Gynecopathology (I)

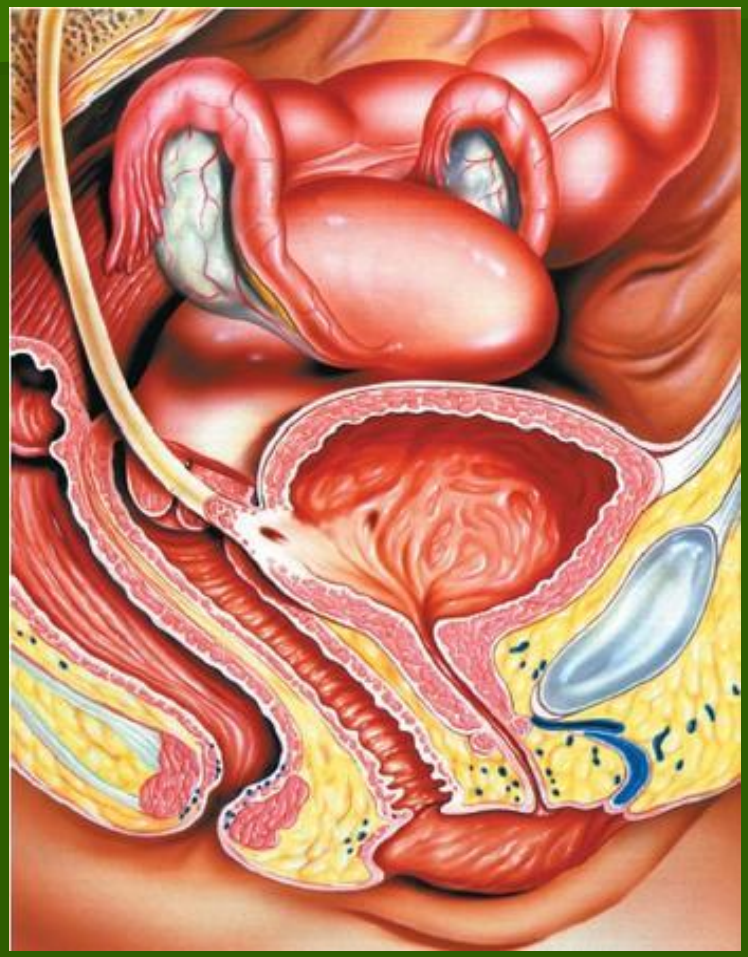
Vulva, Vagina, Cervix, (CIN, Invasive cervical cancer)

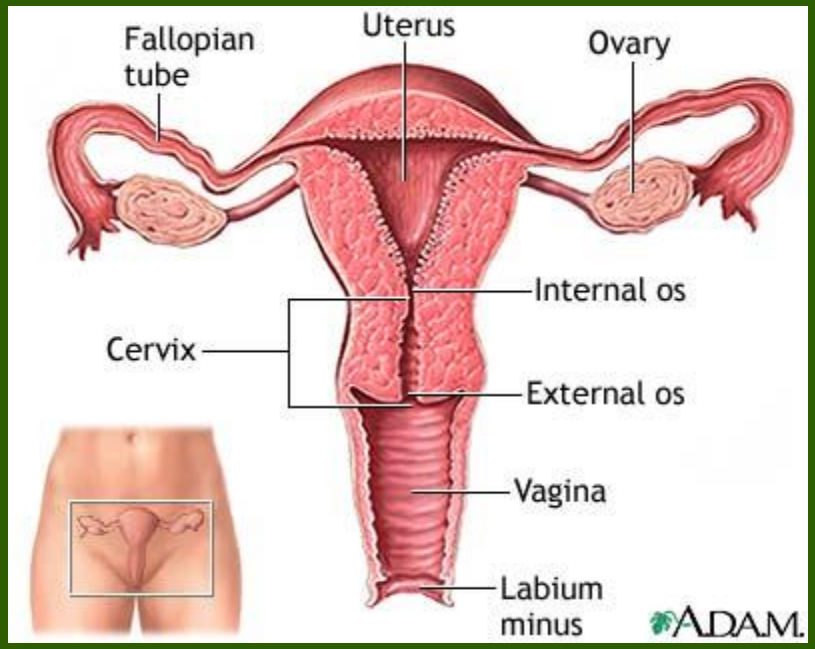
prof.Dr. Zsuzsa Schaff

March 2018

Semmelweis University
2nd Department of Pathology
Budapest

Anatomy




Fallopian tube
Uterus
Ovary
Internal os
Cervix
External os
Vagina
Labium minus
A.D.A.M.

Vulva

- Anatomy
  - Mons pubis, labia majora/minora, clitoris, vestibule, paraurethral glands, Bartholin glands (mucus secrating glands)
- Developmental abnormalities, cysts
  - Bartholin gland cysts, follicular cysts, mucinous cysts
- Inflammations
  - Dermatitis: acute, chronic (lichen simplex chr), lichen sclerosus
- Benign tumors
  - Hydradenoma, syringoma, connective tissue tumors (haemang., fibroma), pigmented lesions
- Malignant tumors
  - Vulvar intraepithelial neoplasia (VIN), squamous cell cc (stage I-IV), malignant melanoma, extramammillary Paget disease

Vulvar Intraepithelial Neoplasia (VIN)

- Incidence of VIN is increasing in the United States and worldwide.[1]
- Mean age of women with VIN is decreasing[2–4]
- Symptoms occur and may be present for a long time prior to diagnosis (median of 1 year)[4]
- HPV 16 appears to be the dominant HPV type associated with high-grade VIN[5]
  - Majority of VIN 1 cases are associated with HPV types 6 and 11[6]
  - HPV 6, 11, 16, or 18 can be found in VIN 2 or 3[7]

