Crevix

Cervicitis (most common, could be due to STI (Chlamydia trachomatis and Neisseria gonorrhea), bacterial vaginosis, candida, non-infectious: irritants, trauma…)

Neoplasia of the cervix	Types
Epithelial cells (most common) (most common by HPV) (tumours most commonly arise from the transformation zone (immature squamous cells)) (HPV-Tropism for immature squamous cells)→ Normal histology: Ectocervix - by SQ mature Transformation - SQ metaplasia-immature - has prolif. activity - HPV hits here first then ecto or endo Endocervix - by glandular mucin secreting column cells	Squamous and colmnar
Stromal cells →	Mesenchymal
Lymphoid tumors →	Primary or secondary

Epithelial cells of cervix neoplasms
HPV infection that has tropism for immature squamous cells.
Low-risk HPV: Transient (mostly), eliminated by immune response within months. On average, 50% of infections are cleared within 8 months, and 90% are cleared within 2 years.
High-risk HPV: Persistent infection (for many years)---- squamous intraepithelial lesions (SILs)----cervical carcinoma Persist for more than 2 years
HPV → detectable by molecular methods (such as PCR for detection of viral DNA) in nearly all cases of cervical intraepithelial neoplasia (CIN) and cervical carcinoma (~5 - 7% of cases are HPV negative).
The 5-7% are due to Genetic mutations, environmental factors, other persistent infections or unknown strains of HPV
Risk factors for CIN and invasive carcinoma (related to HPV exposure): 1. Early age at first intercourse. 2. Multiple sexual partners. 3. Male partner with multiple previous sexual partners. 4. Persistent infection by high-risk strains of HPV; due to immunosuppression, HIV co-infection, and Smoking. 5. African American NOTE: Family history does NOT play a sig. risk in cervical cancer.

Epithelial cells of cervix neoplasms

Risk factors for cervical cancer
• Infection with high-risk HPV strains (eg, 16, 18) • History of sexually transmitted infections • Early onset of sexual activity • Multiple or high-risk sexual partners • Immunosuppression • Oral contraceptive pill use • Low socioeconomic status • Tobacco use
HPV = human papillomavirus.

REFRENCE NO. 6

E6 and E7 oncoproteins cause cancer by inactivating the tumour suppressor proteins p53 (E6) and pRb (E7), disrupting cell cycle regulation and preventing apoptosis.

Integration (NOT ALWAYS) of the viral DNA into the host genome can often lead to increased and more stable expression of E6 and E7 oncoproteins, further driving the carcinogenic process.*

*Malignancy requires → persistent infection + viral integration.

Low-risk HPV variants	High-risk HPV variants
Types 6 and 11	Types 16 (m.c) and 18 account for approximately 70% of cases of CIL and cervical carcinoma Other high-risk types, such as HPV **31, 33, 45, 52, and 58**, also contribute (30%)
Associated with the development of condylomas of the lower genital tract	In general, infections with high-risk HPV types are more likely to persist, which is a risk factor for progression to carcinoma
Express E6 and E7 variants with different or weaker activities and do not integrate into the host genome, remaining instead as free episomal viral DNA (free circular DNA molecules within the nucleus of the cervical cells)	These HPV types also show a propensity to integrate into the host cell genome, an event that is linked to progression. **HOW**? → Integration always disrupts an HPV “E2 gene” at the integration site; that negatively regulates E6 and E7 genes, which leads to their increased expression → Sometimes (less common mechanism) HPV integrates near a host cell oncogene such as MYC, leading to its overexpression as well

Low-risk HPV variants	High-risk HPV variants
	Despite the strong association of HPV infection with cancer of the cervix, HPV is not sufficient to drive the neoplastic process Persistent high-risk HPV infection is the primary initiating event, additional factors are needed for the progression to neoplasia like the integration near MYC or disturbing supressing or activating genes
	Diverse other factors such as: → Immune (immune deficiency) → Hormonal status (long-term OCP). → Coinfection with other sexually transmitted agents (STI) are suspected to play a role Collectively these factors **favor the acquisition of somatically acquired mutations** that involve both **oncogenes** and tumor **suppressor genes** In all types of cancers, somatic or germline mutation at tumor suppressor or oncogenes must occure

