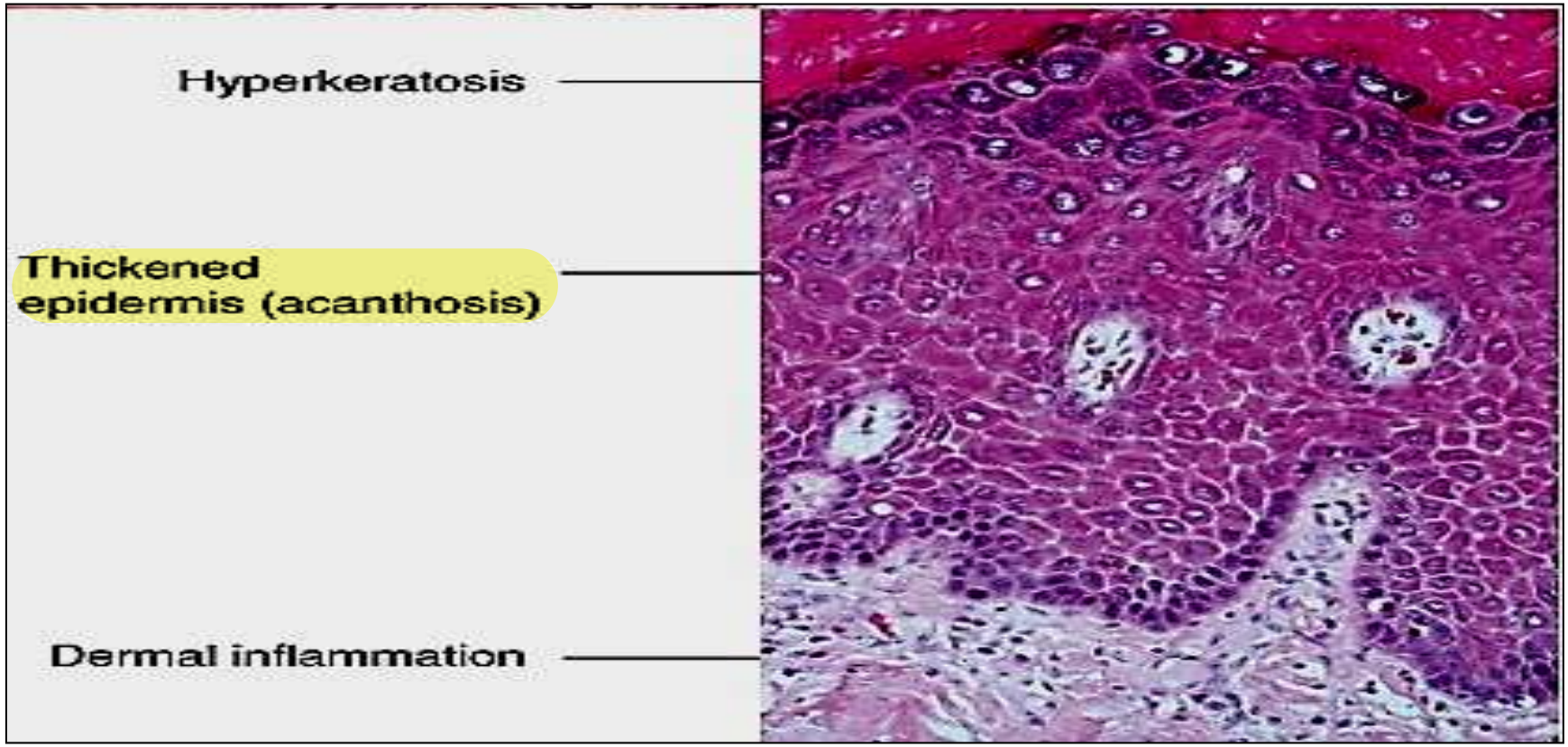
- pathogenesis: uncertain, (?)autoimmune