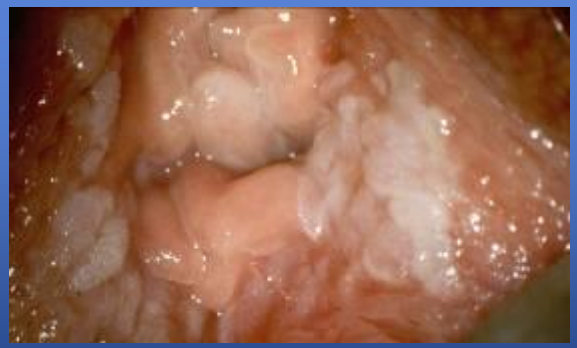
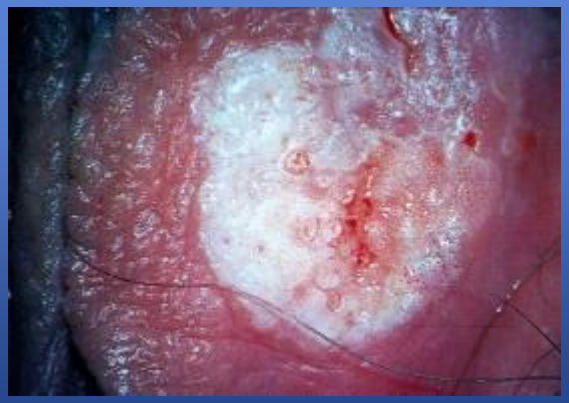
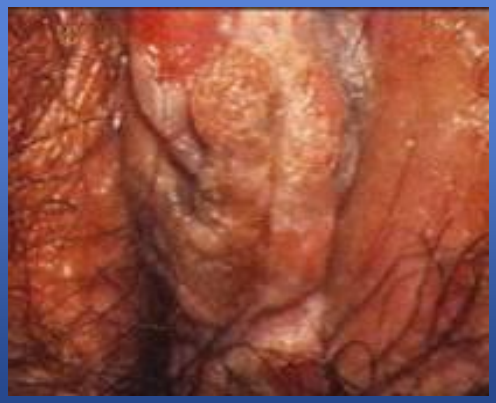


Photo courtesy of Dr. J. Monsonego





Photos courtesy of Dr. E.J. Mayeaux

1. Joura EA. *Curr Opin Obstet Gynecol.* 2002;14:39–43. 2. Sturgeon SR, Brinton LA, Devesa SS, Kurman RJ. *Am J Obstet Gynecol.* 1992;166:1482–1485. 3. Jones RW, Rowan DM, Stewart AW. *Obstet Gynecol.* 2005;106:1319–1326. 4. Herod JJ, Shafi MI, Rollason TP, et al. *Br J Obstet Gynaecol.* May 1996;103:446–452. 5. Buscema J, Naghashfar Z, Sawada E, et al. *Obstet Gynecol.* 1988;71:601–606. 6. Koutsky L. *Am J Med.* 1997;102:3–8. 7. Liaw KL, Kurman RJ, Ronnett B, et al. EUROGIN, April 2006. Paris, France.

Vagina

- Anatomy
  - Hormon-responsive squamous epithelium
- Nonneoplastic conditions and benign tu
  - Cong.anomalies (abscence, septate, atresia, imperforate hymen)
  - Atrophic vaginitis (estrogen deficiency, postmenopausal)
  - Vaginal adenosis (red, granular patches, columnar cells, diethylstilbestrol –DES therapy in utero)
  - Fibroepithelial polyp, mesench tu
- Malignant tumors
  - Squamous cell cc – VAIN, rhabdomyosarcoma

Vaginal Intraepithelial Neoplasia (VaIN)

- Main predisposing factor for VaIN is likely exposure to HPV[1]
- Average age of women with VaIN: 40–60 years[1]
- True incidence unknown, but lower than for CIN[1]
- VaIN is often asymptomatic and difficult to diagnose.[2]
- While untreated VaIN can spontaneously regress, there is a potential for VaIN to progress to invasive vaginal cancer.[2]

1. Winter-Roach B, Monaghan JM, de Lopes A. Colposcopy of the vagina. In: Bosze P, Luesley D, eds. *EAGC Course Book on Colposcopy*. Budapest: Primed-X Press; 2004:120–123. 2. Dodge JA, Eltabbakh GH, Mount SL, et al. *Gynecol Oncol.* Nov 2001;83:363–369.

Cervix I.
Anatomy, Inflammatory to Regenerative changes

- Anatomy (exoocervix – portio vaginalis, endocervix, orificium externum, internum, squamocolumnar junction – tranformation zone)
- Cervicitis – very common
  - Leukorrhea with bacteria and other agents
  - Sexual transmission
- Forms:
  - Acute cervicitis
  - Chronic cervicitis
- Cause:
  - Non-infective:
    - trauma, chemical agents, radiotherapy
  - *„Infective cervicitis"*
    - Candida albicans, Chlamydia trachomatis, Neisseria gonorrhoeae, Gardnerella vaginalis, Strepto, Sta
    - Chlamydia trachomatis
    - Viruses: HPV, HSV, CMV
    - Tbc, sy, Shistosoma („specific")
- Macr: swollen, red,
- Micr: infl infiltration (PMN, ly), erosions, regeneration

Cervix II.
Other non-neoplastic conditions and Polyps

- **Endometriosis**
  - Endometrial tissue in the cervix (glands, stroma)
  - Ages: 20-53 yrs
  - Cause: ?, trauma,
  - Symptomes: incidental, bleeding
  - Macr: blood-filled cysts
- Mesonephric remnants and hyperplasia
  - Remnants in 22% of adult cervices
- **Cervical polyp**
  - Localized overgrowth of endocervical tissue
  - Symptomes: no, or bleeding
  - Micr: surface: glandular or squamous epith, inflammation

