

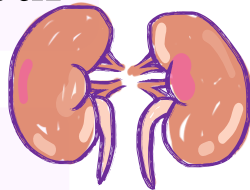
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



Pathology of Lower Female Genital Tract

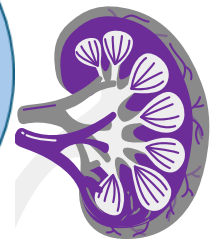
FINAL | Lecture 1

Written by: Awab Al-Hamdan
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﴿ قُلْ بِفَضْلِ اللَّهِ وَبِرَحْمَتِهِ ۖ فَبِذَلِكَ فَلْيَفْرَحُوا هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ ﴾





Pathology of Lower Female Genital Tract

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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

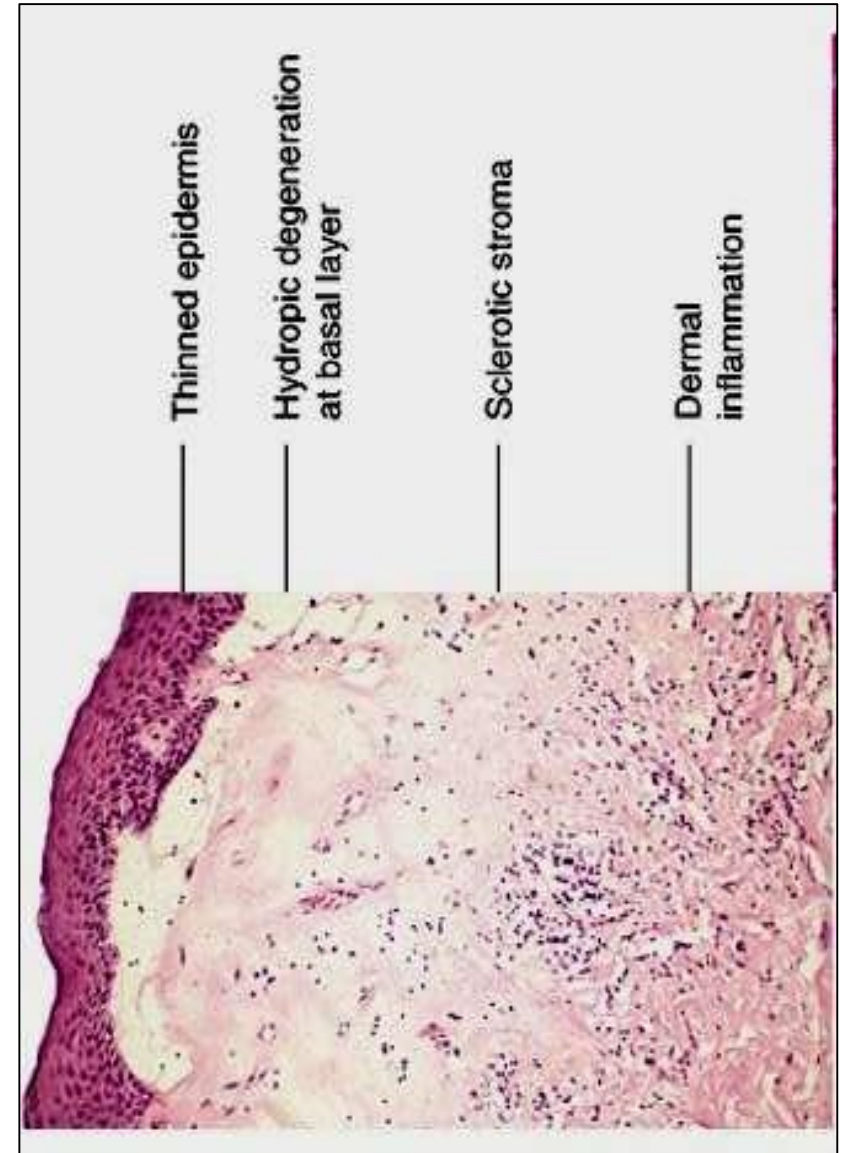
- **Vulvar Diseases:**
- Include non-neoplastic and neoplastic diseases.
- The neoplastic diseases are much less common.
- Of the neoplastic disorders, **squamous cell carcinoma is the most common.**