- is not pre-malignant by itself



Lichen Simplex Chronicus

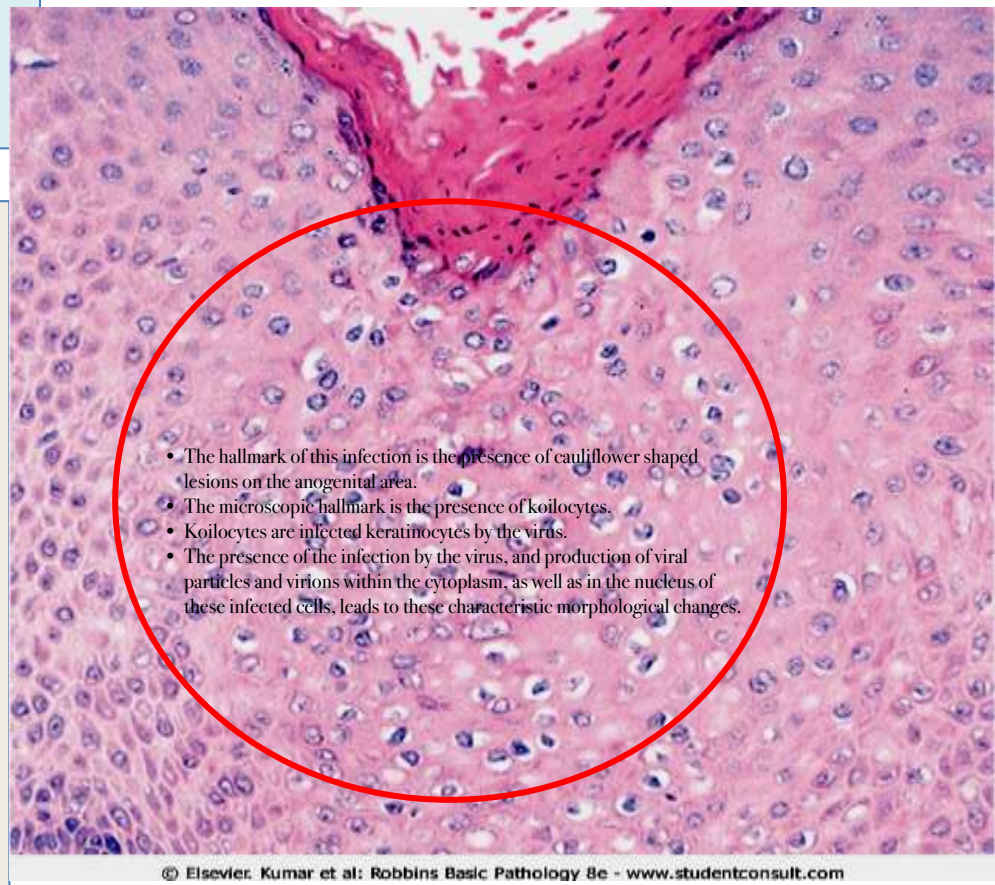
- end result of many inflammatory conditions
- Clinical term: leukoplakia (whitish plaque) This term is used to describe what's happening in the skin.
- epithelial thickening, hyperkeratosis, epithelium shows no atypia. Along with dermal inflammation.
- **no increased predisposition to cancer**, however, maybe present at margins of adjacent cancer.



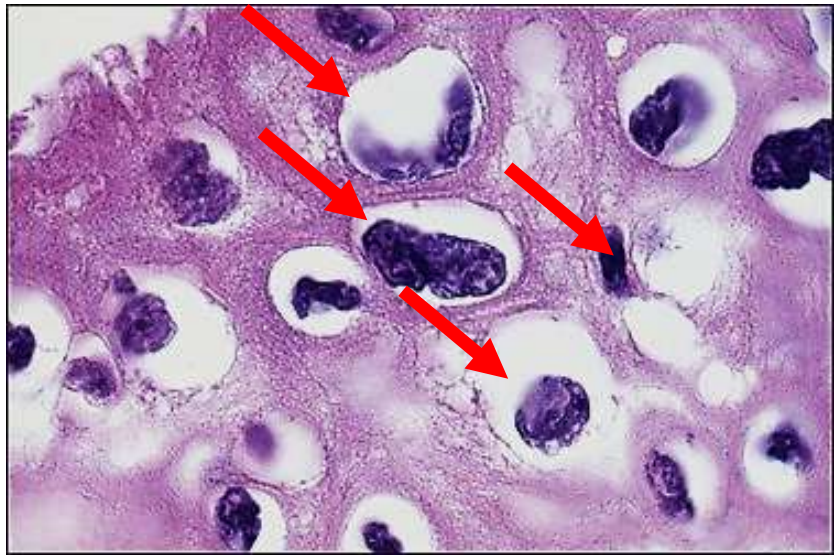
Condyloma

Condyloma acuminatum.

