Pathology of Lower Female Genital Tract

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- **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**

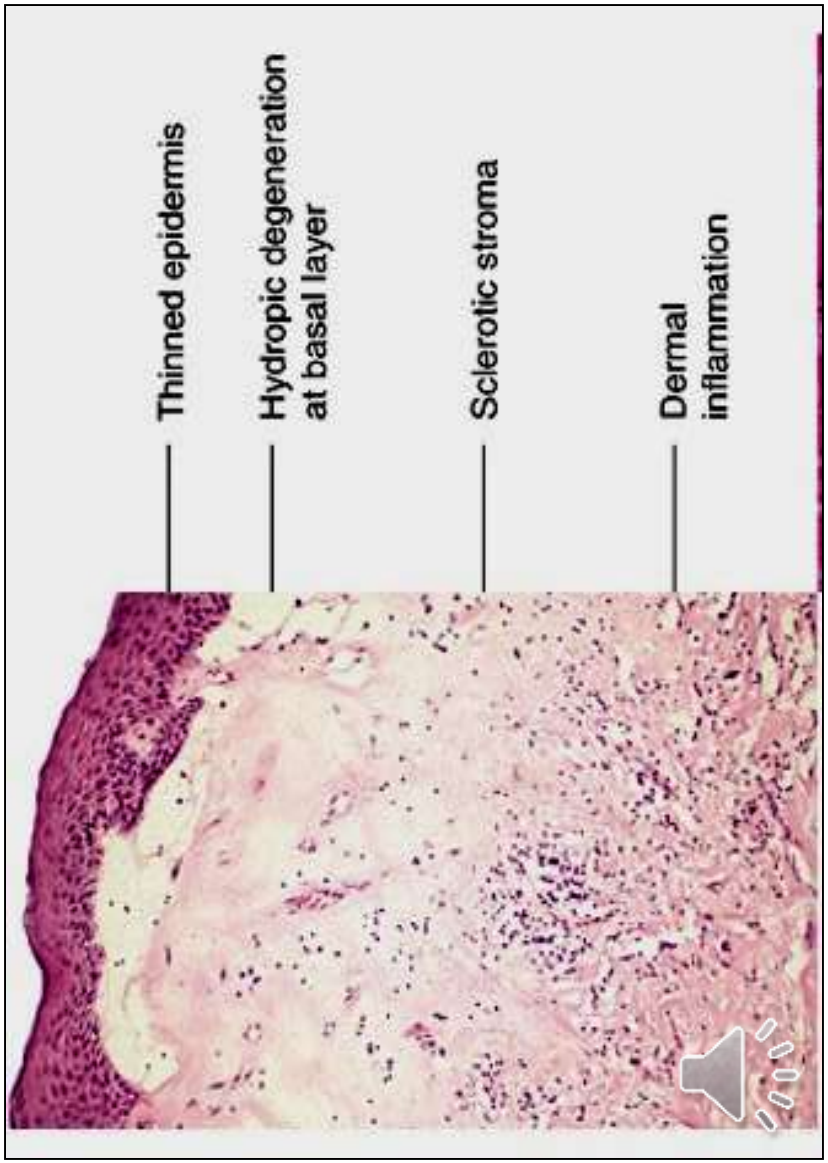
Lichen sclerosus