Non-neoplastic Vulvar Diseases

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

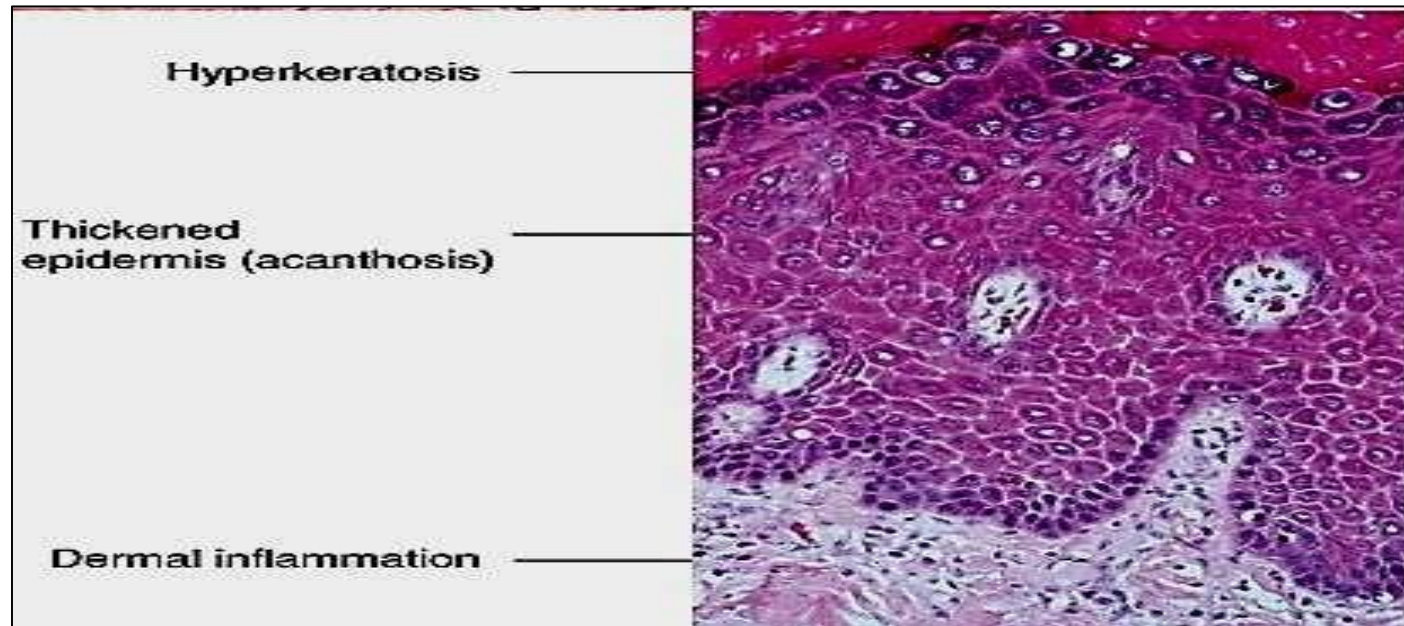
Lichen sclerosis

- **Postmenopausal** women are mainly affected.
- Grossly, white plaques; thinned out skin at the vulvar area.
- Microscopically: thinning of epidermis, disappearance of rete pegs (finger-like epithelial extensions at the epidermal-dermal junction), hydropic degeneration of basal cells, sclerotic stroma beneath the epidermis along with dermal inflammation.
- Pathogenesis: uncertain, (?)autoimmune
- is **not** pre-malignant by itself