Squamous Intraepithelial Lesion (SIL, Cervical Intraepithelial neoplasia):

Dysplasia in the surface epithelium with no disruption of the basement membrane or invasion to the subepithelial stroma

HPV-related carcinogenesis begins with the precancerous epithelial change termed SIL

Usually precedes (SIL peaks in incidence at about 30 years of age) the development of overt cancer by many years, sometimes decades (Invasive carcinoma peaks at about 45 years of age)

Infection of HIV occurs at age of 20 → After 10 years, SLI develops → After 10-15 years , Invasive carcinoma occurs

New 2-tiered classification instead of 3 tiered classification system: both caused by high risk HPV **SIL**

Most high-risk HPV infections do not lead to cancer.

One consideration is that while most women acquire HPV infections in their early 20s, these are usually cleared by the immune system and do not progress to SIL, a process that occurs over many years.

But if HSILs and persistent LSIL are there, they are treated with surgical excision (cone biopsy); due to risk of progression.

So, women with biopsy-documented LSIL are managed conservatively with careful observation (repeat cytology (Pap smear) and/or HPV testing at intervals (e.g., every 6-12 months)) to monitor for persistence or progression, because it often reflects a transient HPV infection that the immune system is likely to clear on its own .

For this reason, HPV DNA screening is only recommended for women aged 30 or older, as a positive test at this age is more likely to identify an individual with a persistent infection that may lead to cervical neoplasia.

So, again, the vast majority are cleared by the immune system , and that viral integration is not present in all infections with high-risk HPV; it is important in the development of invasive lesions.

Low-grade squamous intraepithelial lesion (LSIL)	High-grade squamous intraepithelial lesion (HSIL)
still often referred to as cervical intraepithelial neoplasia I (CIN I)	encompassing cervical intraepithelial neoplasia II and III (CIN II and III) of the previous three-tiered system

Low-grade squamous intraepithelial lesion (LSIL)	High-grade squamous intraepithelial lesion (HSIL)
Does not progress directly to invasive carcinoma	HSIL is considered at high risk for progression to carcinoma
Most LSILs regress and only **10%** progress to HSIL often **goes away on its own** (**60%**) (LSIL (low-grade SIL) often regresses spontaneously.) Persist (**30%**)	HSIL **10%** To carcinoma within 10 years (thus, the progression from HSIL (high-grade SIL) to invasive cancer is a relatively slow process, taking many years in most cases.) Regress by about (**30%**) of the cases Persist (**60%**)
LSIL is 10 times more common than HSIL	

Patient management rests on the histopathologic diagnosis, the decision to treat HSIL and to observe LSIL is based on differences in the natural histories of these two groups of lesions.

Lesion Type	Natural History (If Untreated)
LSIL (CIN 1)	Usually **regresses** (esp. in young women) within 1–2 years
HSIL (CIN 2/3)	More likely to **persist** or **progress** to invasive cancer

Hpv vaccine is given at age of (**9**) by **2** doses and it covers most common Hpv strains (**6, 11,16, 18, 33, 35**), It gives life long or at least 12 years protection

First step:
The Centers for Disease Control and Prevention (CDC) recommends HPV vaccination in 2 or 3 doses depending on age:

- **2** doses for children and adolescents of any gender ages 9 - 14 years. (0m, 6-12m)
- **3** doses for adolescents and adults of any gender ages 15 - 26 years. (0m, 1-2m, 6m)

The quadrivalent HPV vaccine for types 6, 11, 16, and 18, and the more recently introduced 9-valent vaccine (HPV types **6, 11, 16, 18**, **31, 33, 45, 52**, and **58**), which offers a broader protection

Despite its efficacy, vaccination **does not supplant the need for routine cervical cancer screening**—many at-risk women are already infected, and current vaccines protect against only some of the many oncogenic HPV genotypes

SIL is asymptomatic and comes to clinical attention through an abnormal Pap smear result. (gives vaccines first then:)

These cases are followed up by colposcopy, in which **acetic acid** is used to highlight the lesions so they can be biopsied.

HSILs and persistent LSIL are treated with surgical excision **(cone biopsy)**; due to risk of progression. Or follow up.