- postmenopausal women.
- smooth, white plaques; thinned out skin

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

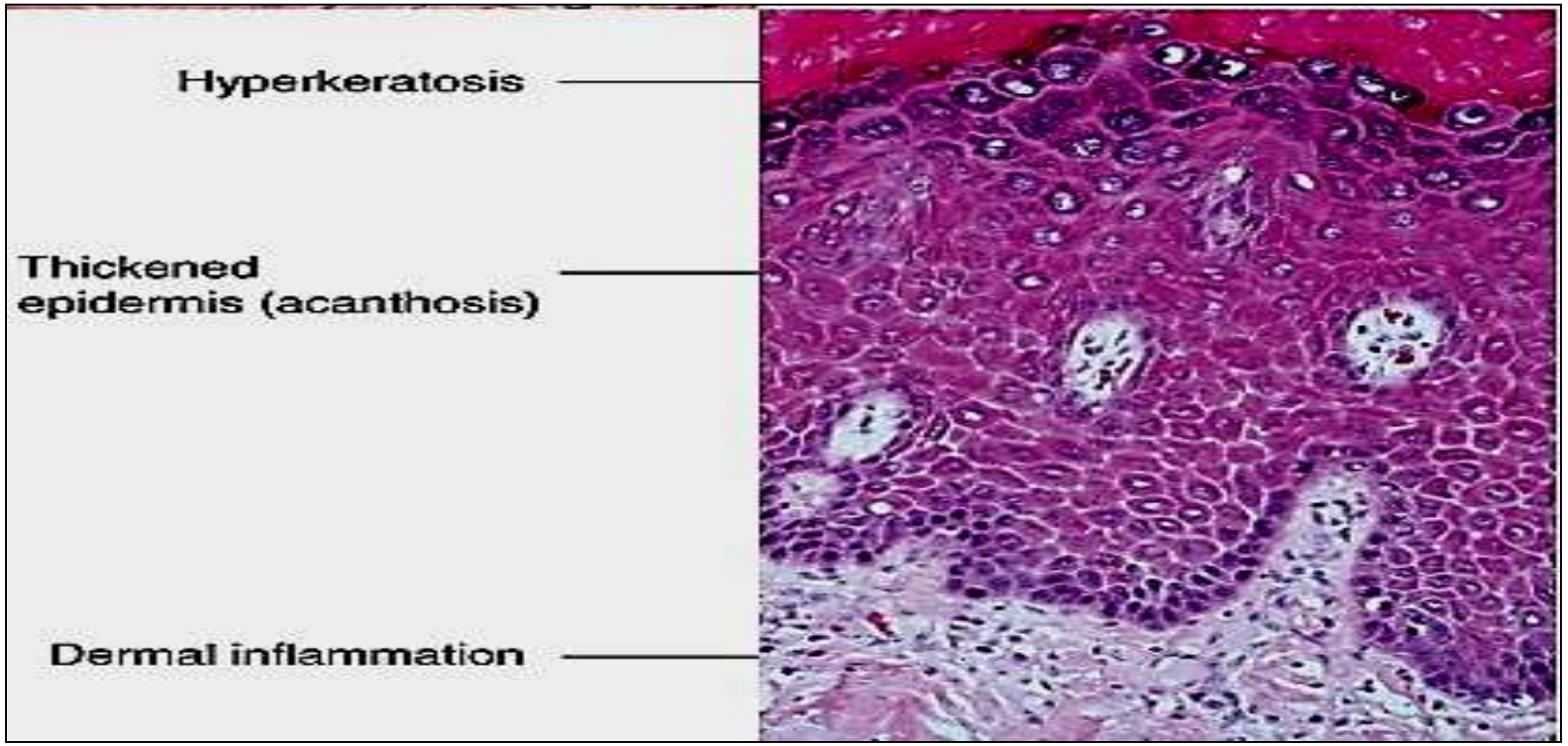
- pathogenesis: uncertain, (?)autoimmune