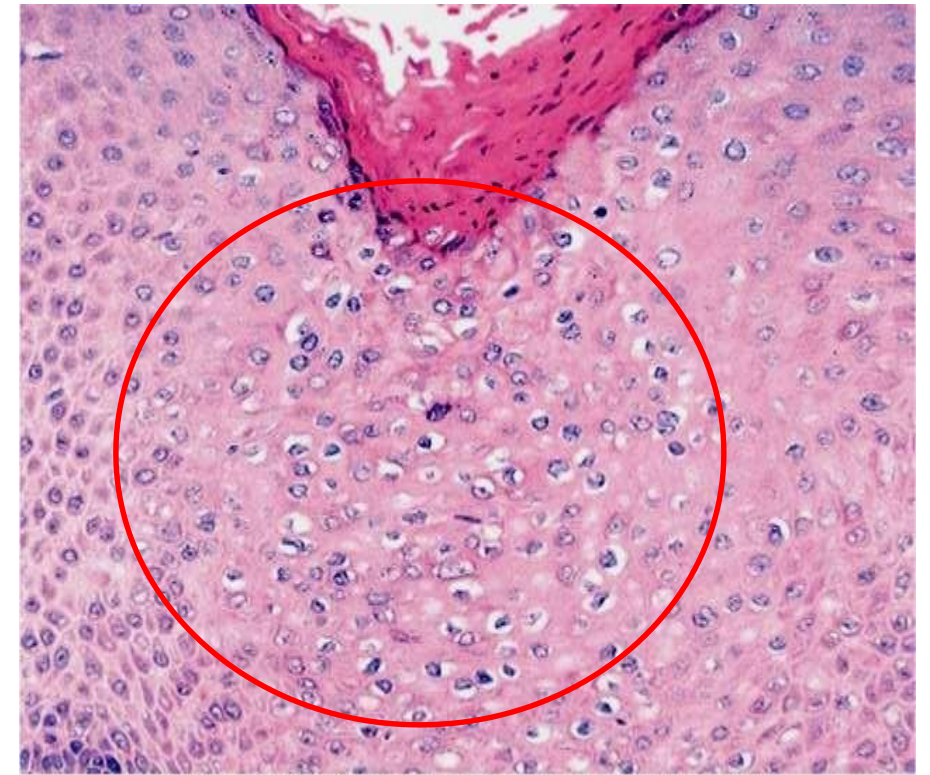
Lichen Simplex Chronicus

- End result of many inflammatory conditions that affect the vulva.
- **Clinical term: leukoplakia** (whitish plaque) on gross examination.
- Microscopically, epithelial thickening (acanthosis) unlike lichen sclerosis, hyperkeratosis (excessive keratin production), epithelium shows **no** atypia, along with dermal inflammation.
- **No increased predisposition to cancer**, however, maybe present at margins of adjacent vulvar cancer.

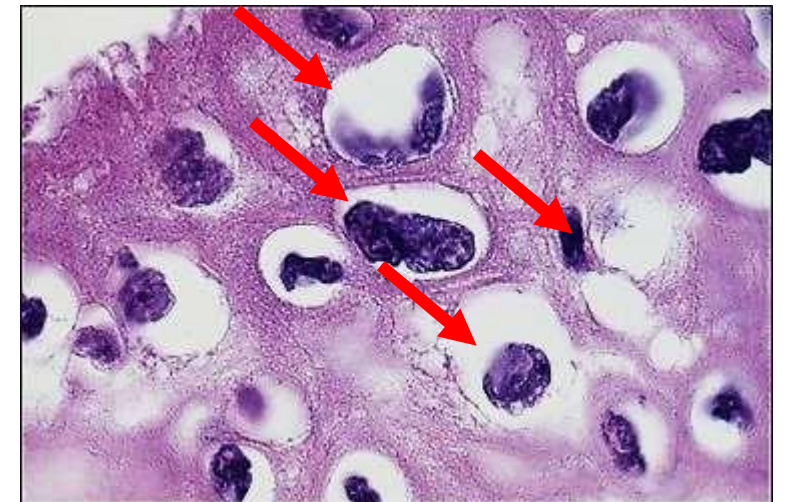


Condyloma

- Anogenital warts.
- Infection by HPV (HPV type 6 and HPV type 11, mainly)
- Cauliflower-like lesion on gross examination is the hallmark of this disease.
- Microscopically, **koilocytosis** (infected keratinocytes showing perinuclear cytoplasmic vacuolization + nuclear pleomorphism; large irregularly outlined hyperchromatic nuclei).
- HPV types isolated from **anogenital cancers (high-risk types)** differ from those found in condylomas (low-risk types).
- Condyloma is **not** precancerous by itself.



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Neoplastic Vulvar Diseases

1 Vulvar Intraepithelial Neoplasia (VIN); precancerous lesion that progresses to greater degrees of dysplasia and eventually to carcinoma in situ.

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 **in both males and females**.
- 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 their pathogenesis and morphology** in all these organs.
- Intraepithelial dysplasia and invasive cancers **within the anogenital tract** produced by HPV are similar in pathogenesis and morphology in all of these locations (**vulva, vagina and cervix**).

HPV & Female Genital Diseases

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

IN: intraepithelial neoplasia

- **High** risk HPV (especially HPV 16 and 18) usually integrate **their genome** into the host genome (**keratinocytes**) 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**
- E6 blocks p53 and E7 blocks RB.
- 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.

