



# Female genital tract-Part1. Pathology of the vulva, vagina and the uterine cervix

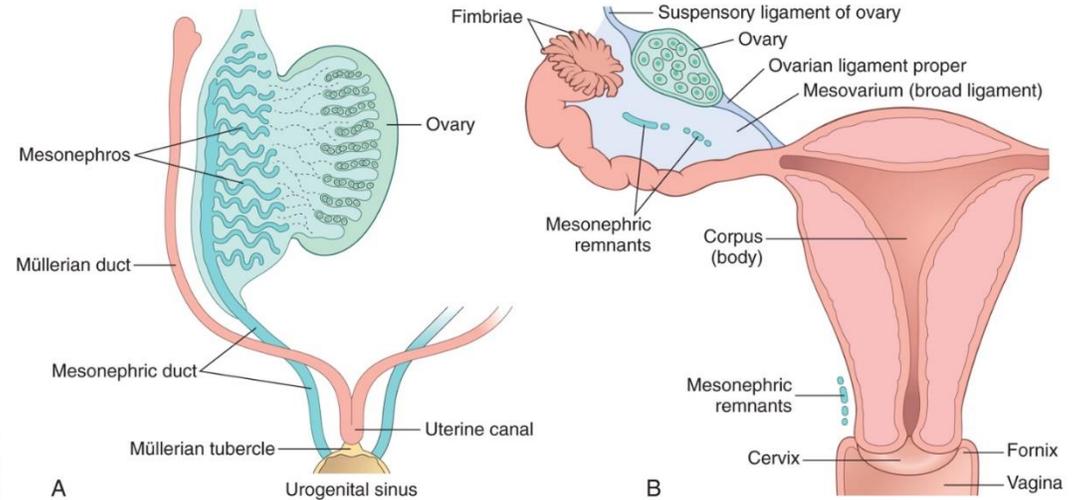
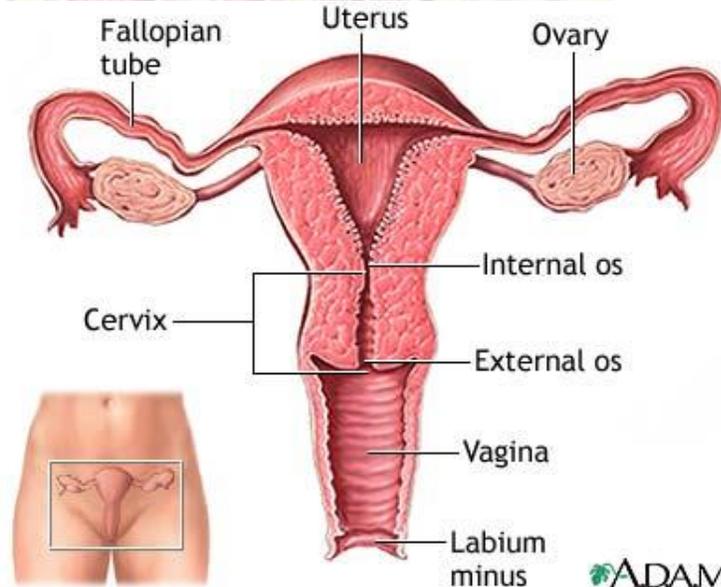
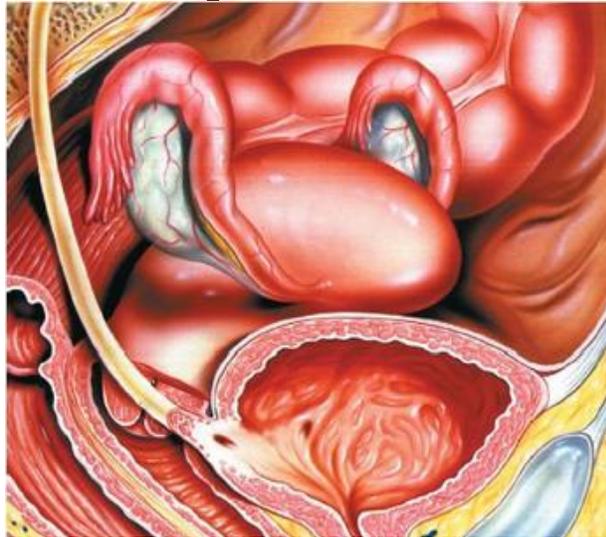
Lilla Madaras MD PhD

Department of Pathology, Forensics and Insurance Medicine

*250 years of EXCELLENCE  
in medical education,  
research & innovation  
and healthcare*

17<sup>th</sup> April 2023

# Anatomy, development



Robbins 9th edition

# Outline

- Infections of the female genital tract
- Vulvar diseases and carcinoma of the vulva, the VIN classification
- Vaginal diseases, VaIN and malignant tumors
- CERVICAL CANCER

# Infections of the Female Genital Tract

- Usually sexually transmitted
- Gonorrhea, trichomoniasis, chancroid, lymphogranuloma venereum, syphilis, granuloma inguinale, mycoplasma, other chlamydia infections, HSV, HPV

# Infections of the lower genital tract

- **Herpes simplex**

- DNA virus
- HSV-1 oropharyngeal infections mainly
- HSV-2 Cervix, vagina, vulva
  - Symptoms: fever, malaise, tender lymph nodes, red papules that progress to vesicles than painful ulcers, purulent discharge
  - healing of skin and mucosal lesions in 1-3 weeks
  - Virus migrates to lumbosacral ganglia where persists → reactivation
  - Transmission during delivery!!!

- **Molluscum contagiosum**

- Poxvirus
- Usually young children, skin anywhere
- In adults: genitals (Sexually transmitted) dome shaped papules with dimple

# Infections of the lower genital tract

- **Candida**
  - Extremely common (part of normal vaginal flora→ disturbance→ candidiasis) in DM, pregnancy, AB treatment
  - Pruritus, curd-like discharge
  - Not STI
- **Trichomonas vaginalis**
  - Flagellated protozoa
  - Yellow, frothy discharge, vaginal discomfort, dysuria, dyspareunia
  - Strawberry cervix on colposcopy (dilated vessels)
- **Gardnerella vaginalis**
  - Gram negative bacillus
  - Bacterial vaginosis (main cause of)
  - Thin, green, malodorous vaginal discharge
  - Preterm delivery if during pregnancy
- Ureaplasma urealyticum, mycoplasma hominis- vaginitis, cervicitis, chorioamnionitis
- Chlamydia- cervicitis, but usually PID

# Pelvic Inflammatory Disease

- Begins in the vulva and vagina
- Pelvic pain, fever, vaginal discharge
- **Neisseria gonorrhoeae**-endocervical or Bartholin gland or periurethral glands from there to adnexae (acute purulent inflammation, Gram negative diplococci within neutrophils, tubo-ovarian abscess, pyosalpinx, later scarring, chronic inflammation, hydrosalpinx) endometrium usually spared!
- **Staphylococci, streptococci** and others- after DC, abortion-bacteraemia, inflammation in deeper tissue layers

VULVA

# Bartholin cyst

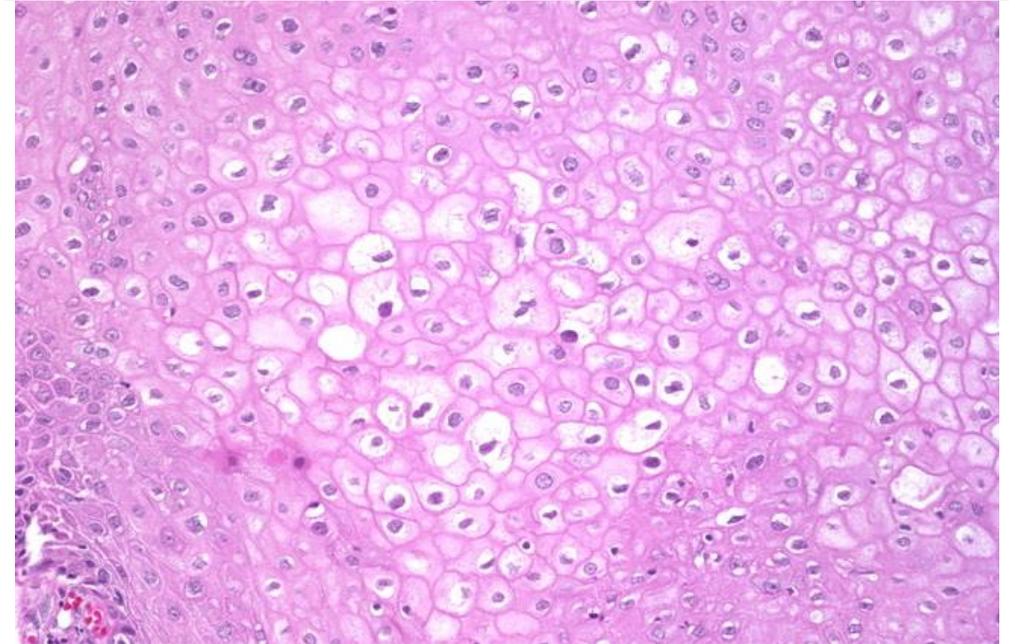
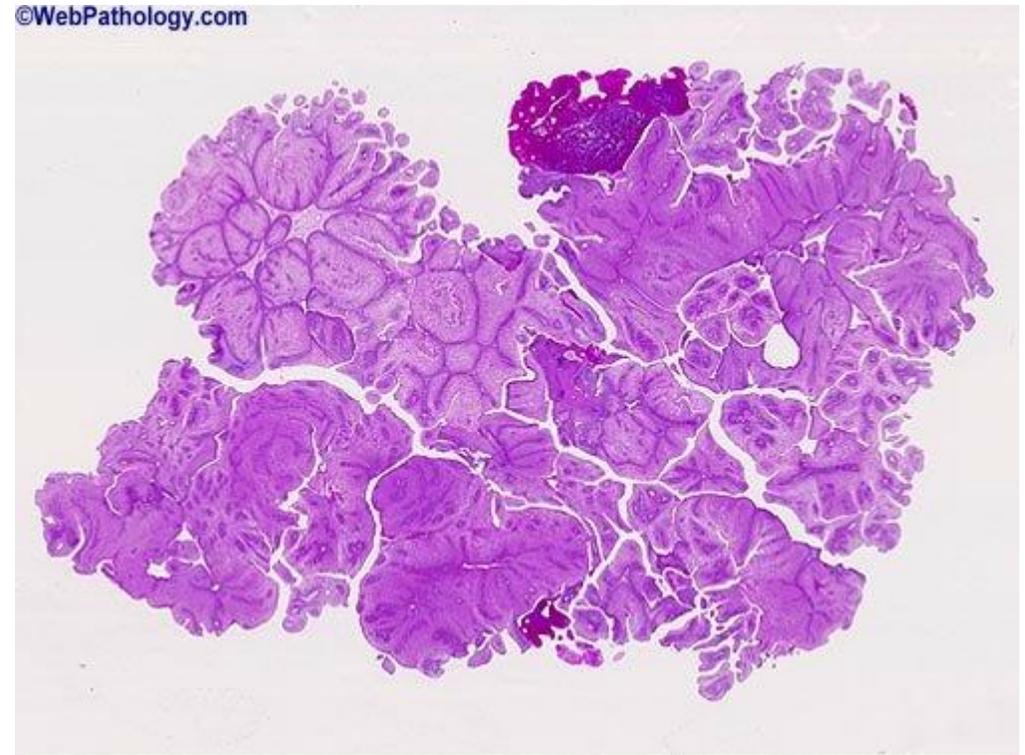
- Acute inflammation of the Bartholin gland may result in abscess
- Inflammation related obstruction may lead to cyst formation
- Transitional or squamous epithelium lined, 3-5 cm in diameter
- Marsupialization or resection

# Leukoplakia

- Clinical term
- White plaques, epithelial thickening
- Pruritus, scaling
- Neoplastic: VIN, Paget disease, carcinoma
- Dermatoses: chronic dermatitis, psoriasis
- Lichen sclerosus

# Exophytic lesions

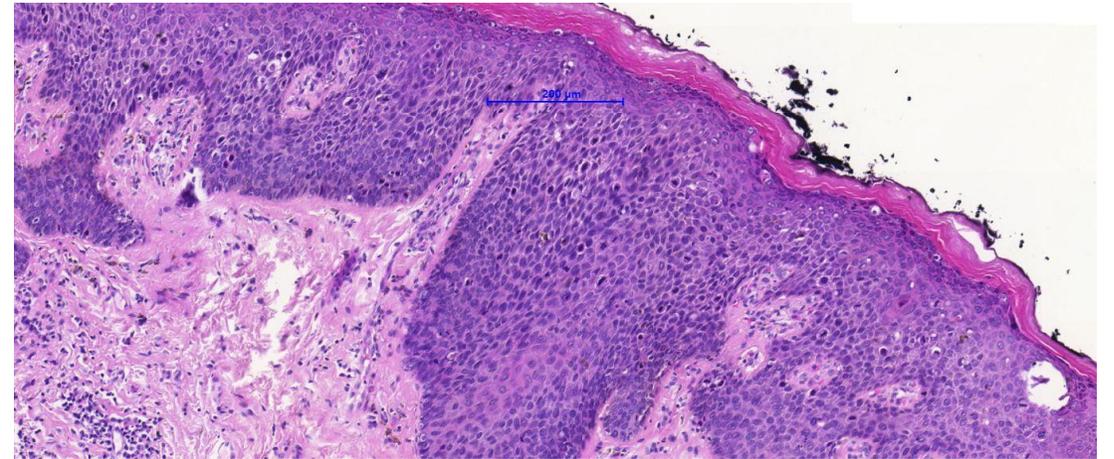
- (Condyloma latum (syphilis))
- Fibroepithelial polyp
- Squamous papillomas)
- **Condyloma acuminatum**
  - Low risk HPV: HPV6, 11 -LSIL
  - Commonly multiple
  - Vulva, perineum, perianal skin, vagina, (cervix-rare)
  - koilocytes



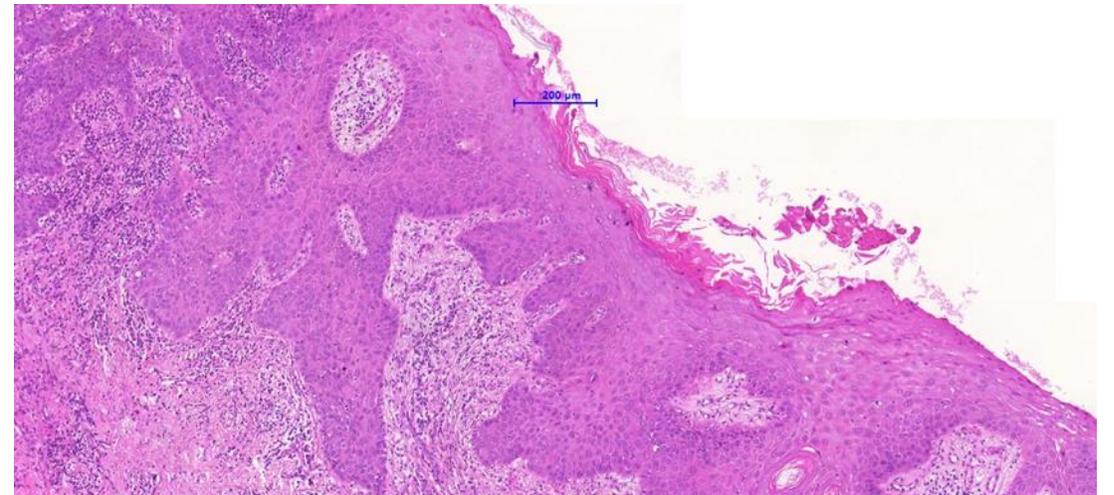
Condyloma acuminatum,  
WebPathology.com

# Neoplasia- VIN (Vulvar Intraepithelial Neoplasia)

- 2 major types
- **Classic VIN**
  - Formerly Bowen disease, carcinoma in situ
  - HR HPV associated
  - younger age group (6th decade)
  - Usually other HPV associated pathologies also
  - Morphology like LSIL-HSIL
  - Background of basaloid and warty squamous cell carcinomas
- **Differentiated VIN**
  - On the basis of long standing lichen sclerosus or epithelial hyperplasia
  - Patients in their 80s
  - Not a HPV associated lesion!!!
  - Role of TP53 mutations
  - Marked atypia of basal layer but orderly maturation of superficial areas



Classic VIN3- HSIL



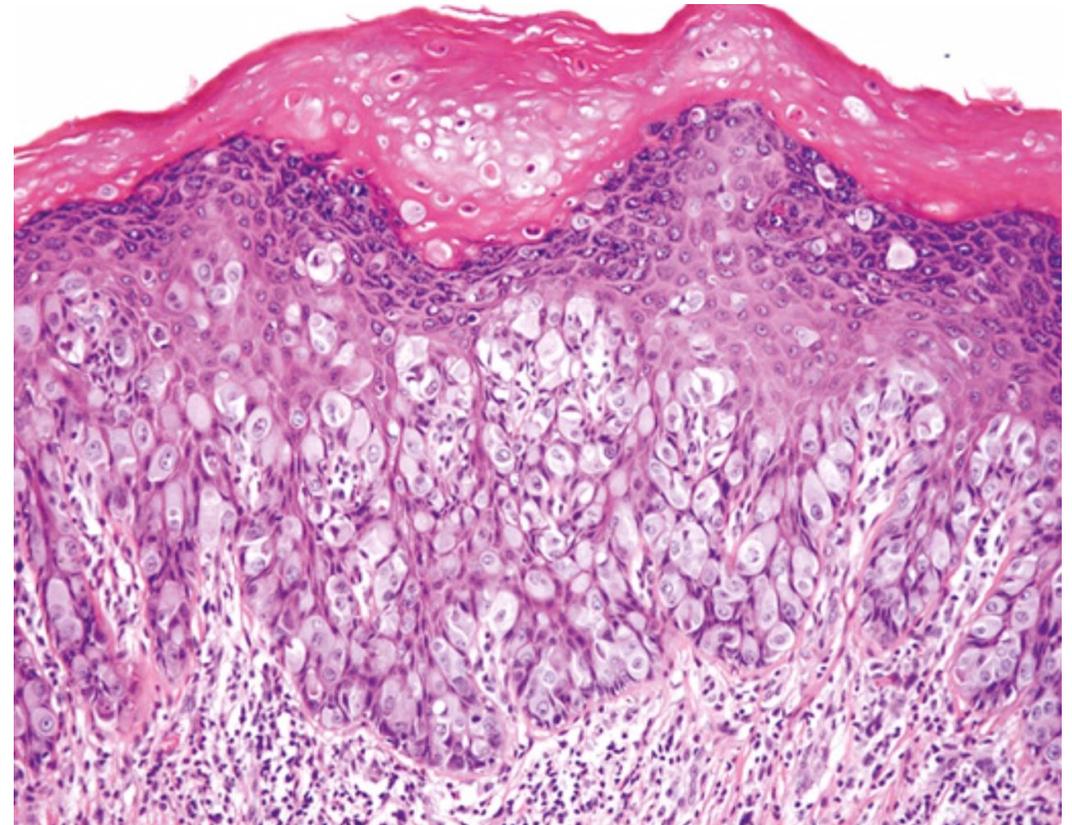
Differentiated VIN

# Neoplasia- Vulvar cancer

- **Squamous cell carcinoma** on the basis of VIN either classic (30%) or differentiated (70%)
- Risk depends on immunity, duration and extent of VIN
- **Spread** to inguinal lymph nodes, pelvic, iliac and paraaortic lymph nodes
- **Distant metastases:** liver, lungs
- Vulvectomy, lymph node dissection
- Prognosis is poor if the tumor is larger than 2 cm with lymph node metastases

# Glandular neoplasia- Extramammary Paget disease

- Red, pruritic, scaling area on labia majora
- Intraepithelial proliferation of large, clear, malignant cells
- Usually confined to the epidermis (unlike breast Paget disease)



VAGINA

# Vaginal diseases- RARE!!!!

- **Developmental anomalies**

- Duplication- failure of müllerian duct fusion
- Vaginal adenosis- small areas of residual endocervical-type epithelium (as embryonal remnants)- clear cell carcinoma (Role of DES)
- Gartner duct cysts- from mesonephric remnants