- **Valuate and treat high-grade cervical intraepithelial neoplasia (CIN 2/3)** , **early-stage cervical carcinoma** and **persistent LSIL**

Colposcopy-------leukoplakia. No need for the acid.

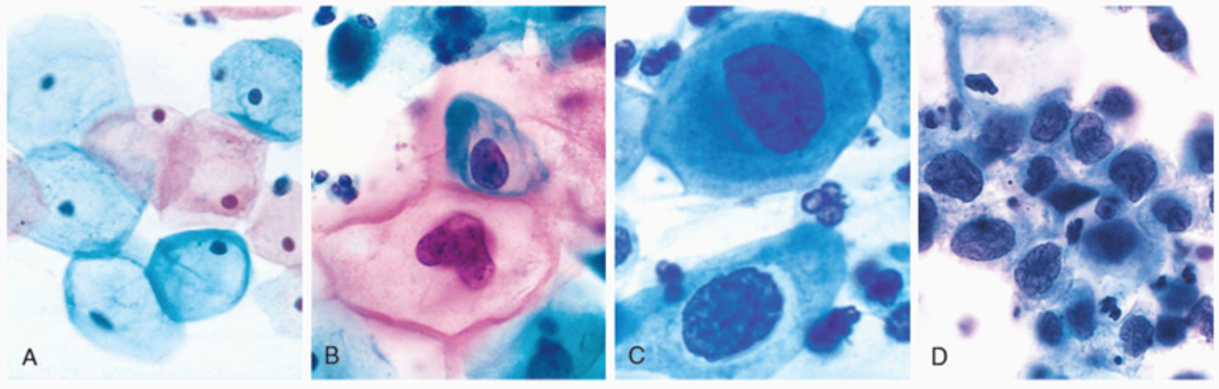
SILs are associated with abnormalities in cytologic preparations that can be detected long before any abnormality is visible on gross inspection:

Second step:

Feature	Pap Smear (Papanicolaou Test) Using Pap stain (Hence the name, but should be Cervical pap smear since pap stain isn't specific) The most successful cancer screening test	HPV DNA Testing (PCR)
What it tests	Scrapes Endo and ecto including **transformation zone cells** to detect **cytologic abnormalities**	Detects **high-risk HPV DNA** via **PCR**
Purpose	Screens for **cellular dysplasia** (SIL/CIN)	Screens for **oncogenic HPV infection**
Effect on cancer	↓ Incidence of **invasive cervical cancer**	Helps identify patients at risk before cytologic changes
Effect on SIL detection	↑ Detection of **SILs (CIN 1–3)** hence the "Increased the incidence of SIL"	Detects **infection before dysplasia** forms
Recommended age	**21–29 years**	**30–65 years** (combined with Pap)
Frequency	Every **3 years**	Every **5 years** (if co-tested with Pap)
Used with	Alone in 21–29 y/o	**Co-testing** with Pap in 30–65 y/o
Screening tool type	**Cytology-based**	**Molecular-based**