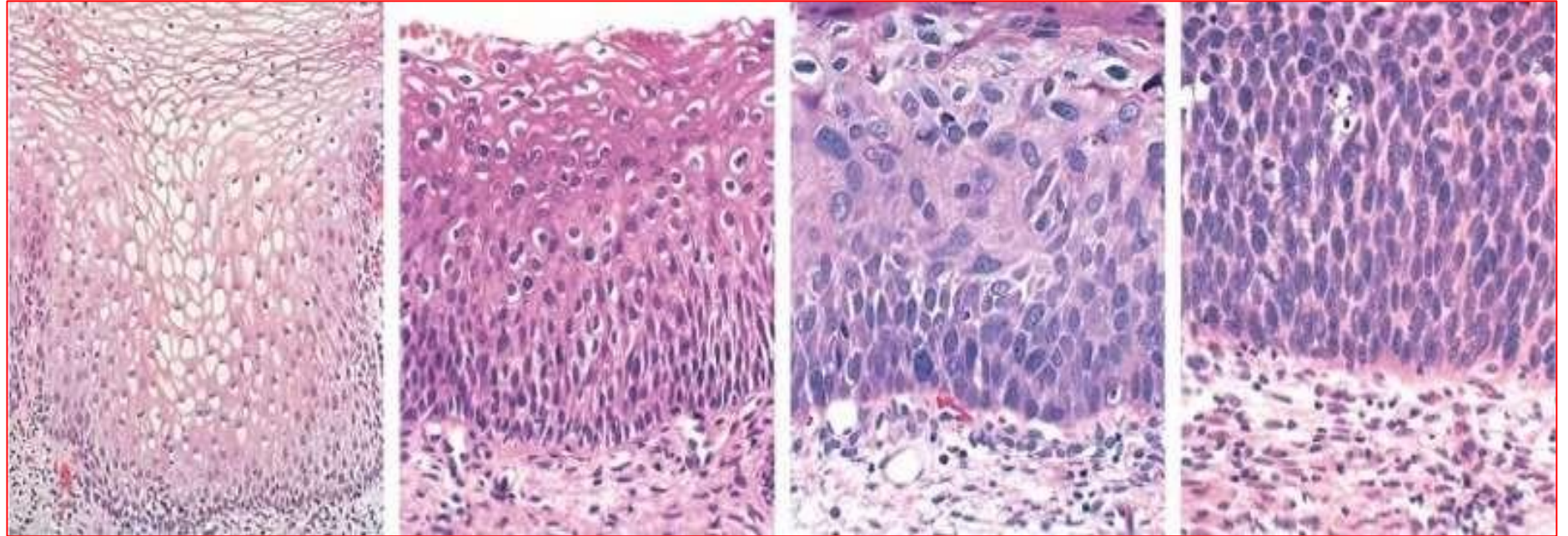
RB: retinoblastoma

Intraepithelial Neoplasia (IN)- concepts:

- High risk HPV causes mutations in cells
- Dysplasia is graded depending on extent of epithelial involvement:
 - ***IN I:** Mild dysplasia (<third of full epithelial thickness, usually within the deeper layers)
 - ***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**; non-invasive severely dysplastic and malignant lesion that remains confined to the basement membrane)

Same concept and similar morphology in all lower genital tract organs
(The same applies for vulva, vagina and cervix regardless of the location) .

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



Nomenclature depends on the site of dysplasia, but again, same morphology and pathogenesis regardless of the location.

Normal

IN 1

IN 2

IN 3

Vulvar dysplasia:

VIN 1

VIN 2

VIN 3

Vaginal dysplasia:

VaIN 1

VaIN 2

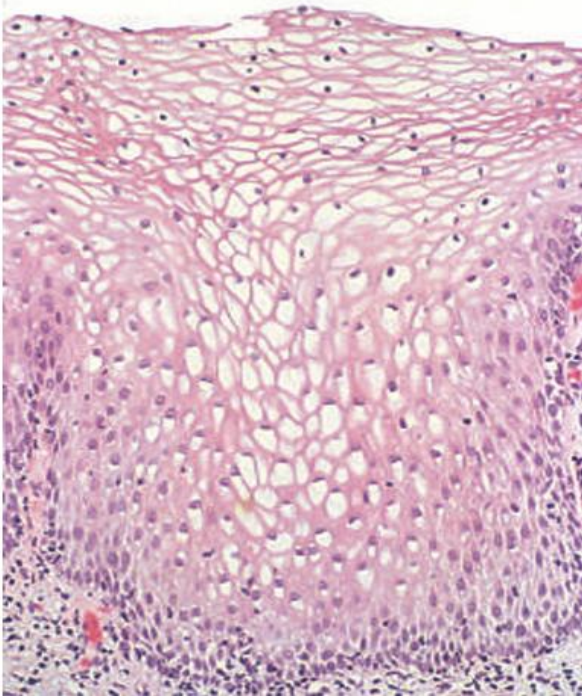
VaIN 3

Cervical dysplasia:

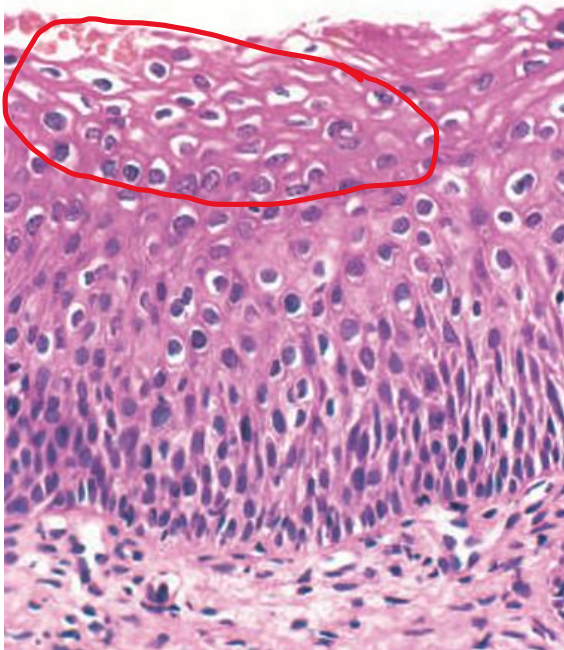
CIN 1

CIN 2

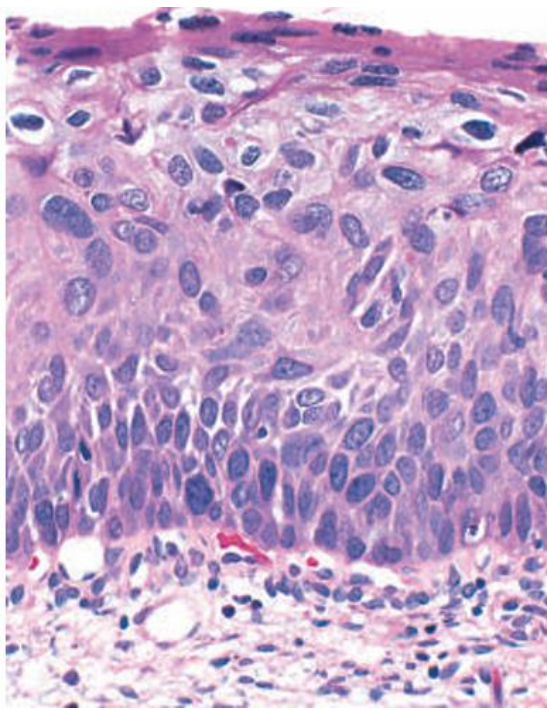
CIN 3



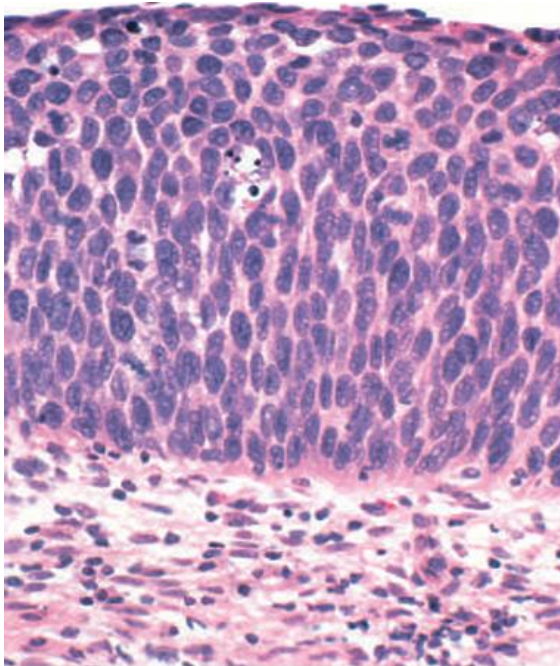
This represents normal stratified squamous epithelium of the female anogenital tract, starting from the vulva, through the vagina and into the **ectocervix** . Normal size of the cells and their dark blue nuclei with ordinary morphology and orientation.



Moving to the lowest grade of dysplasia, IN 1. The size of the cells is different, and the nuclear-to-cytoplasmic ratio (NC ratio) is greater than usual. these changes involve around only a third of the epithelial thickness. One can also appreciate koilocytes superficially as well (red circle).