- **Malignant tumors**

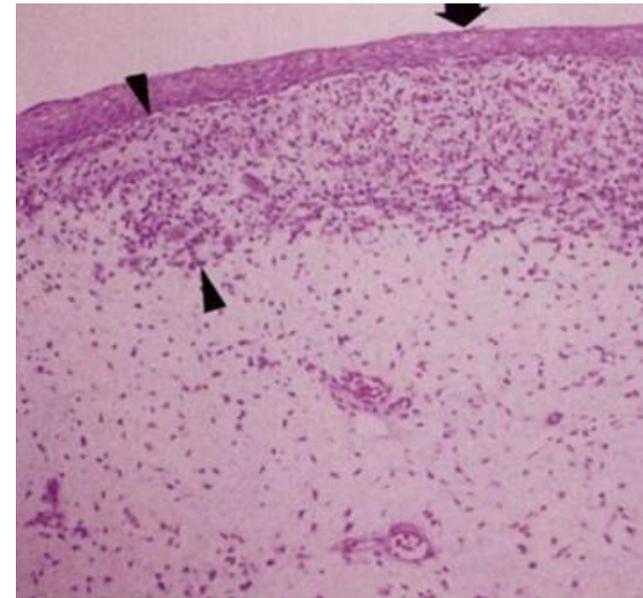
- **Squamous cell carcinoma**
  - HR HPV
  - **Uncommon**
  - Usually with cervical cancer
  - On the basis of VaIN (SILs)

# Vaginal diseases 2

- **Embryonal rhabdomyosarcoma (sarcoma botryoides)**
- Young children
- Grape- like (botryoides) polypoid tumor protruding from the vagina
- Microscopy: characteristic cambium layer: tumor cells condensation below the vaginal epithelium
- Locally invasive



Published in The American journal of case reports 2019  
Recurrent Cervical Sarcoma Botryoides in a 3-Year-Old Female:  
Approach in a Limited Resource Setting



**Cambium layer** (between small arrows)-tumor cell condensation below intact surface epithelium (large arrow)

from the archives of AFIP

CERVIX

# Inflammation

- Normal vaginal and cervical flora dominated by lactobacilli (lactic acid production- pH below 4,5- H<sub>2</sub>O<sub>2</sub> production)
- Predisposing: bleeding, sexual intercourse, AB treatment- higher pH- bacterial (or other microorganisms) overgrowth
- **Gonococci, Herpes simplex, Chlamydiae, Mycoplasmas**

# Endocervical polyp

- Exophytic growth
- Bleeding- as a differential diagnosis, important!
- Fibrous stroma, endocervical glands, surface may be eroded, inflammation

# Cervical cancer



## REVIEW

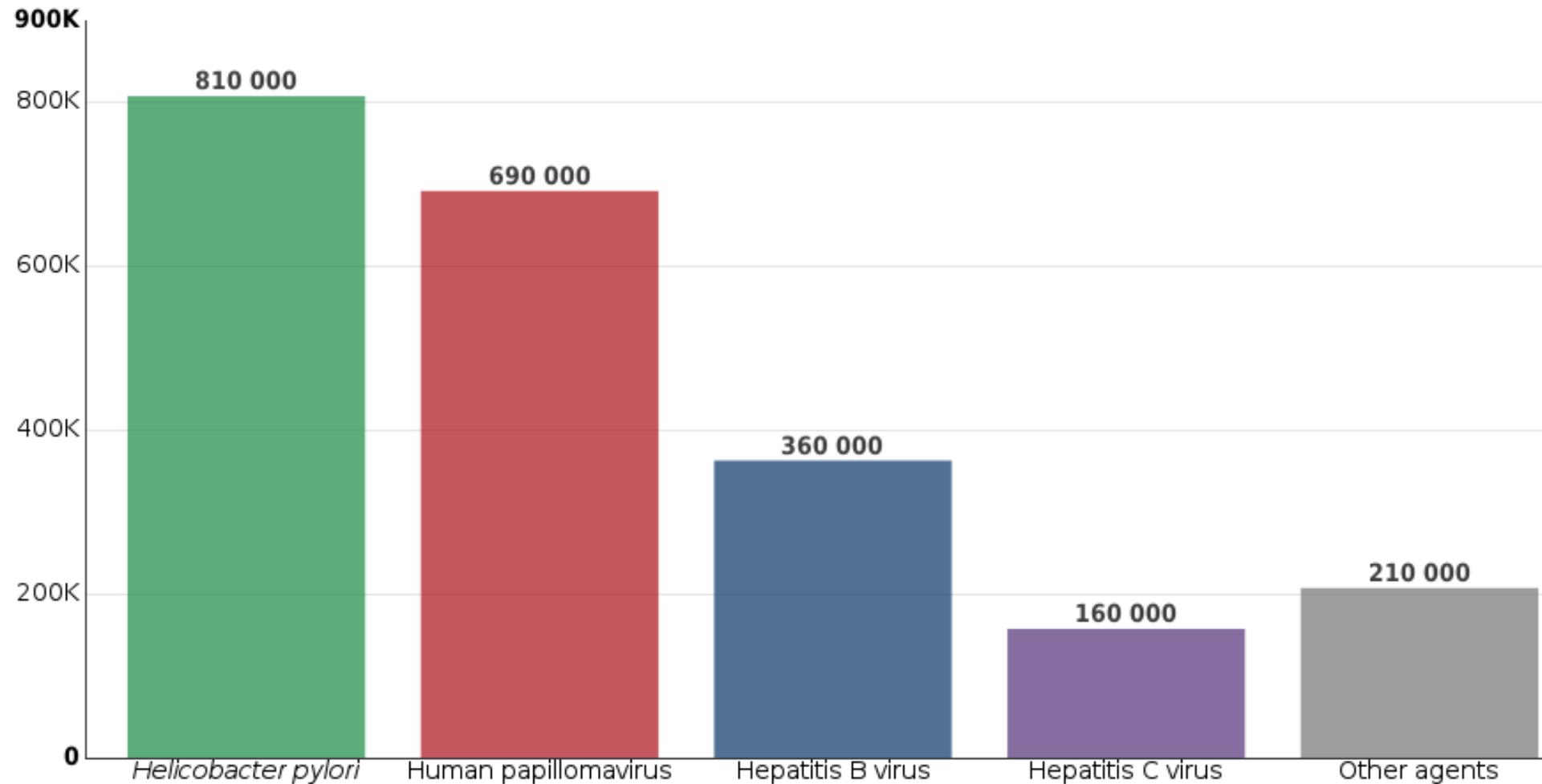
# The most important discoveries of the past 50 years in gynaecological pathology

Steven G Silverberg<sup>1</sup> & C Blake Gilks<sup>2</sup> 

<sup>1</sup>*University of Maryland Medical System, Baltimore, MD, USA, and* <sup>2</sup>*Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, Canada*

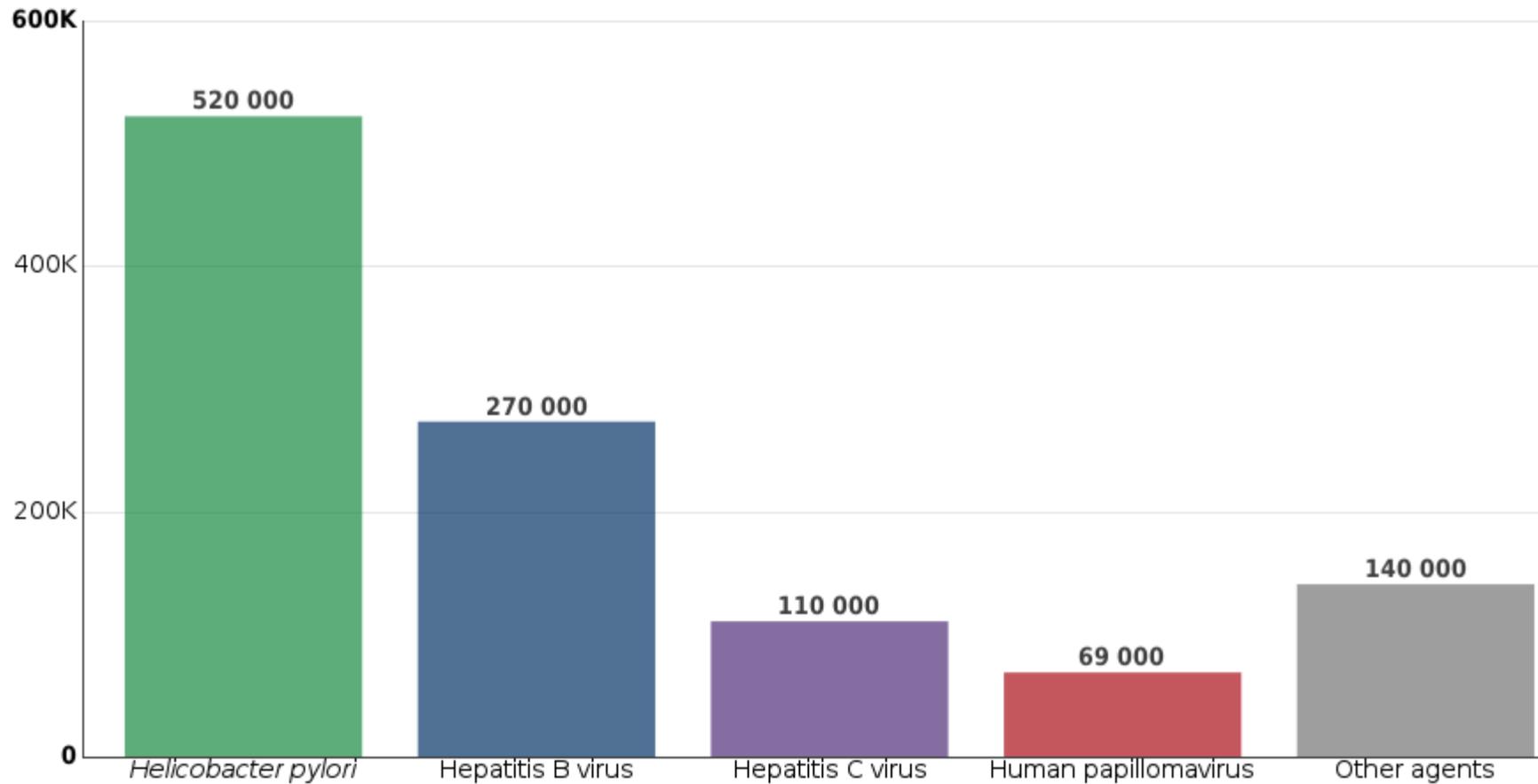
**Number 1:** Discovery of the role of human papillomavirus (HPV) in the aetiology of carcinoma of the lower genital tract

cer cases (all infectious agents) among both sexes in 2018 attributable to infections, in shown by infectious agents



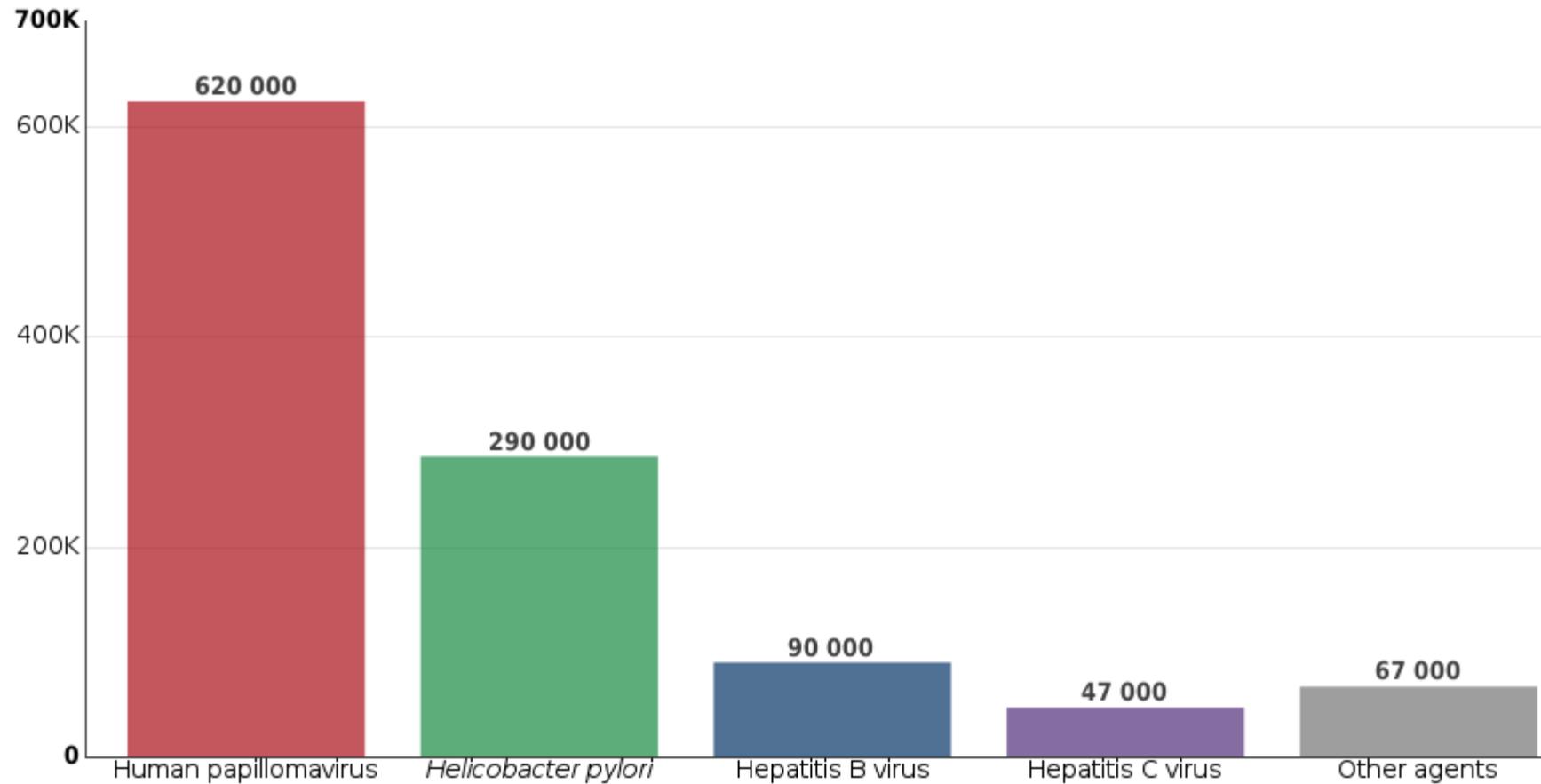
Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)  
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)  
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er cases (all infectious agents) among **males** in 2018 attributable to infections, in the world, by infectious agents



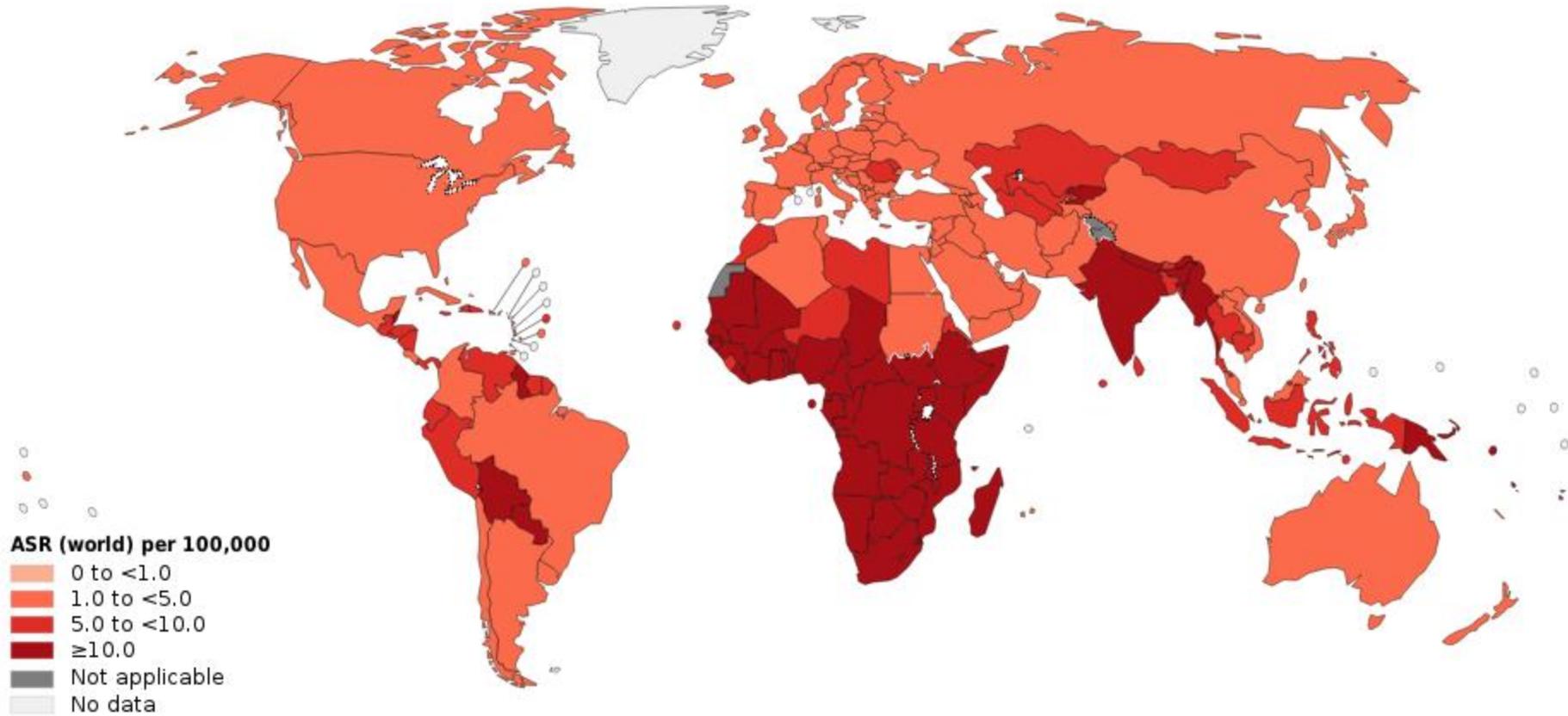
Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)  
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)  
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r cases (all infectious agents) among **females** in 2018 attributable to infections, in the w  
by infectious agents



Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)  
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)  
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Age-standardized rates (worldwide) per 100 000 individual in 2018  
attributable to infections (Human papillomavirus), by country





# HPV brief history

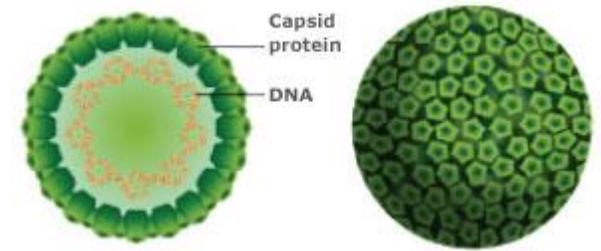
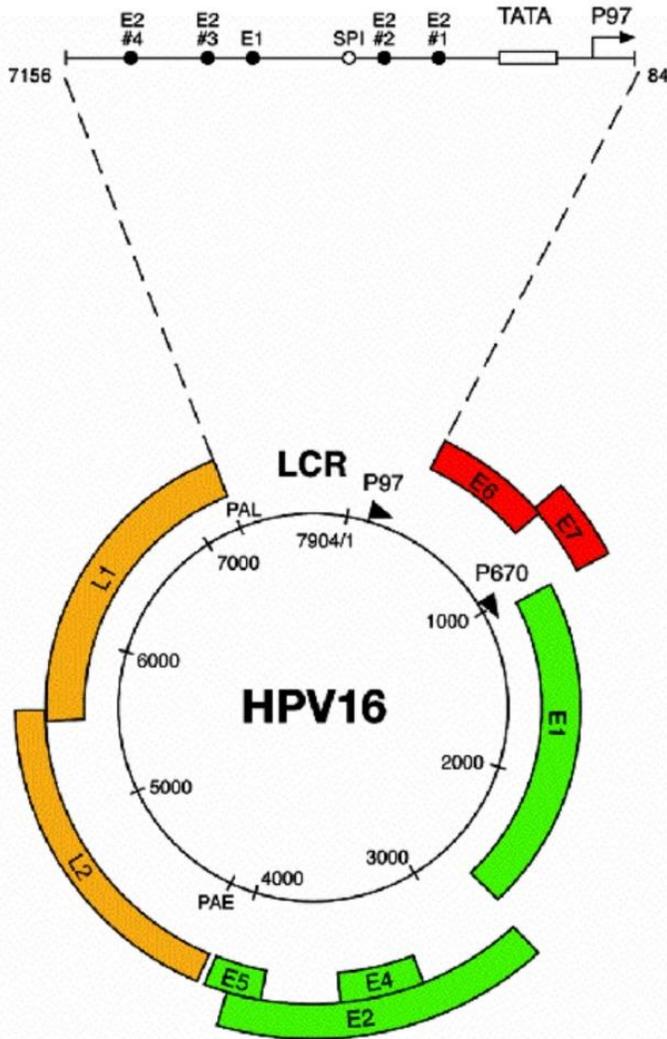
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- Rigoni-Stern (1842) by analyzing death certificates of women in Verona (1760-1839): high frequency of cervical cancer in married women, widows and prostitutes and rare occurrence in virgins and nuns
- 1983. Identification of HPV 16 DNA in cervical squamous cell carcinoma Harald zur Hausen, 25 years later Nobel prize in 2008.