- lichen sclerosus is not pre-malignant by itself



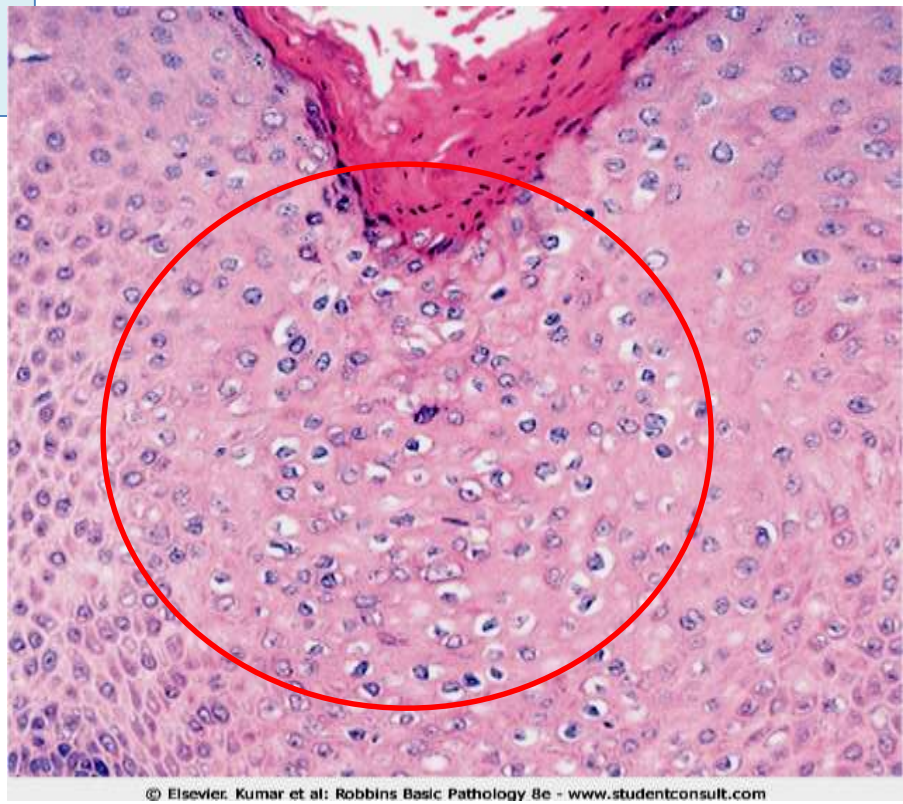
Lichen Simplex Chronicus

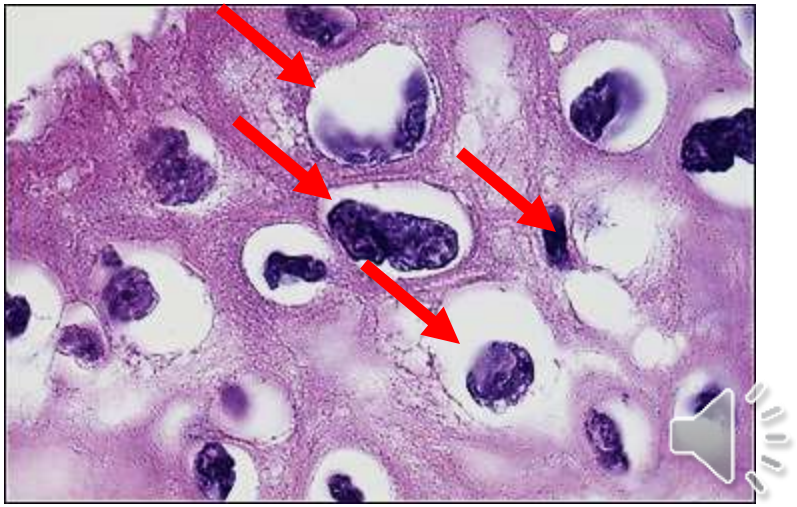
- end result of many inflammatory conditions
- Clinical term: leukoplakia (whitish plaque)
- epithelial thickening, hyperkeratosis, epithelium shows no atypia.
- **no increased predisposition to cancer**, however, maybe present at margins of adjacent cancer.



Condylomas

- Anogenital warts (HPV type 6 and HPV type11)
- koilocytosis (perinuclear cytoplasmic vacuolization + nuclear pleomorphism).
- HPV types isolated from cancers differ from those found in condylomas.
- Condyloma is **not** precancerous by itself.





Neoplastic Vulvar Diseases

1- Vulvar Intraepithelial Neoplasia (VIN)

2- Invasive Carcinoma of Vulva:

Squamous Cell Carcinoma (most common);

adenocarcinomas, melanomas, or basal cell carcinomas

HPV & Female Genital Diseases

- A common sexually transmitted infection of the genital tract.
- Many different types including low risk and high risk (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)
- Condylomas are similar in all these organs.
- Intraepithelial dysplasia and invasive cancers produced by HPV are similar in pathogenesis and morphology in all 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 anogenital neoplasms.