Reaching the intermediate grade, IN 2. More than one third of the epithelial thickness is involved, less cellular differentiation, larger cells, even greater NC ratio than in IN1, more nuclear enlargement and hyperchromasia, with abnormal and irregular nuclear membranes being evident as well.



the highest and worst grade of dysplasia, IN 3. Here, all cells involving the full thickness of the epithelium share the same features already described, however, the NC ratio is the highest, and mitotic figures are also evident. As mentioned previously, this grade is equivalent to carcinoma in situ.

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, also might be present together, affecting the vagina and vulva for example.**
- **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
- ❖ HPV lesions also in vagina and cervix.
- ❖ Poorly differentiated cells
- ❖ This is the form which is what has been discussed so far.

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

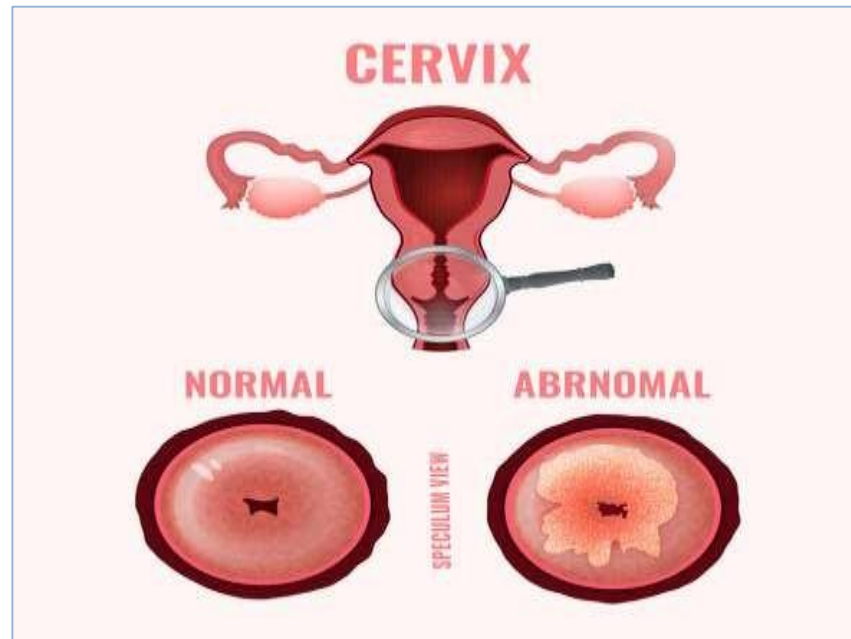
Cervical Diseases

PAP SMEAR TEST

CERVICAL CANCER

Cervical Carcinoma

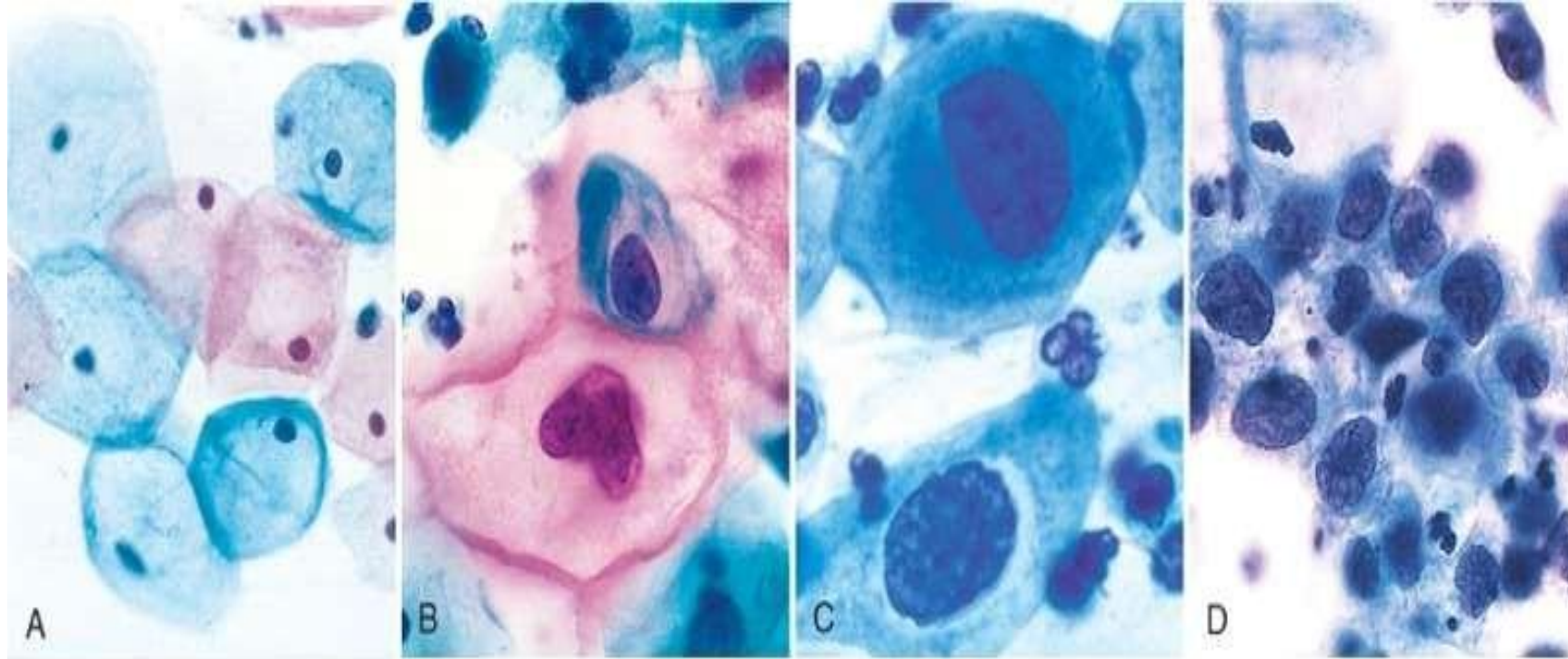
- Used to be the most frequent cancer in women
- Papanicolaou (Pap) cervical smear: a screening test for detection of HPV related lesions of the uterine cervix.
- Cervical cancer incidence dropped (early detection of pre-invasive and early cancer). It helped reduce cervical cancer mortality by 99%.