<https://www.nobelprize.org/prizes/medicine/2008/hausen/lecture/>

- 2006. Vaccine

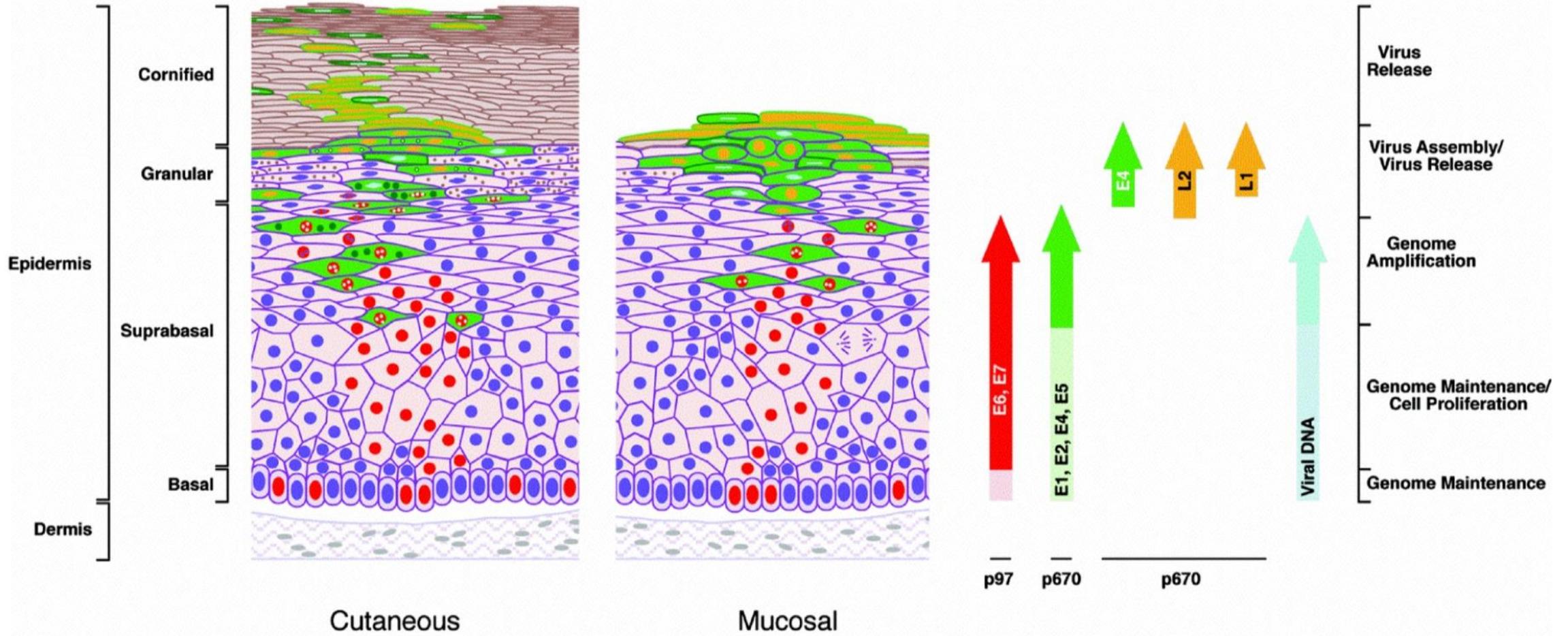
# HPV structure



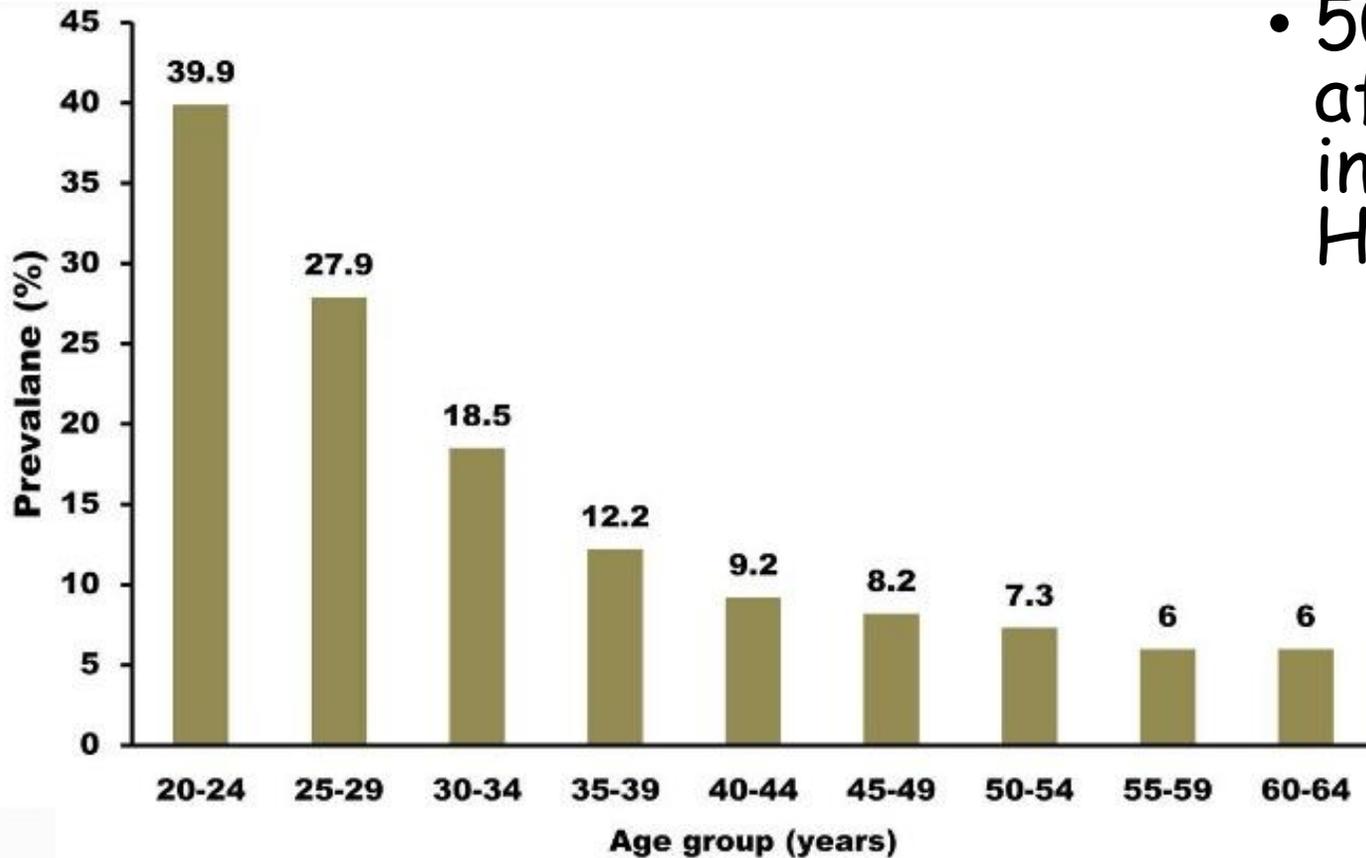
- Non-enveloped DNA virus
- Capsid (surrounds the genome)- 72 capsomeres
- Capsomere: 5 L1 proteins
- (360 L1 proteins and 12 L2 proteins in toto)
- Circular double stranded DNA-8000 bases-8 genes
- Long coding region (LCR) or the Non-coding region-cont. origin of replication, and binding sites for E2 protein!
- Early genes: E1, E2, E4, E5, E6, E7
- Late genes: L1 (major capsid protein), L2 (minor capsid protein)-viral entry, nuclear trafficking

Doorbar J Clin Sci 2006;110:525-41

# HPV- Life cycle



# Prevalence of HPV infection by age groups



- 50% of young girls 4 years after their first sexual intercourse are infected by HPV

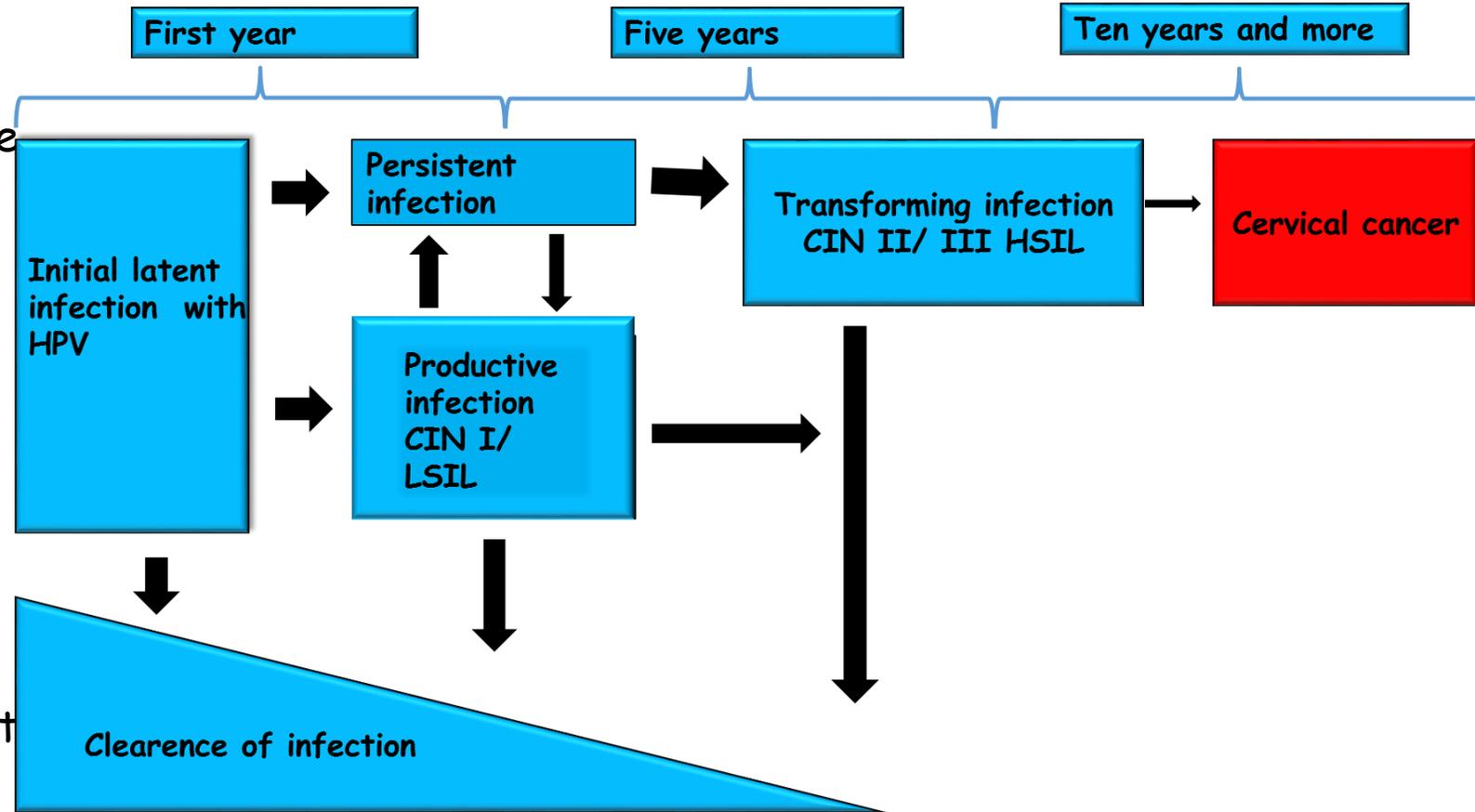
50% of infections cleared within 8 month

90% of infections cleared within 2 years

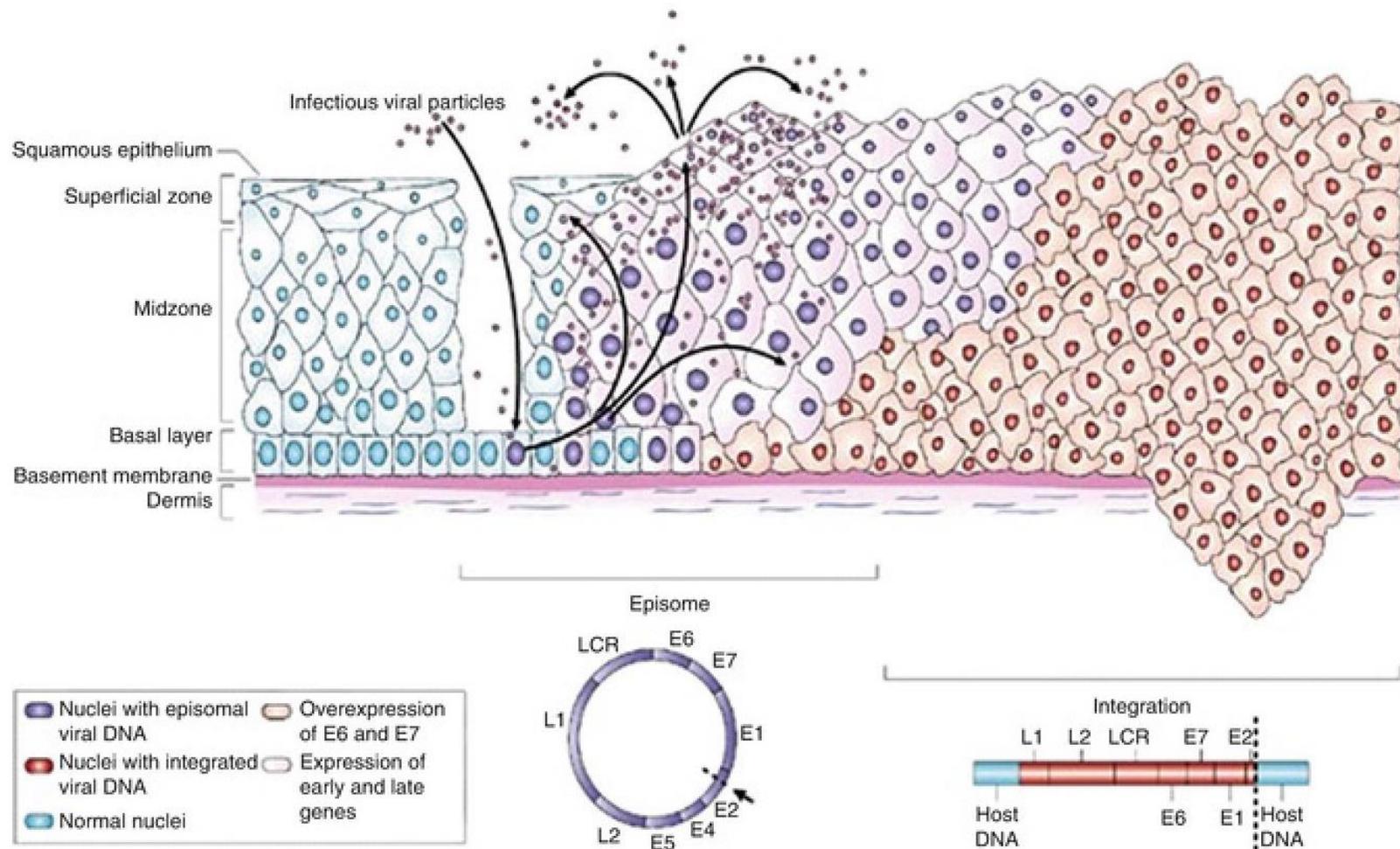
**Productive infections** (the ability of the virus to make daughter viruses): expression of viral gene products regulated as the infected cells move towards the epithelial surface

**Persistent infections**- some can lead to cancer

**Transforming infections**- integrated viral genome-productive life cycle is not completed and deregulated expression of E6 and E7 stimulates uncontrolled cellular proliferation



# HPV- Productive and transforming infection



# Transforming infection to carcinogenesis

- The incorporation of viral DNA to the host genome disrupts the activity of E2 protein
- (The E2 protein normally represses the transcription of E6 and E7), and thus its interruption causes dysregulated expression of these oncoproteins
- E6 and E7- modify the control of the cell cycle and apoptosis- immortalize cells
- Immune evasion : E5 oncogene-modulation of antigen presentation and inflammatory pathways, creating an anti-inflammatory microenvironment

HPV hijacks the cell cycle, kills the guard(ian of the genome- p53), while evades the immune system



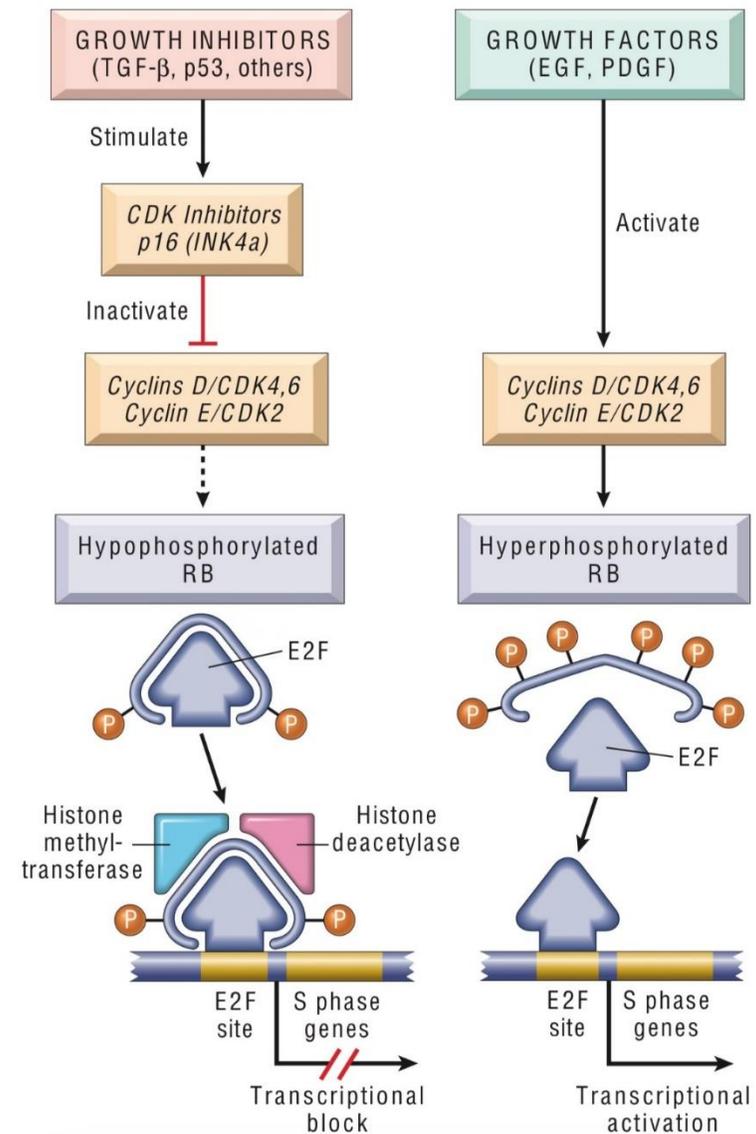


E7



~~RB~~

- Binding and inactivation of cell cycle regulator **retinoblastoma (RB)**
- Binds and inhibits p21 and p27 (cyclin kinase inhibitors)
- All this result in **cell cycle progression and inability of DNA repair**