- **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**

- 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)- consepts:

- High risk HPV causes mutations in cells → Dysplasia is graded depending on extent of epithelial involvement:

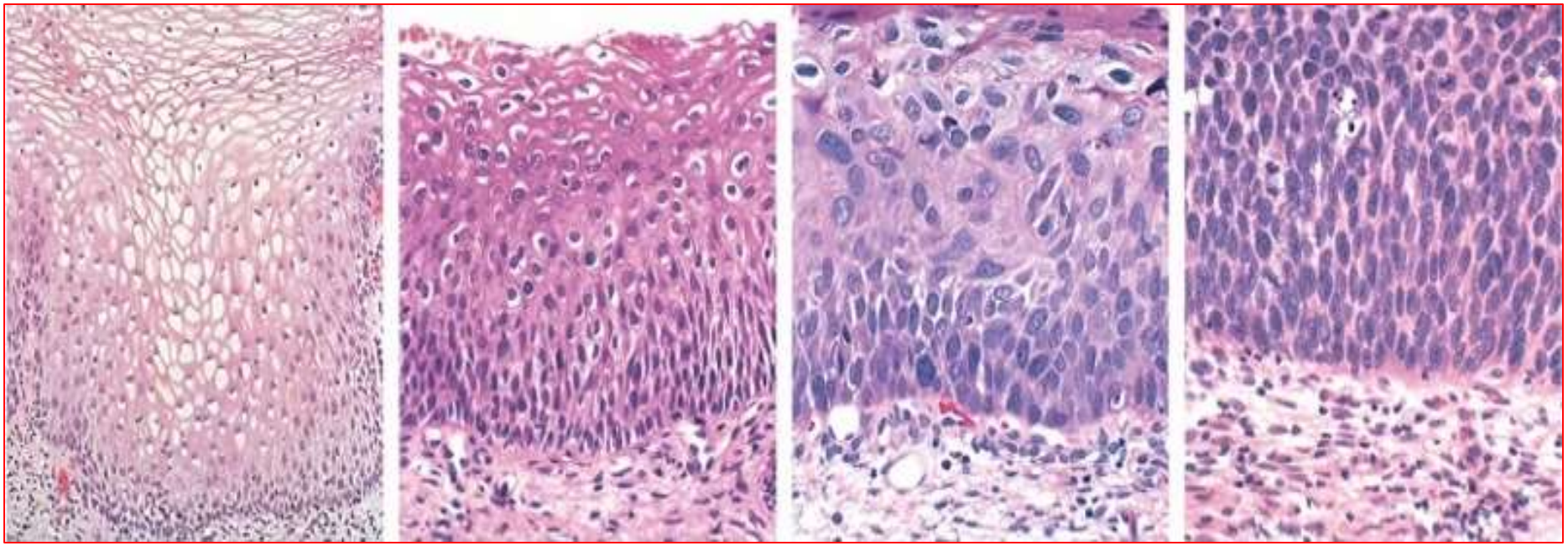
*__IN I__: Mild dysplasia (<third of full epithelial thickness)

*__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**)

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

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

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

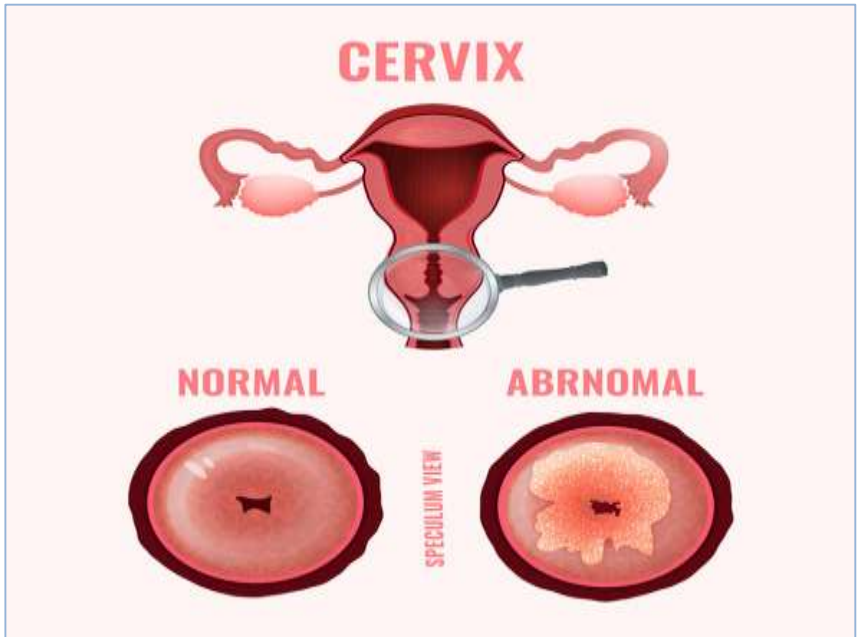
- most common (75% to 90%)
- relatively younger
- HPV-related (types 16 & 18)
- HPV lesions also in vagina and cervix.
- Poorly differentiated cells