- Anogenital warts Both in females and males.
- Infection by HPV (HPV type 6 and HPV type11, mainly)
- koilocytosis (perinuclear cytoplasmic vacuolization + nuclear pleomorphism).
- HPV types isolated from cancers differ from those found in condylomas. Thus viruses that cause condyloma are called low risk HPV types.
- Condyloma is **not** precancerous by itself.



- Cells are abnormal.
- Nucleus is abnormal, larger than normal, with irregular outlines and is hyperchromatic.
- Have perinuclear cytoplasmic vacuoles/halos.
- These changes are called koilocytosis, represent the hallmark of this infection.



Neoplastic Vulvar Diseases

1- Vulvar Intraepithelial Neoplasia (VIN)

2- Invasive Carcinoma of Vulva:

- Types include:

Squamous Cell Carcinoma (most common);
adenocarcinomas; melanomas; basal cell carcinomas

HPV & Female Genital Diseases

- A common sexually transmitted infection of genital tract.
- Many different types of HPV including low risk and high risk types (risk here is for malignancy).
- Low risk HPV → anogenital warts (condylomas)
- High risk types → intraepithelial dysplasia and invasive cancers in all parts of lower female genital tract (vulva; vagina; and cervix) as well as male genital tract.
- Condylomas are similar in all these organs. Regardless of their location in the female genital tract, similar in pathogenesis and morphology.
- Intraepithelial dysplasia and invasive cancers produced by HPV are similar in pathogenesis and morphology in all of these locations.

HPV & Female Genital Diseases

- high-risk HPV types (16, 18, 45, and 31) account for majority of precancerous lesions and invasive anogenital cancers
- peak age of **intraepithelial** neoplasia is about 30 years, whereas invasive cancer is about 45 years (progression to invasion needs 10-15 yr).
- HPV can be detected by molecular methods in nearly all precancerous lesions and invasive HPV-related anogenital neoplasms.

Intraepithelial dysplasia or neoplasia.

- **High** risk HPV (especially HPV 16 and 18) usually integrate into the host genome and express large amounts of certain viral proteins called **E6** and **E7** proteins, which block or inactivate tumor suppressor genes *p53* and *RB*, respectively. → accumulation of **mutations** and DNA damage eventually leads to **malignancy**

Proteins are the important factors in the progression to invasive cancers.

- recently introduced **HPV vaccine** used in USA and Europe is effective in preventing HPV infections and hence cervical cancers and other anogenital HPV-related cancers.

Intraepithelial Neoplasia (IN)- concepts:

- High risk HPV causes mutations in cells

And these mutations cause the development of dysplasia.

- Dysplasia is graded depending on extent of epithelial involvement:

"Dysplasia or intraepithelial neoplasia same thing."

*__IN I__: Mild dysplasia (<third of full epithelial thickness)

*__IN II__: Moderate dysplasia (up to 2/3 of full epithelial thickness)

*__IN III__: Severe dysplasia in full epithelial thickness (is equivalent to **carcinoma in situ**)

Cells are malignant (severely dysplastic) but still confined within the basement membrane, so the cells are not invasive yet.