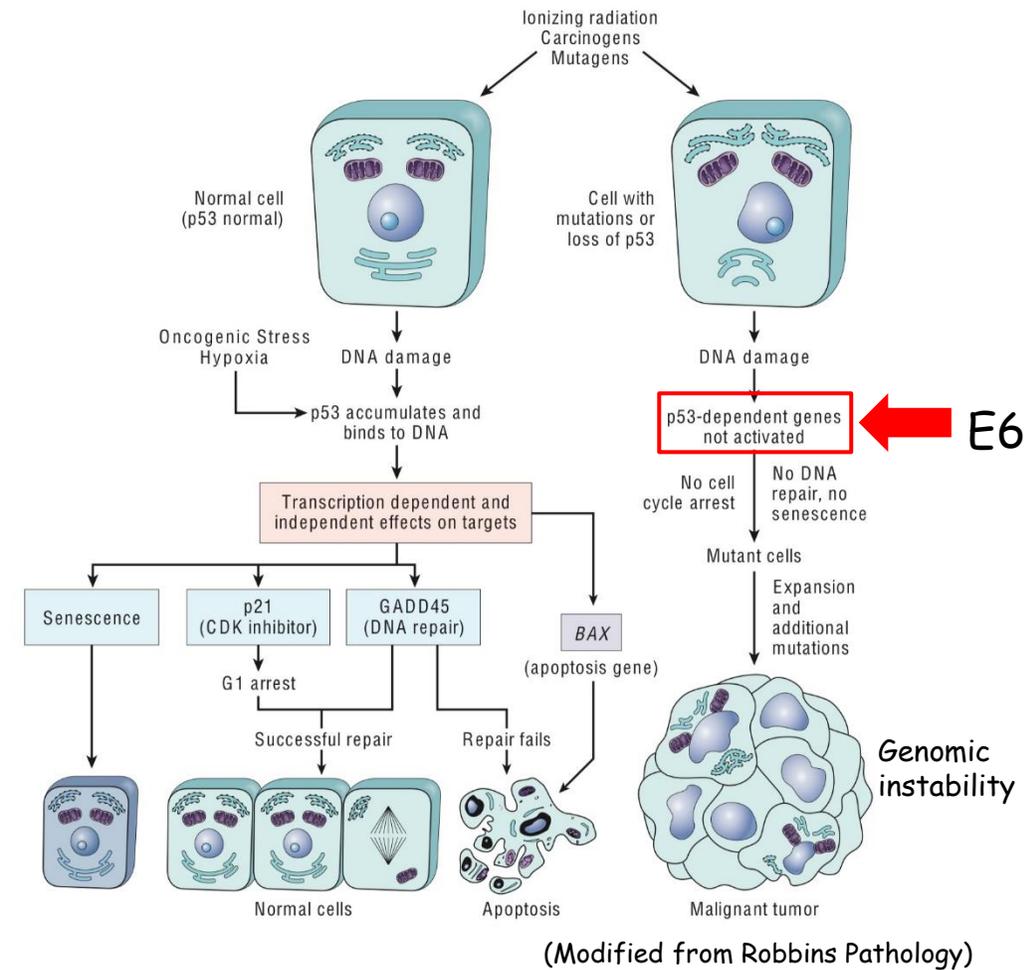


Role of RB: in G0 and G1 binds to and inactivates E2F family of transcription factors that mediate the transcription of genes responsible for S-phase progression. During late G1 RB is phosphorylated by CDKs and hyperphosphorylated RB releases E2F

E6 → ~~p53~~



- Encourages the ubiquitin-dependent proteosomal degradation of p53
- Upregulates telomerase expression-immortalization



Through the normal action of p53 the cell cycle is halted → DNA repair or apoptosis follows

# E5 → immune evasion

- viroporin, a channel protein able to modulate ion homeostasis, vesicle trafficking, virion production, and viral genome entry
- **Immune evasion**: modulation of antigen presentation and inflammatory pathways creating an **anti-inflammatory microenvironment**

Review

## How Human Papillomavirus Replication and Immune Evasion Strategies Take Advantage of the Host DNA Damage Repair Machinery

Valentina Bordignon <sup>1,\*</sup>, Enea Gino Di Domenico <sup>1</sup> , Elisabetta Trento <sup>1</sup>, Giovanna D'Agosto <sup>1</sup>, Iliaria Cavallo <sup>1</sup>, Martina Pontone <sup>1</sup>, Fulvia Pimpinelli <sup>1</sup>, Luciano Mariani <sup>2</sup> and Fabrizio Ensoli <sup>1</sup>

<sup>1</sup> Clinical Pathology and Microbiology Unit, San Gallicano Dermatology Institute, IRCCS, IFO, Via Elio Chianesi 53, 00144 Rome, Italy; enea.didomenico@ifogov.it (E.G.D.D.); elisabetta.trento@ifogov.it (E.T.); giovanna.dagosto@ifogov.it (G.D.); ilaria.cavallo90@gmail.com (I.C.); martina.pontone@ifogov.it (M.P.); fulvia.pimpinelli@ifogov.it (F.P.); fabrizio.ensoli@ifogov.it (F.E.)

<sup>2</sup> HPV Unit, Department of Gynaecologic Oncology, National Cancer Institute Regina Elena, IRCCS, IFO, Via Elio Chianesi 53, 00144 Rome, Italy; luciano.mariani@ifogov.it

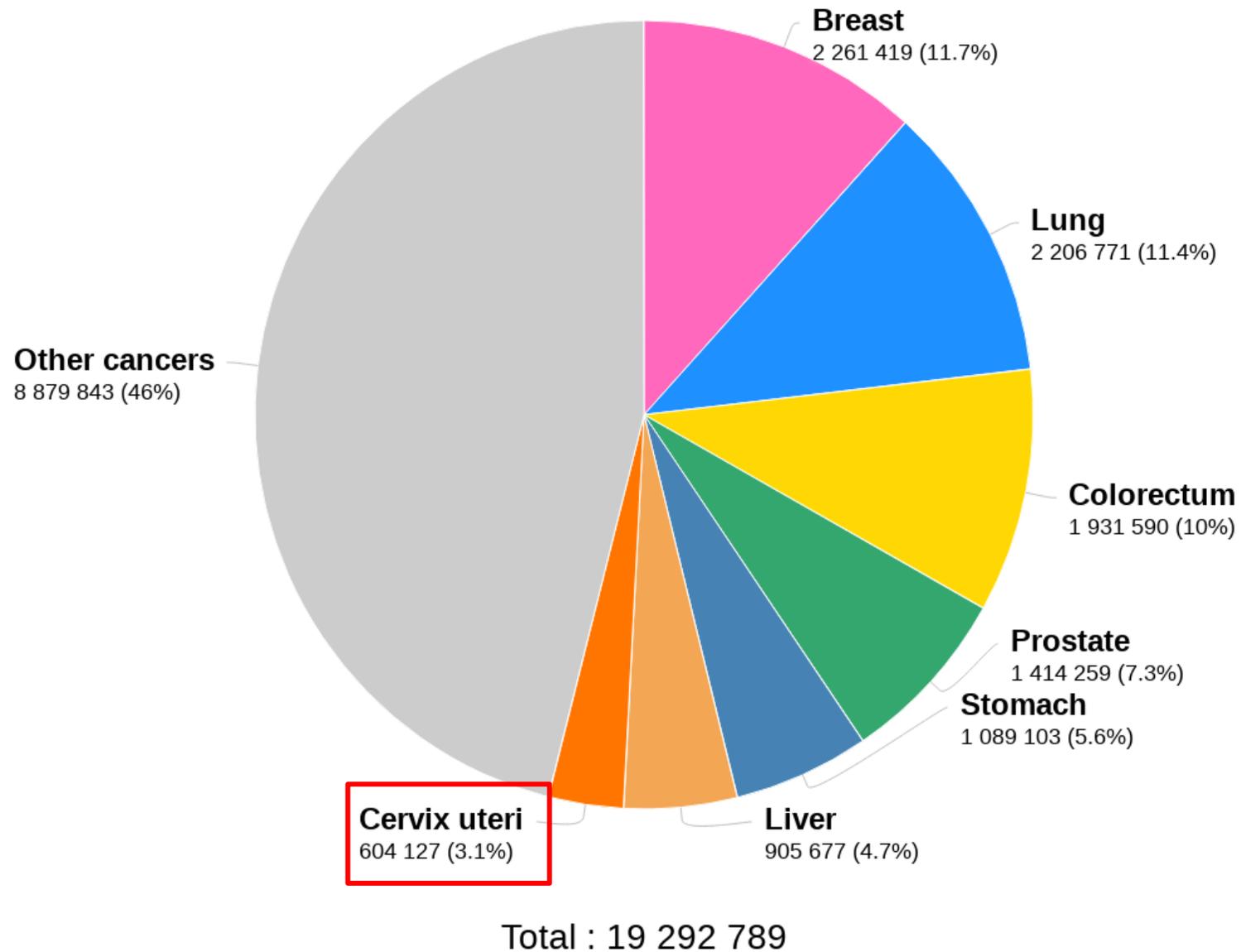
\* Correspondence: valentina.bordignon@ifogov.it; Tel.: +39-06-5266-5245; Fax: +39-06-5266-6812

Received: 13 November 2017; Accepted: 16 December 2017; Published: 19 December 2017

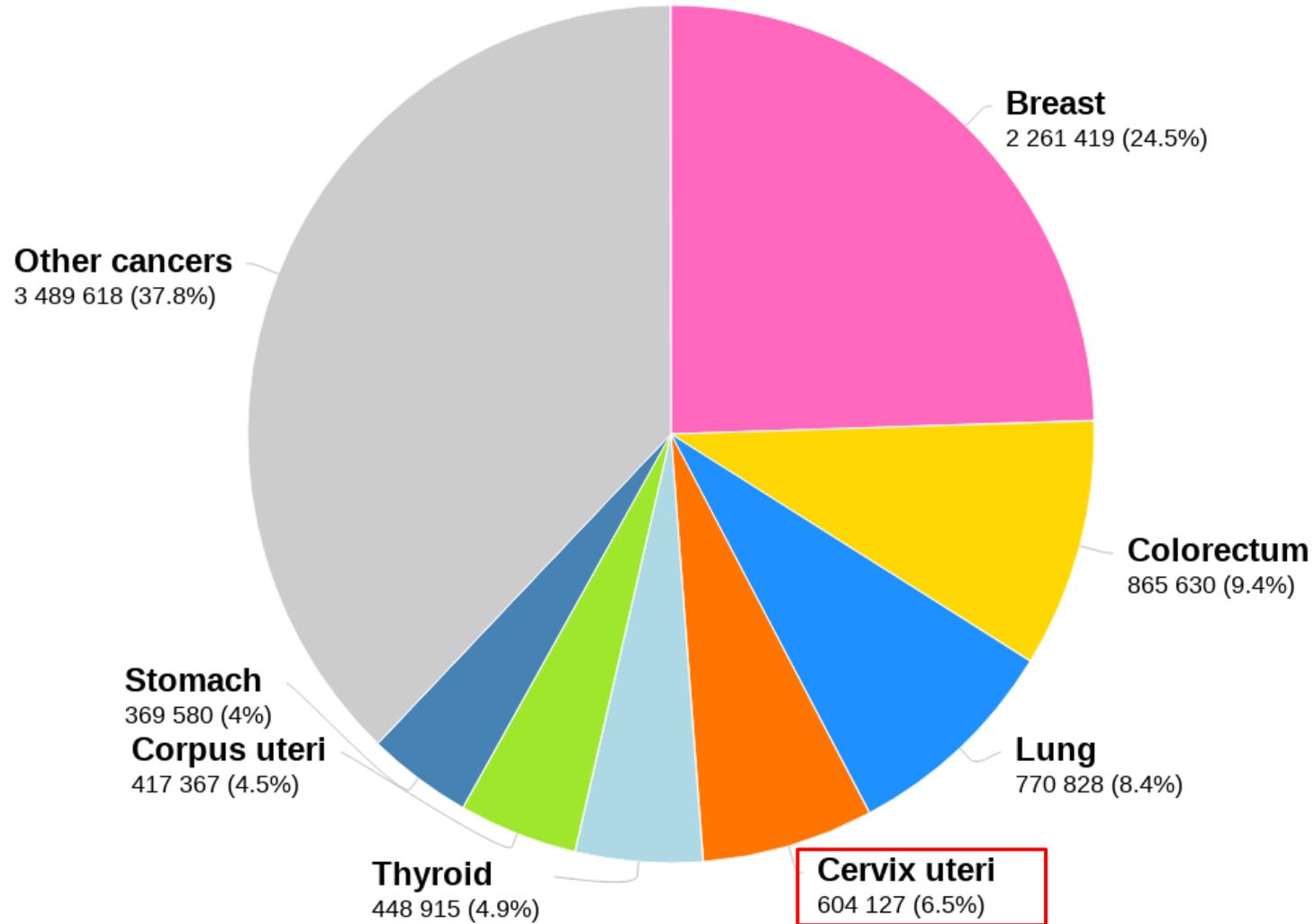
- chronic infection
- no systemic clinical manifestations, rarely kills the host
- periodically shed large amounts of infectious virus for transmission to naive individuals

HPVs evade the host defense systems by avoiding recognition and interfering adaptive immunity

Estimated number of **new cases** in 2020, World, **both sexes**, all ages

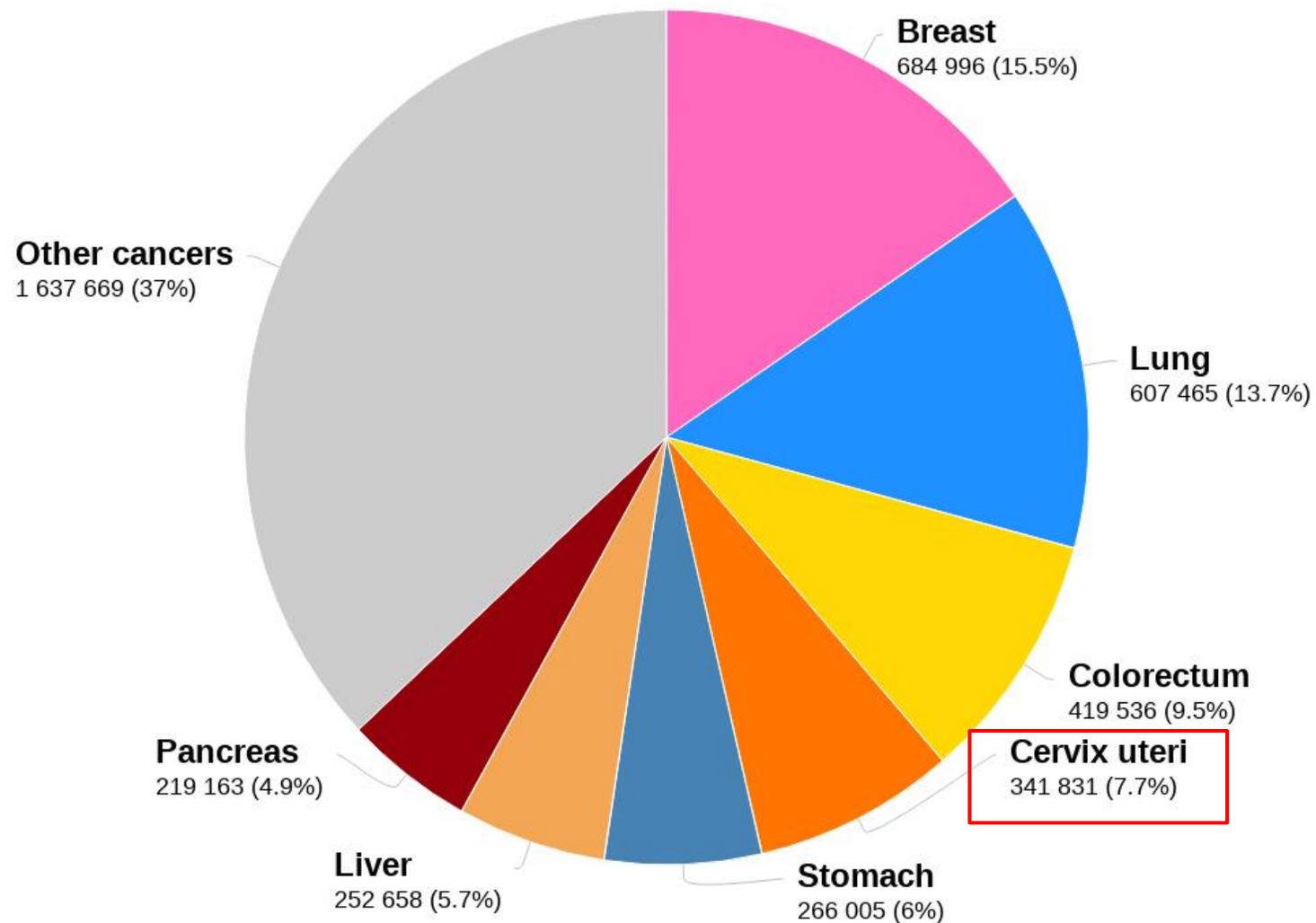


# Estimated number of new cases in 2020, World, females, all ages



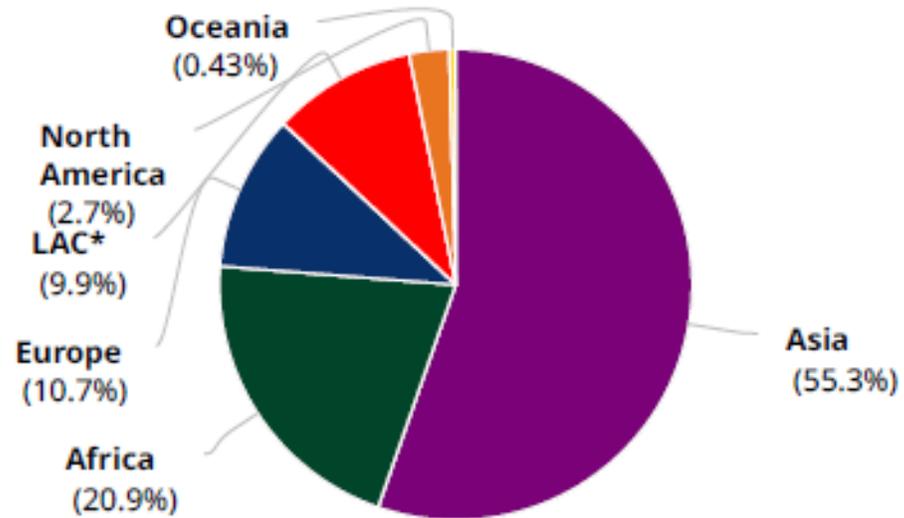
Total : 9 227 484

Estimated number of deaths in 2020, World, females, all ages



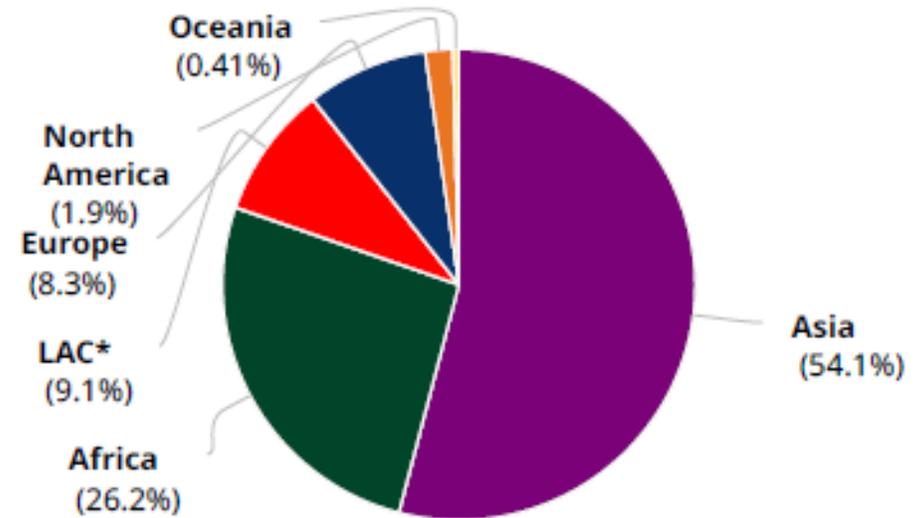
Total : 4 429 323

## Incidence, both sexes



	Population	Number
Asia	315 346	
Africa	119 284	
Europe	61 072	
*Latin America and the Caribbean	56 187	
North America	15 502	
Oceania	2 456	
<b>Total</b>		<b>569 847</b>