2- Well-differentiated SCC

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

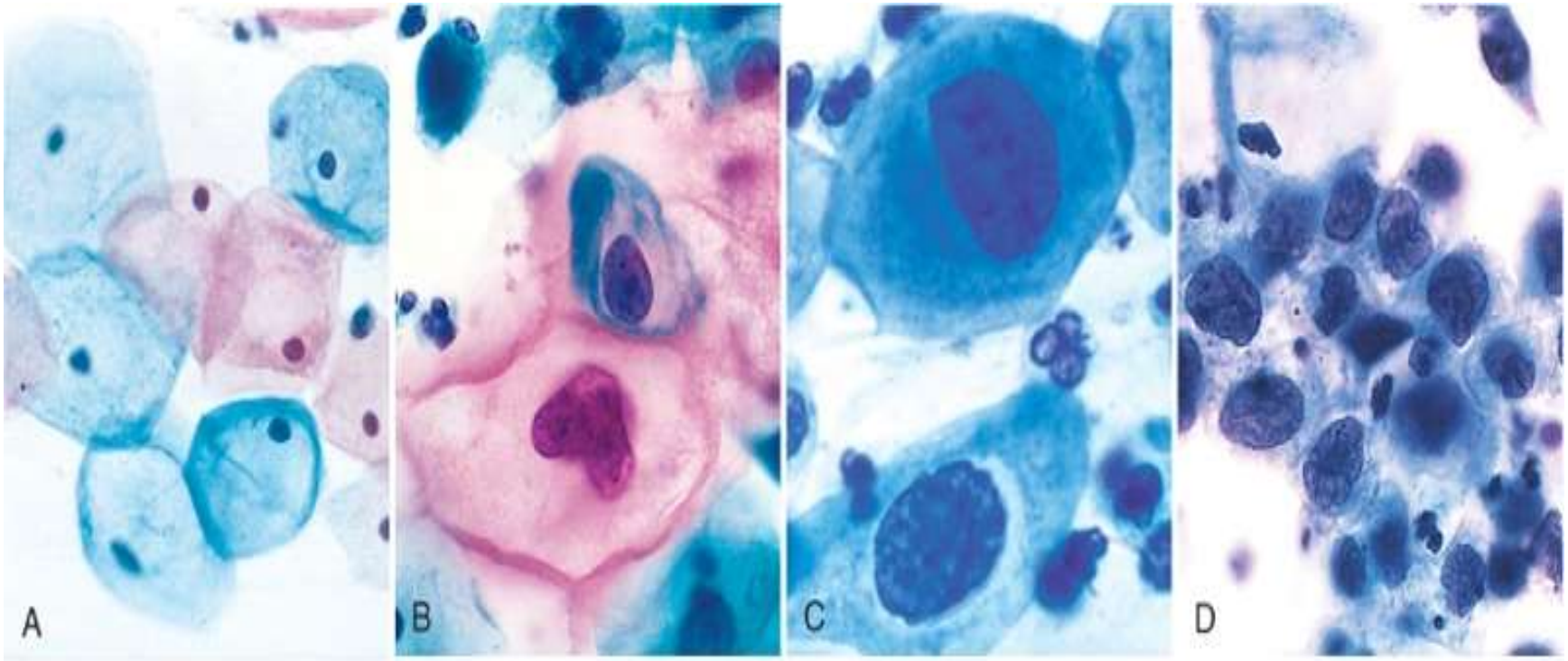
Cervical Carcinoma

- 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



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