Pre-invasive & Carcinoma of the cervix

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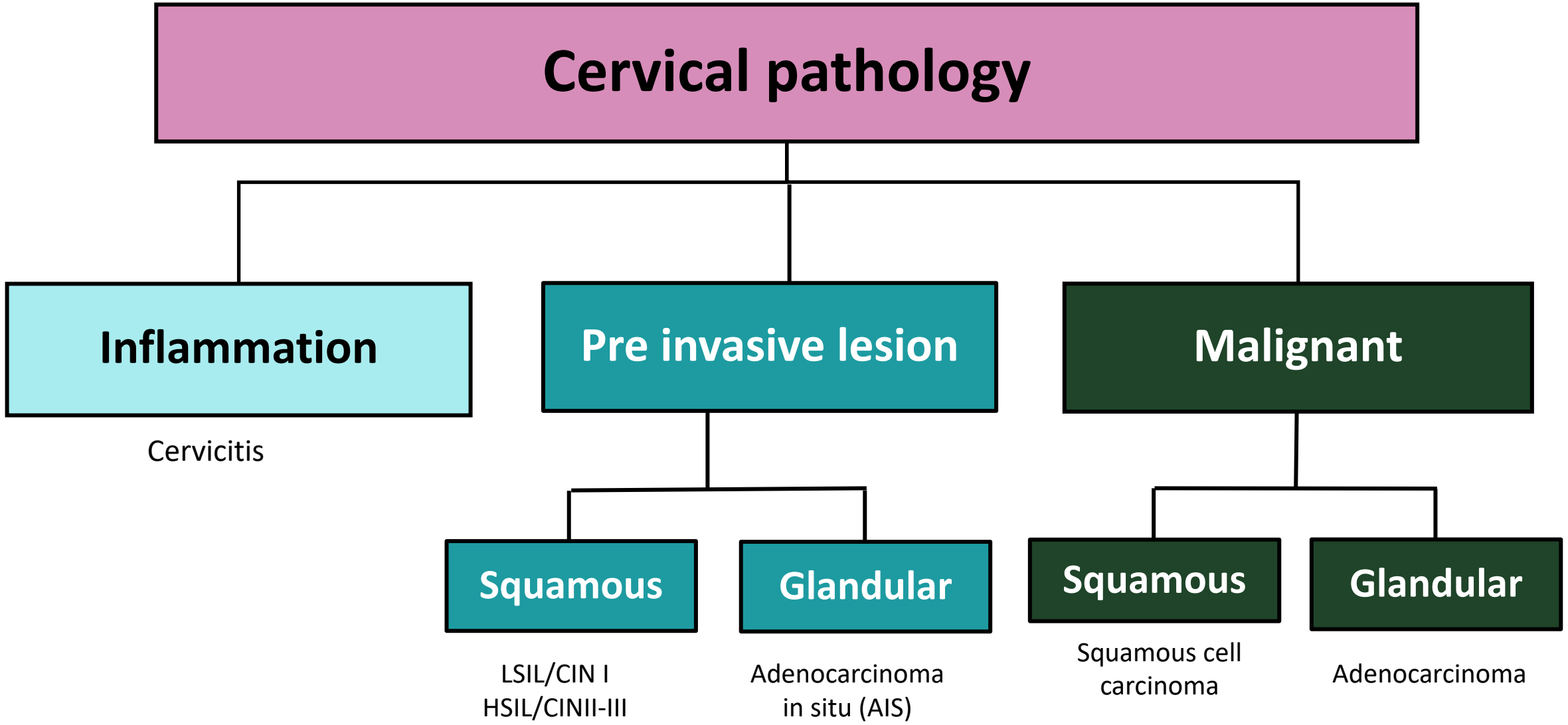
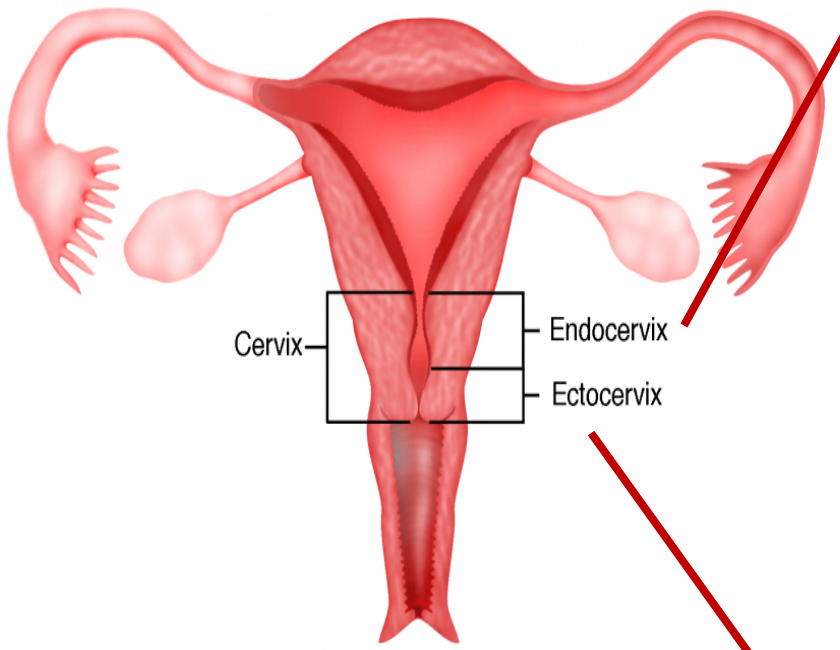
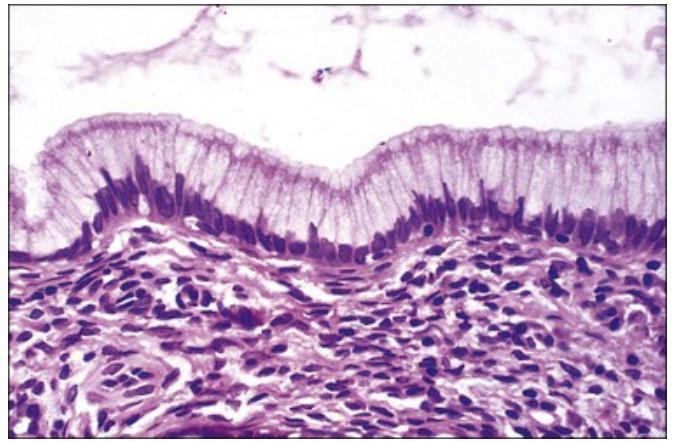
Learning outcome

1. Describe **the terminologies** of pre-invasive cervical lesions (CIN/SIL)
2. Describe the **epidemiology and risk factors** of cervical cancer
3. Describe the **high-risk HPV types** and how HPV affect cell cycle
4. Describe the **pathogenesis** of cervical cancer
5. Identify **gross and histological features** of cervical cancer


Cervical pathology
Inflammation
Pre invasive lesion
Malignant
Cervicitis
Squamous
Glandular
Squamous
Glandular
LSIL/CIN I
HSIL/CINII-III
Adenocarcinoma
in situ (AIS)
Squamous cell
carcinoma
Adenocarcinoma

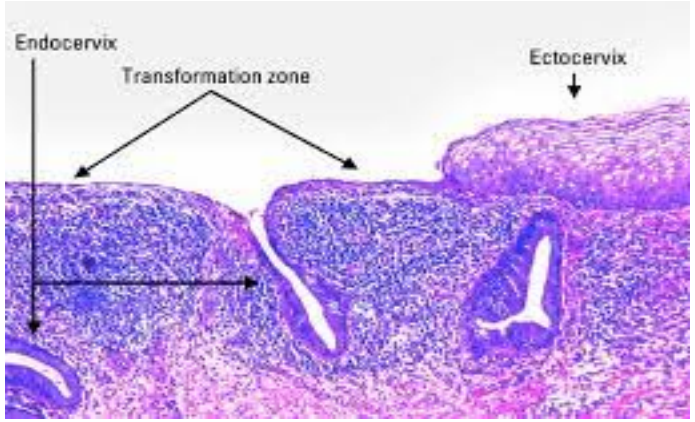


Endocervix is lined by columnar, mucus-secreting epithelium.



Squamo-columnar junction:

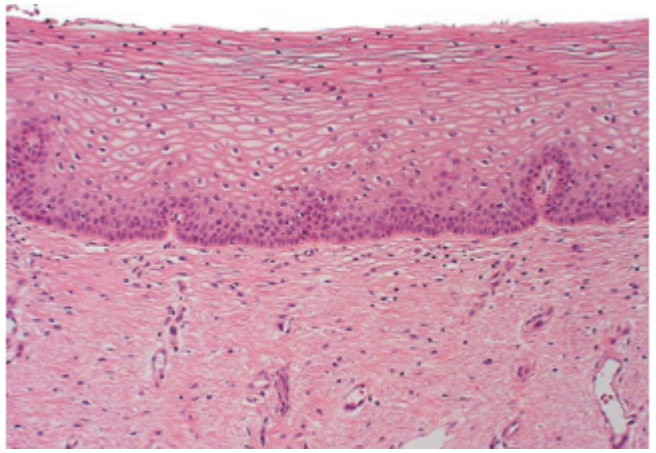
- Junctional mucosa of the ectocervix and endocervix- consists of gradual transition between squamous and columnar epithelial.



Transformation zone:

- **The extend of transformed metaplastic squamous epithelium**
- **This area is susceptible to the effects of oncogenic HPV.**

Ectocervix is covered by a mature squamous epithelium



Terminology

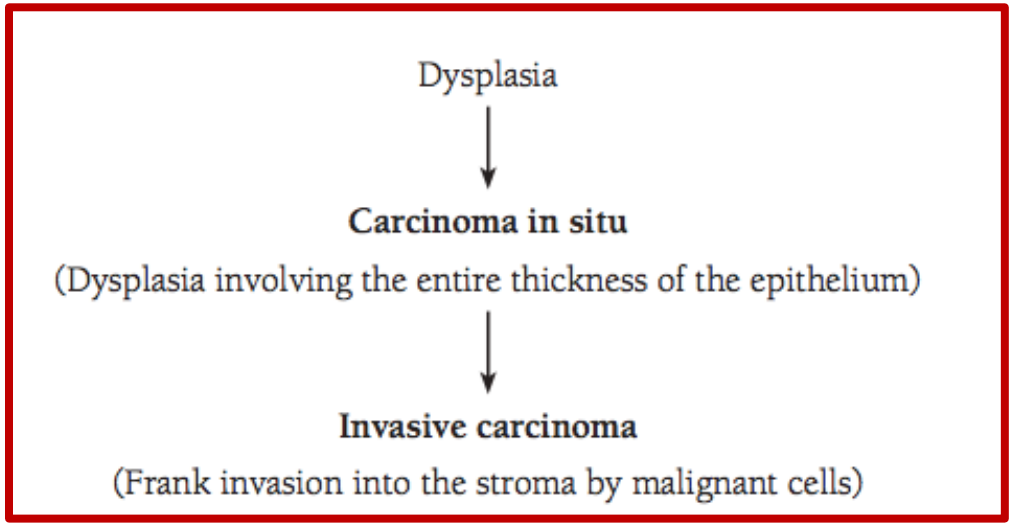
- Terminology used to classify pre-invasive lesions of the cervix has frequently changed.
- Initially it was known as **non-invasive epithelial abnormalities** (1886)
- **Carcinoma in situ/CIS** severe dysplasia (1930s)

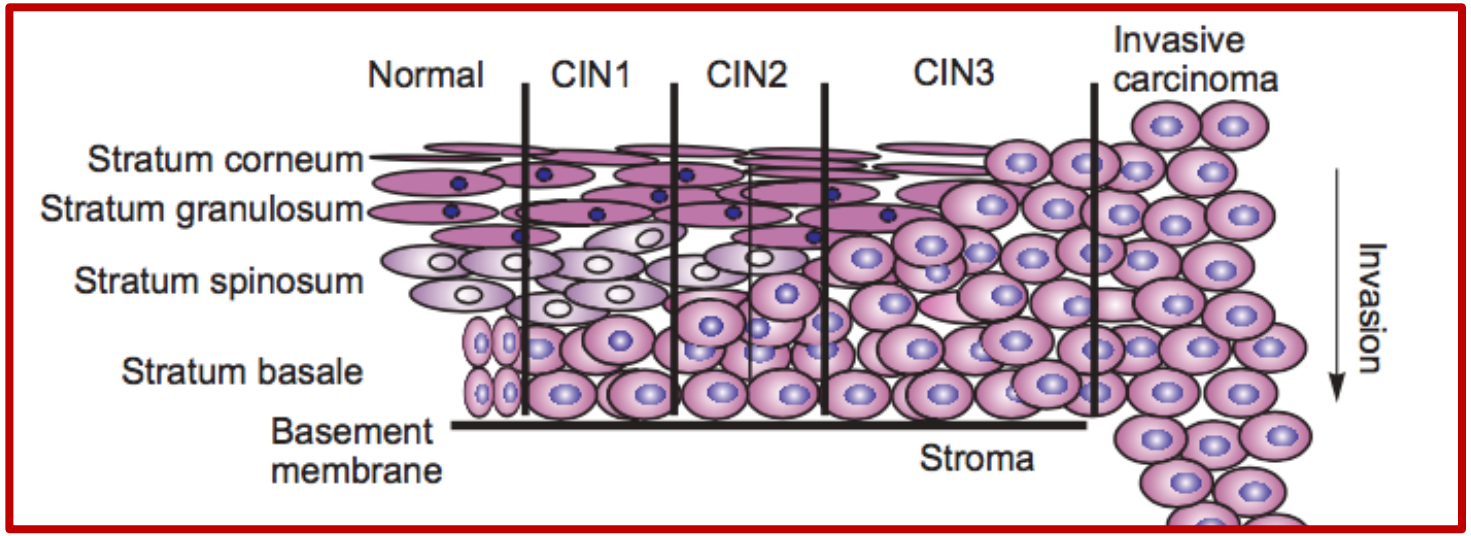
Dysplasia: disordered growth, loss architecture orientation

- This was followed by the three-tier classification system-**cervical intraepithelial neoplasia** (CIN)
  - mild dysplasia termed CIN I
  - moderate dysplasia termed CIN II
  - severe dysplasia termed CIN III.

- Recently simplified to a two-tiered system-squamous intraepithelial lesion (SIL)
  - CIN I renamed as low-grade squamous intraepithelial lesion (LSIL)
  - CIN II and CIN III combined into one category referred to as high-grade squamous intraepithelial lesion (HSIL)

- Cervical carcinoma: malignant epithelial tumour arise from cervical. It show malignant morphology with evidence of invasion to the stroma.