Cervical benign and non-neoplastic conditions

- Inflammatory (cervicitis) to regenerative changes
  - Infective cervicitis
- Lesions in the endocervical glandular epithelium
  - Deep nabothian cysts (2-10 mm mucus-filled cysts located on the surface of normal endocervical glands. Occasionally are located deeply, lined by flattened endocervical glandular cells, with accumulated mucus)
  - Glandular hyperplasia
- Lesions related to exogenic stimuli
  - Microglandular hyperplasia
  - Arias-Stella reaction (papillary, cribriform pattern, large cells, associated with pregnancy, contraceptive use)
  - Decidual change (progesteron induced alteration)
  - Radiation changes (acute or chr)
- Benign tumors
  - Papilloma, condyloma acum. (HPV)
  - Leiomyoma (less common than in the uterine body)
  - Blue nevus (small benign lesion, 0,5% of uteri, asymptomatic, incidental, blue, flat, 2-3 mm – but up to 2 cm)

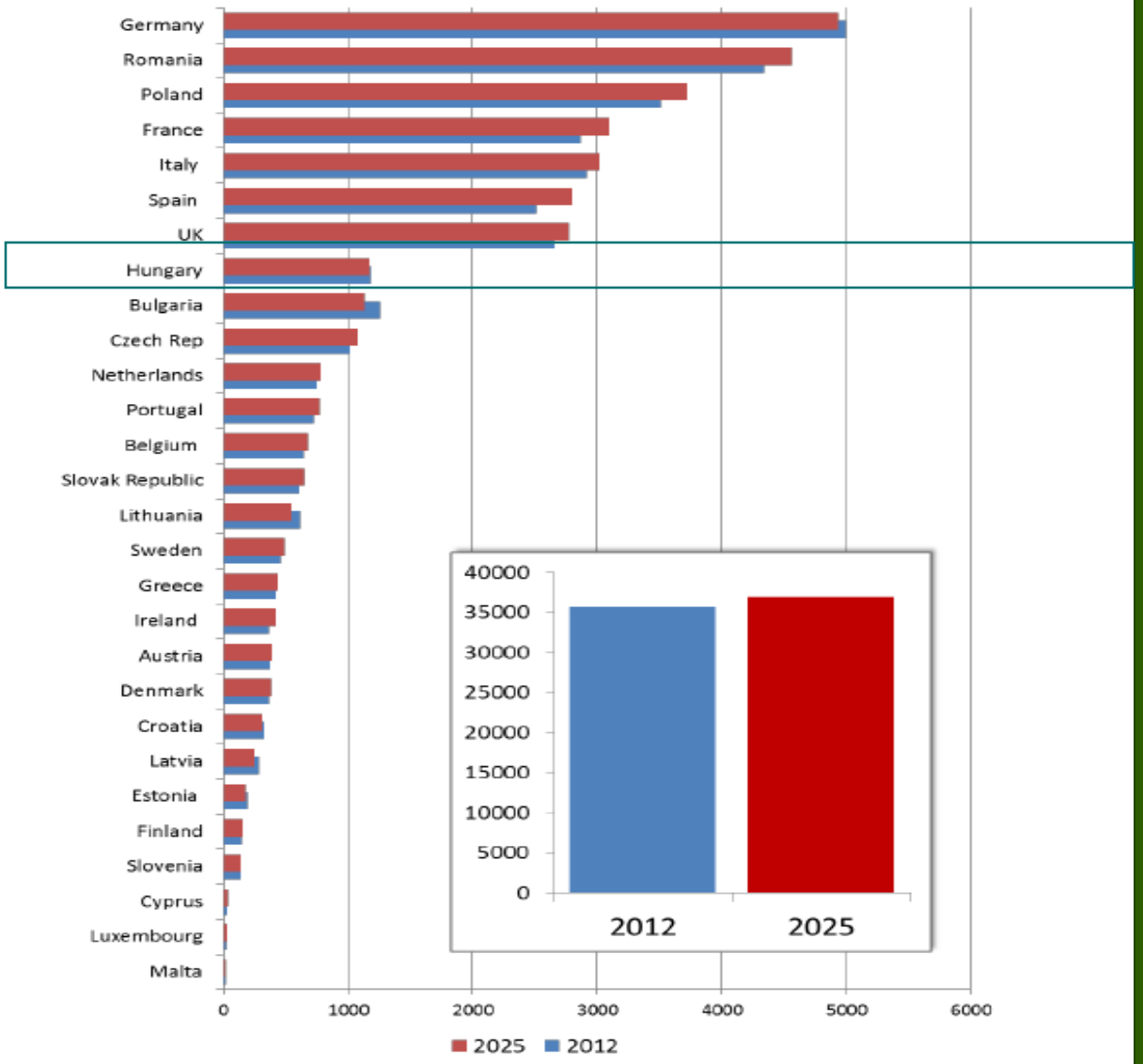
Cervical Cancer
Impact of Cervical Cancer

- **Morbidity**
  - Global prevalence: ~2.3 million[1]
  - Global incidence: ~500,000[1,2]
  - Globally, cervical cancer is second to breast cancer as the leading cause of cancer in women.[2]
- **Mortality**
  - 3rd most common cause of overall female cancer-related mortality worldwide[2]

1. World Health Organization. Geneva, Switzerland: World Health Organization; 2003:1–74. 2. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004. 3. Ries LAG, Eisner MP, Kosary CL, et al. (eds). *SEER Cancer Statistics Review, 1975–2002*, National Cancer Institute. Bethesda, MD; 2005.