## Mortality, both sexes

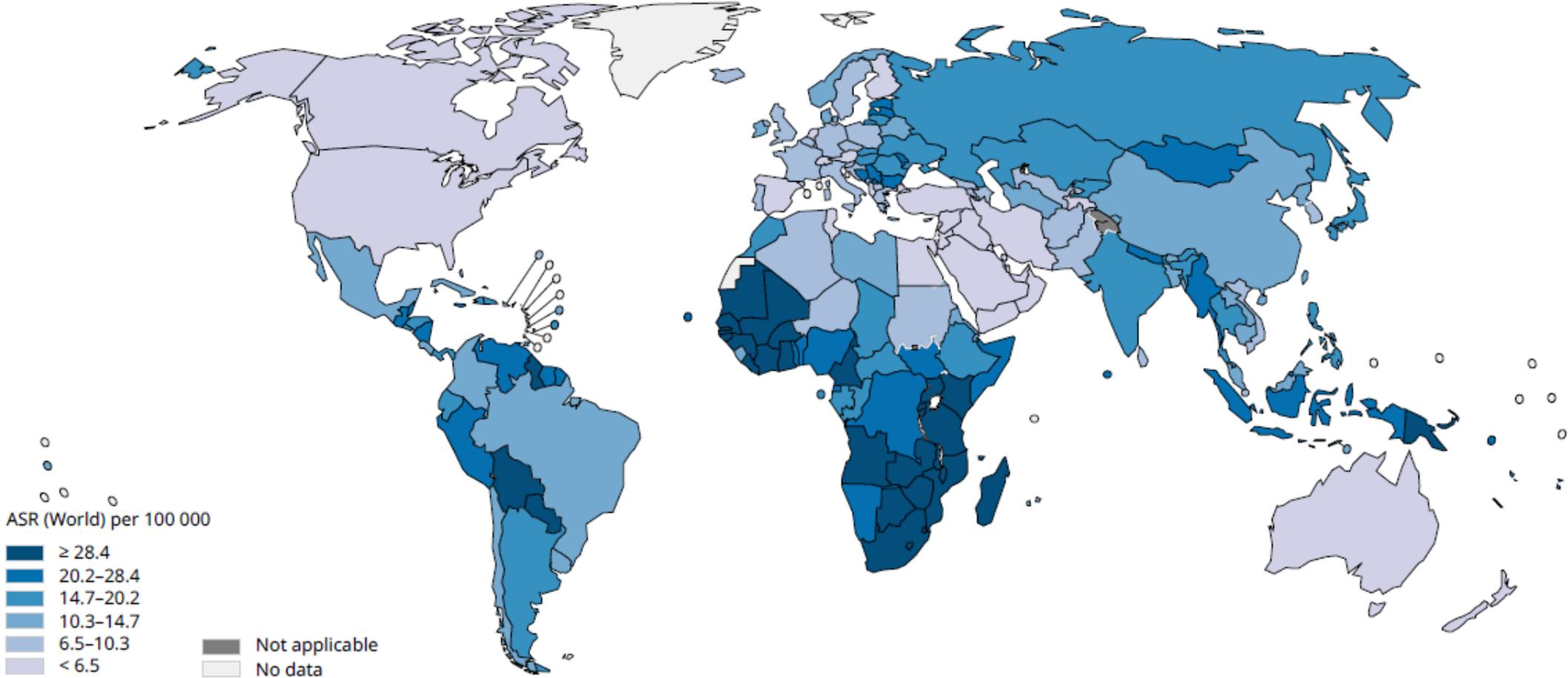


	Population	Number
Asia	168 411	
Africa	81 687	
*Latin America and the Caribbean	28 318	
Europe	25 829	
North America	5 852	
Oceania	1 268	
<b>Total</b>		<b>311 365</b>

[The Global Cancer Observatory](#) - All Rights Reserved, March, 2019.

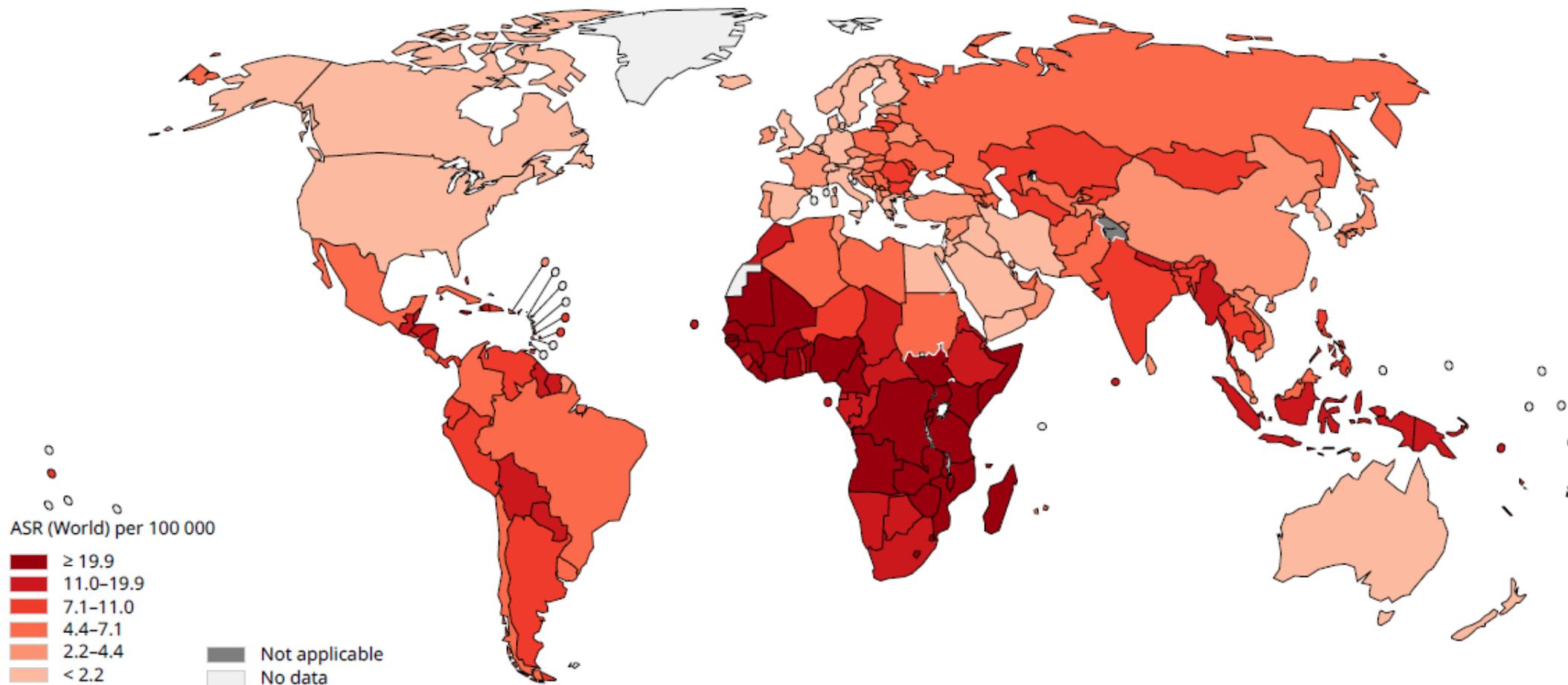
# CERVICAL CANCER IS A MAJOR GLOBAL HEALTH ISSUE

Age standardized (World) incidence rates, cervix uteri, all ages



# CERVICAL CANCER IS A MAJOR GLOBAL HEALTH ISSUE

Age standardized (World) mortality rates, cervix uteri, all ages



Data source: GLOBOCAN 2018

Graph production: IARC (<http://gco.iarc.fr/today>)

World Health Organization



© International Agency for Research on Cancer 2018

# A cervical cancer-free future: First-ever global commitment to eliminate a cancer

17 November 2020 News release

To eliminate cervical cancer as a public health problem, all countries must reach and maintain an incidence rate of fewer than **4 new cases of cervical cancer per 100 000 women per year**. Achieving that goal rests on **three key pillars** and their corresponding targets:

**Vaccination: 90%** of girls fully vaccinated with the HPV vaccine by the age of 15 years;

**Screening: 70%** of women screened using a high-performance test by the age of 35 years, and again by the age of 45 years;

**Treatment: 90%** of women with pre-cancer treated and 90% of women with invasive cancer managed.

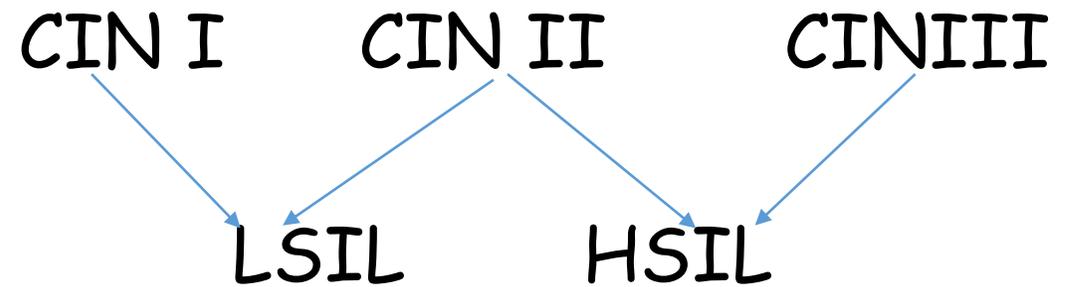
Each country should meet the **90–70–90 targets** by 2030 to get on the path towards eliminating cervical cancer by the end of this century.



- Over 200 HPV types
- 14 types considered high risk (oncogenic)
- High risk (oncogenic) HPV- squamous cell carcinoma of vulva, vagina, cervix, penis, anus, tonsilla and oropharynx
- **MOST IMPORTANT: HPV 16 and 18**
- Other high risk HPVs: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, (66, and 68)
- **Co-carcinogens:**
  - Multiple sexual partners
  - Young age at first intercourse
  - High parity
  - Immunosuppression, HIV co-infection
  - Oral contraceptives
  - Smoking

# Cervical intraepithelial neoplasia

- CIN I: mild dysplasia
- CIN II : moderate dysplasia
- CIN III: severe dysplasia



2 tier system

LSIL: low-grade squamous intraepithelial lesion

HSIL: high-grade squamous intraepithelial lesion

(Lower Anogenital Squamous Terminology project)

# LSIL

- 80% associated with high-risk HPV (HPV 16)
- Productive HPV infection (no transformation, no cell cycle disruption)
- 60% regress
- 30% persist
- 10% progress to HSIL (but not cancer directly)

# HSIL

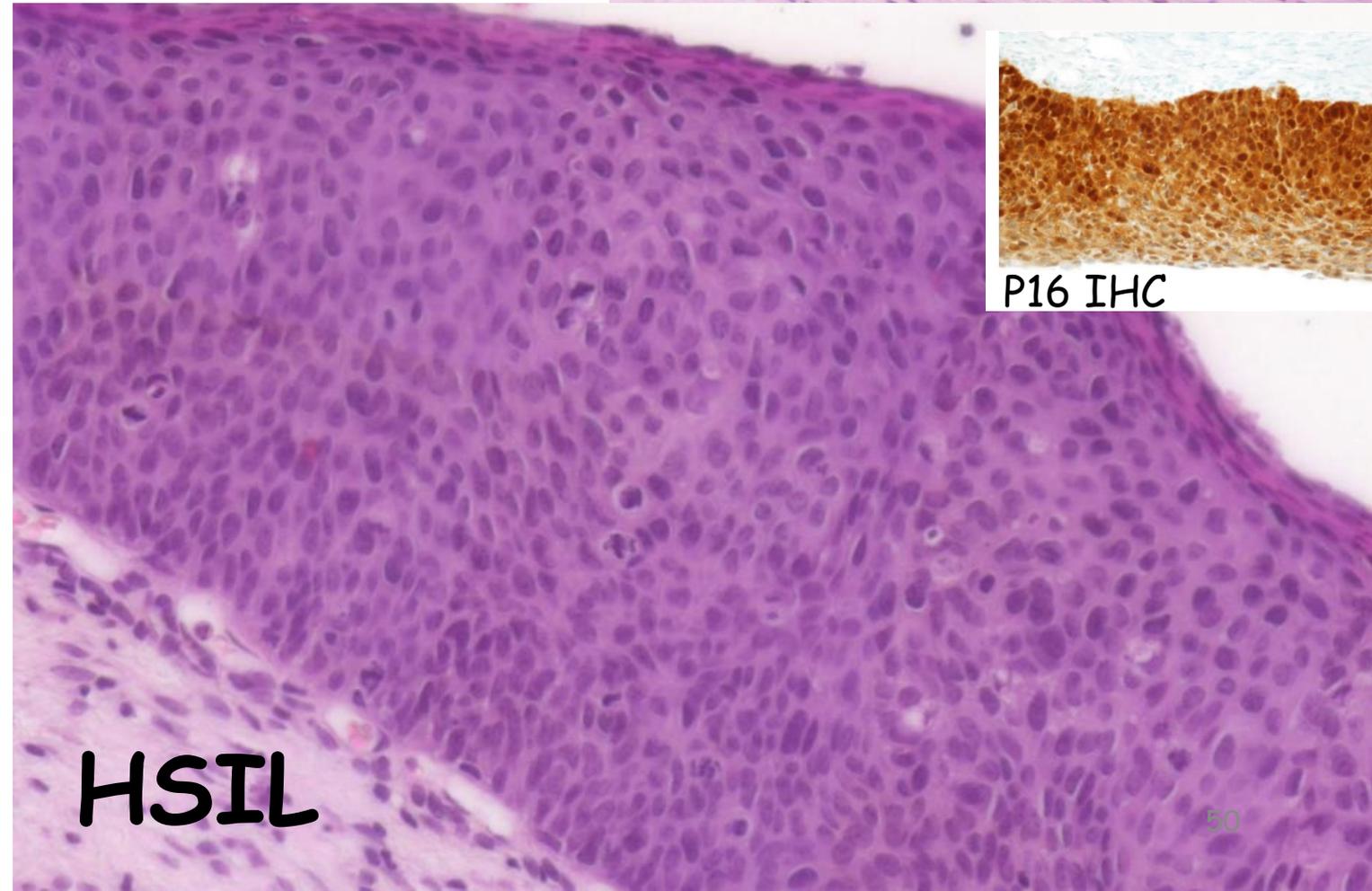
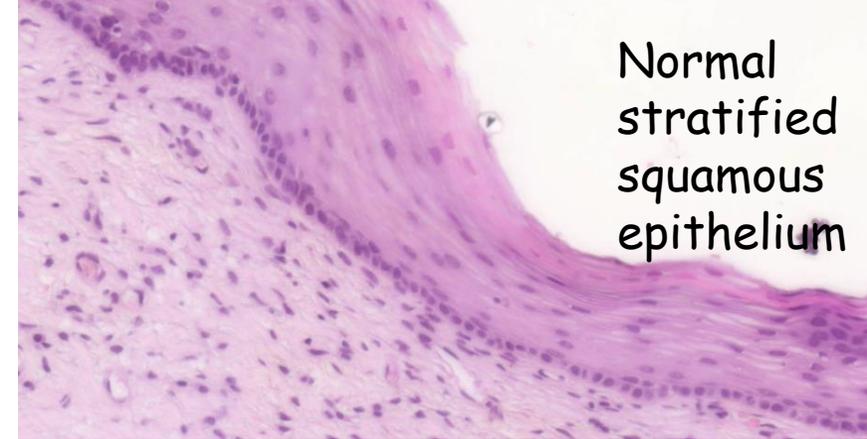
- 100% associated with high-risk HPV
- Transforming infection, deregulation of cell cycle, cellular proliferation, decreased cellular maturation and virus replication
- 30% regress
- 60% persist
- 10% progress to cancer (in several months to 10 years, depending on other factors too)



CIN III (HSIL) from the archive of the 2nd Dept. Of Pathology, Semmelweis University, Budapest, Hungary

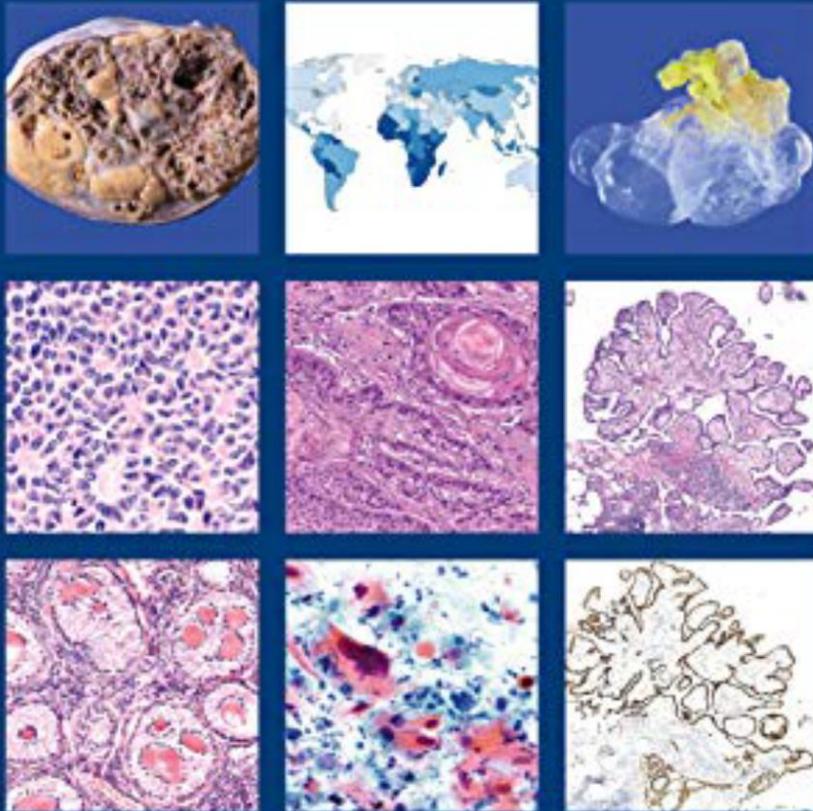
# High-grade dysplasia- HSIL

- Loss of cellular orientation
- Cells resembling basal cells
- Increased nuclear size  
(N/C ratio increased)
- Hyperchromasia
- Nucleoli
- Mitoses in abnormal location
- Increased mitotic count
- Occasional bizarre cells
- Polymorphism



# Female Genital Tumours

Edited by the WHO Classification of Tumours Editorial Board



## WHO classification of tumours of the uterine cervix

<b>Squamous epithelial tumours</b>		8140/3 Adenocarcinoma NOS
	Squamous metaplasia	8483/3* Adenocarcinoma, HPV-associated
	Atrophy	8482/3 Adenocarcinoma, HPV-independent, gastric type
	Condyloma acuminatum	8310/3 Adenocarcinoma, HPV-independent, clear cell type
8077/0	Low-grade squamous intraepithelial lesion	9110/3 Adenocarcinoma, HPV-independent, mesonephric type
8077/0	Cervical intraepithelial neoplasia, grade 1	8484/3* Adenocarcinoma, HPV-independent, NOS
8077/2	High-grade squamous intraepithelial lesion	8380/3 Endometrioid adenocarcinoma NOS
8077/2	Cervical intraepithelial neoplasia, grade 2	
8077/2	Cervical intraepithelial neoplasia, grade 3	
8085/3	Squamous cell carcinoma, HPV-associated	
8086/3	Squamous cell carcinoma, HPV-independent	
8070/3	Squamous cell carcinoma NOS	
<b>Glandular tumours and precursors</b>		
	Endocervical polyp	
	Müllerian papilloma	
	Nabothian cyst	
	Tunnel clusters	
	Microglandular hyperplasia	
	Lobular endocervical glandular hyperplasia	
	Diffuse laminar endocervical hyperplasia	
	Mesonephric remnants and hyperplasia	
	Arias-Stella reaction	
	Endocervicosis	
	Tubeometrioid metaplasia	
	Ectopic prostate tissue	
8140/2	Adenocarcinoma in situ NOS	
8483/2*	Adenocarcinoma in situ, HPV-associated	
8484/2*	Adenocarcinoma in situ, HPV-independent	
		8980/3 Carcinosarcoma NOS
		8560/3 Adenosquamous carcinoma
		8430/3 Mucoepidermoid carcinoma
		8098/3 Adenoid basal carcinoma
		8020/3 Carcinoma, undifferentiated, NOS
		<b>Mixed epithelial and mesenchymal tumours</b>
		8932/0 Adenomyoma NOS
		Mesonephric-type adenomyoma
		Endocervical-type adenomyoma
		8933/3 Adenosarcoma
		<b>Germ cell tumours</b>
		9064/3 Germ cell tumour NOS
		9080/0 Mature teratoma NOS
		9084/0 Dermoid cyst NOS
		9071/3 Endodermal sinus tumour
		9071/3 Yolk sac tumour NOS
		9100/3 Choriocarcinoma NOS

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) {1149}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. Subtype labels are indented.

\* Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in June 2020.

# Cervical carcinoma

- 70-80% squamous cell carcinoma (precursor: HSIL)
- 15-25% adenocarcinoma (precursor: AIS-adenocarcinoma in situ)
- 5%: neuroendocrine cc, adenosquamous cc and others
- Mean age of patients with squamous cell cc 45 y

# Squamous cell carcinoma of the cervix

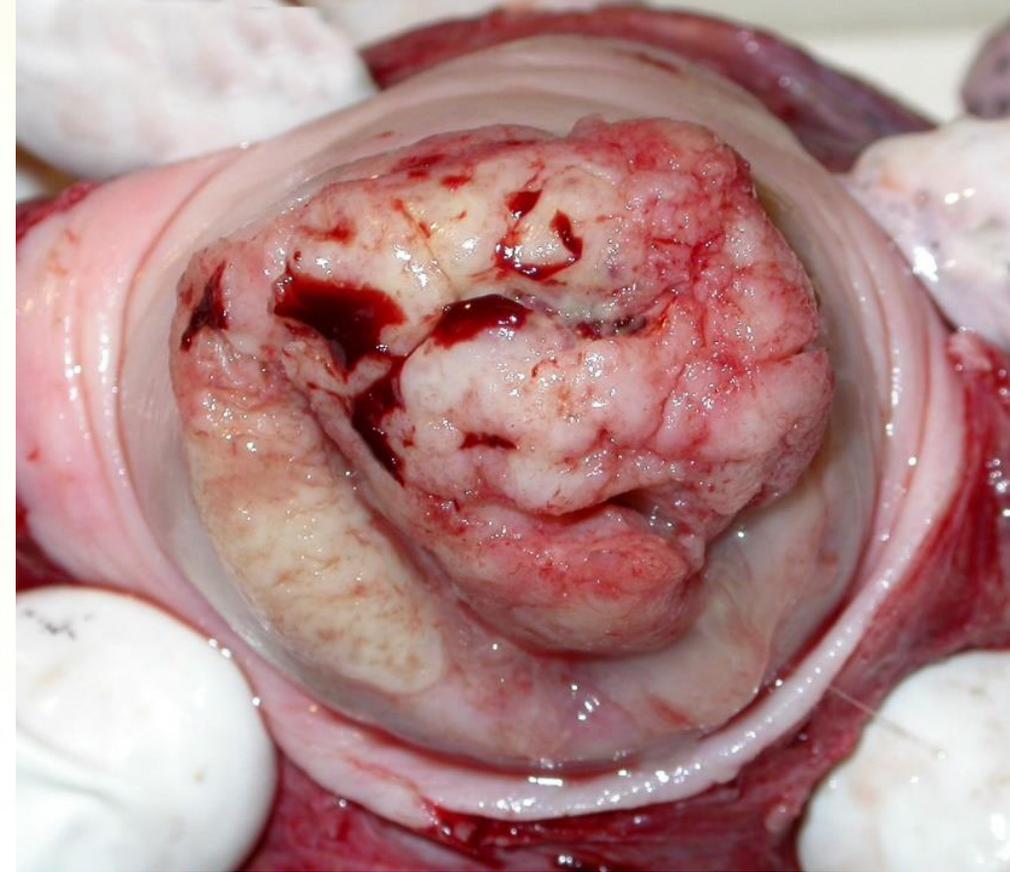
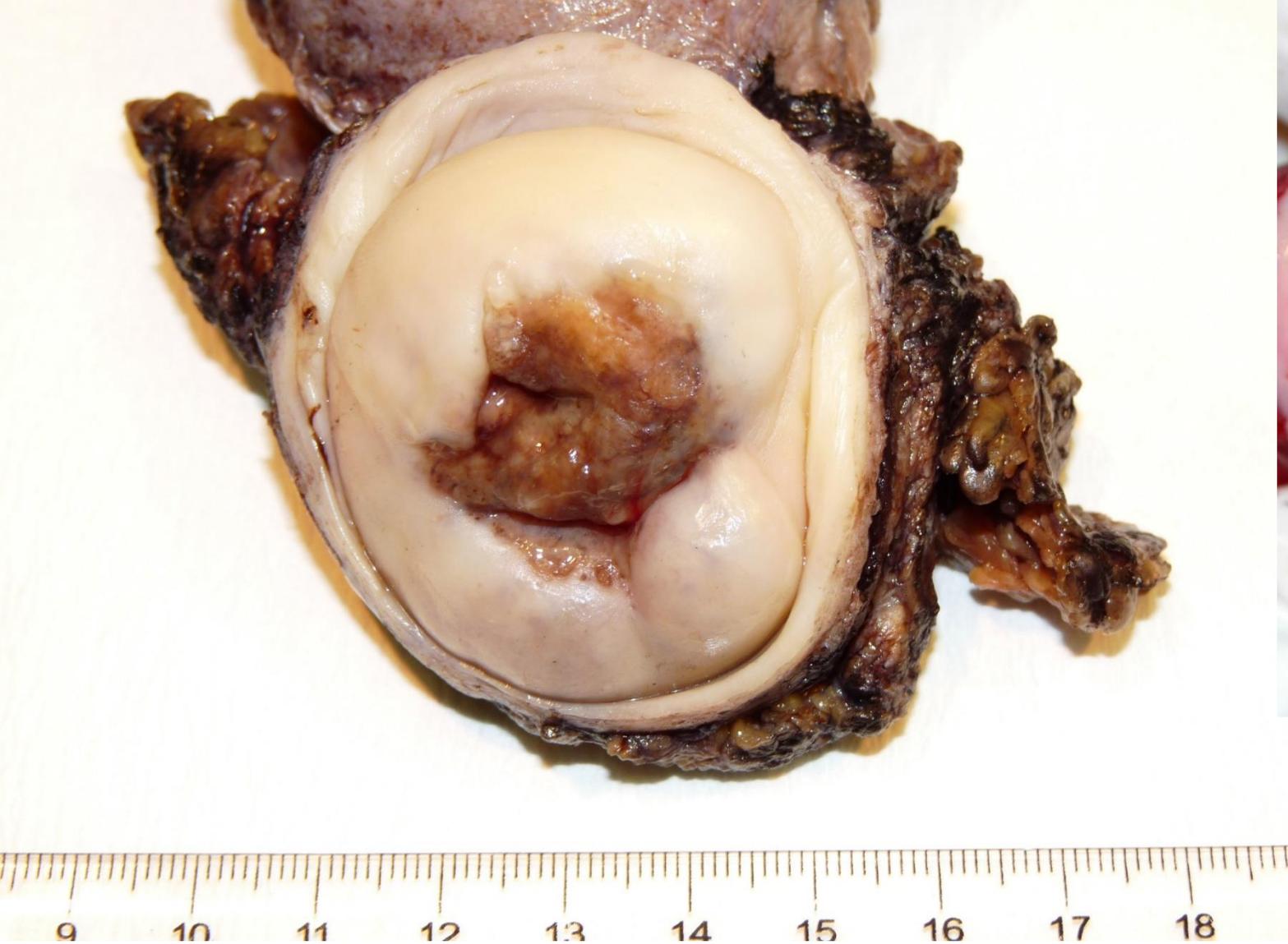
- Almost 100% high-risk HPV associated (unlike sq c cc of the vulva)
- WHO subtypes and grade irrelevant in management
- Most important: stage (measurements in early lesions!)
- Presentation:
  - Abnormal Pap smear
  - Bleeding (intermenstrual or postcoital)
  - Renal obstruction
  - Lymphedema
- Usually in women who do not participate in regular screening
- Prognosis: stage dependent (Stage Ia 95%, while Stage III and IV less than 50%)

# Management of cervical cancer

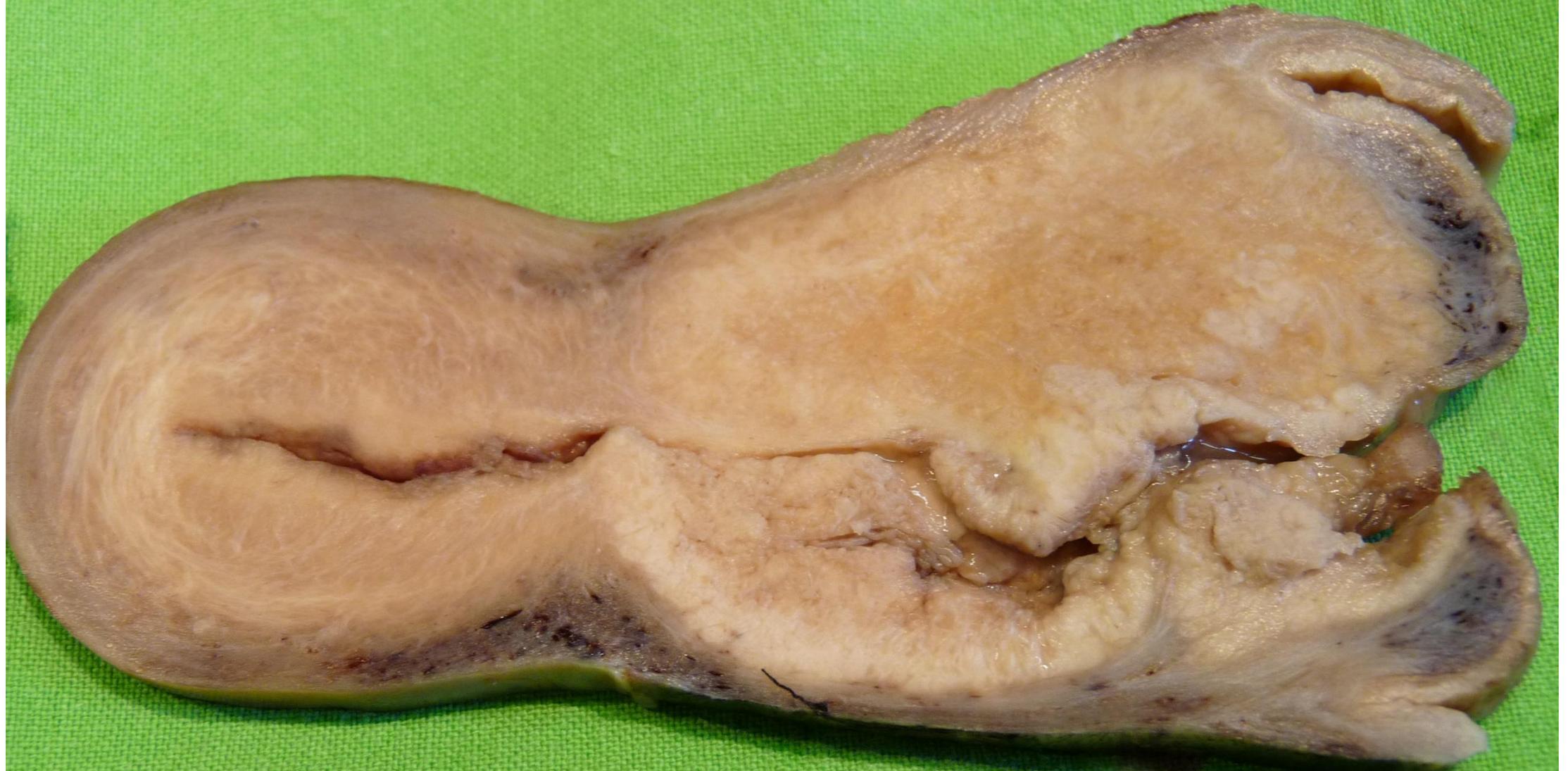
- Stage dependent
- Conisation or hysterectomy- early stage
- Wertheim surgery: radical hysterectomy with lymph node dissection
- Irradiation: if tumor larger than 4 cm
- Exenteration

# Disease course

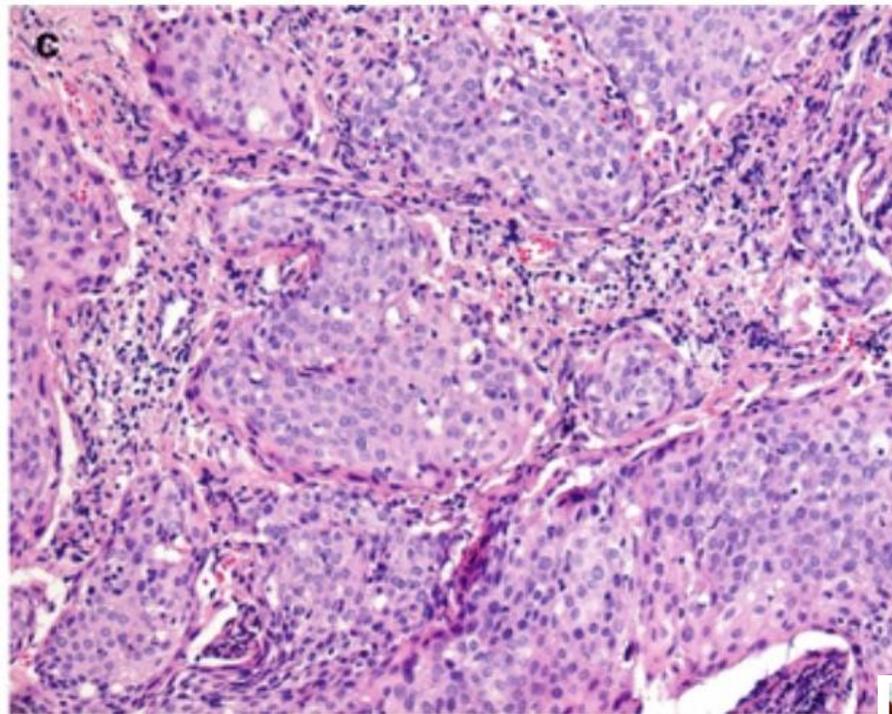
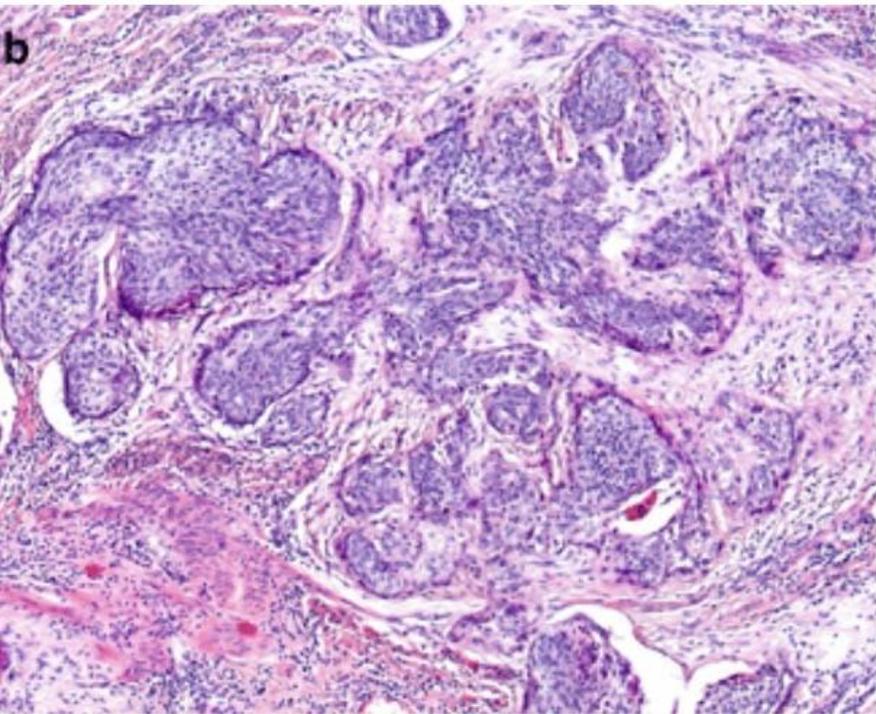
- Usually locally infiltrative
- Distant metastases rare (liver, lungs, bone marrow etc.)
- Local extension into urinary bladder, ureter, (leading to obstruction, uremia), paracervical soft tissues, vagina, rectum
- LVI, lymph node metastases



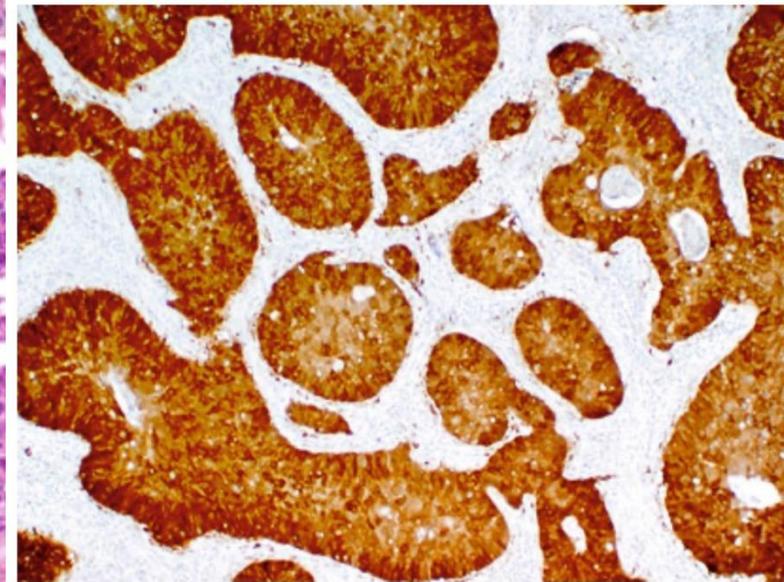
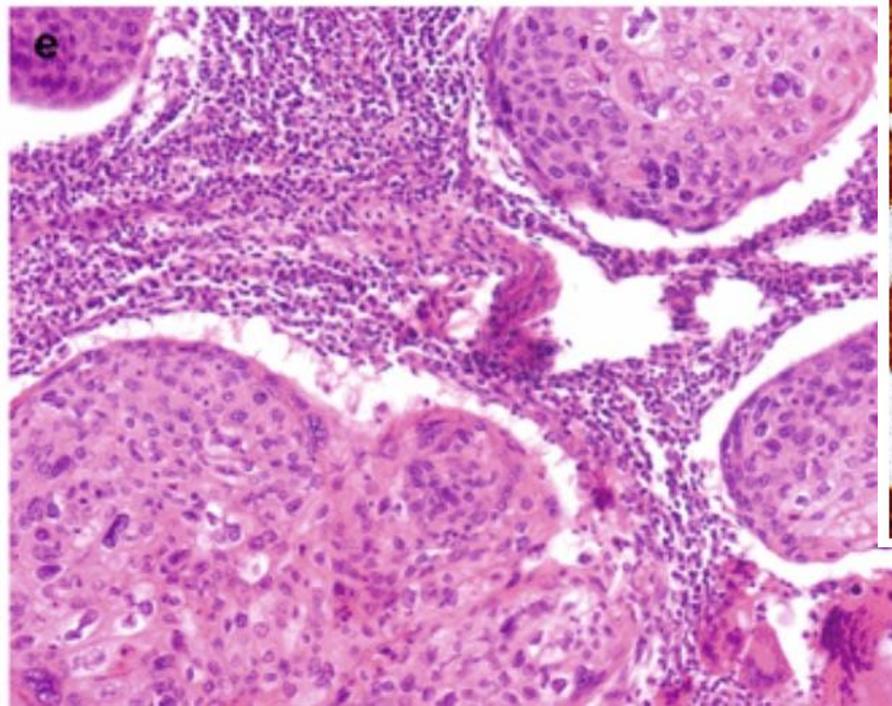
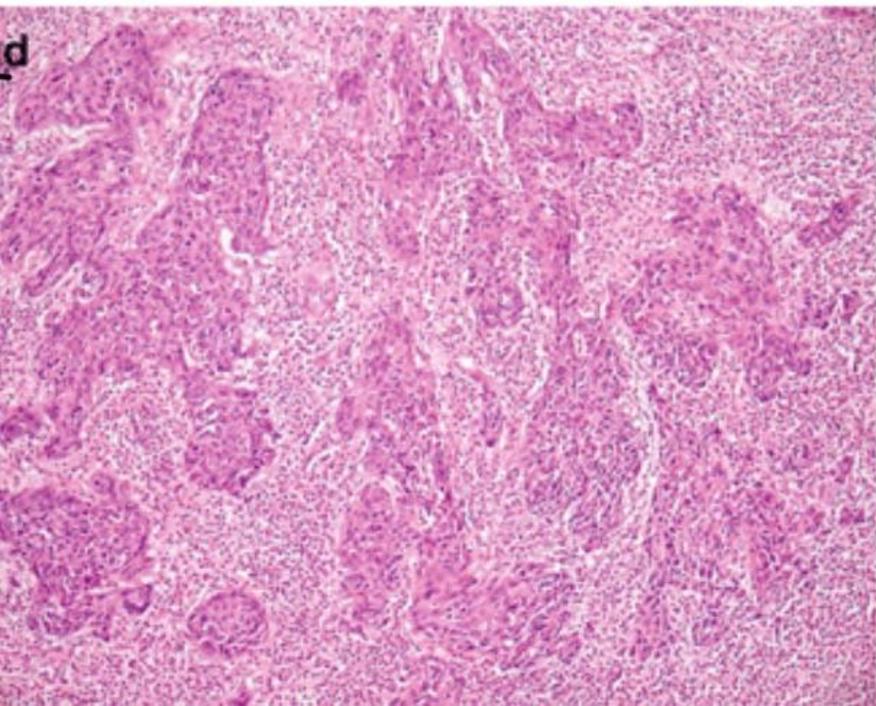
Cervical cancer-squamous cell carcinoma  
from the archive of the 2nd Dept. Of Pathology,  
Semmelweis University, Budapest, Hungary