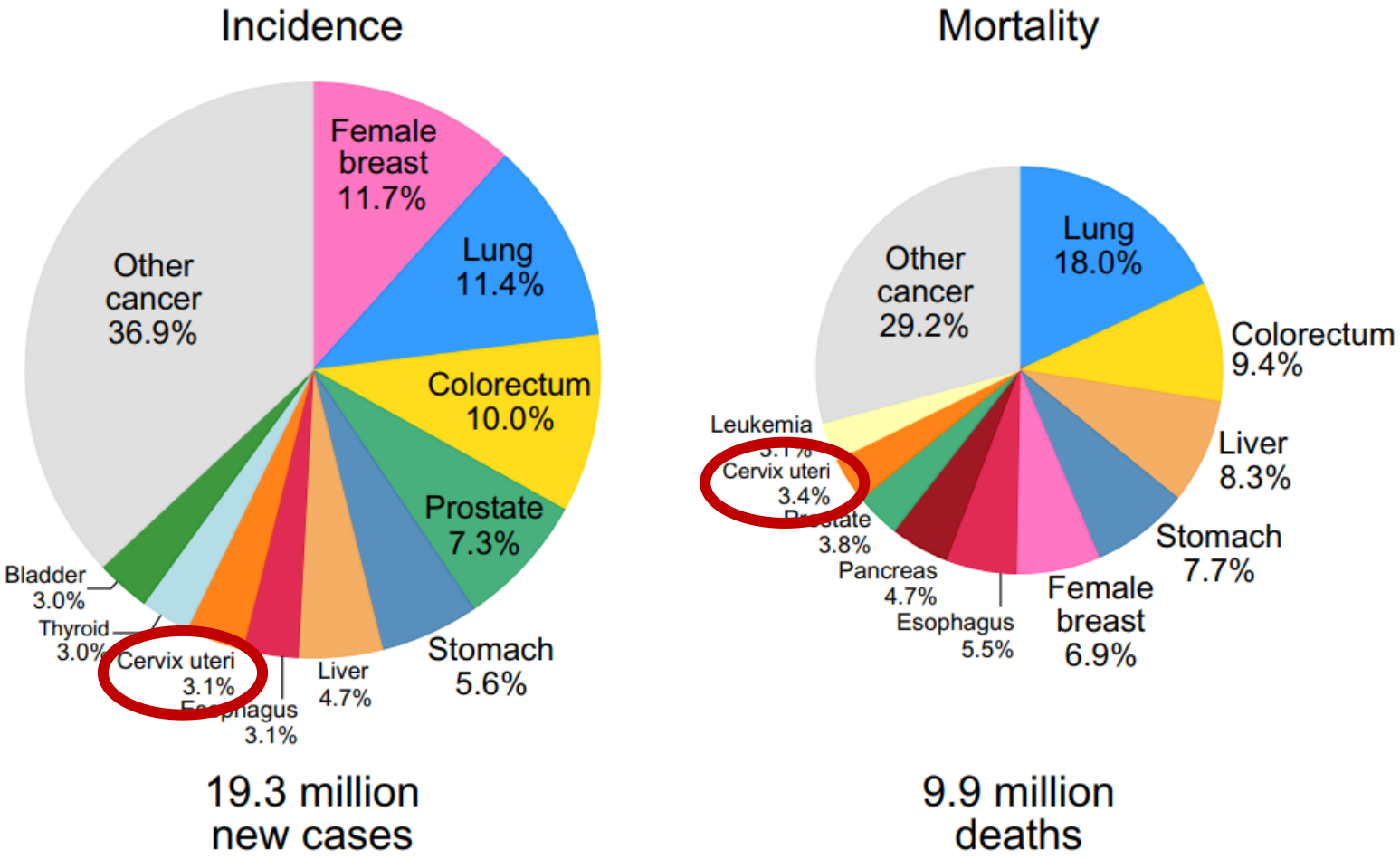


CERVICAL INTRAEPITHELIAL NEOPLASIA

Dysplasia/carcinoma in situ	Cervical intraepithelial neoplasia (CIN)	Squamous intraepithelial lesion (SIL), Current classification
Mild dysplasia	CIN I	Low grade SIL (LSIL)
Moderate dysplasia	CIN II	High – grade SIL (HSIL)
Severe dysplasia	CIN III	High – grade SIL (HSIL)
Carcinama in situ	CIN III	High – grade SIL (HSIL)

Epidemiology of cervical cancer

Both sexes

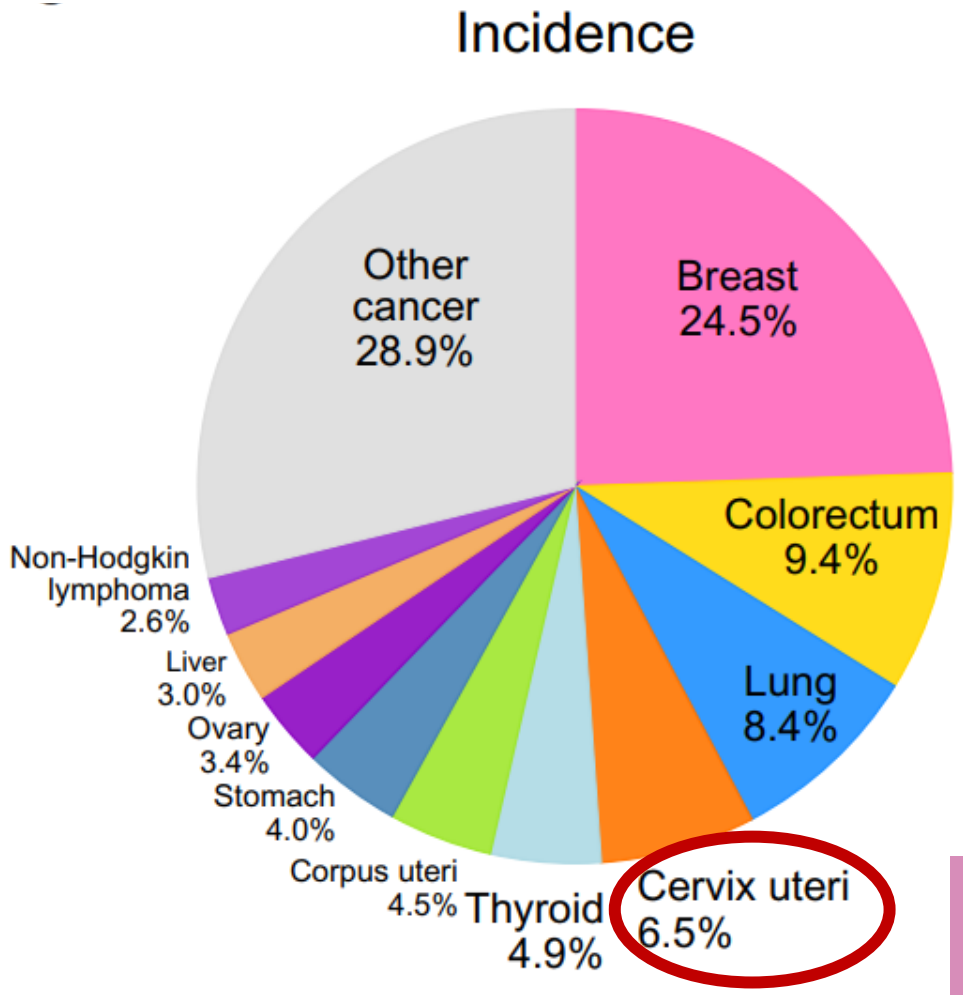


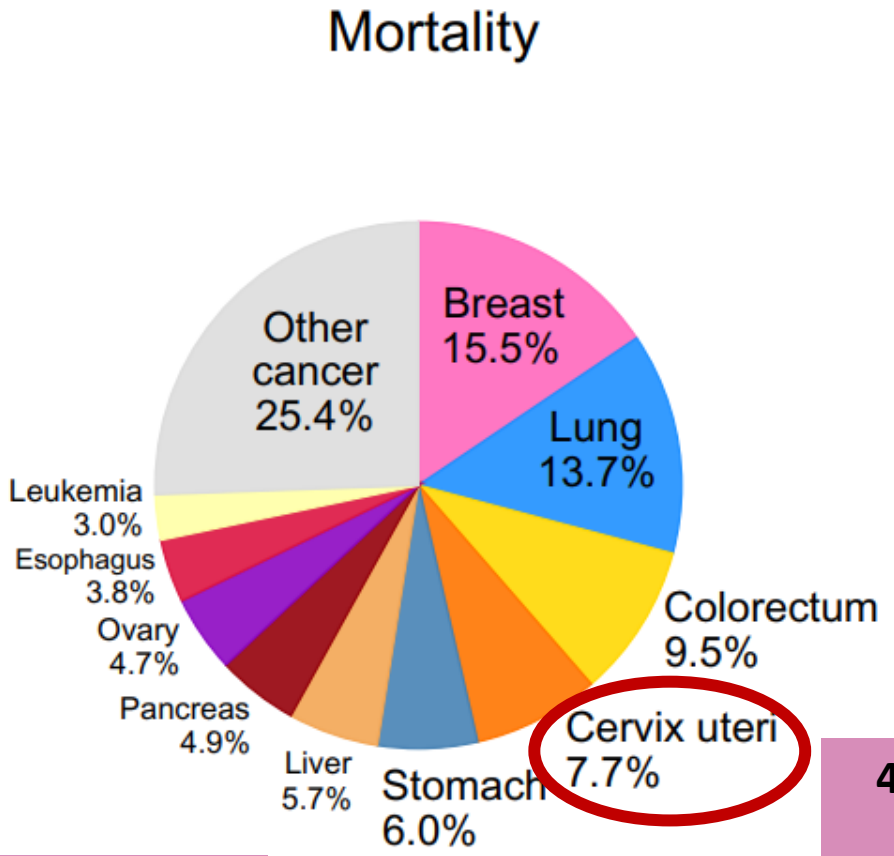
8th most frequently diagnosed cancer worldwide

9th leading cause of cancer death in women

Cancer in both sexes: Global Cancer Statistics 2020: GLOBOCAN

In 2020: The estimated new cases of cervical cancer is 604,000 and causing 342,000 deaths worldwide





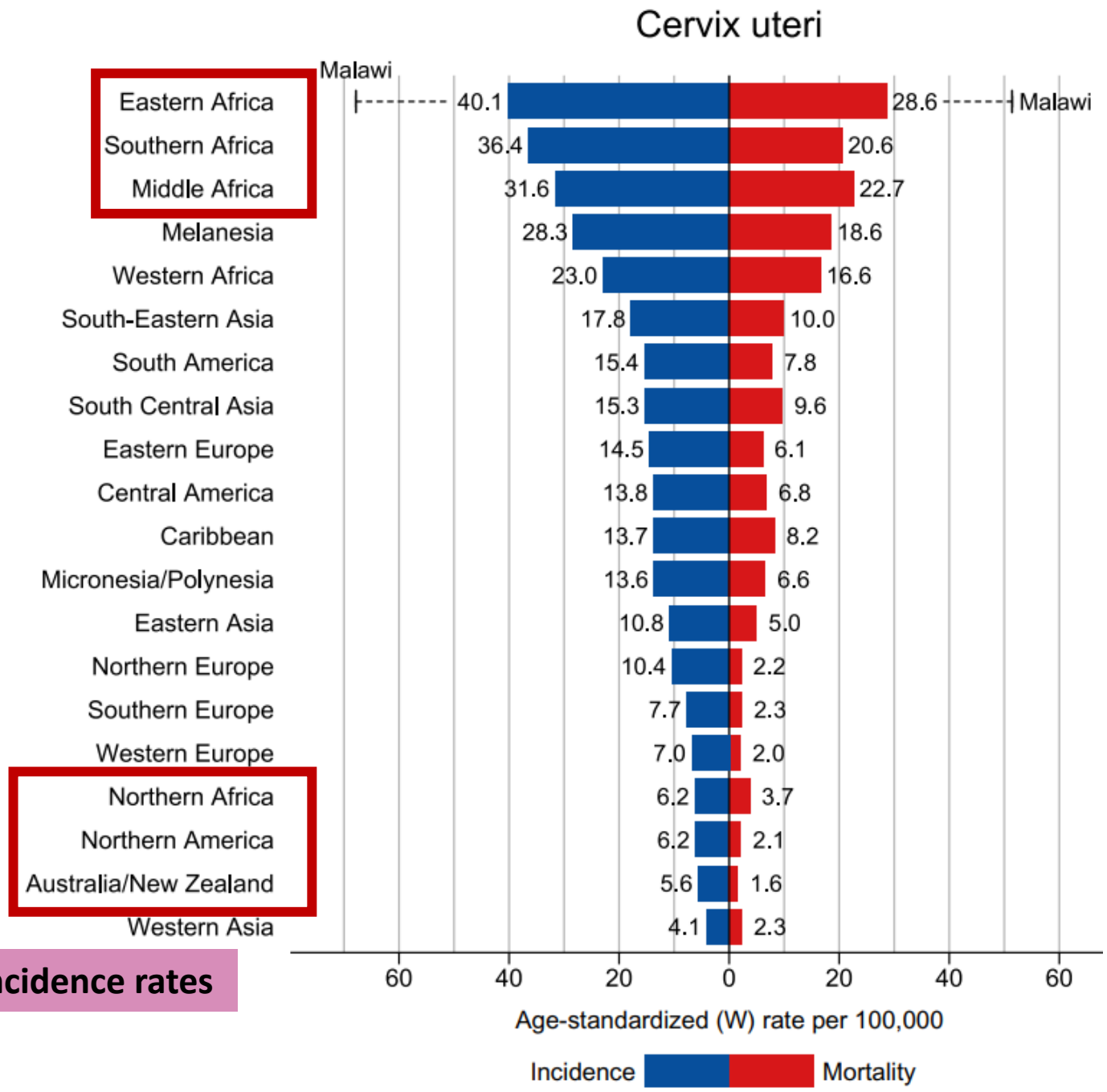
4th most frequently diagnosed cancer in women

4th leading cause of cancer death in women

Cancer among women: Global Cancer Statistics 2020: GLOBOCAN

Highest incidence and mortality

- Low socioeconomic levels
- Low awareness
- Poor genital hygiene
- High parity
- High STD

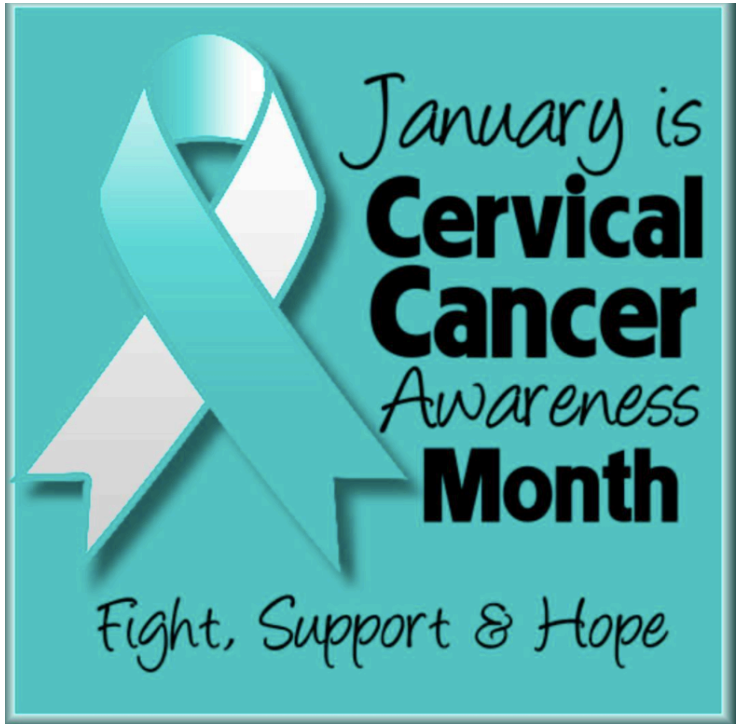


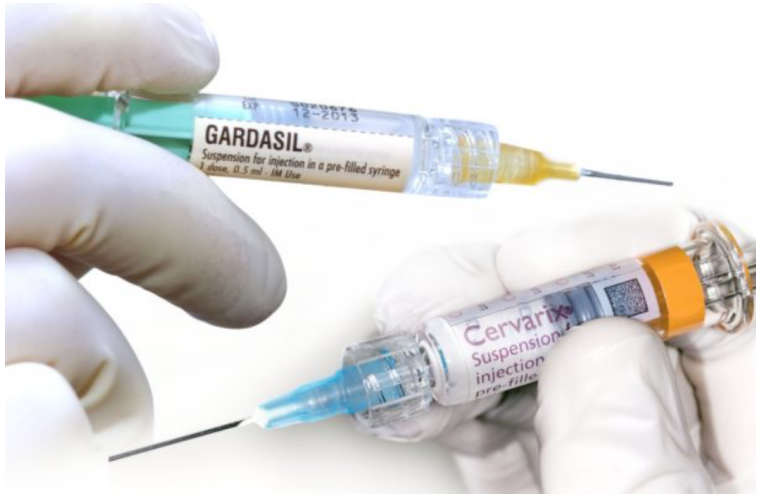
Lowest incidence rates

- Incidence & mortality rates declined in most areas for the past few decade, due to:
  - Increasing average socioeconomic levels
  - Improvements in genital hygiene
  - Reduced parity
  - Diminishing prevalence of STD

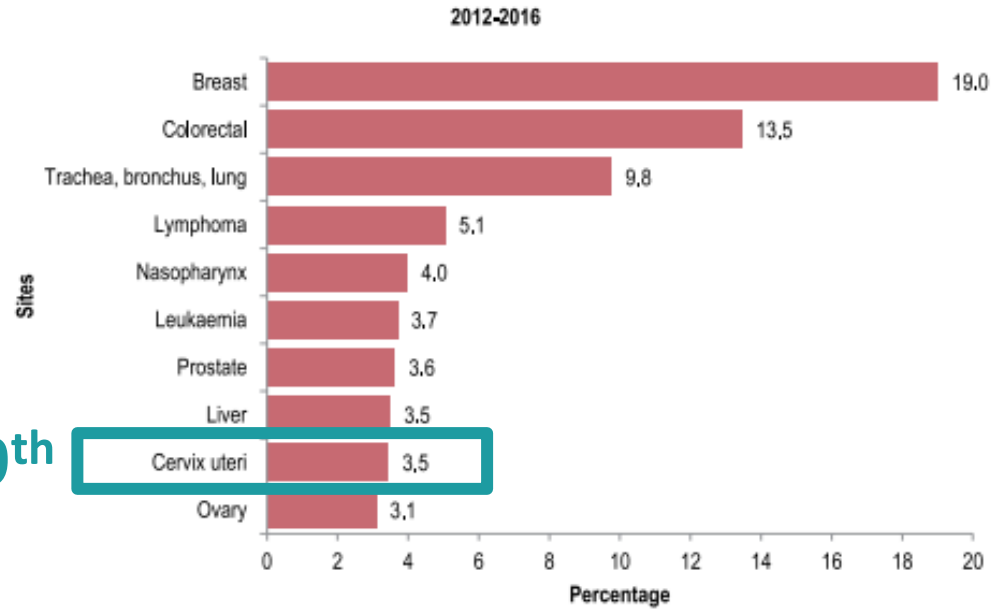
- **Cervical cancer screening programs** accelerated the declines upon their implementation

- Cervical ca is considered nearly completely preventable because of the highly effective primary (HPV vaccine) and secondary (screening) prevention measures.