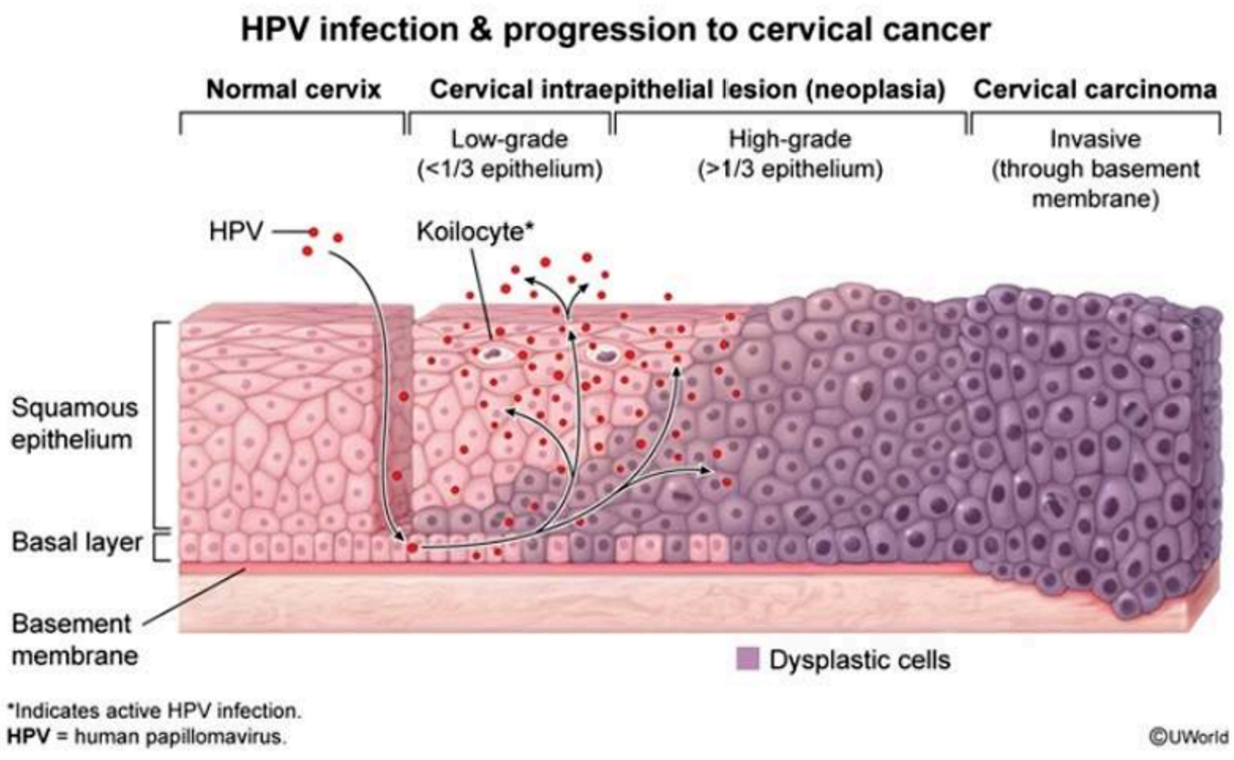
Grade	Name	Extent of Dysplasia	Key Histologic Features
CIN I	**LSIL (Low-Grade SIL)**	Lower **1/3 of the squamous epithelium**	Dysplastic changes in lower third + **koilocytic change** in superficial layers
CIN II	**HSIL (High-Grade SIL)**	Dysplasia extends to the **middle 1/3** of the epithelium	Superficial cells still show **differentiation** and **occasional koilocytosis**
CIN III	**HSIL (High-Grade SIL)**	Dysplasia involves **>2/3 or full thickness** of epithelium	**Loss of differentiation**, ↑ cell/nuclear size variation, **chromatin heterogeneity**, **abnormal mitoses**, disorganized cells in **all layers** with basement membrane invasion -> Then it turns into invasive cervical carcinoma

Pap smear



A: Normal B: LSIL C: HSIL D: HSIL

Note the reduction in cytoplasm and the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. This observation reflects the progressive loss of cellular differentiation on the surface of the cervical lesions from which these cells are exfoliated.