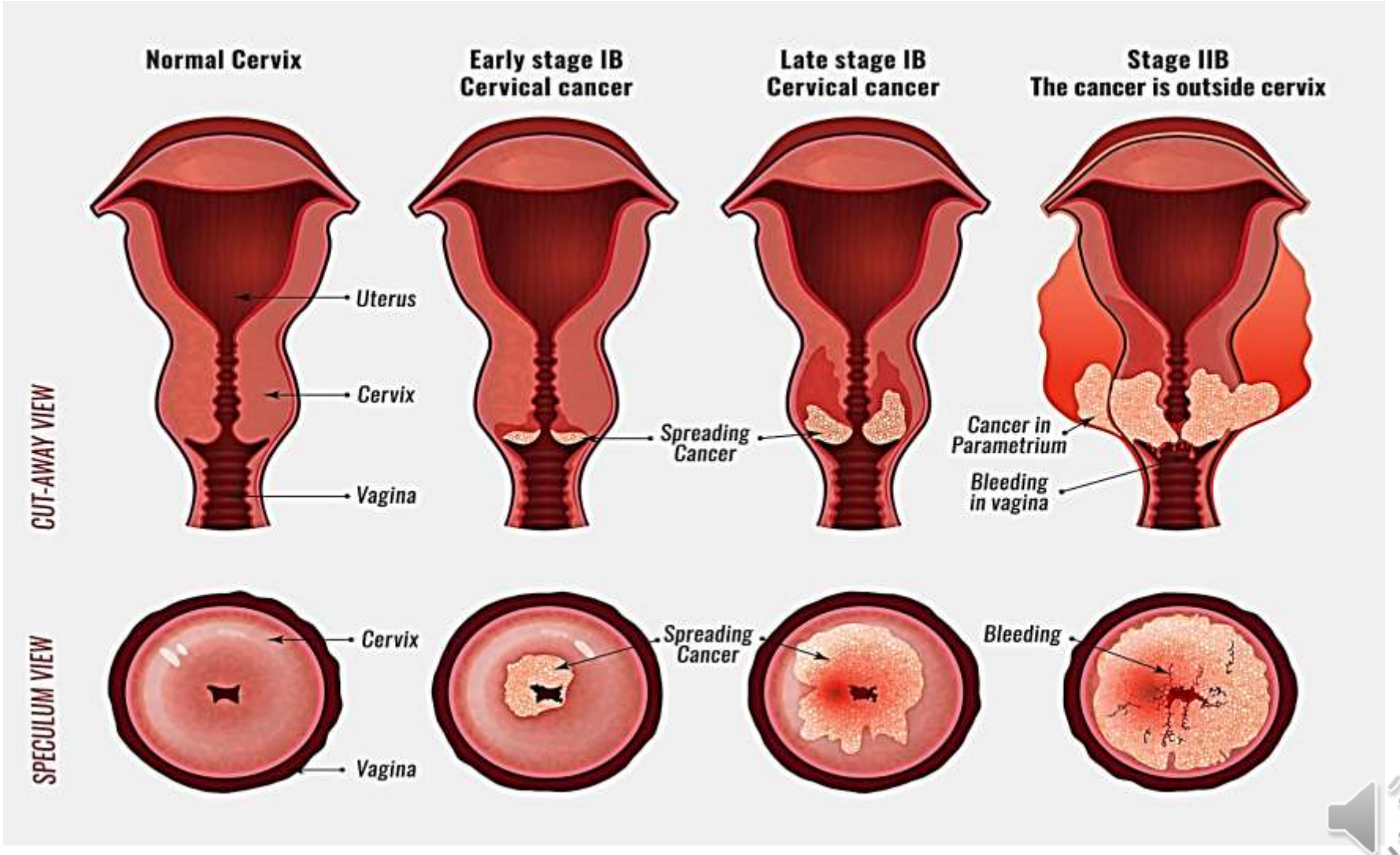
Normal **CIN I** **CIN II** **CIN III**

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%;
- stage 1→ 90%;
- stage 2→82%;
- stage 3→ 35%;
- and stage 4→ 10%.

- Radiotherapy and Chemotherapy in advanced cases