In Malaysia



9th

Figure 14. Comparison of ten most common cancers, all residents, Malaysia, 2007-2011 and 2012-2016

Table 33. Cervix Uteri: Cancer incidence summary by year, Malaysia

All residents	No.	CR	ASR	CumR
2007-2011	4,325	6.8	7.6	0.9
2012-2016	3,981	6.0	6.2	0.7
2012	811	6.1	6.3	0.7
2013	746	5.5	5.7	0.6
2014	870	6.5	6.6	0.7
2015	797	5.8	5.9	0.7
2016	757	5.5	5.6	0.6

Risk factors cervical cancer

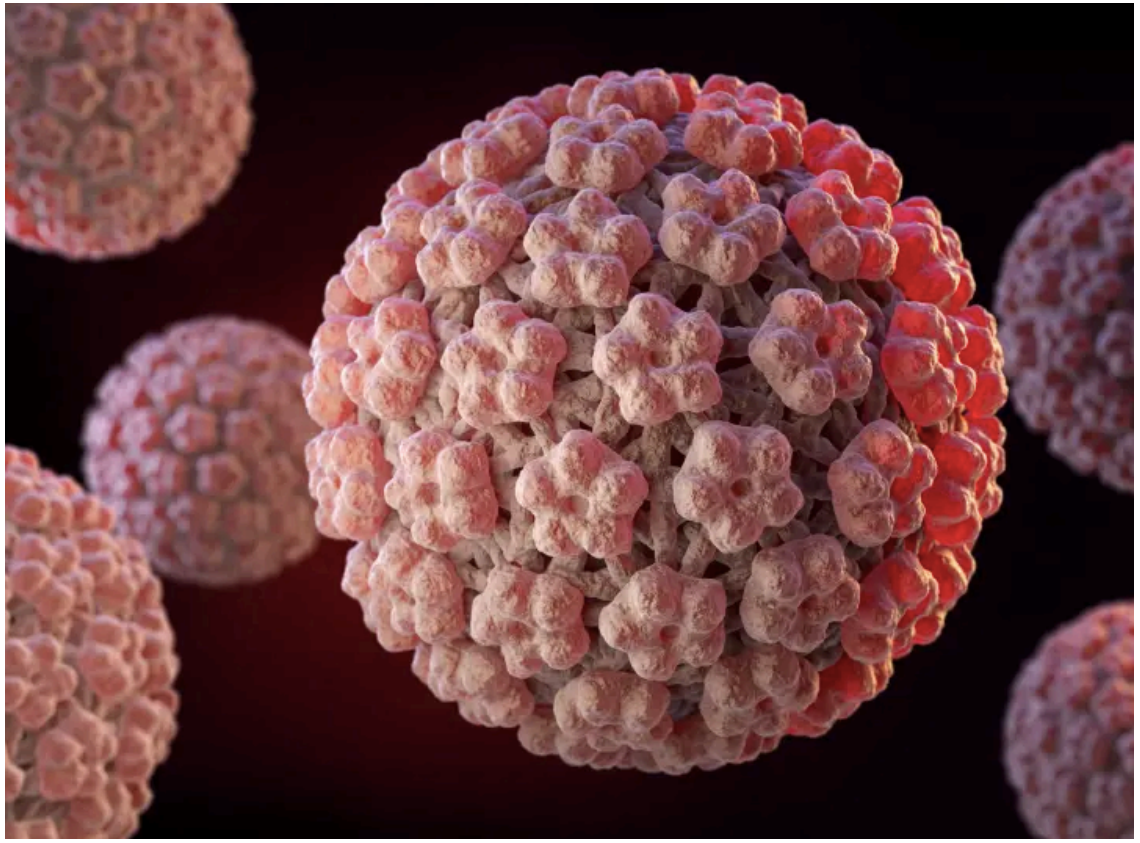
- **Major risk factors** for cervical cancer are infection with specific HR-HPV
- Sexual activity
  - Number of sexual partners
  - Early sexual activity (especially <16 years of age)

Cofactors

- Sexually transmitted diseases (e.g HIV, Chlamydia trachomatis)
- Early age of first pregnancy
- High number childbirths
- Low socioeconomic class
- Cigarette smoking
- Human immunodeficiency virus
- Immunosuppression from any cause
- Long term oral contraceptive usage

HR-HPV: High risk Human Papilloma Virus

HUMAN PAPILLOMAVIRUS (HPV)



- Small **double stranded DNA virus** with circular genome.
- 70 genetically distinct types of HPV have been identified.
- HPV variants are based on their propensity to induce carcinogenesis:
  - **High-risk HPVs type 16, 18**
  - **Low-risk HPVs type 6, 11**

- **Genital HPV infections** are extremely common
- Most of them are asymptomatic
- Other common sites to HPV infection
  - Squamo-columnar junction of the **anus** (anal sex)
  - Squamous cells of **oropharyngeal**, tonsillar crypts (oral sex)

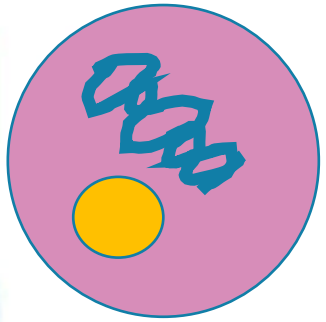
PATHOGENESIS OF CERVICAL NEOPLASIA

The physical state of virus differs in different lesions

HPV infection of basal epithelial cells

Low risk HPV 6,11,42,44

Episomal form (extrachromosomal form)



Condyloma accuminata

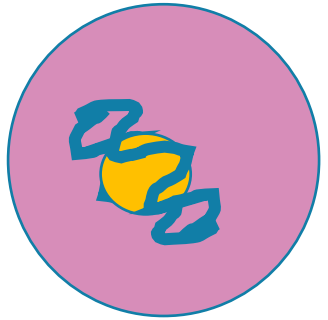
Regression

High risk HPV 16,18,31,33,35

viral DNA is integrated with host DNA

Invasive carcinoma

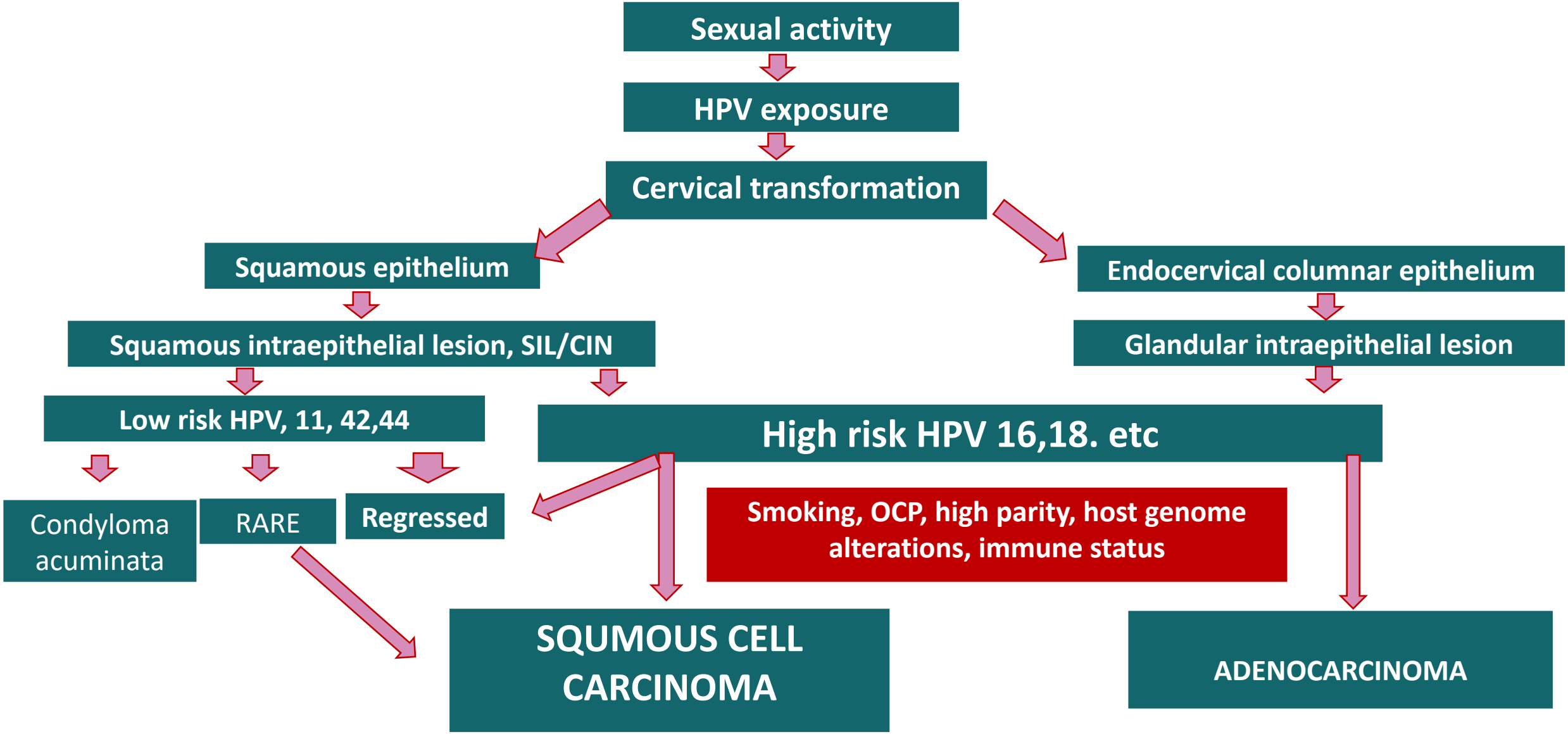
Types 16 (60%) and 18 (10%) risk to develop carcinoma



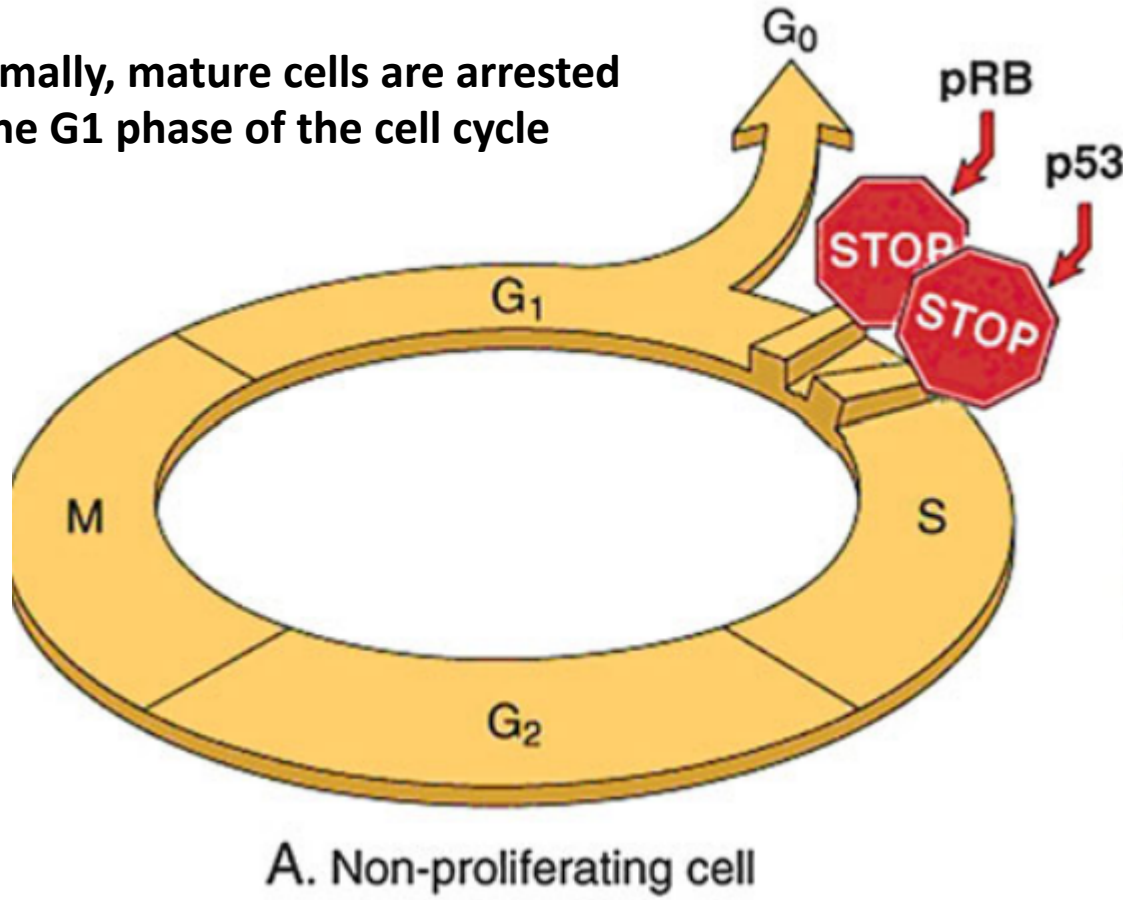
Pathogenesis cervical carcinoma

- Most HPV infections are transient
- 50% of HPV infections are cleared within 8 months and 90% of infections are cleared within 2 years
- HR-HPVs take longer to clear (average 10 months) than low-risk HPVs (8 months)
- Persistent infection, increases the risk of development cervical precursor lesions & subsequent carcinoma.
- Sites in the cervix that are susceptible to HPV infection include
  - Squamous epithelial in trauma or reparative → virus may access basal cells
  - Immature metaplastic squamous cells (squamo-columnar junction)

Pathogenesis of cervical carcinoma



Normally, mature cells are arrested in the G1 phase of the cell cycle



A. Non-proliferating cell

P53

- Tumour suppressor protein
- Guardian of genome
- Repair damaged DNA (if repairable)
- Induces apoptosis if DNA damage unrepairable

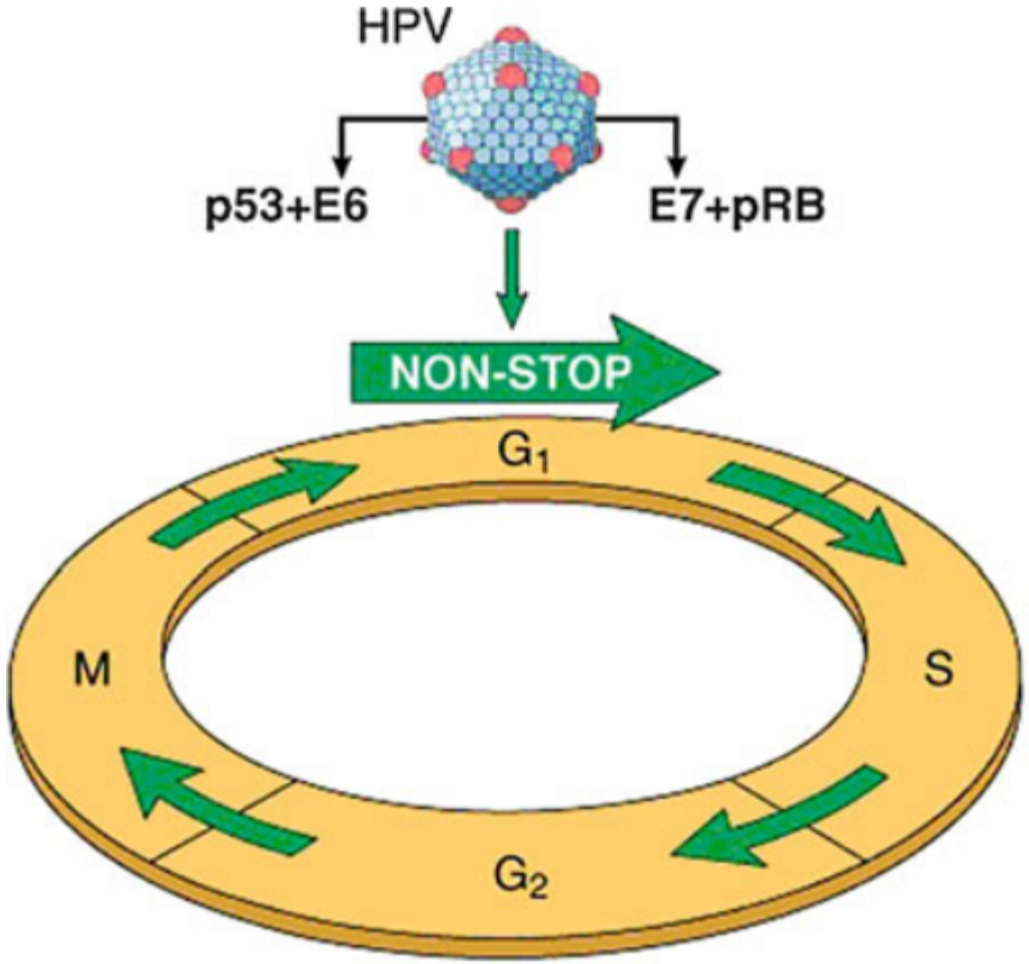
RB

- Tumour suppressor protein
- Controls the rate of cells entering cycle

IN NON-INFECTED CELL

The obedience of cellular DNA replication is maintained by p53.