Cervical cancer incidence

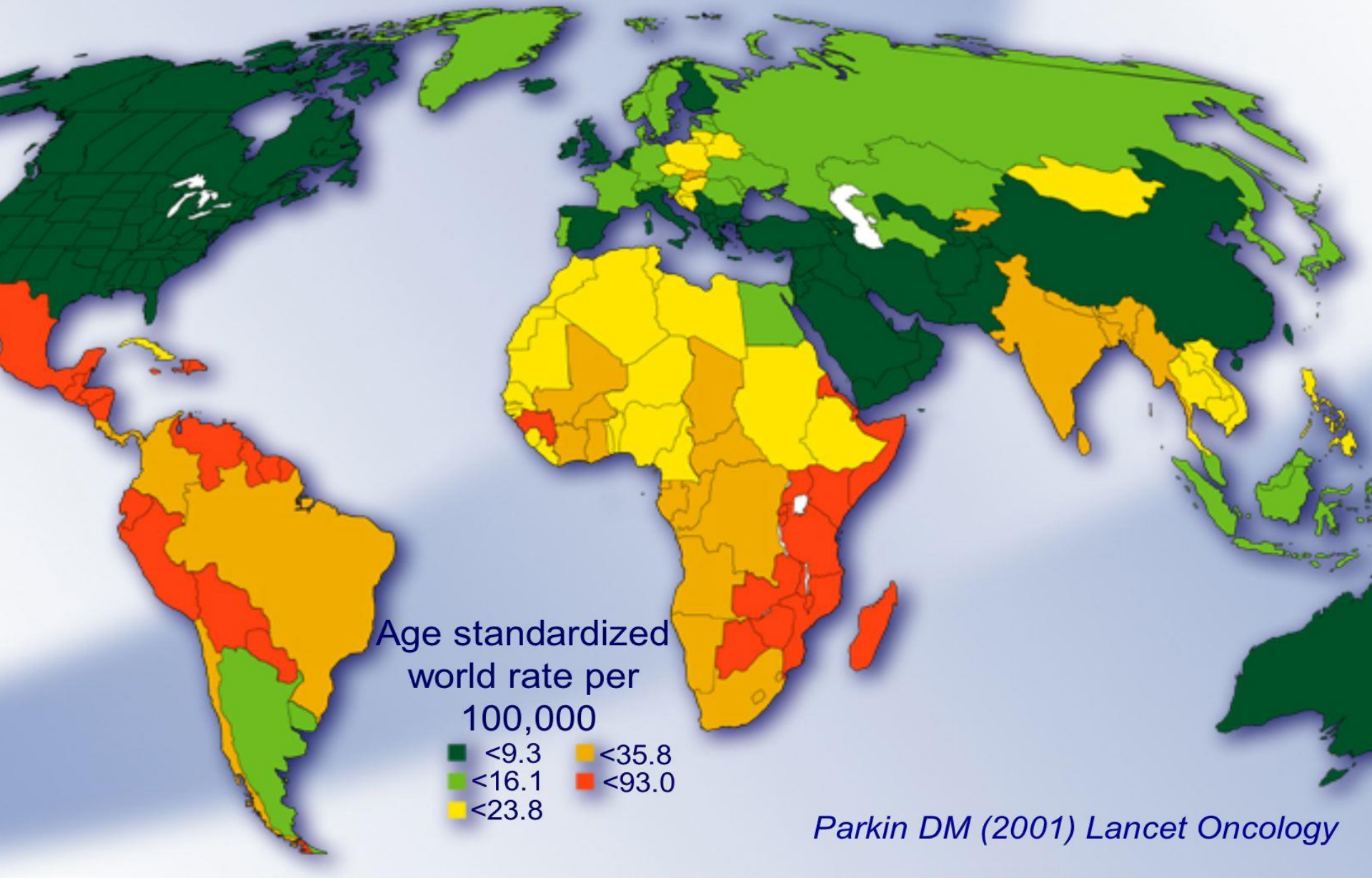
Figure 1.4.2. Estimated number of **new cervical cancers in women** in the EU countries in 2025 compared to 2012. (Population forecasts were extracted from the *United Nations, World Population prospects, the 2012 revision)*



Source: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 22/March/2016.

European Commission. Cancer Screening in the European Union Report on the implementation of the Council Recommendation on cancer screening. 2017. https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf

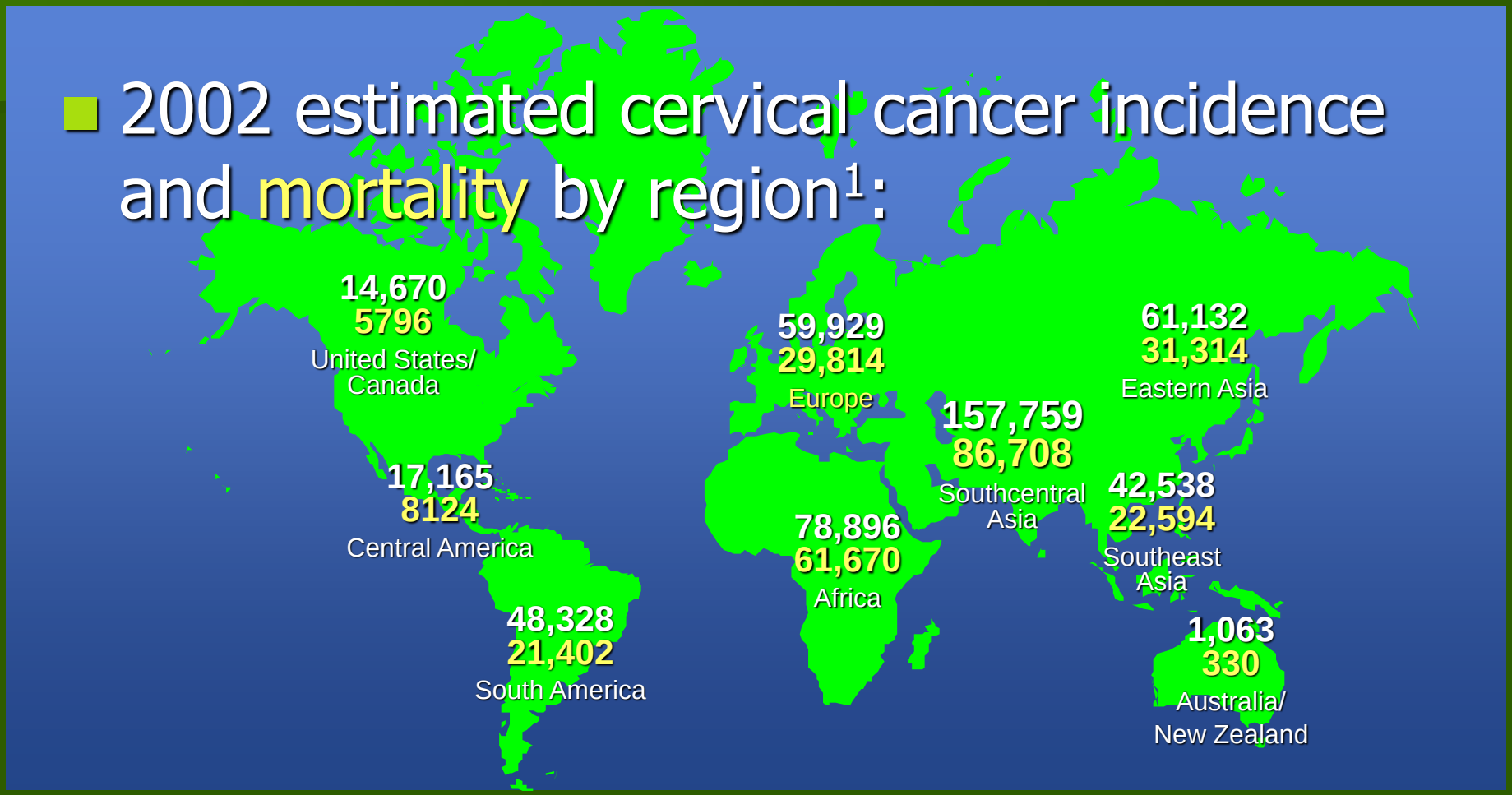
ge-standardized Cervical Cancer Incidence



Parkin DM (2001) Lancet Oncology

Cervical Cancer Incidence and Mortality Estimates by Region

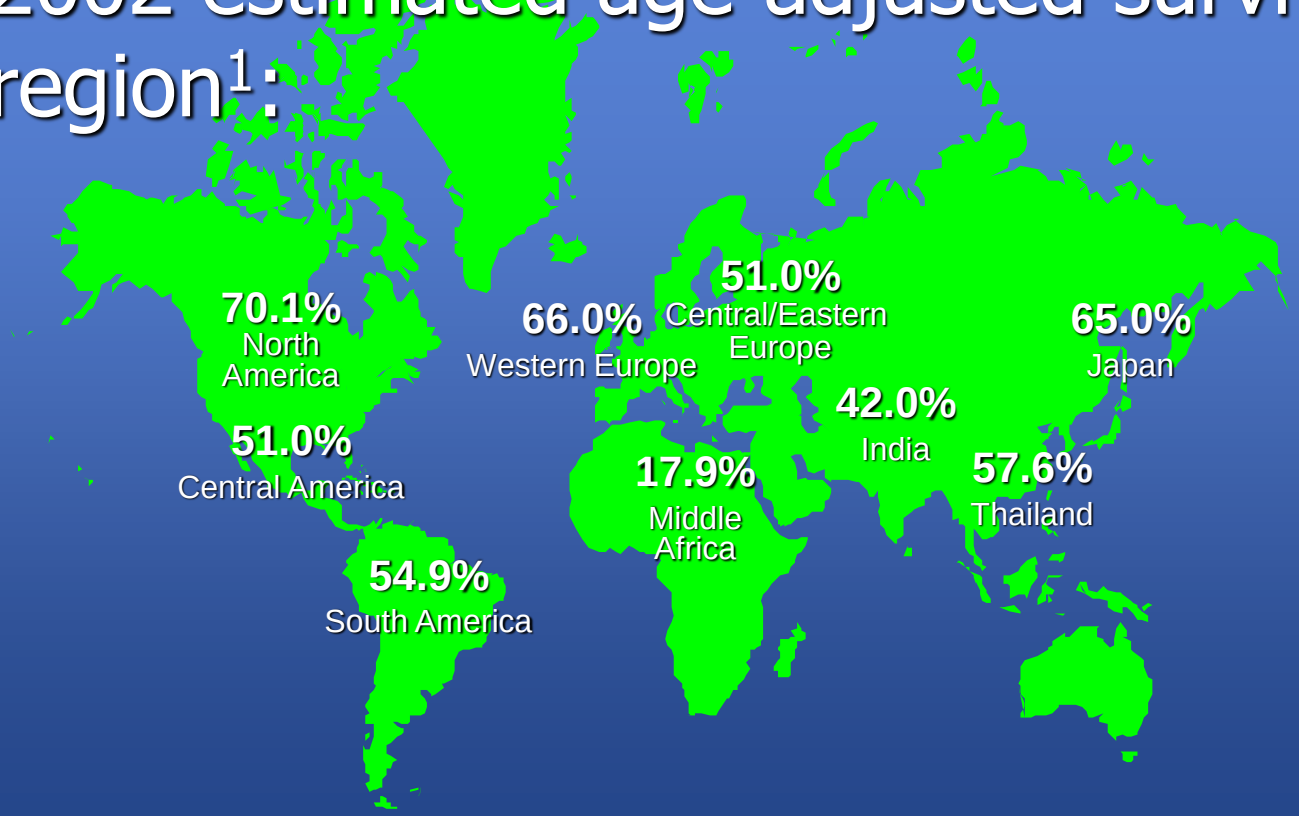
- 2002 estimated cervical cancer incidence and mortality by region[1]:



1. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004.

Cervical Cancer: Age-Adjusted Survival

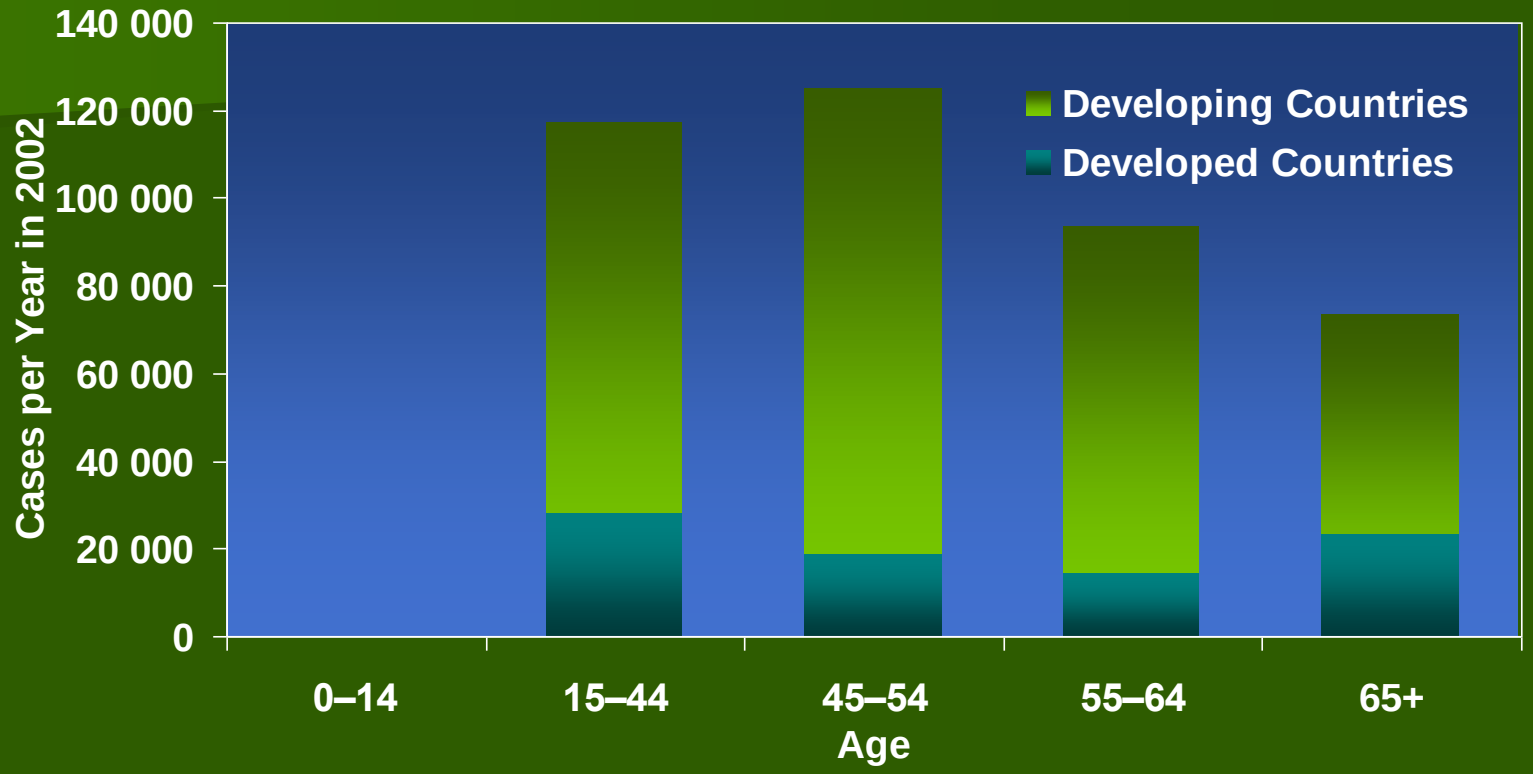
- 2002 estimated age-adjusted survival by region[1]:



Age-adjusted survival: 61.2% in more developed countries; 41.4% in developing countries[1]

1. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004.