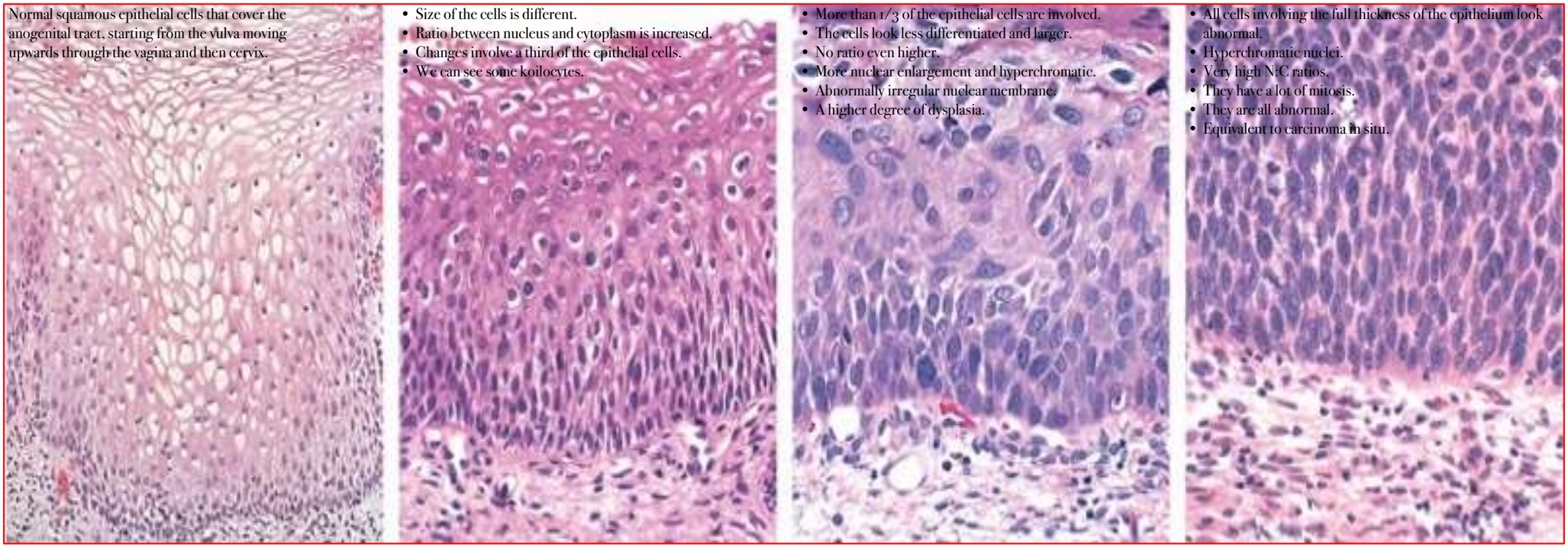
Why are we discussing intraepithelial neoplasia without any classification into vulva, vagina or cervix?

Same concept and similar morphology in all lower genital tract organs.

Same pathogenesis which is high risk HPV infection, also same grades, the only difference would be the nomenclature of the lesion.

Under the microscope we can't distinguish what are these changes if we look at the difference between the cells

Dysplasia = increased N/C ratio, nuclear enlargement, hyperchromasia, and abnormal nuclear membranes



Normal	IN 1	IN 2	IN 3
Vulvar dysplasia:	VIN 1	VIN 2	VIN 3
Vaginal dysplasia:	VaIN 1	VaIN 2	VaIN 3
Cervical dysplasia:	CIN 1	CIN 2	CIN 3

Cervical intraepithelial neoplasia.

High-grade Intraepithelial Neoplasia and Carcinoma of Ano-genital Organs

- high grade IN= IN II or IN III.
- IN III = carcinoma in situ
- may be multiple foci, or it may coexist with an invasive lesion.
- IN may be present for many years before progression to cancer.
- ?genetic, immunologic, environmental influences (e.g., cigarette smoking or superinfection with new strains of HPV) determine the course.

Vulvar Squamous cell carcinoma SCC

there are two biologic forms:

1- Basaloid or poorly differentiated SCC

- most common (90%)
- relatively younger
- HPV-related (Types 16 and 18.)
- HPV lesions also in vagina and cervix.
- Poorly differentiated cells

2- Well-differentiated SCC

- Less common
- older women (60-70s).
- **Not** HPV-related
- Maybe found adjacent to lichen simplex or sclerosus
- well to moderately differentiated cells