In response to errors of DNA replication or other DNA damage, p53 arrests the cell cycle to allow for DNA repair.



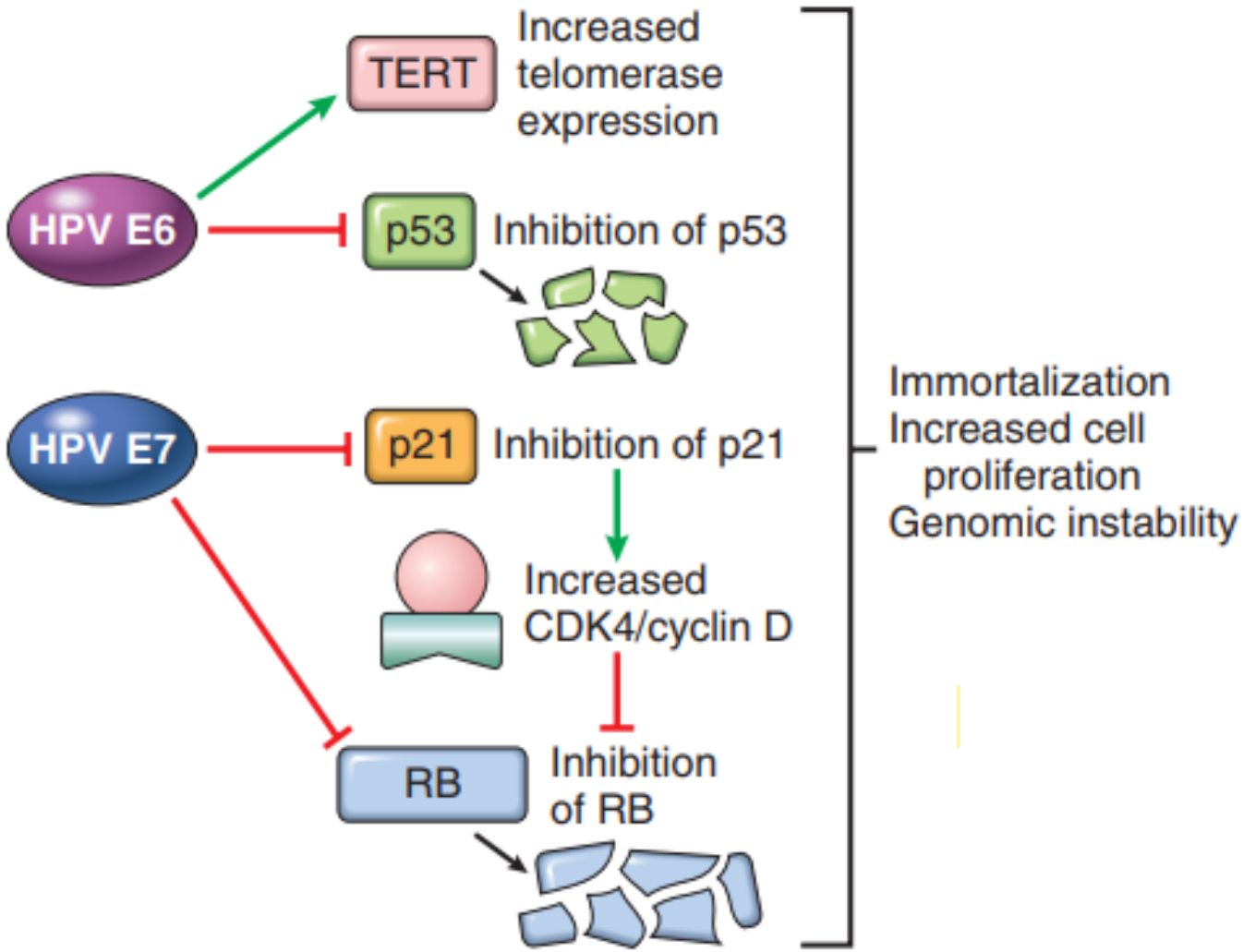
B. HPV stimulates uncontrolled DNA replication and cell proliferation

Normally, mature cells are arrested in the G1 phase of the cell cycle, but they continue to actively progress through the cell cycle when infected with HPV

INFECTED CELLS:

- **Activation of the host cell cycle by HPV oncoproteins E6 and E7.**
- **Binding of p53 by E6 and RB by E7 protein removes the breaks on the cell cycle.**
- **Leading to continuous cellular proliferation and accumulation and propagation of DNA errors**

Pathogenesis of cervical carcinoma

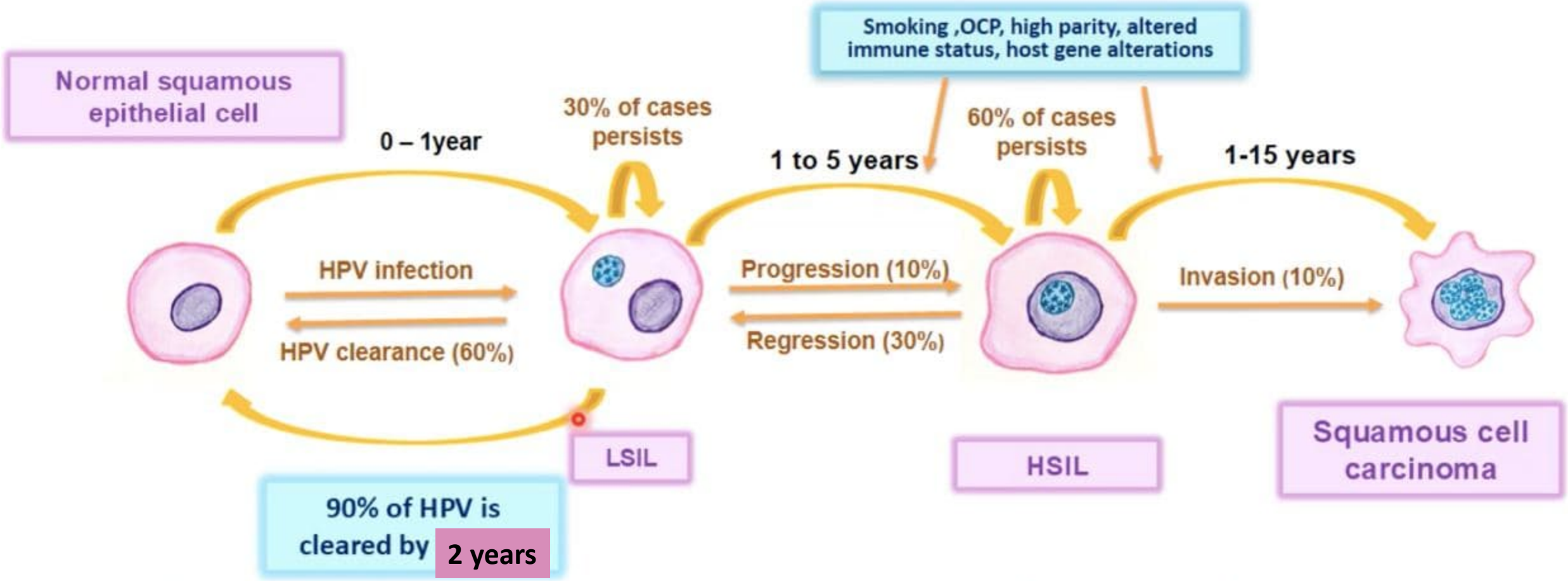


Cervical carcinoma

TERT, Telomerase reverse transcriptase

PATHOGENESIS OF CERVICAL NEOPLASIA

HPV PATHOPHYSIOLOGY



This lesion may exist in the non-invasive stage for as long as 20 years & shed abnormal cells that can be detected on cytologic examination by Papanicolaou smear screening

LSIL- lowgrade squamous intraepithelial lesion; HSIL- High grade squamous epithelial lesion

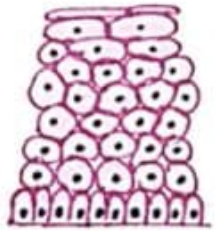
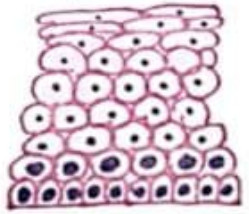
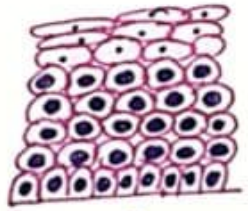
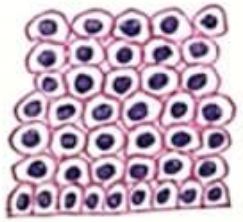
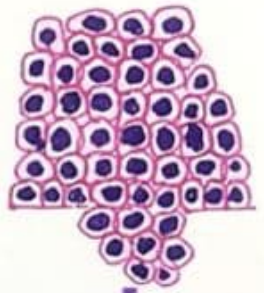
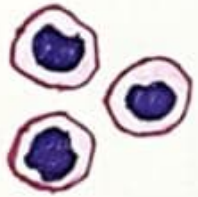
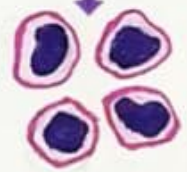
Pathologic Findings

SIL frequently detected on the **posterior lip of the cervix**

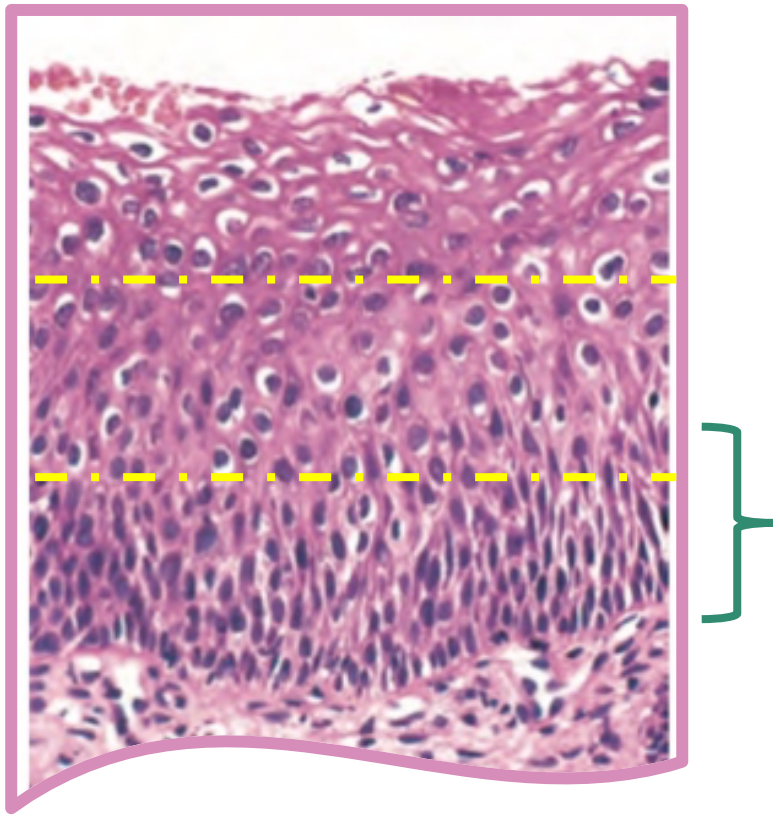
The diagnosis of SIL is based on identification of nuclear atypia accompanied by cytoplasmic “halos”

- Nuclear atypia (hallmark):
  - Nuclear enlargement
  - Hyperchromatic nuclei (dark staining chromatin)
  - Coarse chromatin granules
  - Variation in nuclear size and shape
- Cytoplasmic “halos” (perinuclear vacuoles)
  - cytopathic change created in part by an HPV-encoded protein E5 that localizes to the membranes of the endoplasmic reticulum.
  - Nuclear alterations associated with perinuclear halos are termed koilocytic atypia

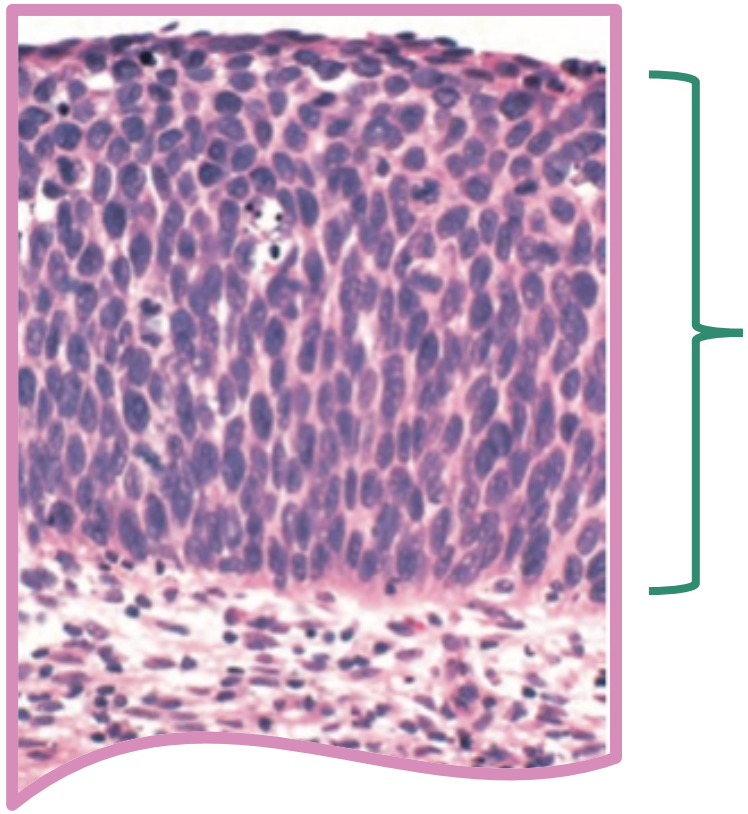
CERVICAL INTRAEPITHELIAL NEOPLASIA

	NORMAL SQUAMOUS EPITHELIUM	MILD DYSPLASIA	MODERATE DYSPLASIA	SEVERE DYSPLASIA	INVASIVE CARCINOMA
Histology					
Pap smear cytology					
	NORMAL SQUAMOUS EPITHELIUM	CIN I (LSIL)	CIN II (HSIL)	CIN III (HSIL)	INVASIVE CARCINOMA

The grading of SIL into low or high grade is based on expansion of the immature cell layer from its normal, basal location.