Cervical cancer- Squamous cell carcinoma  
from the archive of the 2nd Dept. Of Pathology,  
Semmelweis University, Budapest, Hungary



Invasive squamous cell carcinoma of the cervix



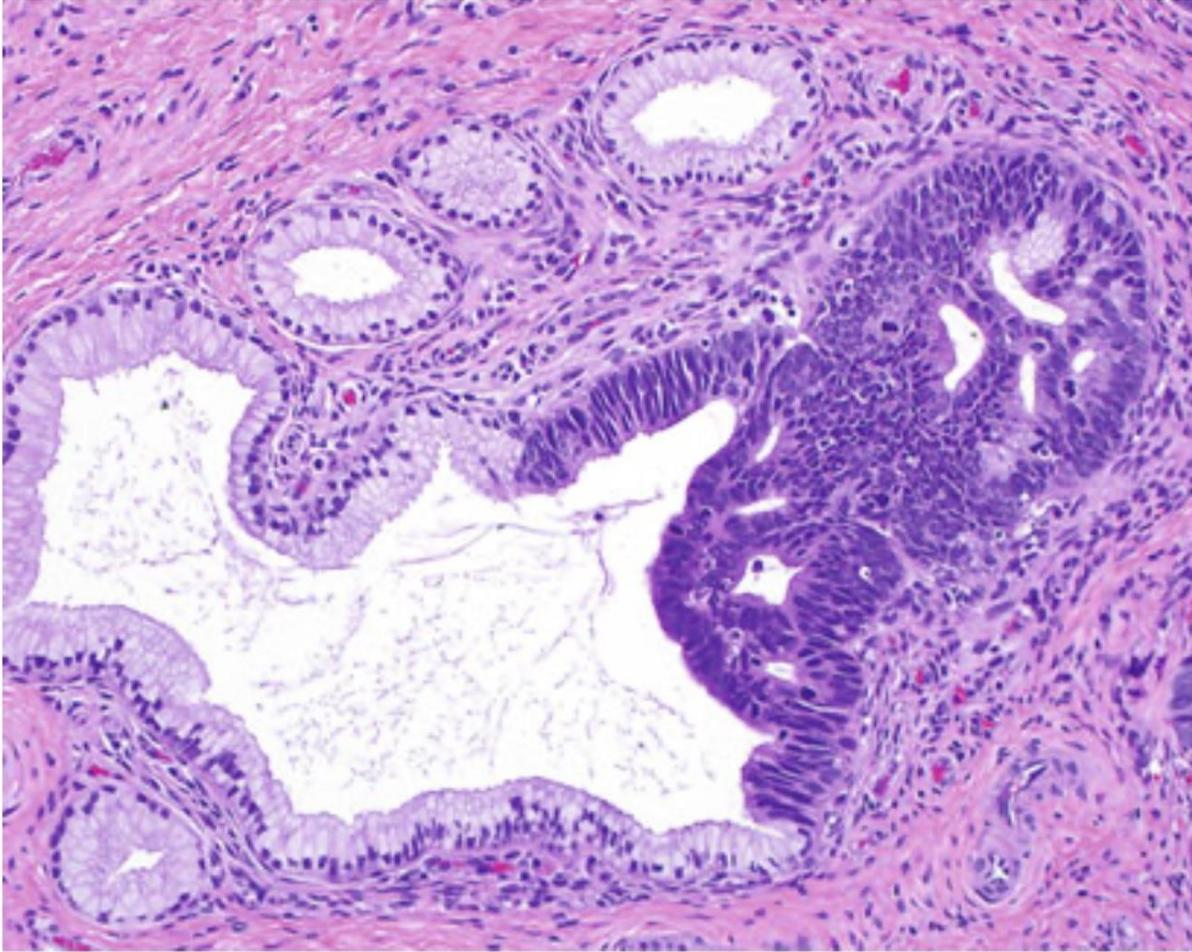
p16 immunohistochemistry

# Endocervical adenocarcinoma

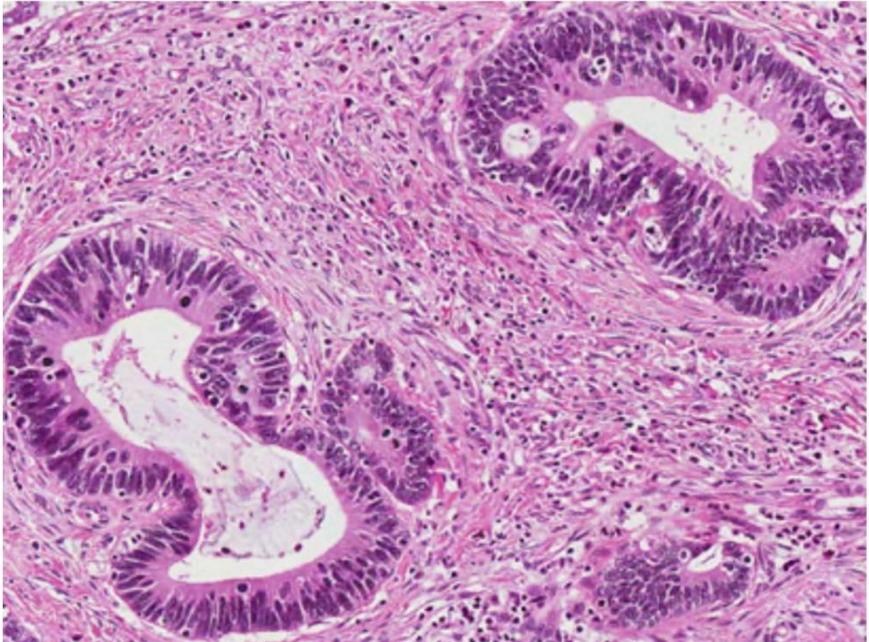
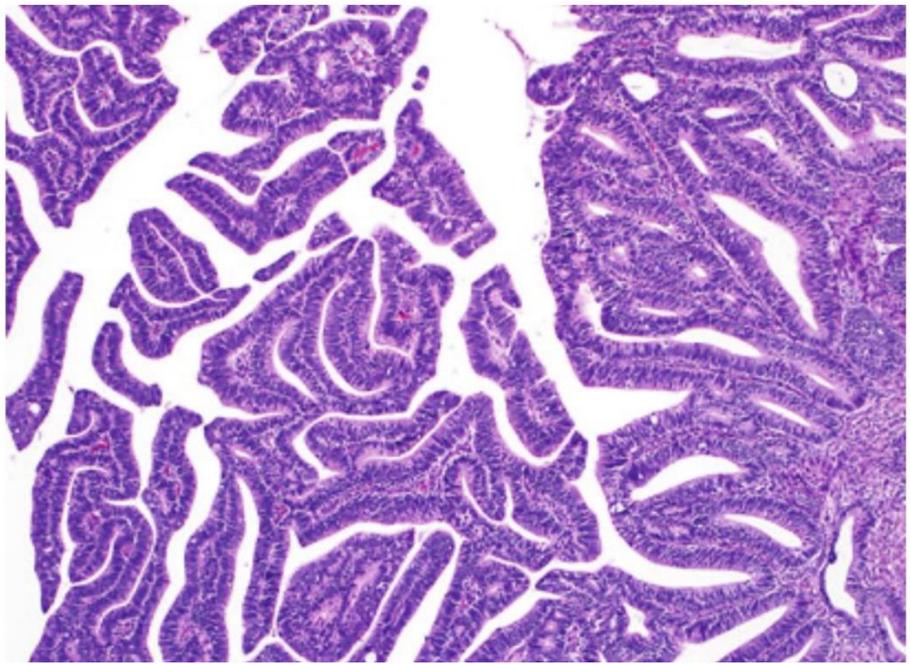
- 20-25% of cervical cancer cases
- HR HPV18 mainly
- Precursor: adenocarcinoma in situ (AIS)
- Most common (80-90%): Usual type endocervical adenocarcinoma
- Some types non-HPV related e.g Gastric type mucinous carcinoma



Endocervical adenocarcinoma, from the archive of the 2nd Dept. of Pathology, Semmelweis University, Budapest Hungary



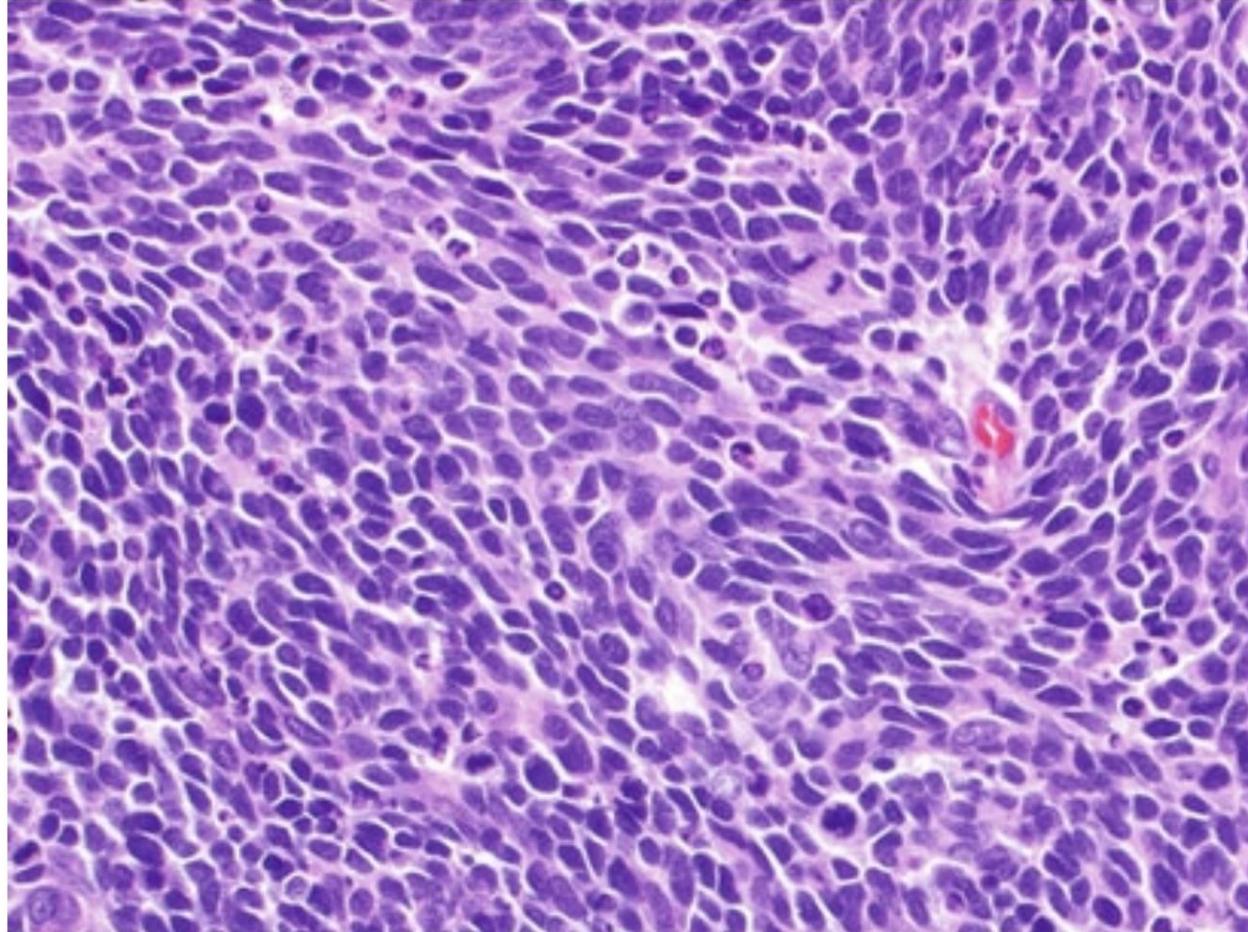
Endocervical adenocarcinoma in situ,  
usual type



HR HPV related usual type endocervical  
adenocarcinoma

# Neuroendocrine tumors (NETs)

- Rare (2%)
- Low grade e.g carcinoid tumor
- High grade: Small cell neuroendocrine carcinoma (the most common form)



Small cell neuroendocrine carcinoma of the uterine cervix

# PREVENTION- Screening

# The Development of Cytology based population screening

- Pap smear: George N. Papanicolau „New cancer diagnosis“ 1928.
- Simultaneously Aurel Babes in Bucharest
- From 1940. every women admitted to the gynecological service of Cornell was required to have a vaginal smear and the samples were examined by Papanicolau
- By mid-1950s screening by cervical exfoliative cytology introduced in US- Reduction of mortality clearly detected
- 2001. The Bethesda Classification



## Liquid based cytology

Monolayer or near monolayer of cervical samples to provide optimal platform to computer assisted image-analysis

Most of the debris, blood and exudate removed by filtration

ThinPrep® (Hologic), SurePath®(BD Diagnostics)

**Table 10** TBS 2014 Classification (Nayar and Wilbur 2015)

### Specimen type:

Indicate conventional smear (Pap smear) versus liquid-based preparation versus other

### Specimen adequacy:

Satisfactory for evaluation

Unsatisfactory for evaluation (*specify reason*)

### General categorization (optional)

Negative for intraepithelial lesion or malignancy

Other: See interpretation/result

Epithelial cell abnormality: See interpretation/result (*specify* "squamous" or "glandular" as appropriate)

### Interpretation/result

#### Negative for intraepithelial lesion or malignancy

Nonneoplastic findings (*optional to report*)

Nonneoplastic cellular variations

Reactive cellular changes

Glandular cells status posthysterectomy

Organisms

#### Other

Endometrial cells (*in a women > 45 yrs of age*)

#### Epithelial cell abnormalities

Squamous cell

ASC

– Of undetermined significance (ASC-US)

– Cannot exclude HSIL (ASC-H)

LSIL (*encompassing: HPV/mild dysplasia/CIN1*)

HSIL (*encompassing: moderate and severe dysplasia, CIS: CIN 2 and CIN 3*)

Squamous cell carcinoma

Glandular cell

Atypical

– Endocervical cells (*NOS or specify in comments*)

– Endometrial cells (*NOS or specify in comments*)

– Glandular cells (*NOS or specify in comments*)

Atypical

– Endocervical cells, favor neoplastic

– Glandular cells, favor neoplastic

Endocervical AIS

Adenocarcinoma

– Endocervical

– Endometrial

– Extrauterine

– Not otherwise specified (NOS)

#### Other malignant neoplasms: (*specify*)

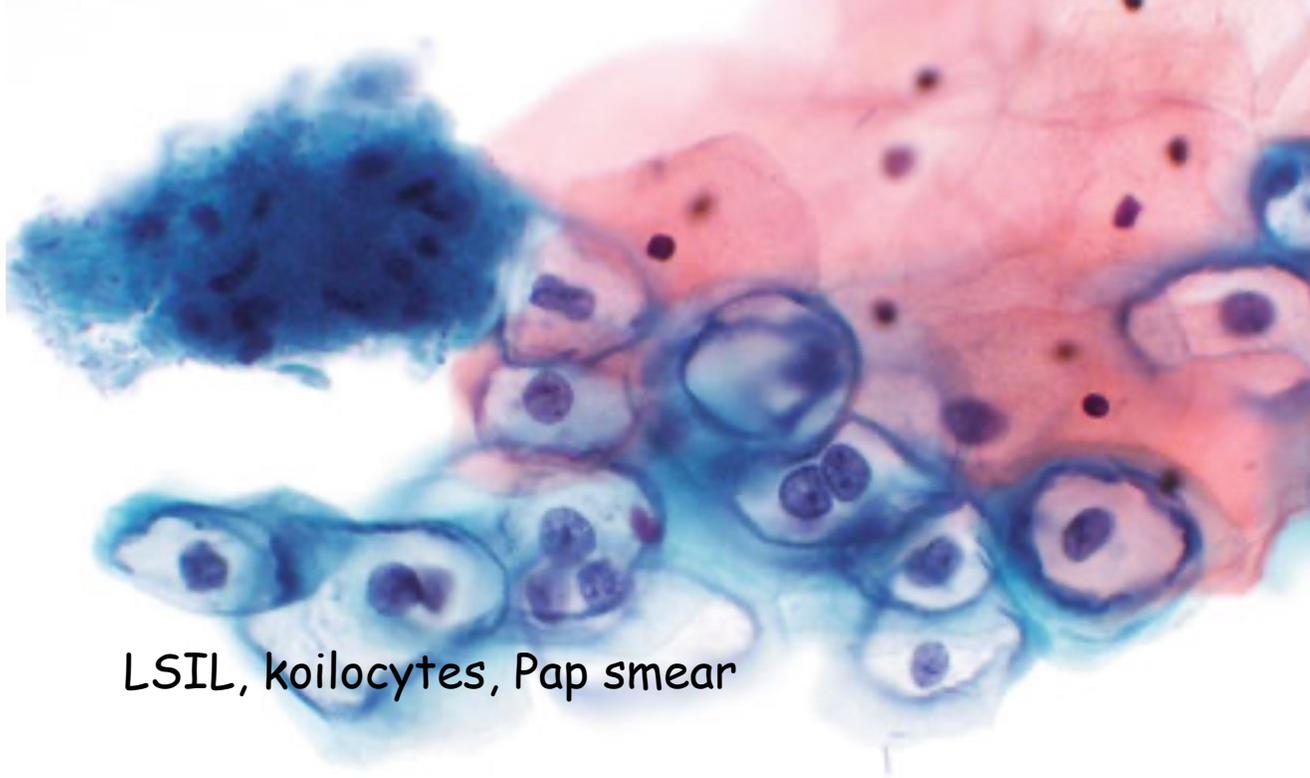
#### Adjunctive testing:

*Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician*

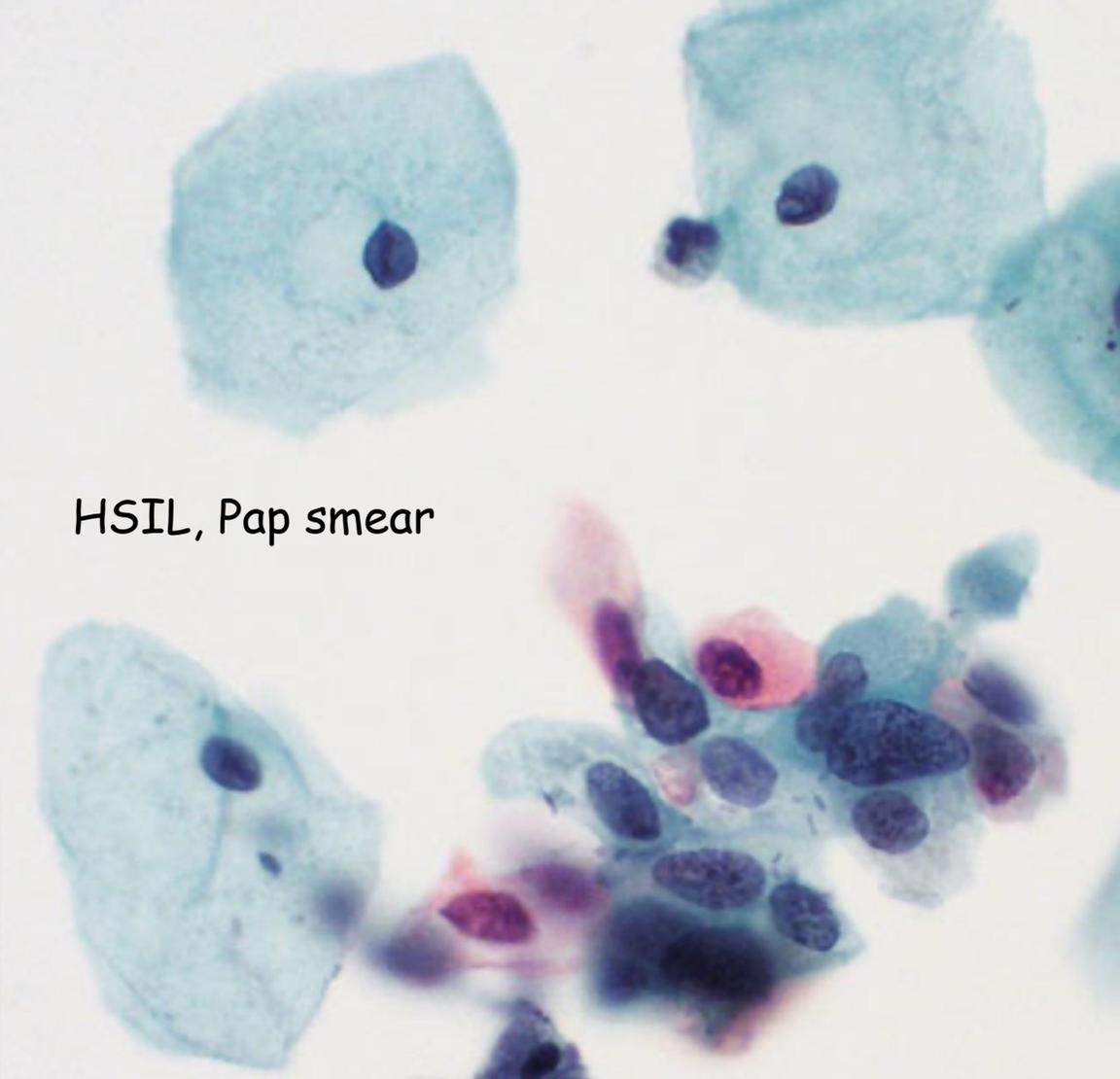
#### Computer-assisted interpretation of cervical cytology

*If case examined by an automated device, specify device, and result*

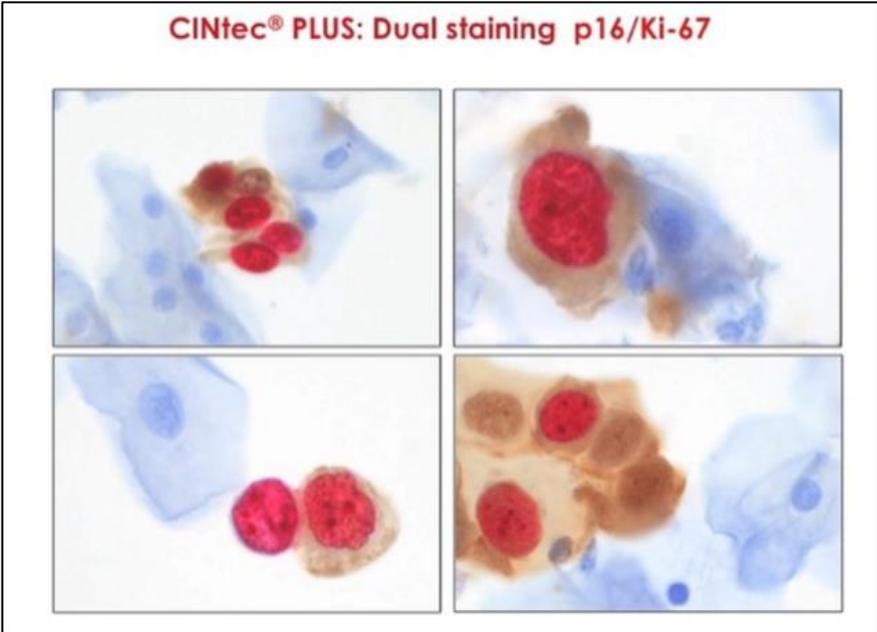
#### Educational notes and comments appended to cytology reports (*optional*)



LSIL, koilocytes, Pap smear



HSIL, Pap smear



# Management

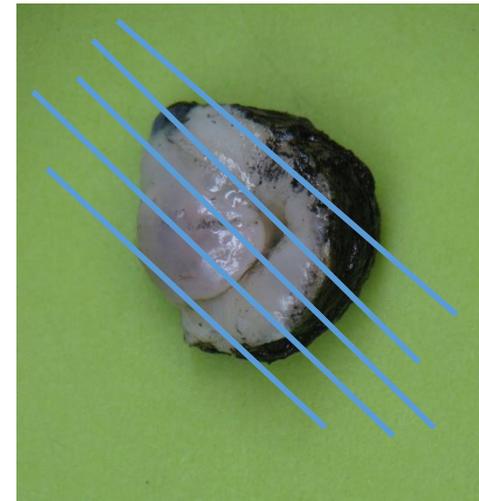
- HPV testing: high throughput molecular essays
  - Indication: 1. primary cervical screening 2. „test of cure“ (monitoring the success of treatment-after removal of HPV-induced cervical lesion) 3. triage of equivocal or low grade cytological abnormalities
  - Possible on various biospecimens: liquid based cytology samples, clinician taken swabs, self-taken samples (for hard-to-reach women), urine
  - Higher sensitivity, but lower specificity than Pap smear

# HPV Biomarkers

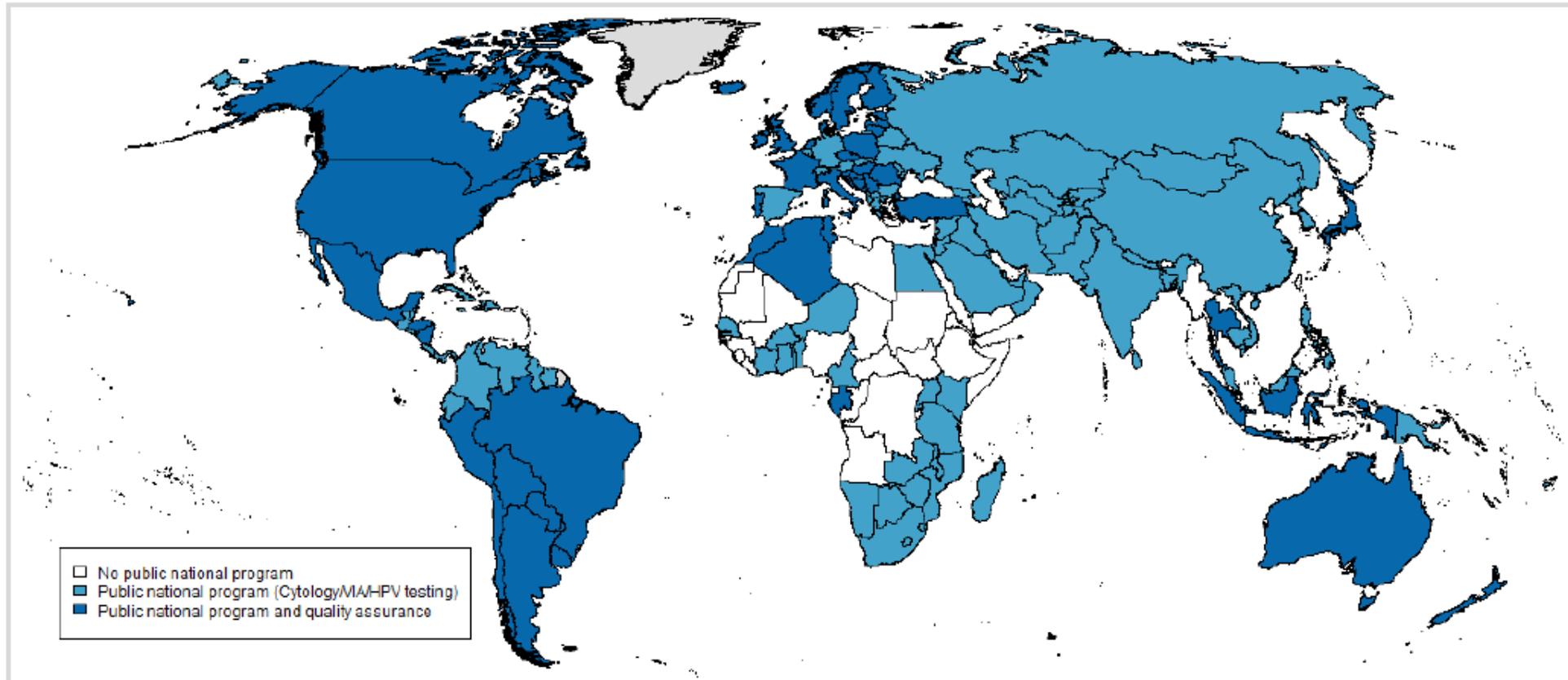
Type of biomarker	Test/Technique	Remarks
HPV DNA testing	Hybrid capture 2 (Qiagen) detects 13 high-risk HPVs	Detects 13 high-risk HPVs
	Cervista HPV HR (Hologic) detects 14 high-risk HPVs	Detects 14 high-risk HPVs
	Cervista HPV 16/18 (Hologic)	Specifically identifies HPV 16 and 18
	Cobas 4800 HPV (Roche diagnostics)	Targets 14 high-risk HPVs
HPV RNA testing	APITMA (Gen-Probe) and OncoTect (IncellDX)	Based on reverse transcriptase and PCR technique. Can detect E6 and E7 mRNA from 14 and 13 high-risk HPA serotypes, respectively
	PreTect HPV-Proofer (Norchip) and NucliSENS EasyQ (bioMerieux)	Rely on nucleic acid sequence-based amplification (NAS-BA) and are able to detect E6/E7 transcripts from HPV 16, 18, 31, 33, and 45
HPV protein testing	OncoE6 (Arbor Vita Corporation)	Detects E6 protein encoded by HPV 16, 18, and 45
	Cytoactiv assay (cytoimmune diagnostics)	Measures loss of expression of L1 which has been identified as a potential marker of progressive lesions
Cellular biomarkers	P16/K1-67 immunocytochemistry assay	p16 is a CDK-I while K1-67 is a proliferation antigen expressed in the G2 and M phases of the cell cycle. They are co-expressed in dysplastic lesions and constitute a highly sensitive and specific test for CIN 2 or worse lesions
	ProExCTM assay (Becton-Dickinson)	Recognizes minichromosome maintenance protein 2 and topoisomerase II $\alpha$ , which are expressed in cells with abnormal S-phases such as HPV-infected cells with increased E6/E7 synthesis.
	Fluorescence <i>in situ</i> hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA)	Can be used to detect gain of chromosomes 3q and 5p which carry the TERC and TERT genes
Epigenetic biomarkers	Differential methylation hybridization (DMH)	Allows identification of SOX1, NKX6-1, PAX1, WX1, and LMXIA genes that are often methylated in cervical cancer and precancerous lesions
	Restriction landmark genomic scanning (RLGS)	Detection of methylated NOL4 and LHFPL4 genes
	Demethylating agent expression microarray	Identifies methylation of SPARC and TFP2 genes

# Some principles...

- Age 21 first screening
- After age 30 negative Pap smear and HPV negative every 5 years
- Negative Pap smear, but HR HPV, test every 6-12 months
- If Pap abnormal- colposcopy (magnifying glass), acetic acid test, biopsy
- If biopsy result is LSIL-follow
- If biopsy result is HSIL-conization



# Worldwide status of cervical cancer screening programmes

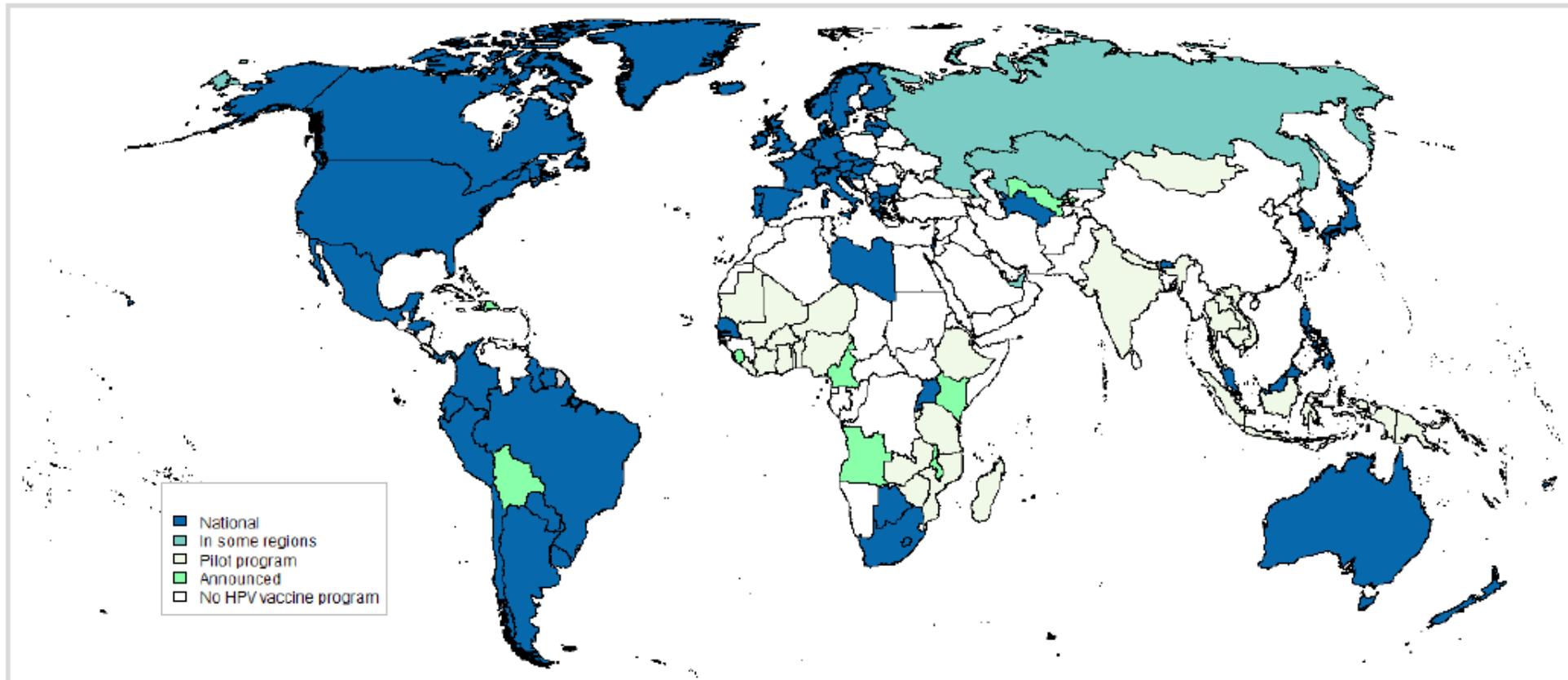


Data accessed on 31 Dec 2016.

# Prevention-vaccination

- **Quadrivalent vaccine: Gardasil<sup>®</sup>** (HPV 6, 11, 16, and 18)
  - The L1 capsid proteins are produced in yeast cells (*Saccharomyces cerevisiae*) and mixed with an aluminum adjuvant.
  - For both males and females who are 9-26 years of age
  - three doses at 0, 2, and 6 months.
- **Bivalent vaccine: Cervarix<sup>®</sup>** (HPV 16 and 18)
  - The VLPs in this preparation are generated in insect cells with baculovirus and an adjuvant with  $ASO_4$  and monophosphoryl lipid A via bacterial cell walls
  - For girls and women 10-25 years of age and is given in three doses at 0, 1, and 6 months.
- **Nonavalent vaccine: Gardasil 9<sup>®</sup>** (HPV 16, 18, 31, 33, 45, 52, and 58) and (HPV 6, 11)
  - protection from 70 to 90% of cervical cancer-causing HPV infections

# Worldwide status of HPV vaccination programmes



Data accessed on 31 Dec 2016.

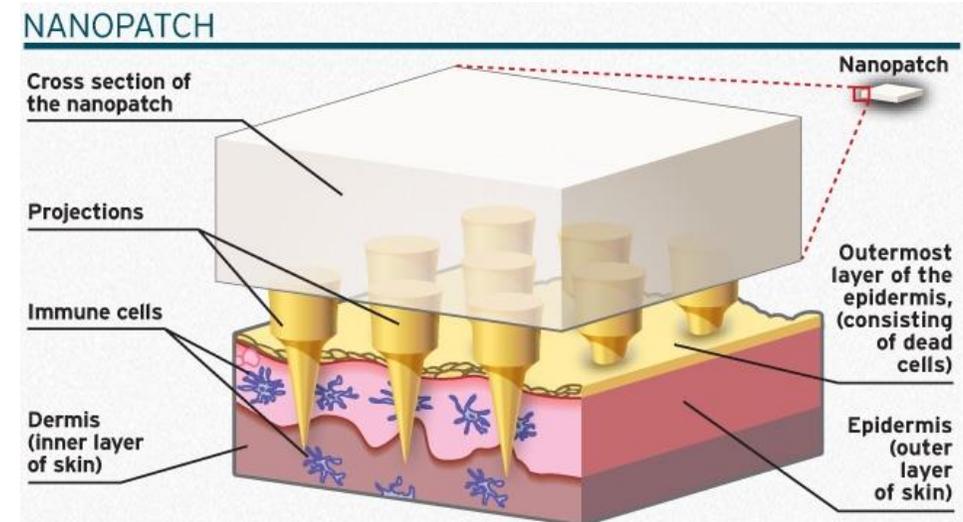
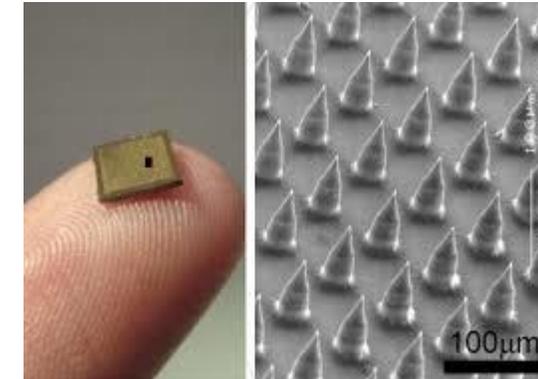
# An alternative form of vaccination- Nanopatch™



Immune response and reactogenicity of an unadjuvanted intradermally delivered human papillomavirus vaccine using a first generation Nanopatch™ in rhesus macaques: An exploratory, pre-clinical feasibility assessment

Brian K. Meyer<sup>a,\*</sup>, Mark A.F. Kendall<sup>b,c,1</sup>, Donna M. Williams<sup>a</sup>, Andrew J. Bett<sup>d</sup>, Sheri Dubey<sup>d</sup>, Renee C. Gentzel<sup>e</sup>, Danilo Casimiro<sup>d,2</sup>, Angus Forster<sup>c</sup>, Holly Corbett<sup>b,3</sup>, Michael Crichton<sup>b,c,4</sup>, S. Ben Baker<sup>b,c,5</sup>, Robert K. Evans<sup>a,6</sup>, Akhilesh Bhambhani<sup>a</sup>

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<sup>d</sup> Infectious Disease and Vaccines, MRL, Merck & Co., Inc., 770 Sumneytown Pike, West Point, PA 19486, USA  
<sup>e</sup> Movement Disorders and Translation, MRL, Merck & Co., Inc., 770 Sumneytown Pike, West Point, PA 19486, USA



<https://www.youtube.com/watch?v=BGRy5VU-LfI>