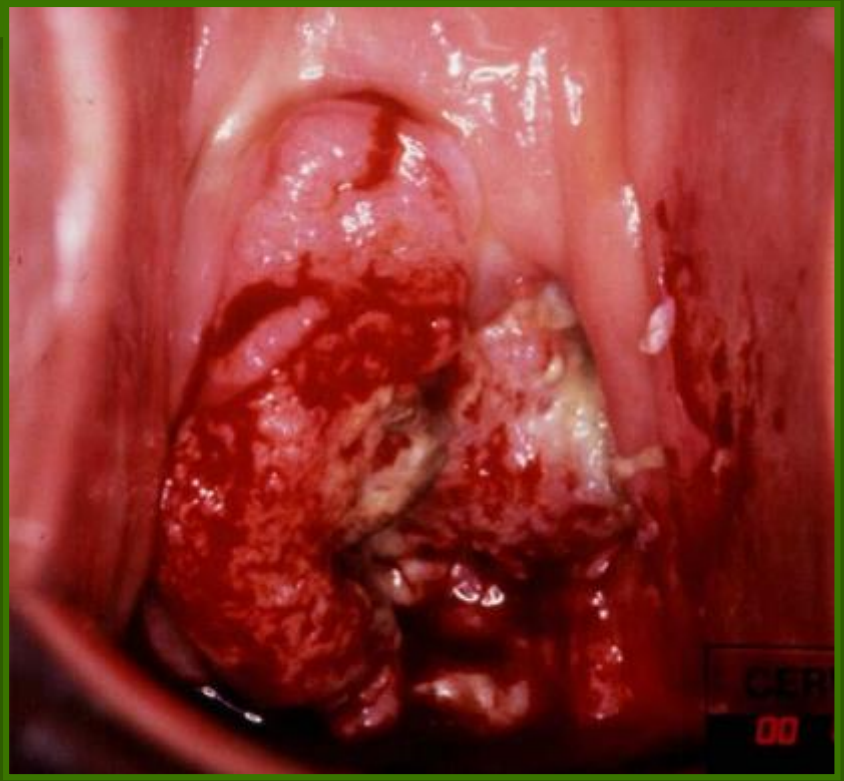
Age Distribution of New Cervical Cancer Cases[1]



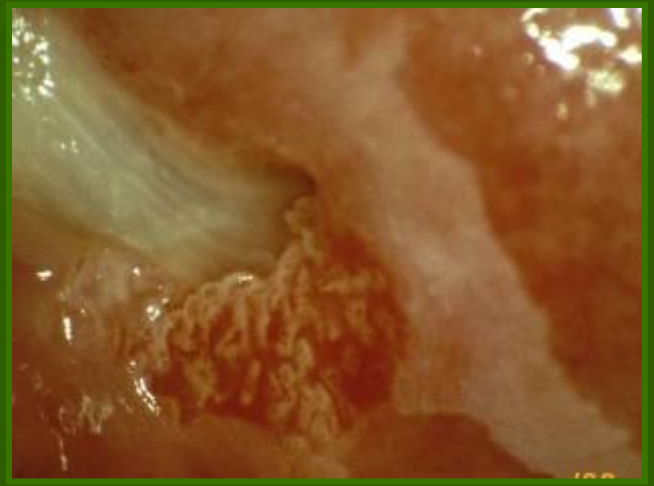
	Age Group				
	0–14	15–44	45–54	55–64	65+
Developing	133	117,242	125,040	93,485	73,369
Developed	0	27,828	18,513	14,021	23,075

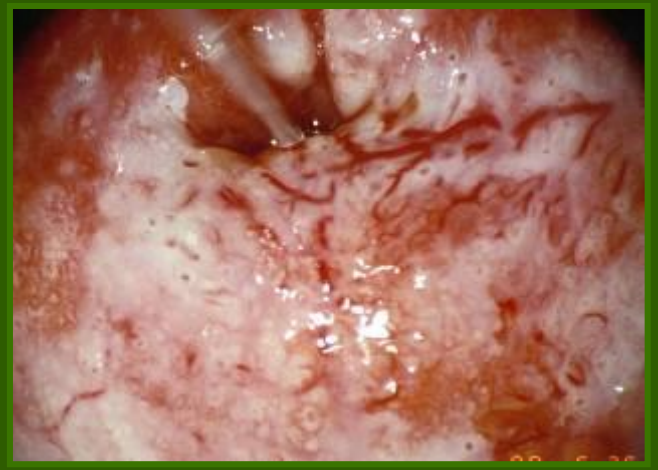
1. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004.

Colposcopy: Invasive Cervical Carcinoma



From IARC, 2003.[1]