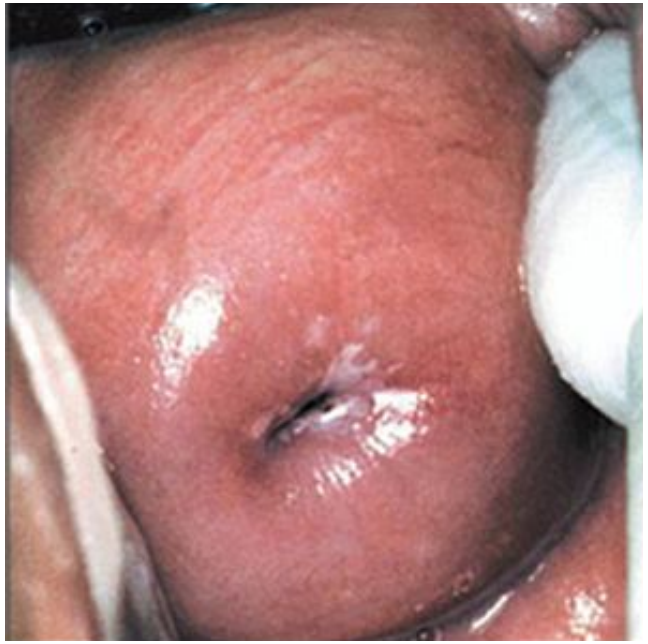
LSIL: immature squamous cells are confined to the lower 1/3 of the epithelium



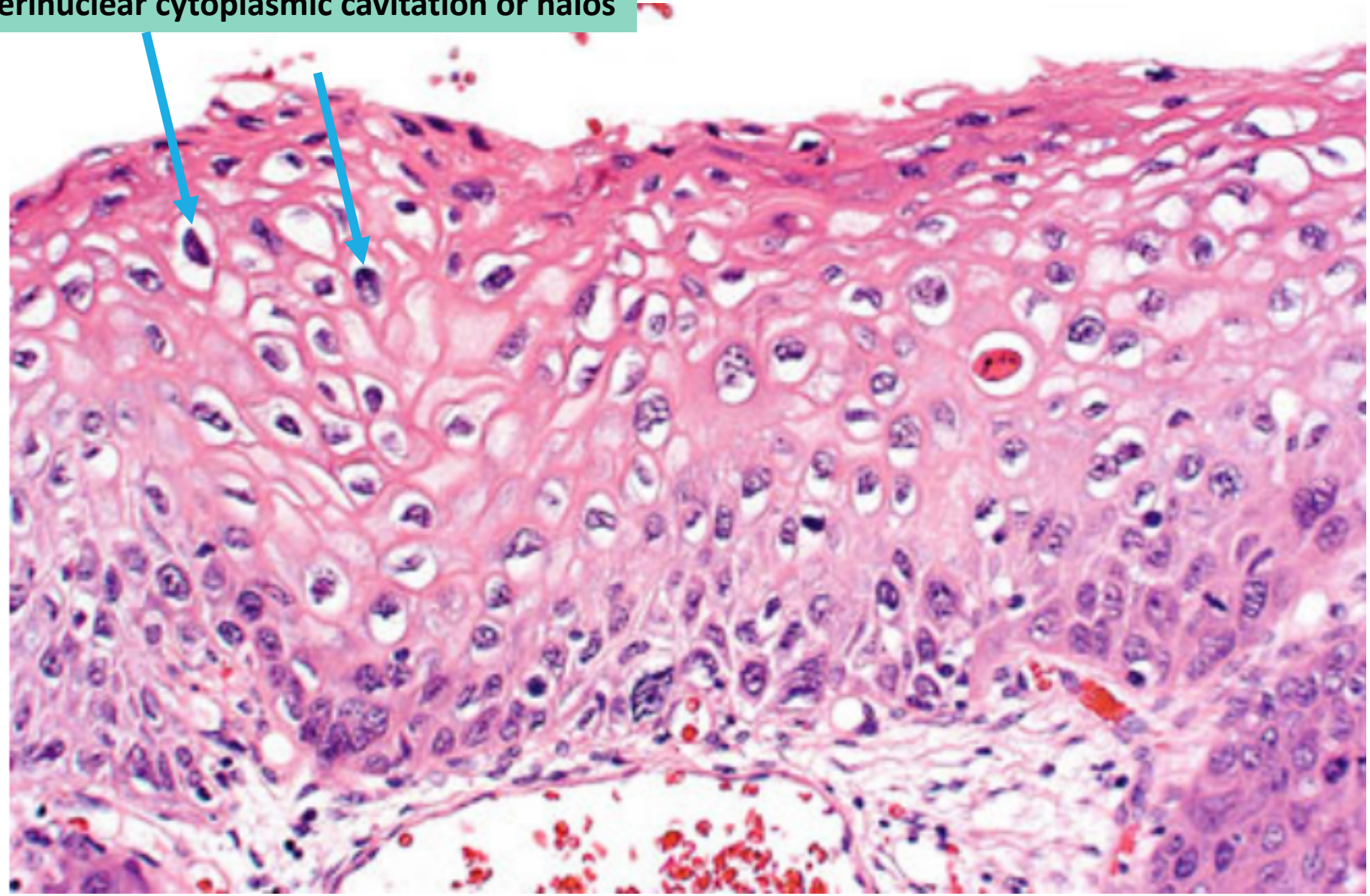
HSIL: immature squamous cells at upper 2/3 to full thickness of the epithelial.

Pathological features: Low grade SIL

- LSIL is approximately 10X more common than HSIL
- LSIL does not progress directly to invasive carcinoma.
- In most cases regress spontaneously
- Only a small percentage progress to HSIL.
- LSIL represents a productive HPV infection in which there is a high level of viral replication, but only mild alterations in the growth of host cells.
- For these reasons, LSIL is not treated like a premalignant lesion.

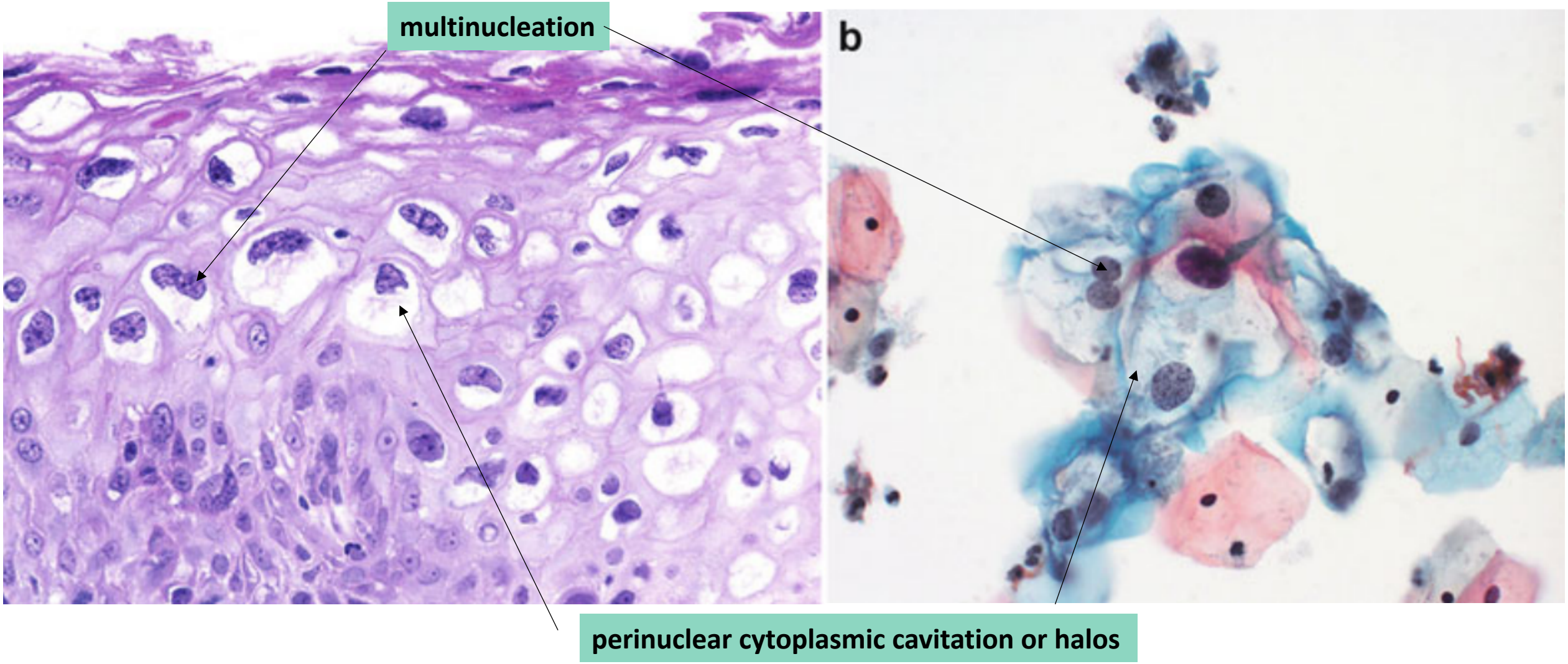


Colposcopy CINI/LSIL



The most significant feature of LSIL is **nuclear atypia** characterized by

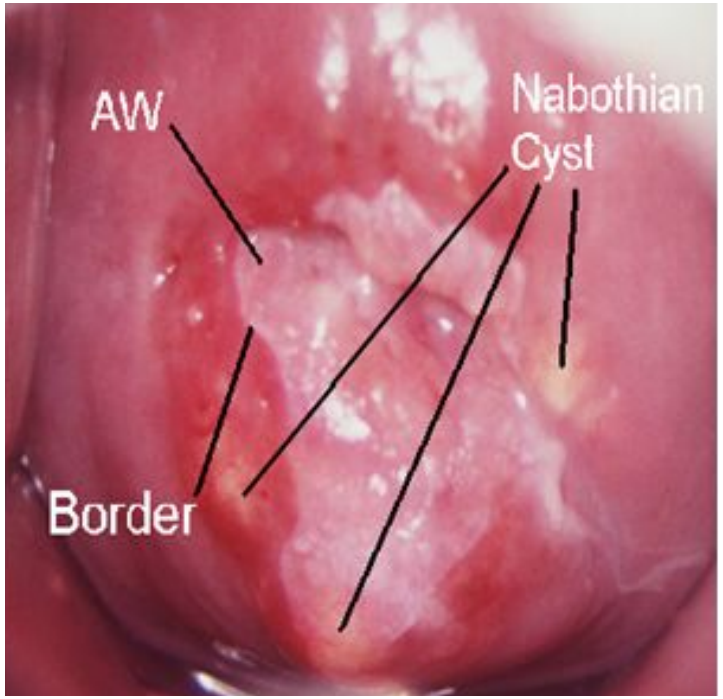
- Nuclear enlargement
- Hyperchromasia
- Nuclear irregularity,
- Variation in nuclear size



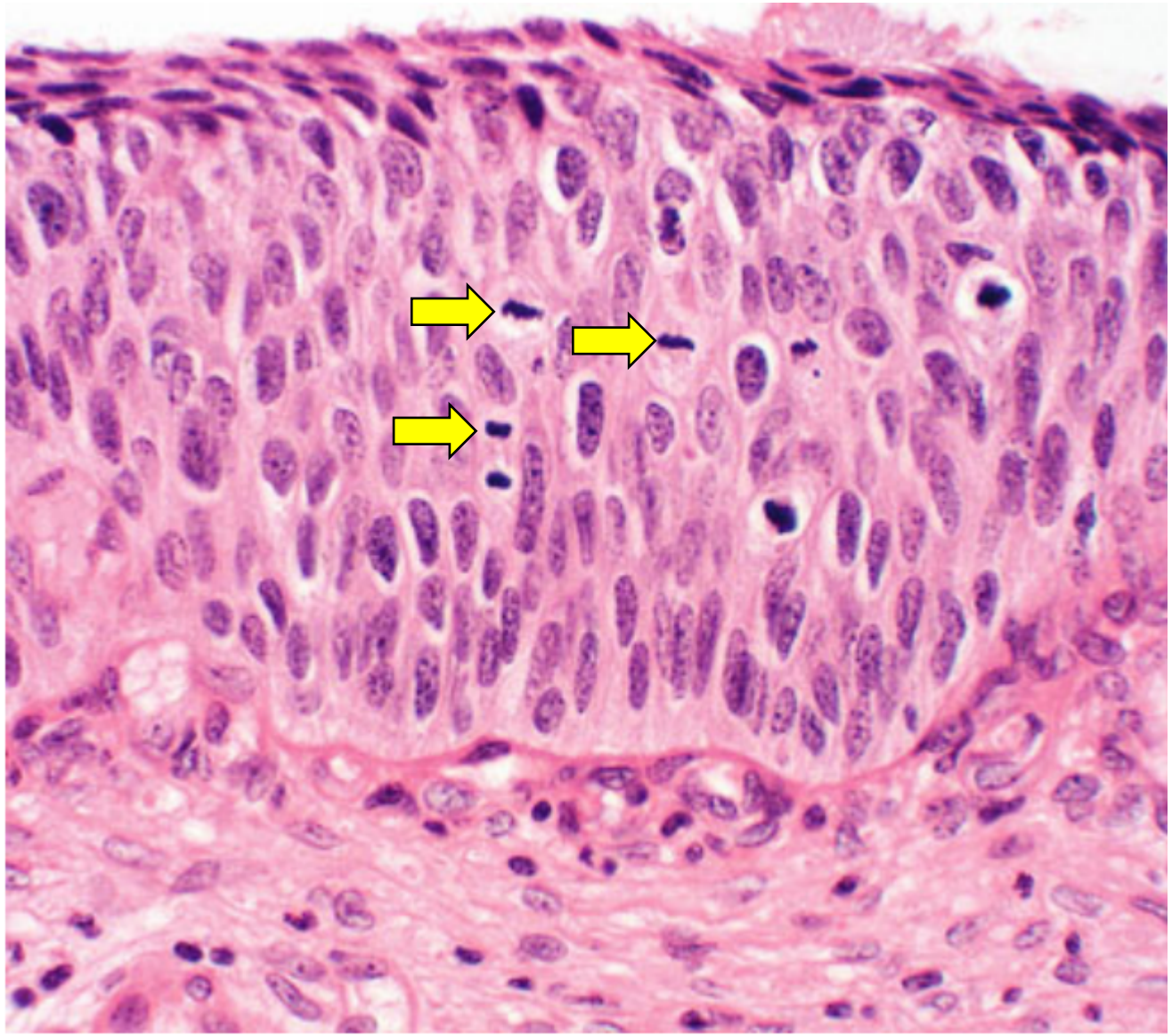
Koilocytosis in LSIL. The cytological features of a productive HPV infection include multinucleation and perinuclear cytoplasmic cavitation or halos. The combination of nuclear atypia and cytoplasmic halos is referred to as koilocytosis. (left) Koilocytosis on histology, (right) Koilocytosis on cytology (pap smear)

High grade SIL

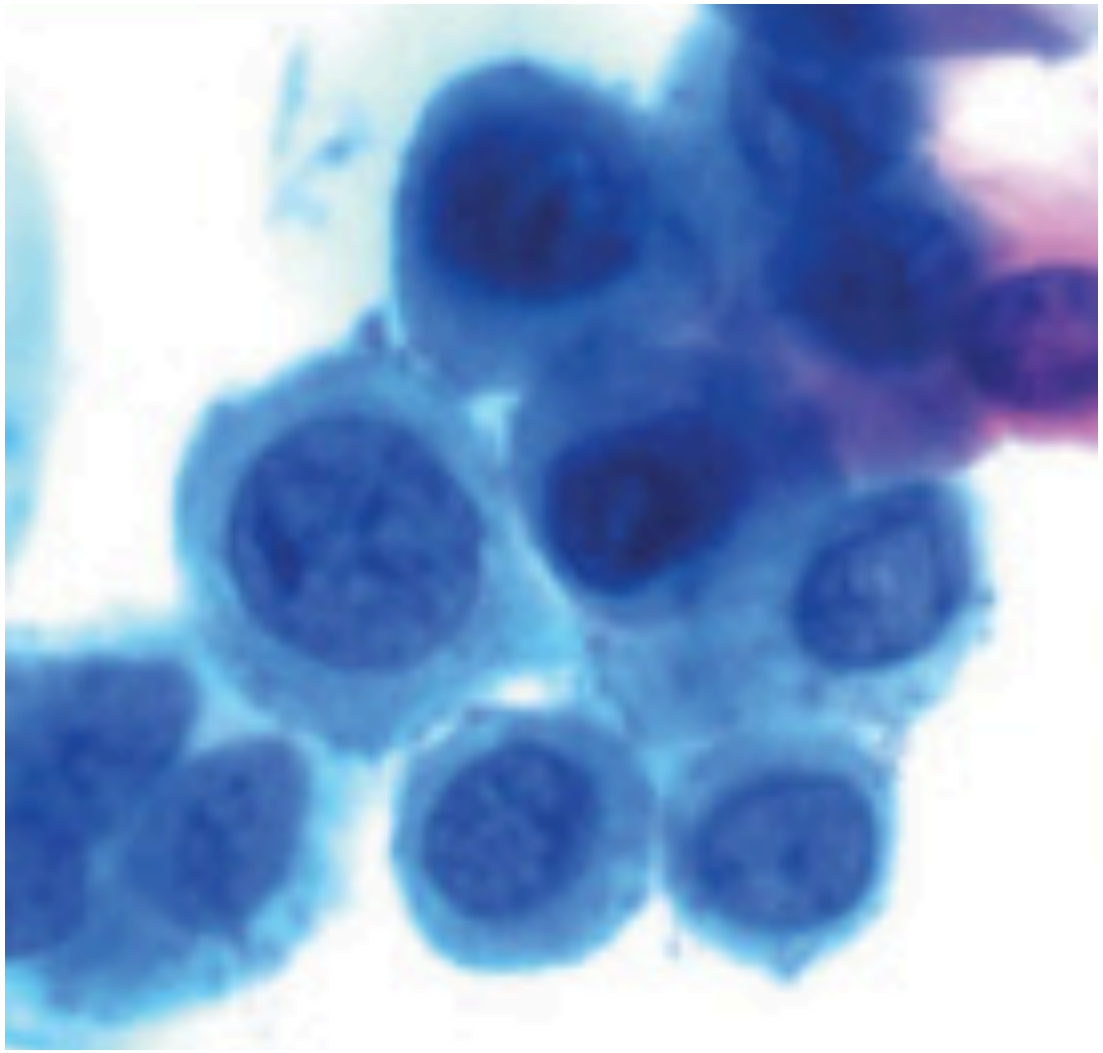
- High risk for progression to carcinoma but has lower rate of viral replication as compared with LSIL
- HSIL involved in progressive deregulation of the cell cycle by HPV, lead to:
  - Increased cellular proliferation
  - Decreased or arrested epithelial maturation
  - Derangement of the cell cycle may become irreversible and lead to a fully transformed malignant phenotype.
- Although the majority of HSILs develop from LSILs, approximately 20% of cases of HSIL develop de novo, independent of any pre-existing LSIL.