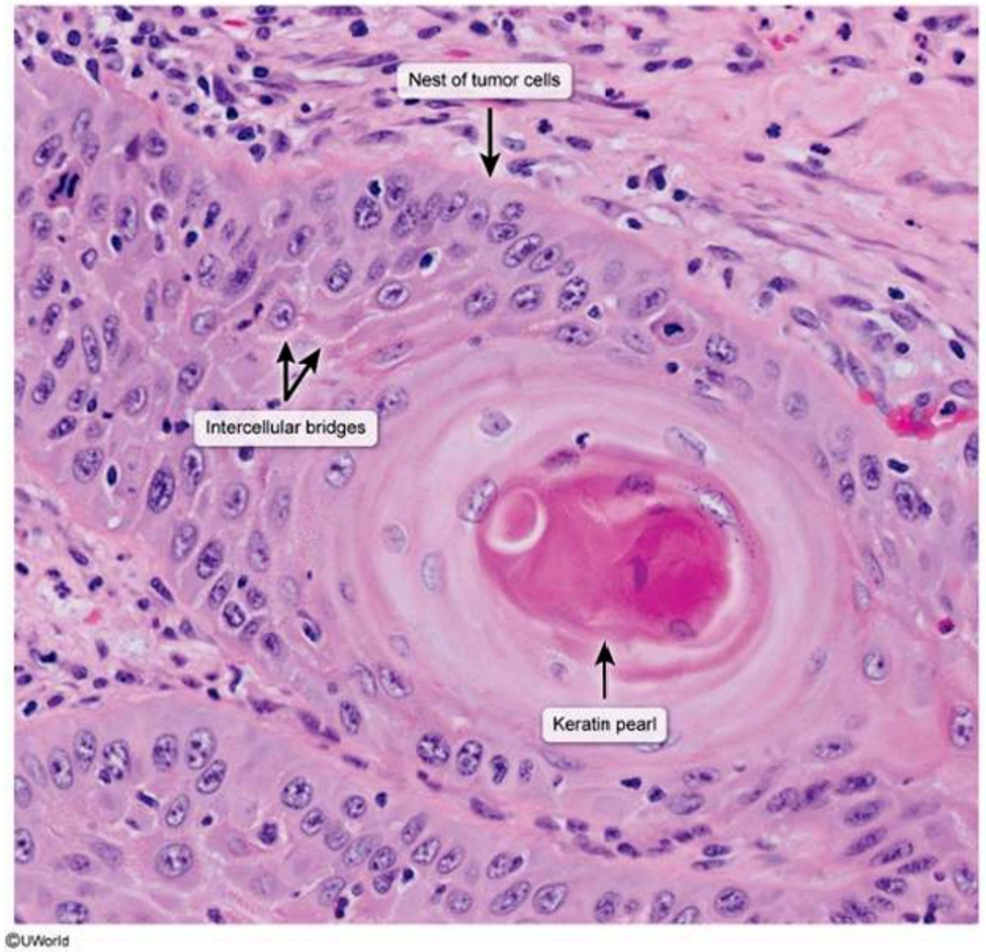


Carcinoma of the vuvla (RECALL)
Represents about 3% of all female genital tract cancers. Not common.
Squamous cell carcinomas (90%). First most common - Not only in vulva.
Adenocarcinomas. Second.
Basal cell carcinoma. Third.

Carcinoma of the vagina (RECALL)
Squamous cell carcinomas. First most common - Not only in vulva. (DRIVEN BY HPV INFX)
Adenocarcinomas. (DRIVEN BY DES/AGE)
Sarcoma botryoides (embryonal rhabdomyosarcoma of the vagina)

Invasive Carcinoma of the Cervix
Squamous cell carcinomas (75%). Well-differentiated (keratinizing). Keratin pearls. (DRIVEN BY HPV INFX)
Adenocarcinomas and mixed adenosquamous carcinomas (20%). (DRIVEN BY HPV INFX)
Small cell **neuroendocrine** carcinomas (<5%).

Squamous cell carcinoma



Just like SIL, **all** of these types of carcinomas are associated with high-risk HPV

Squamous cell carcinoma (Sym)
Has a peak incidence at the age of about 45 years
Preceded by SIL (Asym)
Progression of SIL to invasive carcinoma is variable and unpredictable and requires (persistent) high-risk HPV infection (types 16, 18, 31, and 33); as well as mutations in tumour suppressor genes and oncogenes
Cigarette smoking
Immunodeficiency (human immunodeficiency virus (HIV) infection, suggesting that immune surveillance plays a role in preventing progression)
Exophytic cervical tumour
Grading: well-differentiated, moderately differentiated, poorly differentiated
Ulceration or bleeding, leukorrhea, painful coitus (dyspareunia), or dysuria

Squamous cell carcinoma (Sym)
Spread to pelvic lymph nodes: correlates with the depth of tumor invasion and the presence of tumor cells in vascular spaces (LVI)
The risk of metastasis increases from less than 1% for tumors less than 3 mm in depth to more than 10% after invasion exceeds 3 mm
Mortality is most strongly predicted by tumor stage
The primary treatment is hysterectomy and lymph node dissection, CONE restriction is not enough.
Radiation and chemotherapy are also of benefit in instances where surgery alone is not curative