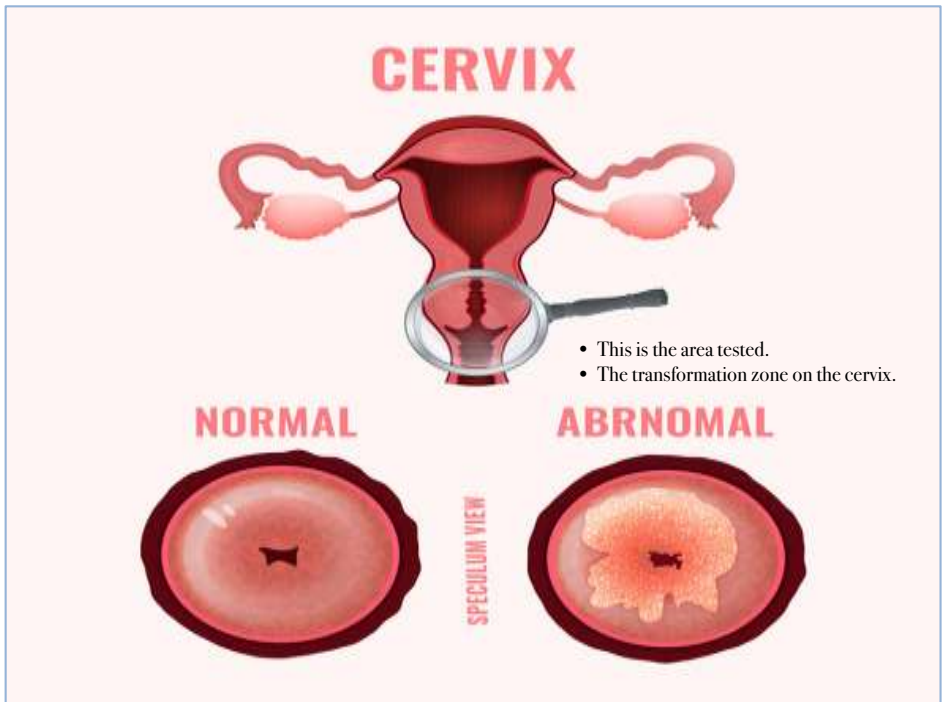
Cervical Diseases

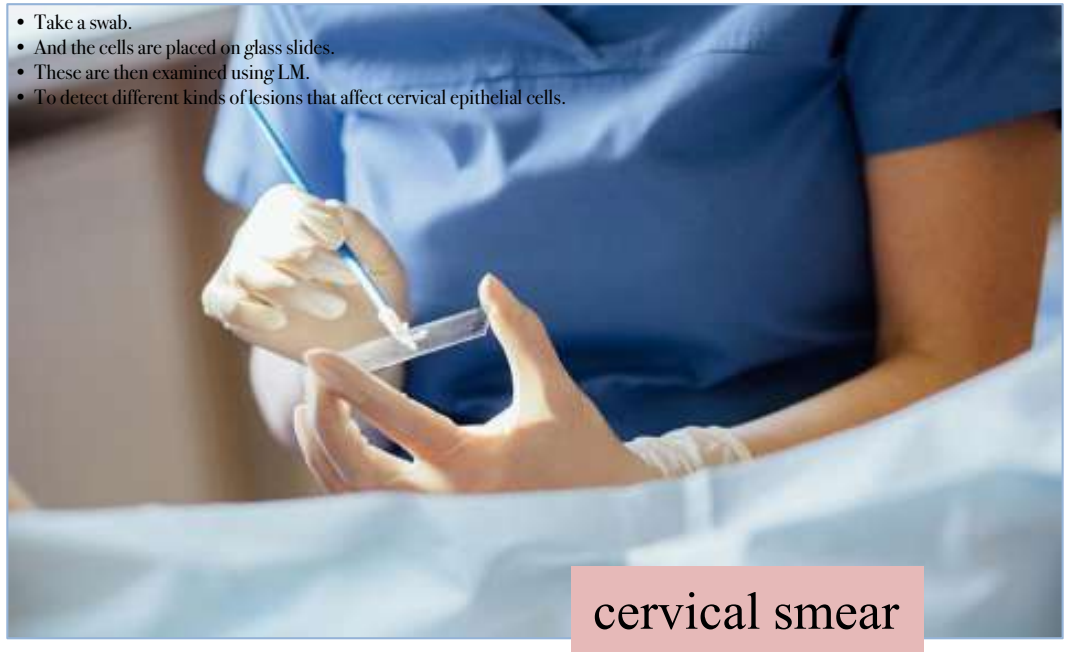
PAP SMEAR TEST

CERVICAL CANCER

Cervical Carcinoma

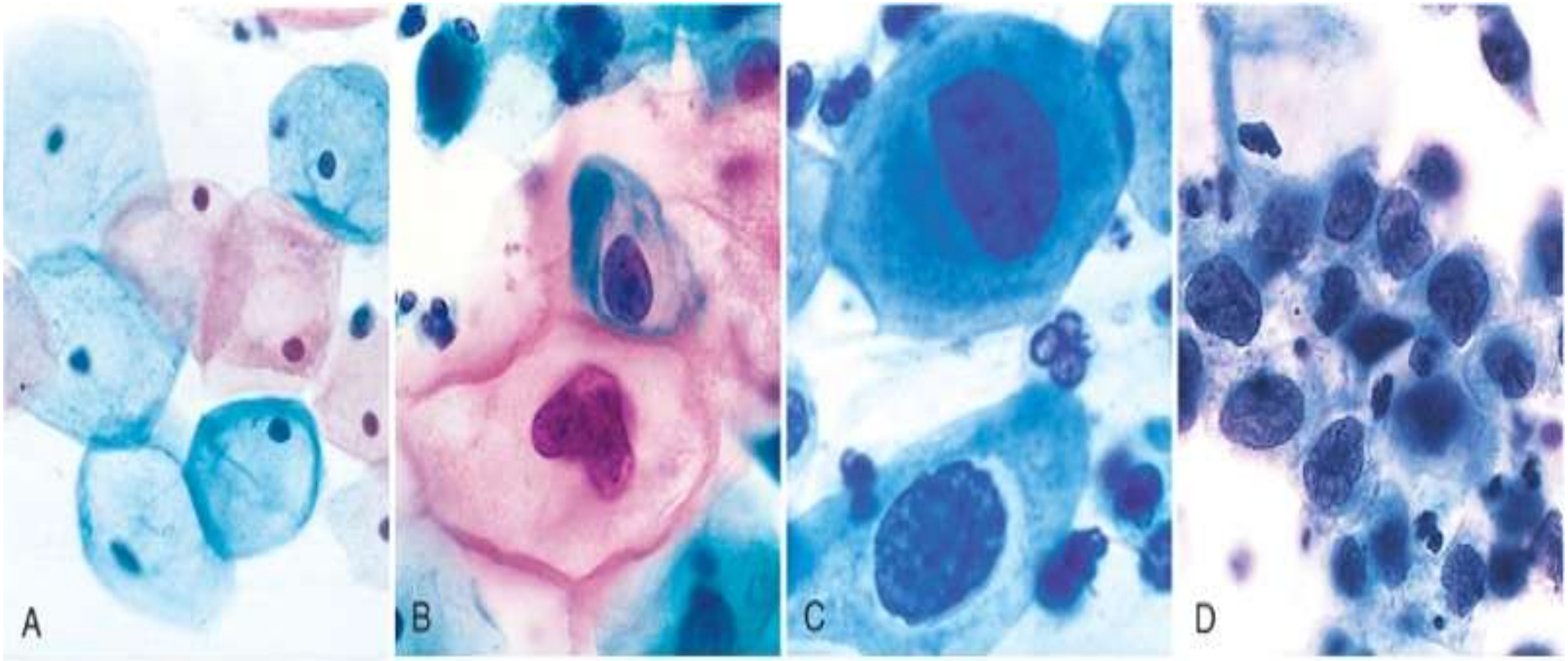
- Used to be the most frequent cancer in women
- Papanicolaou (Pap) cervical smear: a screening test for detection of HPV related lesions of the uterine cervix.
- Cervical cancer incidence dropped (early detection of pre-invasive and early cancer). It helped reduce cervical ca mortality by 99%.