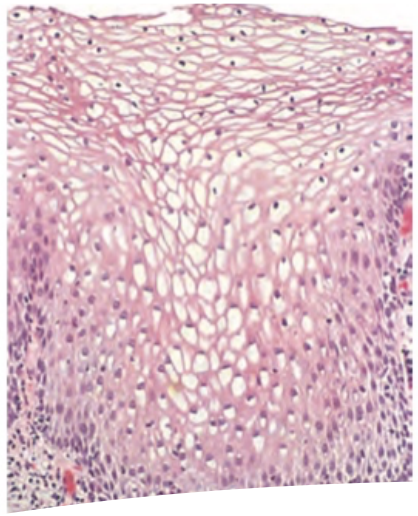
Colposcopy CINII/HSIL



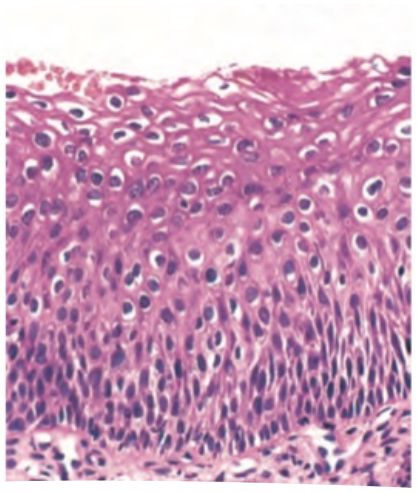
HSIL with numerous mitoses in the middle portion of the epithelium and immature basaloid cells extending almost to the surface (full thickness)



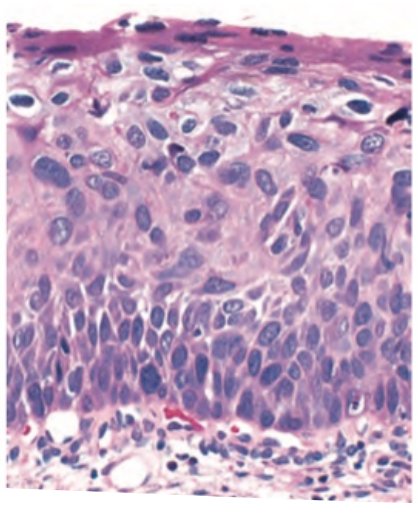
Pap smear HSIL:
-High N:C ratio
-Hyperchromasia



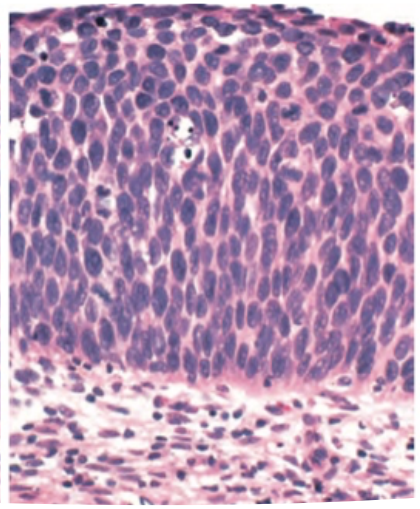
Normal



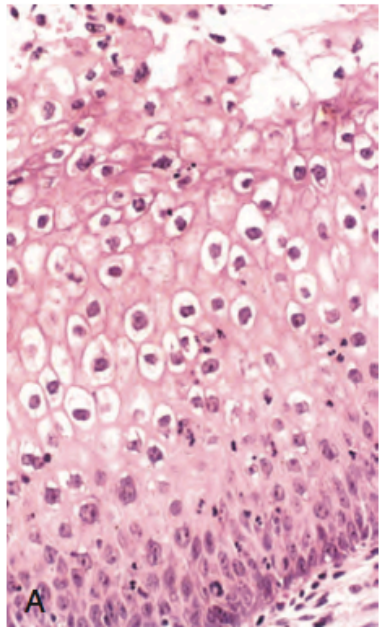
LSIL/CIN 1



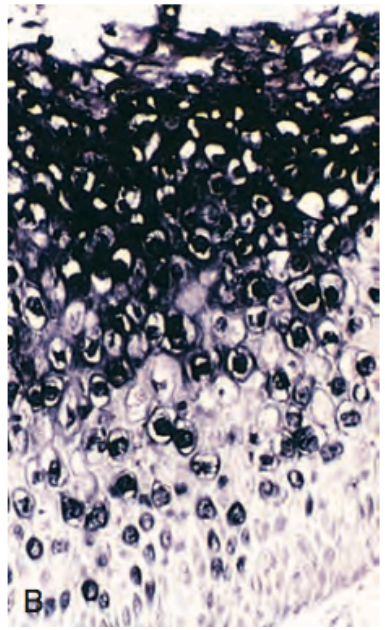
HSIL/CIN II



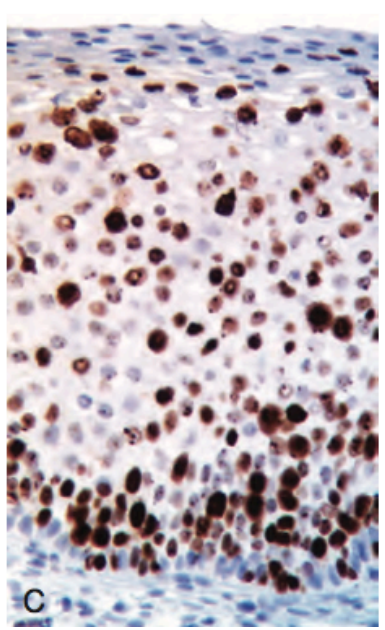
HSIL/CIN III



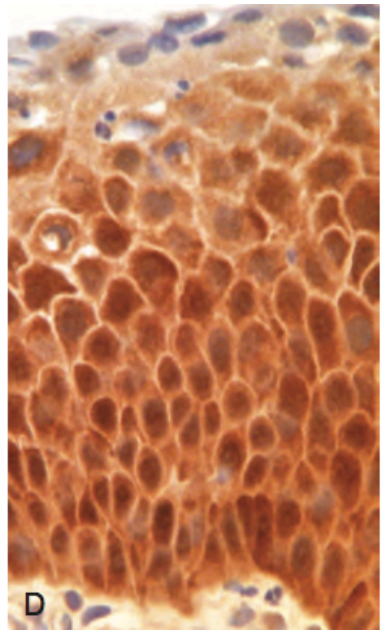
LSIL



In situ hybridization
HPV DNA



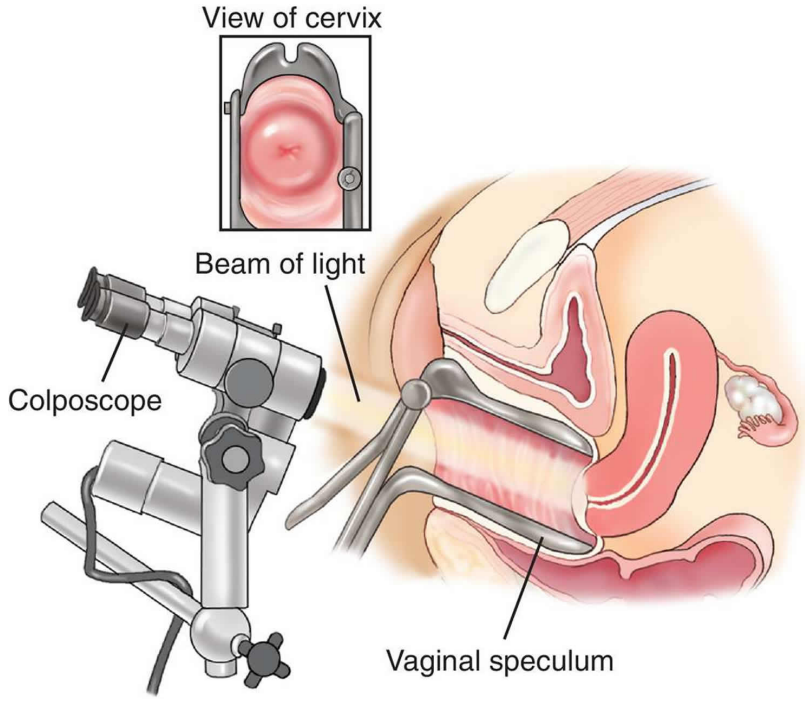
Ki-67



p16

Management

- Asymptomatic.
- Pap smear cytology usefull screening for SIL
- Abnormal pap smear → referred for colposcopy & cervical biopsies.
- **Colposcopy** and **directed biopsy** allows the clinician TRO invasive cancer & determine the limits of preinvasive disease.
- Conservative ablative treatment modalities: **cryosurgery, laser ablation & loop electrosurgical excision procedure (LEEP**) can be used to treat pre-invasive disease.



Colposcopic examination:
-Viewing the cervix with long focal-length dissecting-type microscope after applied acetic acid
-The solution acts to remove and dissolve the cervical mucus and causes SIL to become whiter than the surrounding epithelium (acetowhite).

Invasive Carcinoma of the Cervix

- 80% of cervical carcinomas are squamous cell carcinoma (**SCC)** followed by **adenocarcinomas (15%),** adeno-squamous ca and small cell neuroendocrine ca.
- The peak incidence of **SCC** is 45 years.
- Progression of SIL to invasive carcinoma is variable and unpredictable.
- The only reliable way to monitor the disease course is with frequent physical examinations with Pap smears and biopsy of suspicious lesions.
- The incidence of SCC has decreased in countries with organized screening programs

Symptoms suggestive of cervical cancer are:

- Post-coital bleeding (most common symptom)
- Intermenstrual bleeding
- Postmenopausal bleeding
- Vaginal discharge (blood stained)
- Pelvic pain

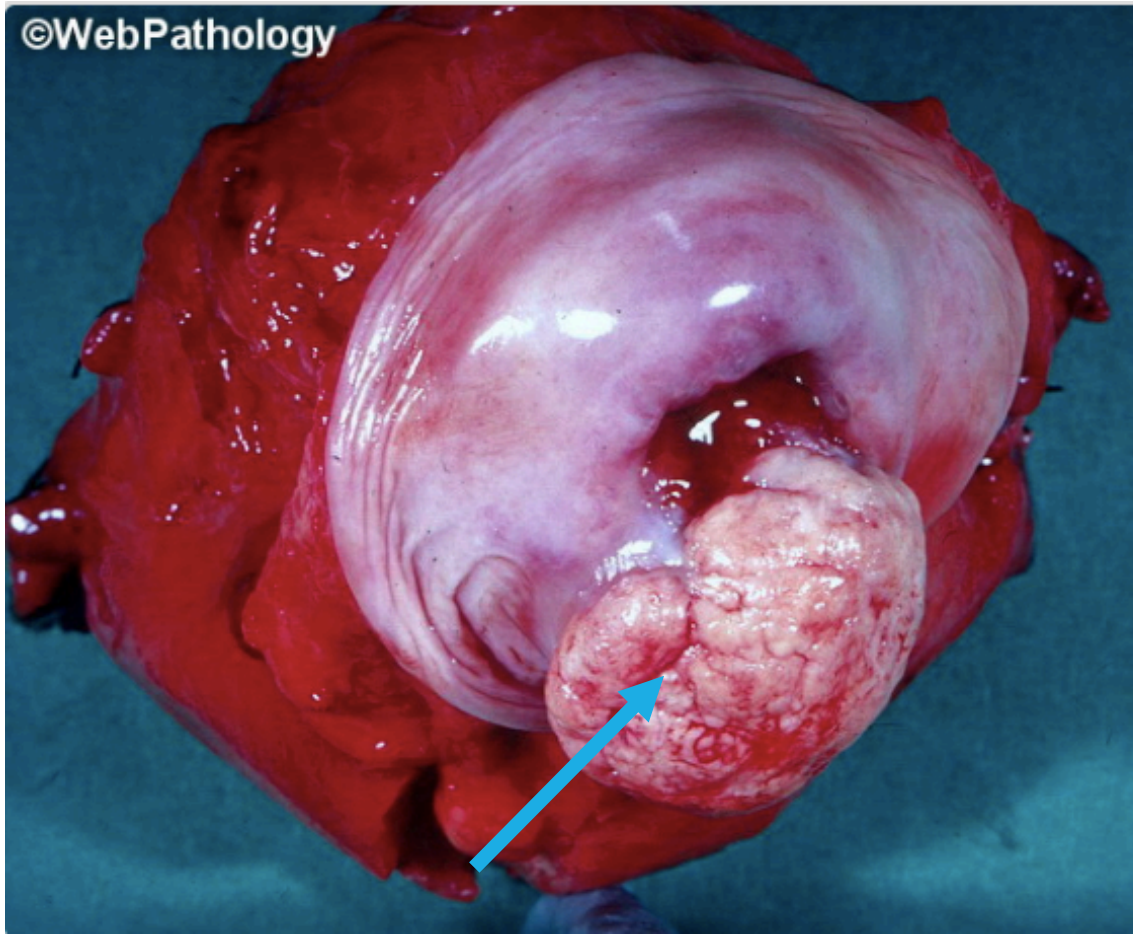
Examination

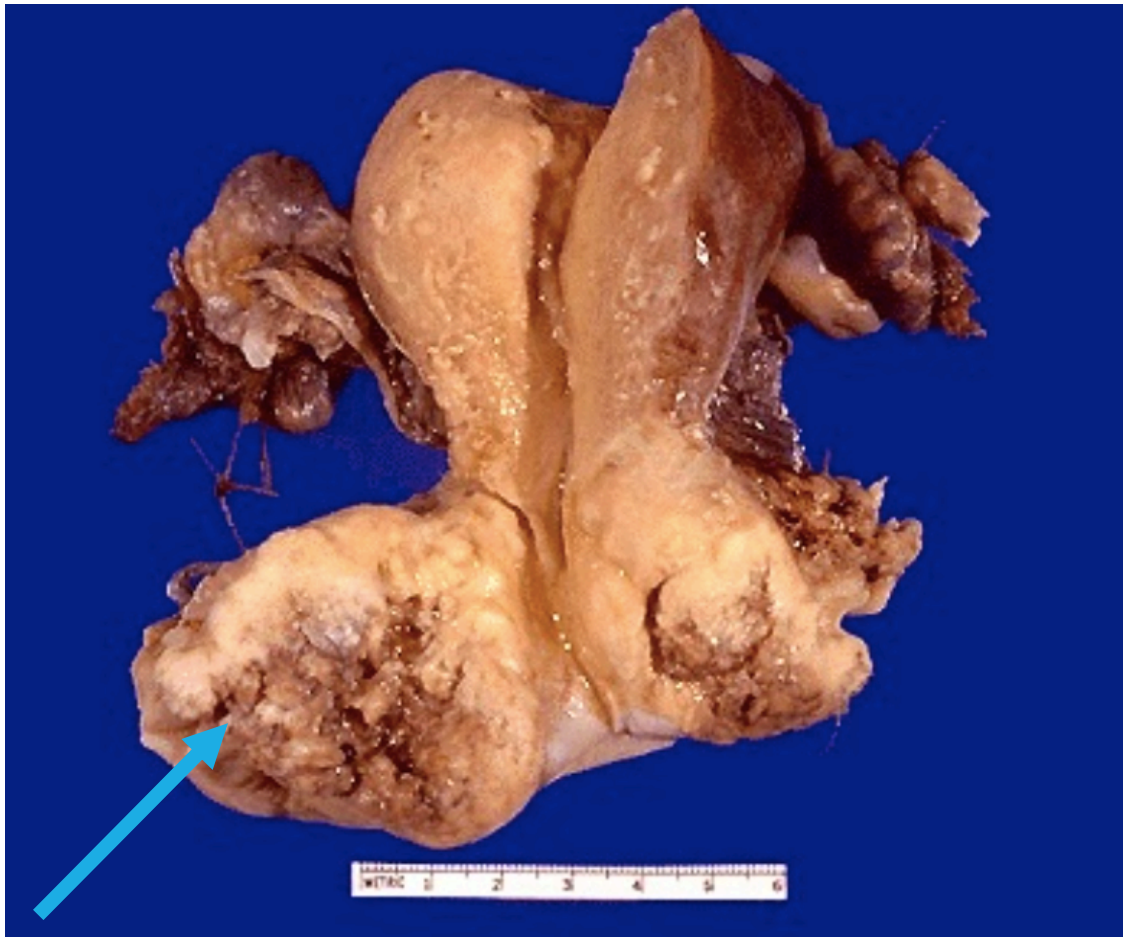
- Examination of the cervix with a speculum is mandatory.
- A suspicious cervix, or a woman with persistent symptoms is referred to colposcopy for a more detailed examination and biopsies.

Imaging:

- all patients with a diagnosis of cervical cancer > stage 1a1 have an MRI cervix to define local spread
- CT of abdomen and chest to look for signs of distant spread.