Pap smear test

- As shown in the image, the transformation zone of the cervix is examined, and we can see what a normal and abnormal (either non-invasive or invasive) speculum view of the cervix look like.
- The clinician takes a cervical swap, and the sample is placed on multiple glass slides, for it to be then processed and examined by a pathologist using a light microscope.
- This aids in the detection of these lesions that affect the cervical epithelial cells.

Cervical Pap smear pictures



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Normal

CIN I

CIN II

CIN III

CIN: Cervical
intraepithelial
neoplasia

These are koilocytes, as shown by the perinuclear halo, as well as the abnormal and irregular nucleus shape.

The NC ratio is higher, the cell is becoming more abnormal, and chromatin is darkening (hyperchromasia)

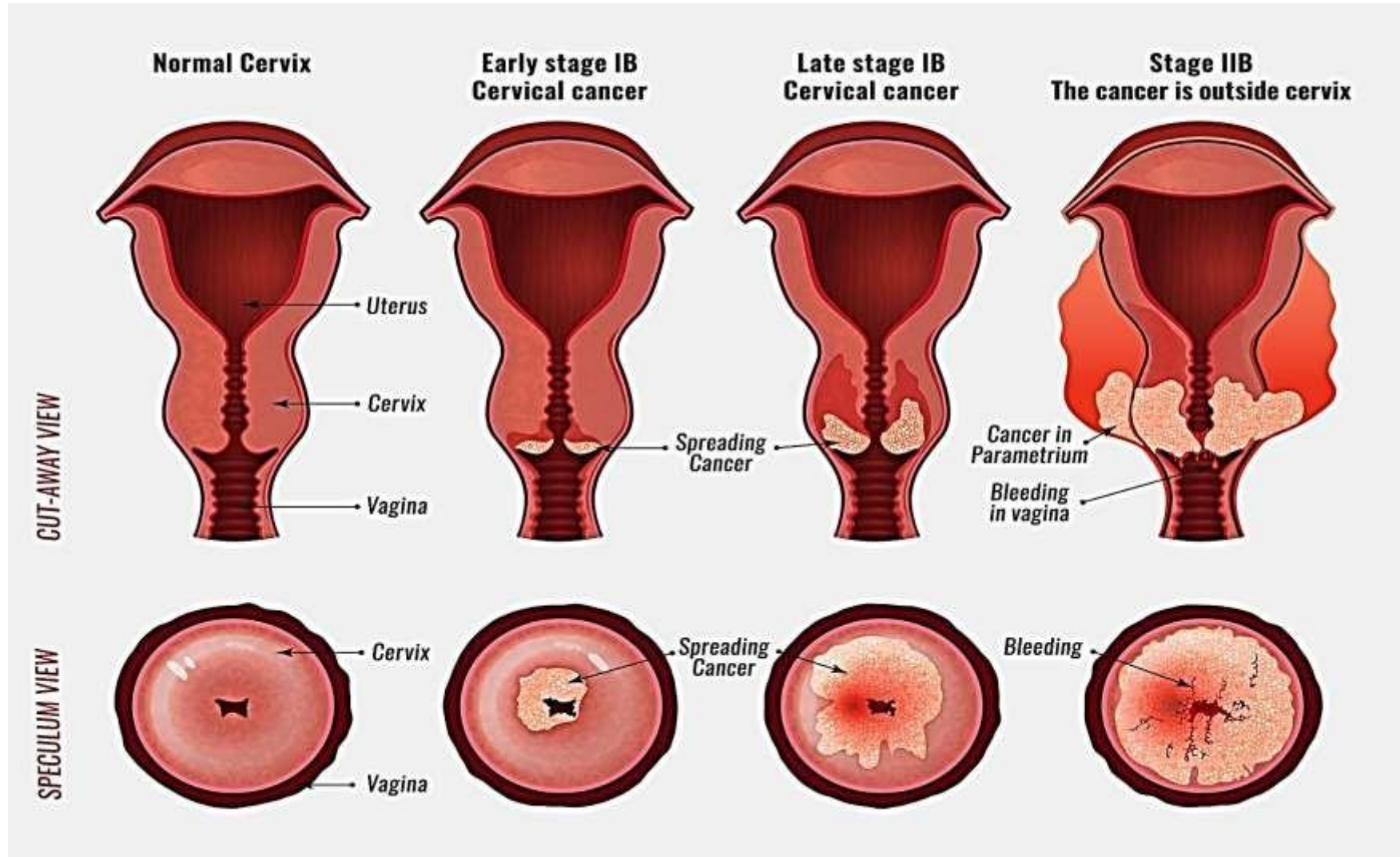
Even greater NC ratio (little cytoplasm and large nucleus), and very abnormally looking chromatin.