cervical smear

Cervical Pap smear pictures

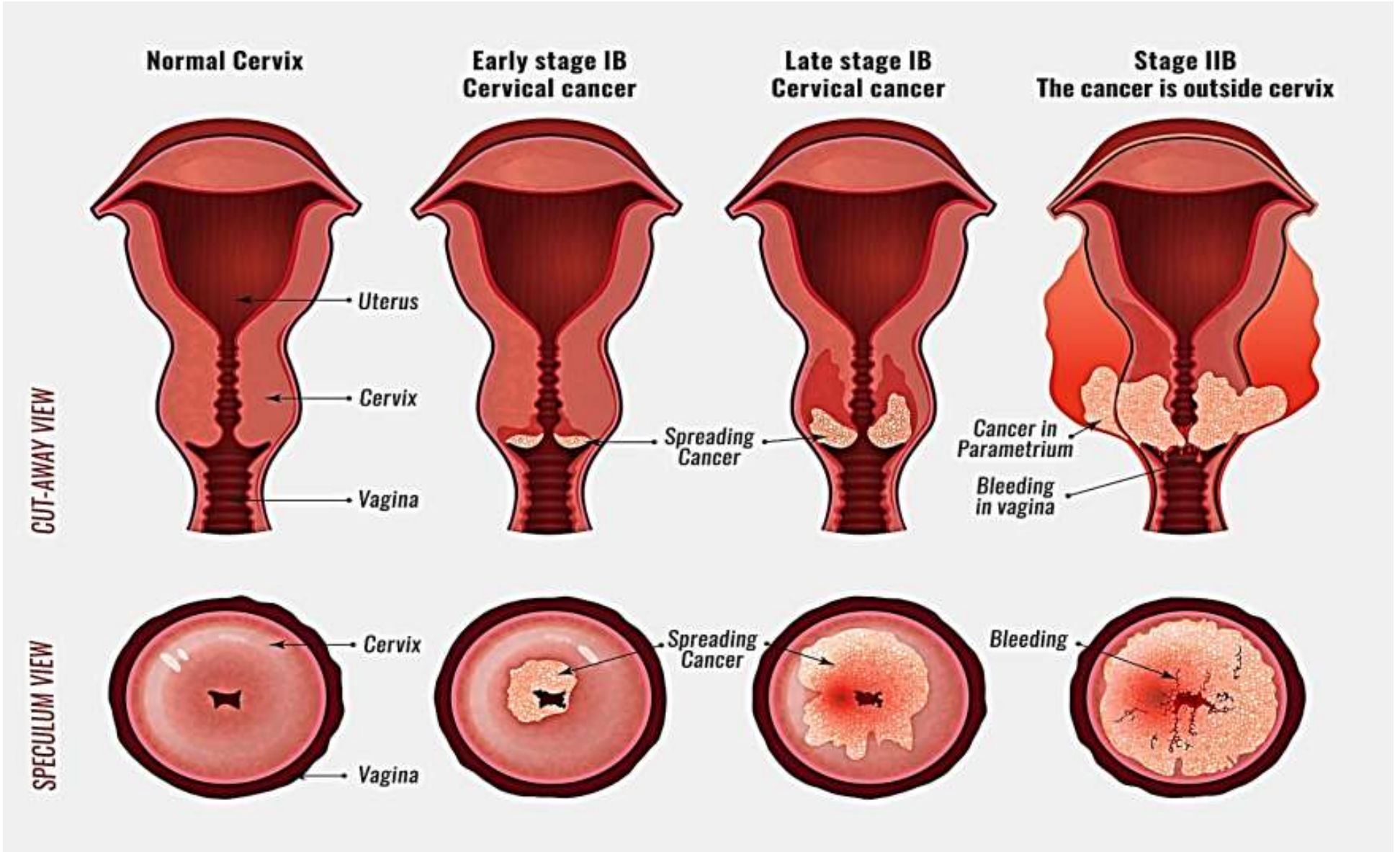


Normal **CIN I** **CIN II** **CIN III**

Cervical Cancer

- Types: most common are **SCC (75%),** followed by adenocarcinomas and adenosquamous carcinomas (20%), and neuroendocrine carcinomas (<5%).
- SCC now has peak incidence at 45 years, almost **10 to 15 years after detection of their precursors: cervical intraepithelial neoplasia (CIN)**

Cervical cancer stage is one of the most important prognostic factors



Clinical Aspects of Cervical Cancers

- CIN: treatment by **laser or cone biopsy**
- Invasive cancer: surgical excision
- 5-year survival drops with increased stage:

- Pre-invasive (CIN)→ 100%; That's why screen tests using Pap smear is very important in this regard.
- stage 1→ 90%;
- stage 2→82%;
- stage 3→ 35%;
- and stage 4→ 10%.

As we move more, meaning there is extensive spread and progression of the cancer, enlargement of the cancer, and spreading outside the cervix, all affect survival of the patient, dropping it significantly.

- Radiotherapy and Chemotherapy in advanced cases