Gross: Squamous cell carcinoma





Cervical os with surrounding, invasive, exophytic cervical carcinoma (blue arrow).

Geography-where are you?

Low power: what is the organ
The border of lesion-pushing, encapsulated, infiltrative

Architecture: How is the house is built?

How the tumour cells arranged-acinar, nested, sheets, solid, cribriform..
Shape and size of the CELLS-polygonal, round, spindle..
Amount and the colour of cytoplasm-scant, abundant, granular, eosinophilic..
Shape and size of the NUCLEI
Chromatin texture & colour-fine, coarse, salt and pepper
Other features-

Landscape: what else is in and around?

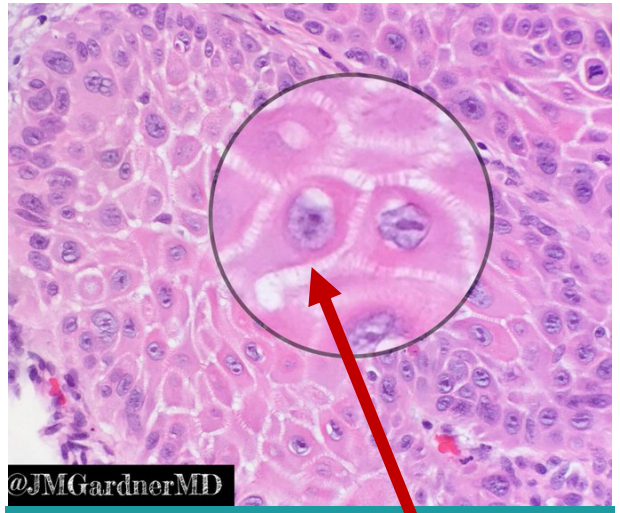
Necrosis, hemorrhage
Calcification
Stroma
Special features

Final diagnosis

Histologically

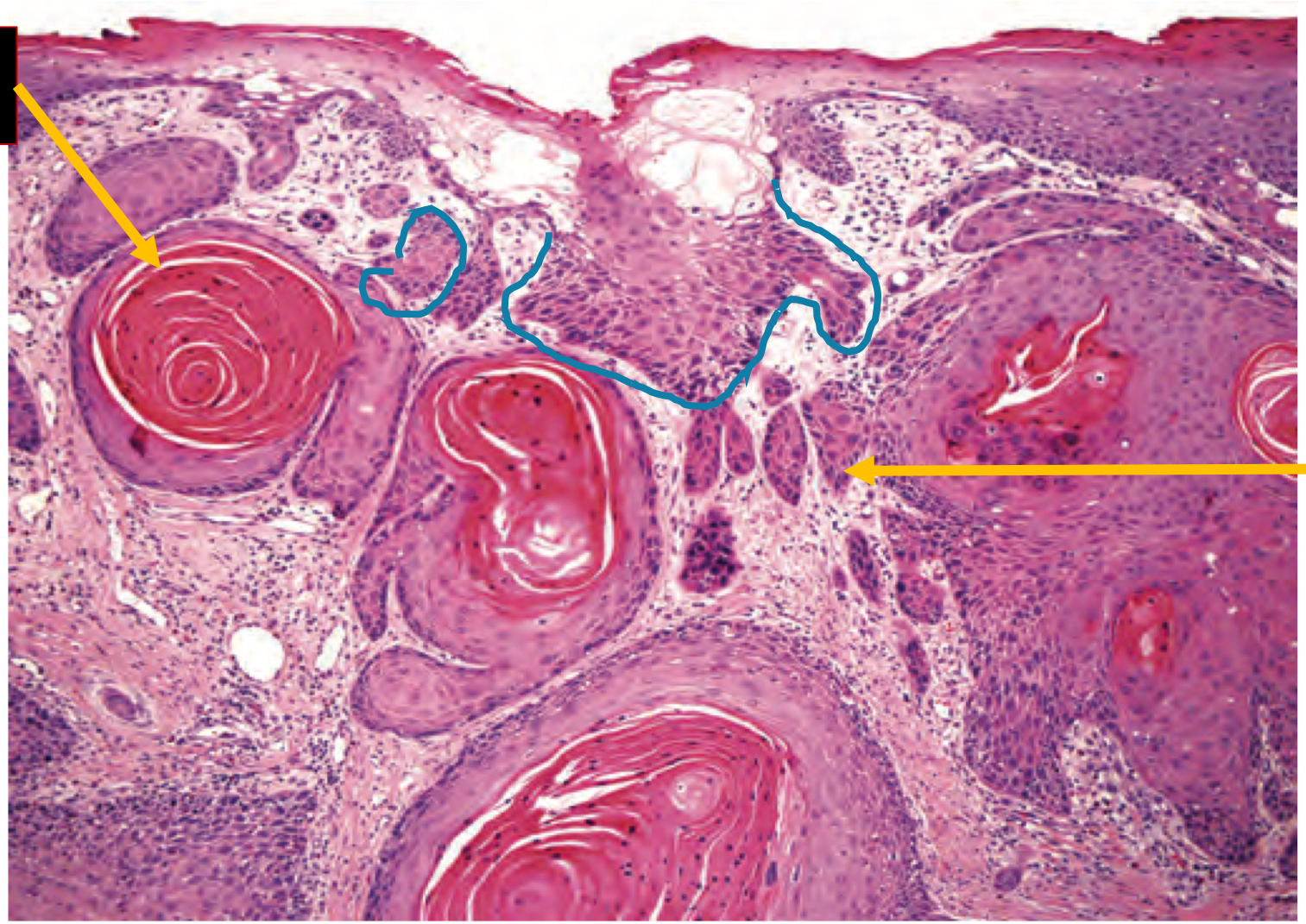
- Infiltrating nests and clusters of atypical squamous epithelium into the underlying tissue
- Presents of keratin pearls, individual cell keratinization (abundant eosinophilic cytoplasm), intercellular bridges
- Cells – enlarged nuclei, High NC ratio, pleomorphic, hyperchromatic
- Mitosis seen
- Stroma reactive/ desmoplastic reaction

Please labelled the structure as labelled



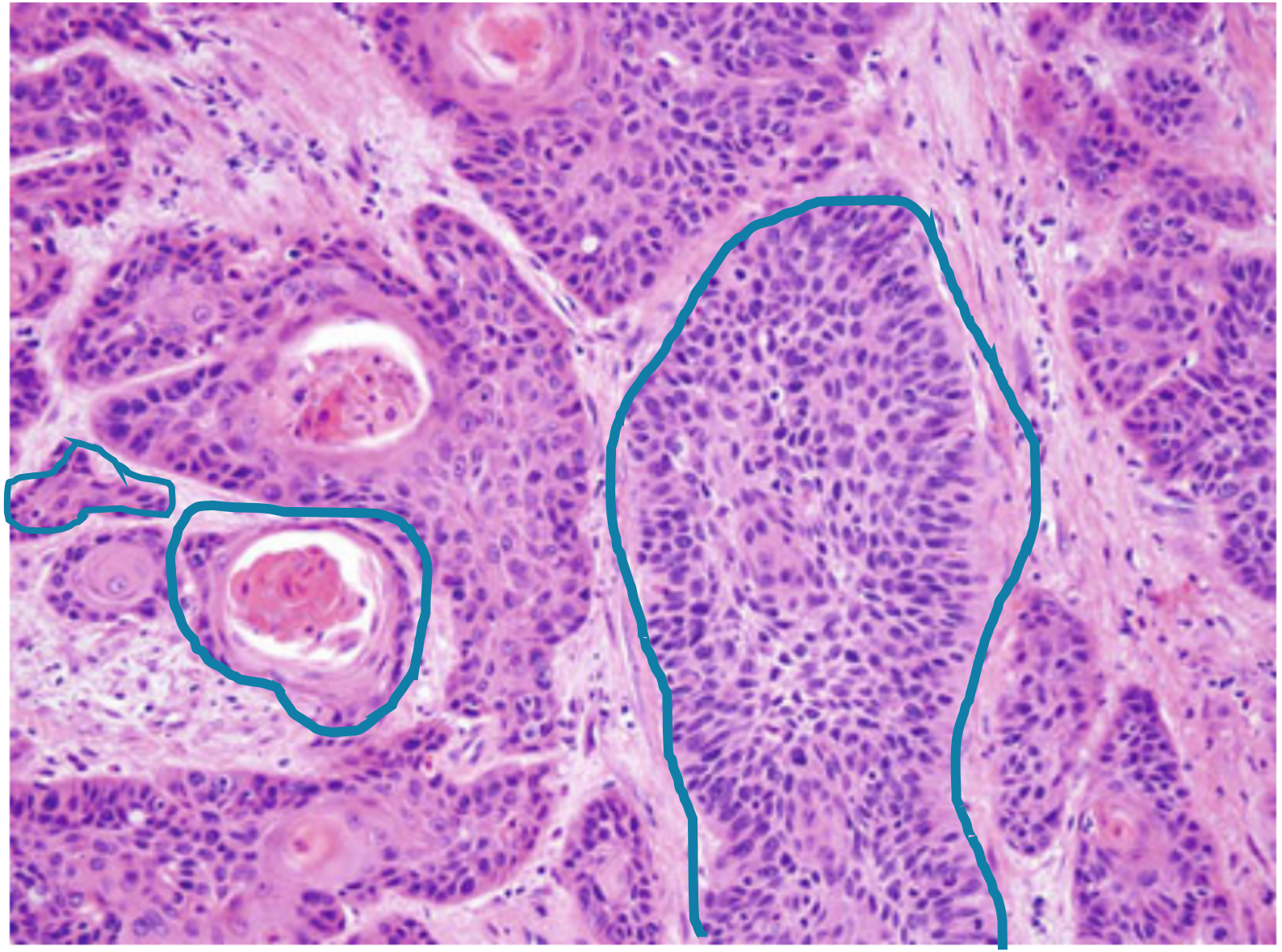
Intercellular bridges

Keratin pearls

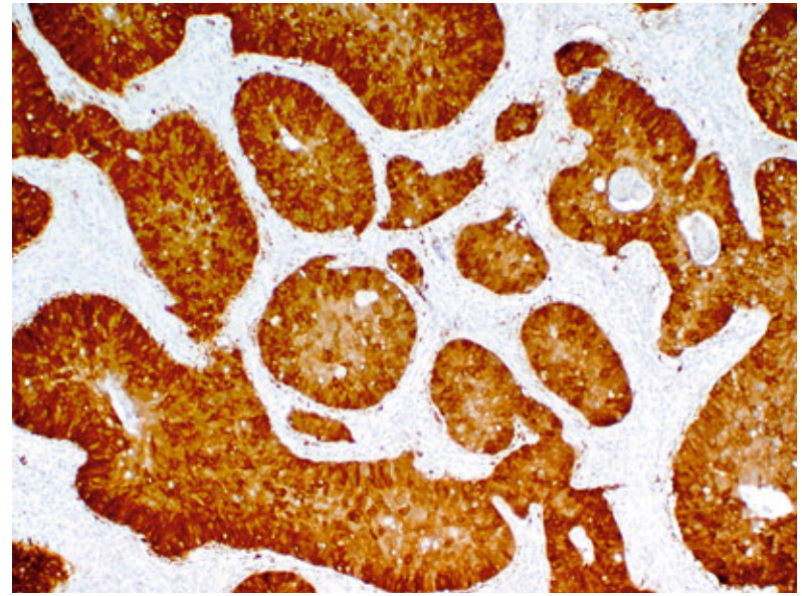


Infiltration of tumour cells

What is the diagnosis?
-Squamous cell carcinoma, well differentiated



Keratinizing SCC of the cervix, well differentiated, composed of islands and nests of neoplastic squamous epithelium with central keratin pearls

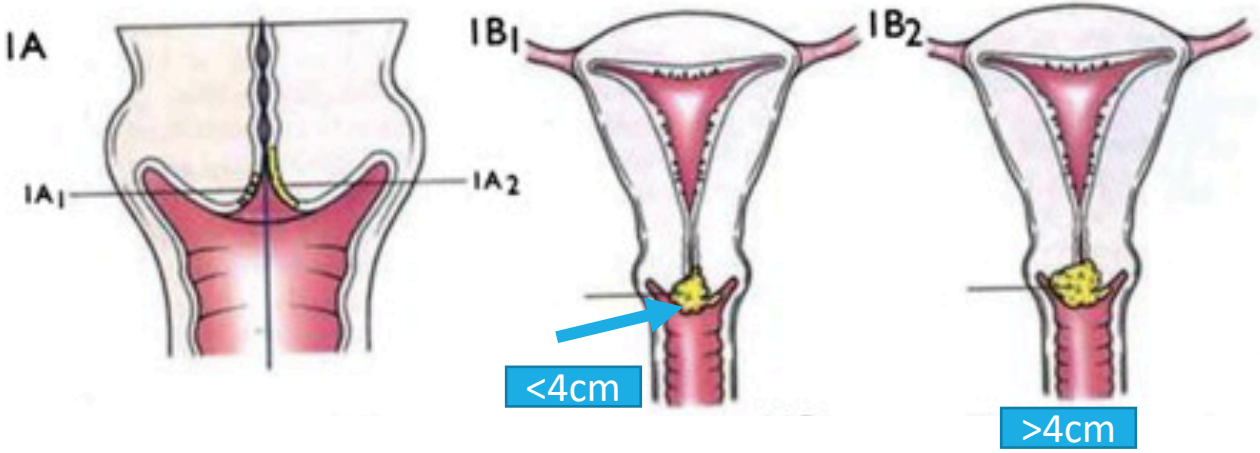


SCC positive for p16. Tumor exhibits characteristic diffuse and strong nuclear and cytoplasmic positive

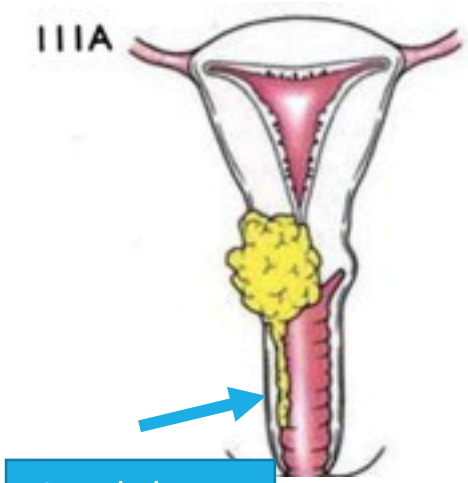
Grading

Well differentiated (grade 1)	Moderately differentiated (grade 2)	Poorly differentiated (grade 3)
• Histological and cytological features **closely resemble normal** squamous epithelium • varying proportions of basal & squamous cells with **intercellular bridges** • **Keratinisation** is a prominent • Few mitotic figures are seen • Atypical mitoses extremely rare • multinucleated epithelial cells are extremely rare • Nuclear and cellular pleomorphism is minimal.	This is a neoplasm with features intermediate btwn well differentiated and poorly differentiated. Compared with well-differentiated squamous cell carcinomas, moderate differentiated have • less intercellular bridges • less keratinisation • more mitotic figures and some are abnormal in form • more nuclear and cellular pleomorphism	• Histologically and cytologically there is only a **slight resemblance** normal squamous epithelium. • Intercellular bridges are extremely scarce • **Keratinization is rarely** present • Mitotic activity is frequent and atypical mitoses can readily be found • Multinucleated cells may be frequent. • Cellular and nuclear pleomorphism are obvious

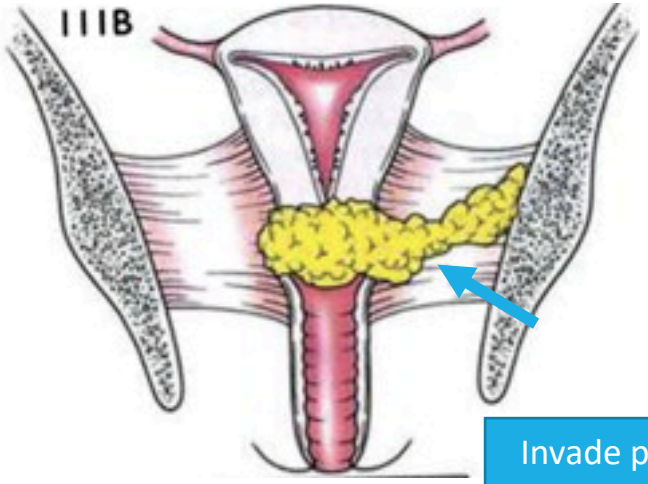
TNM & FIGO STAGING (Four-stage system of the International Federation of Gynecology and Obstetrics)



TNM Categories	FIGO Stages	Definition
T1a[b,c]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[d]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion

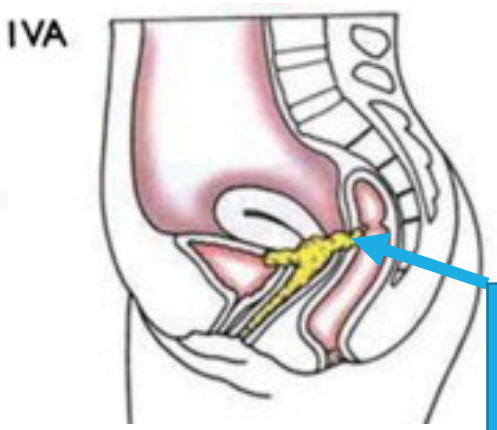


Invade lower 1/3 vagina

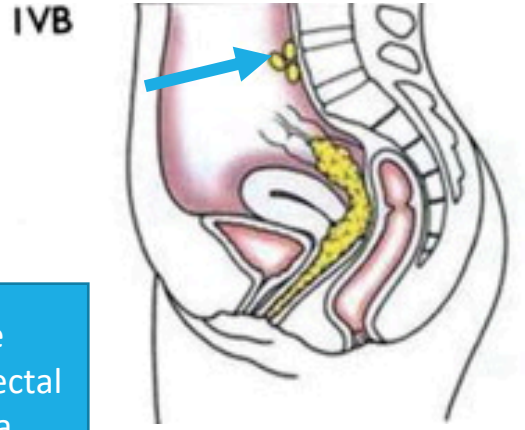


Invade pelvic wall

T3		III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
	T3a	IIIA	Tumour involves lower third of vagina
	T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non-functioning kidney



Invade bladder/rectal mucosa

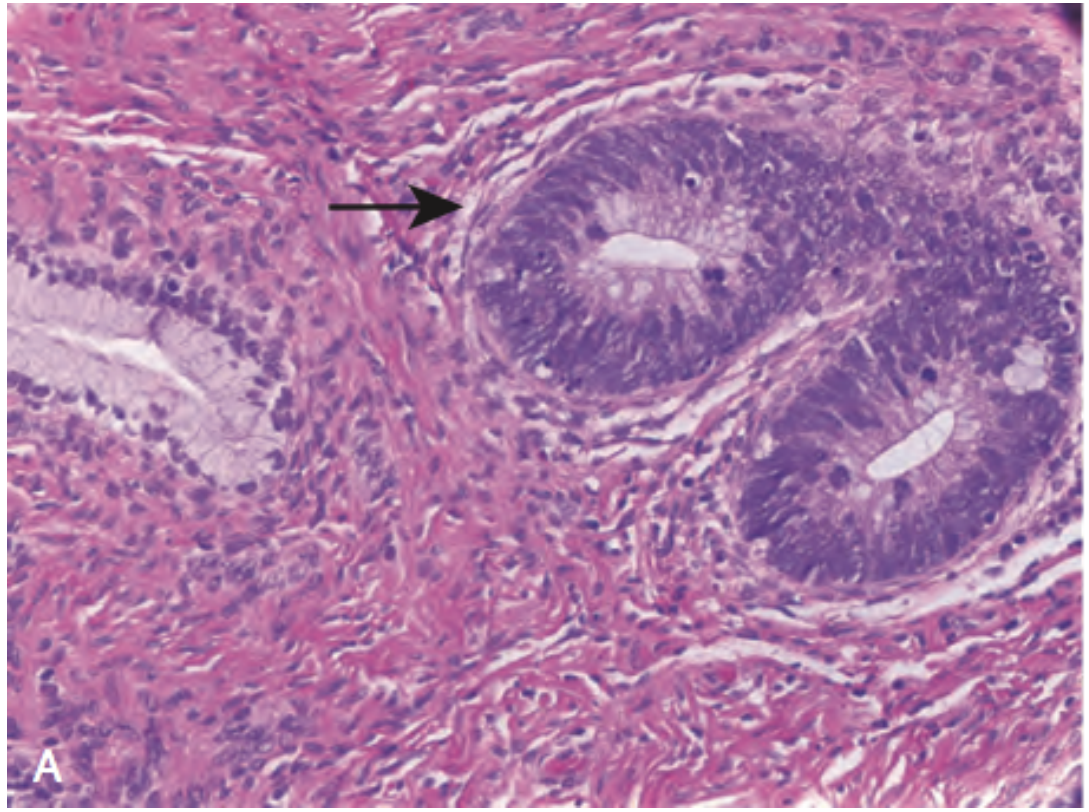


T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]
	IVB	Metastases

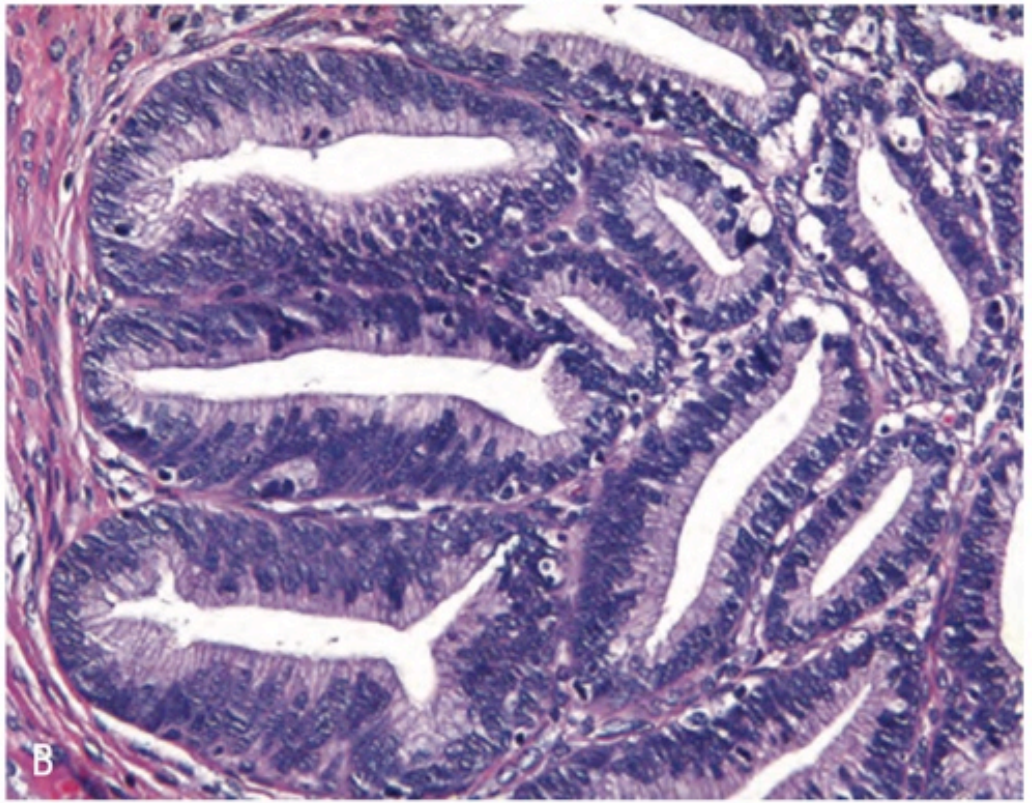
Treatment

- The treatment of invasive cervical carcinoma is largely dependent on stage at presentation.
- Early-stage cancer: treated surgically
- Advanced stages may be treated by **radical hysterectomy** with or without adjuvant therapy or by chemoradiation alone.
- Prognostic factors include **stage, tumor size, lymph-vascular space invasion, lymph node involvement, and patient factors such as age and performance status**
- Survival is stage-dependent, with a 91.8% 5-year survival for localized disease vs. a 16.9% survival for distant disease

Cervical adenocarcinoma



Adenocarcinoma in situ (AIS): dark glands with atypical, enlarged nuclei

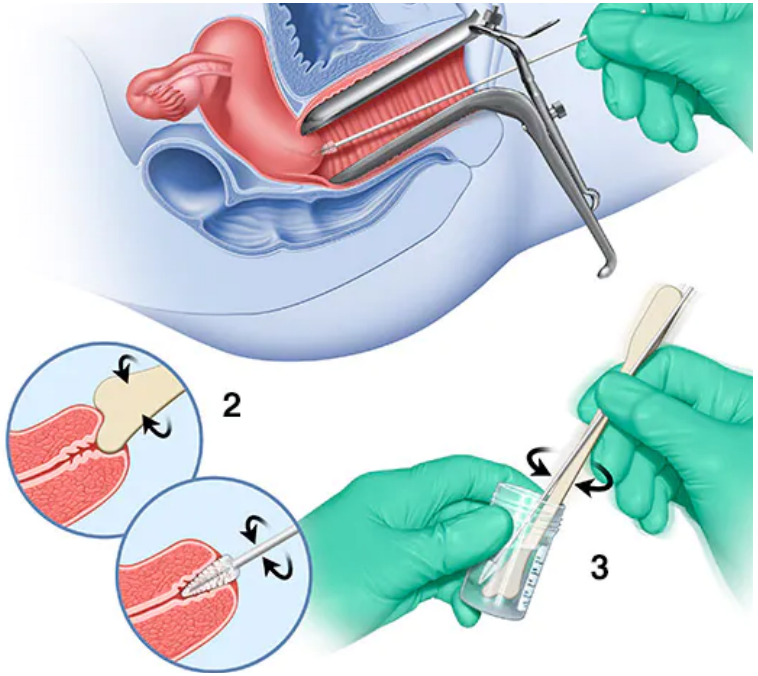


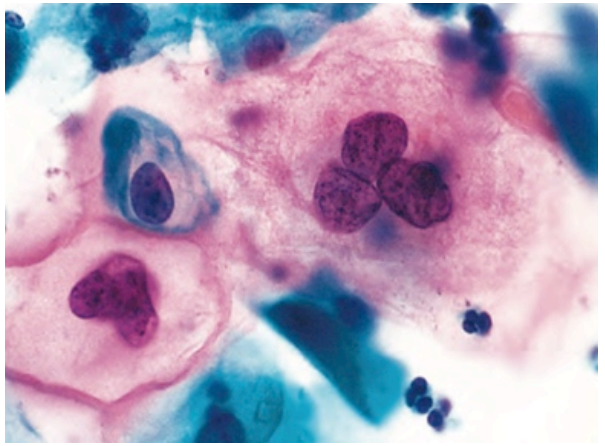
Invasive adenocarcinoma: malignant endocervical cells with large, hyperchromatic nuclei and relatively mucin-depleted cytoplasm,

Cervical Cancer Screening: Pap smear & HPV DNA

PAP SMEAR CYTOLOGY

- Cytologic cancer screening has significantly reduced mortality from cervical cancer.
- Objective were prevention and early detection of cervical cancer and ensuring early treatment
- Method: Using a **spatula or brush**, the transformation zone of the cervix is circumferentially scraped and the cells are smeared down onto a slide → further processing → screened microscopically.





HPV DNA

- New cervical cancer screening (molecular method) in detecting the HPV DNA in the cervical scrape.
- HPV testing has a **higher sensitivity** but lower specificity
- HPV DNA testing may be added to cervical cytology for screening in women **30 years of age or older**.
- Self-sampling by women or by health-care professional.

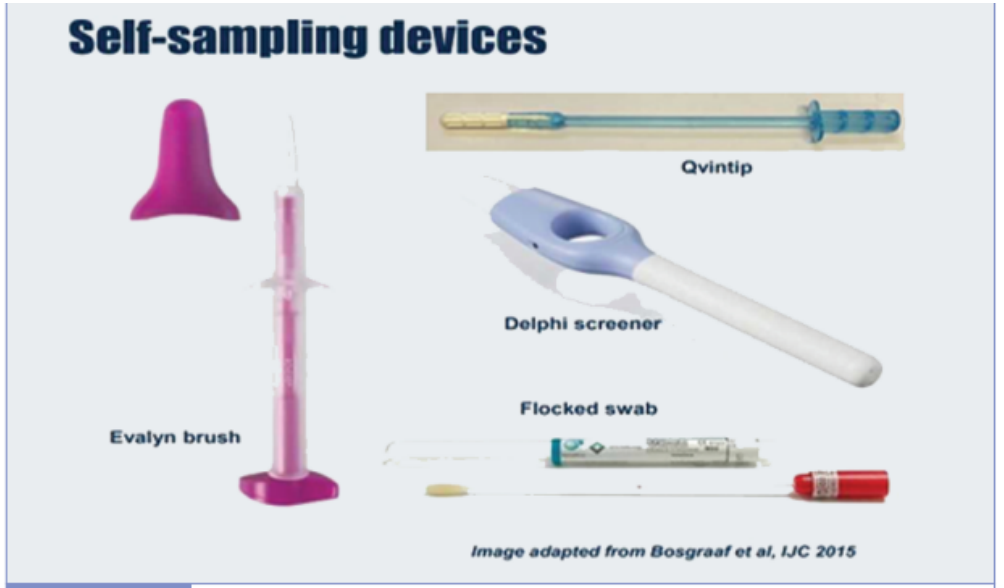
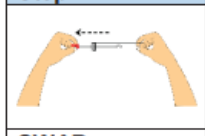
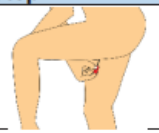
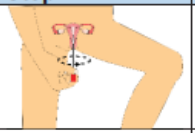
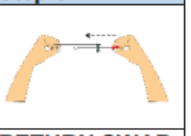


Figure 2 : Self-sampling devices

General guide for self-sampling technique (depend on the self-sampling devices available in the health facilities)

Step 1	Step 2	Step 3	Step 4	Step 5
				
SWAB • Remove the swab out of its plastic tube • Twist and pull	**POSITION** • Undress from the waist down • Remove your underwear • While holding the swab in your hand, get into a comfortable position	**INSERTING THE SWAB** • With your other hand, gently spread open the folds of skin at the opening of your birth canal • Insert the swab approximately 5cm (about half the length of your finger) • This is similar to inserting a tampon	**TAKING THE SAMPLE** • Rotate the swab gently for 10-30 seconds. There should be very little pain or discomfort • If you have any problems, speak to the nurse	**RETURN SWAB** • Put the swab back into the tube • Give the tube to the nurse

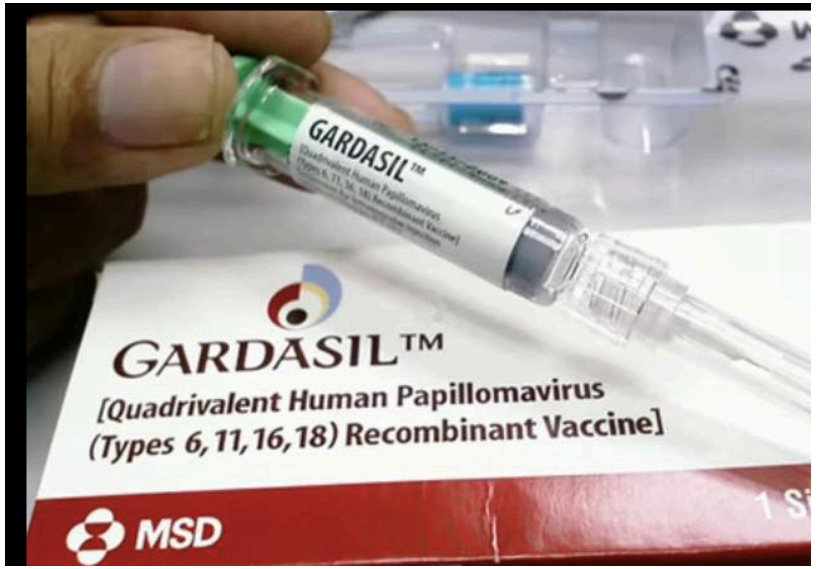
- Recommendations for the frequency of Pap screening vary.
- General the first smear should be at 21 years of age or within 3 years of onset of sexual activity, and thereafter **every 3 years**.
- After **30 years of age**, women who have had normal cytology results and are negative for HPV → screened **every 5 years**.
- Women who have a normal cytology result but test positive for high-risk HPV DNA →repeated every 6 to 12 months

Pap test is abnormal, what's next?

- Refer for **colposcopic examination** of the cervix and vagina is performed to identify the lesion and **biopsies**.
- Biopsy-confirmed LSIL can be followed in a **conservative fashion/local ablation**.
- HSIL is treated with **cervical conization** (superficial excision)

Cervical cancer Prevention: Vaccination

- Part of cervical cancer prevention
- Recommended for all girls and boys by age of 11 to 12 years, & up to 26 years of age.
- Two HPV vaccines (FDA-licensed)- Cervarix & Gardasil
- Both provide nearly complete protection **against high-risk oncogenic** HPV types 16 and 18 (also covered HPV types 6 and 11)
- The vaccines offer **protection for up to 10 years**.
- Because the HPV vaccines do not protect against all high-risk HPV types, current guidelines recommend that cervical cancer screening be continued as in the past.



Summary

- Transformation zone
- CIN/SIL
- HPV infection is transient
- Persistent HR-HPV can dev pre-invasive lesion and invasive lesion
- Screening program is really benefit in detecting precancerous cervical lesion and improve patient survival.

References

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