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 (the extent of spread) is one of the most important prognostic factors

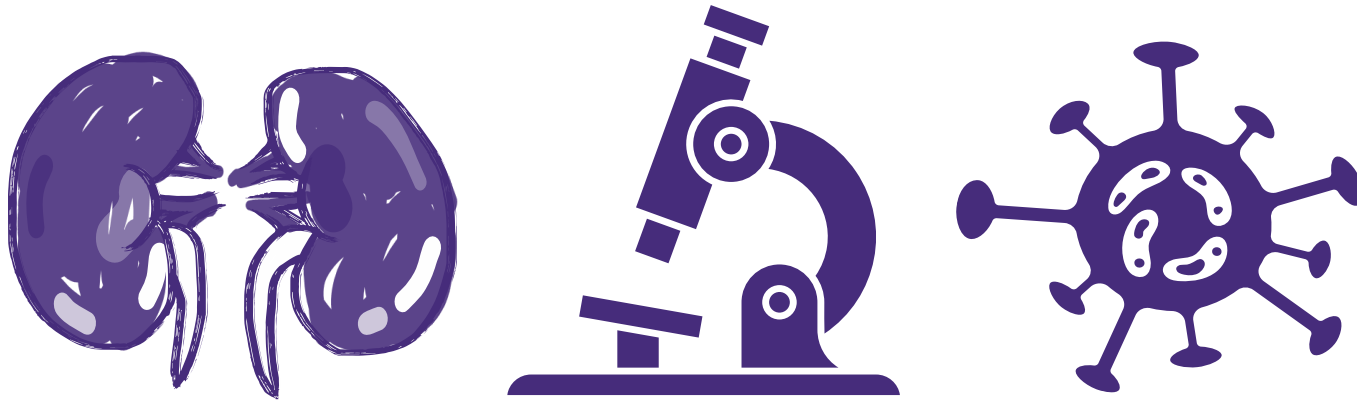
The higher the stage, the more the growth, spread and invasion of adjacent structures and potential metastasis



Clinical Aspects of Cervical Cancers

- CIN: treatment by **laser or cone biopsy** (surgical procedure)
- Invasive cancer: surgical excision of the cervix
- 5-year survival drops with increased stage:
 - Pre-invasive (CIN) → 100%;
 - stage 1 → 90%;
 - stage 2 → 82%;
 - stage 3 → 35%;
 - and stage 4 → 10%.
- Radiotherapy and Chemotherapy in advanced cases

CIN: Cervical intraepithelial neoplasia



PATHOLOGY
QUIZ
LECTURE 1

External Resources

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