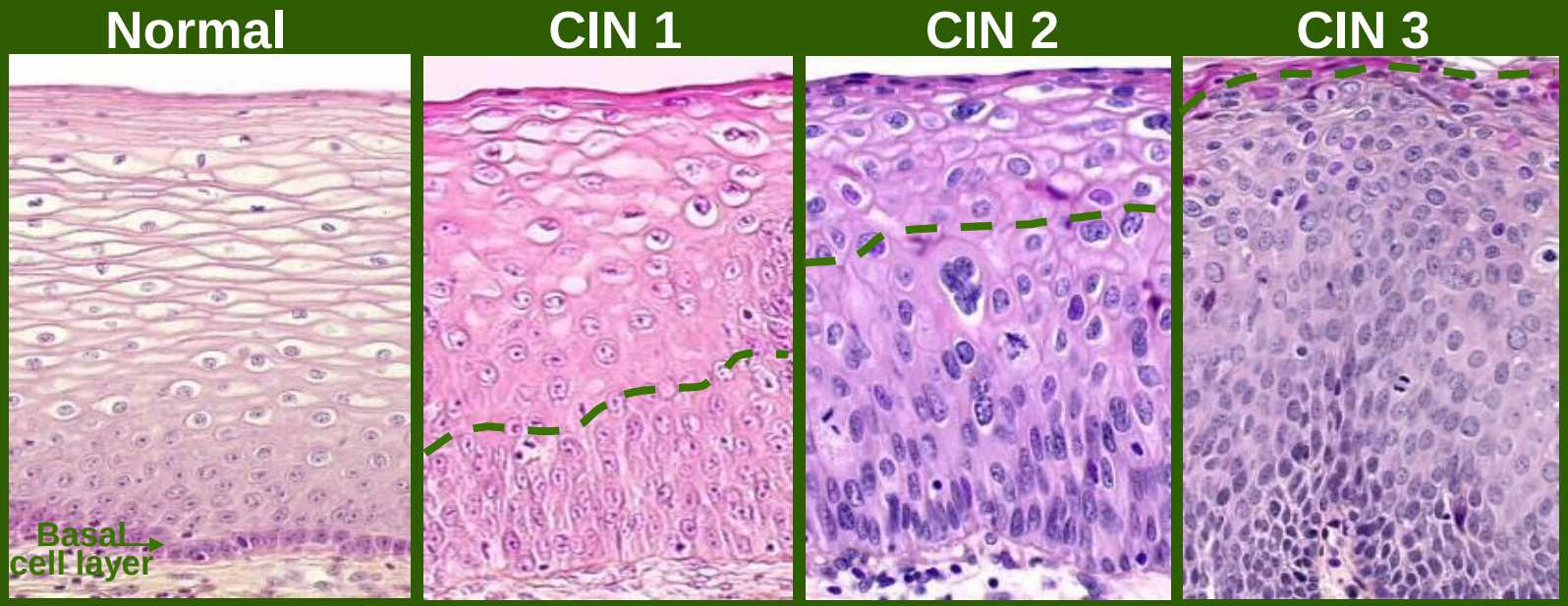


Photos courtesy of Dr. J. Monsonego

1. Reprinted with permission from Sellors JW, Sankaranarayanan R, eds. Colposcopy and Treatment of Cervical Intraepithelial Neoplasia. A Beginner's Manual. Lyon, France: International Agency for Research on Cancer; 2003.

Histopathology: CIN[1]

- CIN 1: Mild dysplasia; includes condyloma (anogenital warts)
- CIN 2: Moderate dysplasia
- CIN 3: Severe dysplasia; CIS; FIGO stage 0



All figures reprinted with permission from Frappart, et al. Histopathology and Cytopathology of the Uterine Cervix. Digital Atlas, Lyon, France: IARC *Press*, 2004.

Cytology findings confirmed by histology[4]

1. Frappart L, Fontaniere B, Lucas E, Sankaranarayanan R, eds. Lyon, France: International Agency for Research on Cancer; 2004. 2. Bonnez W. In: Richman DD, Whitley RJ, Hayden FJ, eds. Washington, DC: American Society for Microbiology Press; 2002:557–596. 3. Canadian Cancer Society. Cervical Cancer: What you need to know. Available at: http://www.cancer.ca/vgn/images/portal/ cit_86751114/ 63/40/151140772cw_library_wyntk_cervical_en.pdf. Accessed March 13, 2006. 4. Wright TC Jr, Cox JT, Massad LS, et al, for the ASCCP-Sponsored Consensus Congress. *JAMA*. 2002;287:2120–2129.

Classification Terminology for Cervical Cytology: The 2001 **Bethesda System**

Normal

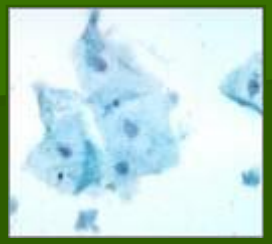


Photo courtesy of Marion M. Haber, MD.

ASCUS

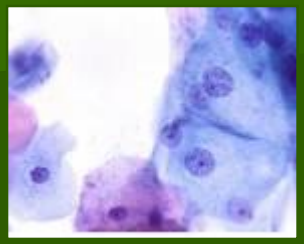


Photo courtesy of American Society of Cytopathology.

LSIL

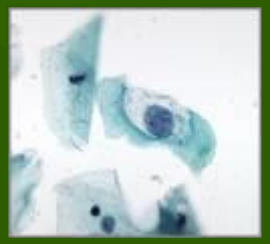


Photo courtesy of Marion M. Haber, MD.

HSIL

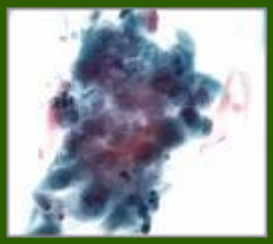


Photo courtesy of Marion M. Haber, MD.

Squamous cells[1]

- Atypical squamous cells (ASCs)
  - ASCs of undetermined significance (ASCUS)
  - ASC, cannot exclude high-grade SILs (ASC-H)
- Squamous intraepithelial lesions (SIL)
  - Low-grade SIL (LSIL): Mild dysplasia, cervical intraepithelial neoplasia 1 (CIN 1)
  - High-grade SIL (HSIL): Moderate and severe dysplasia, CIN 2/3, carcinoma in situ (CIS)

Glandular cells1

- Atypical glandular cells (AGCs)
- AGCs, favor neoplastic
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma

Cytology findings should be confirmed by histology.[2]

1. Solomon D, Davey D, Kurman R, et al, for the Forum Group Members and the Bethesda 2001 Workshop. *JAMA*. 2002;287:2114–2119. 2. Wright TC Jr, Cox JT, Massad LS, et al, for the ASCCP-Sponsored Consensus Congress. *JAMA*. 2002;287:2120–2129.

Comparison of Terminology for Cervical Dysplasia Reported by Cytology and Histology

No clear correspondence between classification of cytology and histology results

Bethesda classification (cytology)[1]	Normal	ASC	LSIL	HSIL	Invasive cancer

If confirmed by histology

CIN (WHO (histopathology)	Normal	Condyloma	CIN 1 (mild dysplasia)	CIN 2 (moderate dysplasia)	CIN 3 (severe dysplasia/CIS)	Invasive cancer

- Chance of having biopsy-confirmed CIN 2/3 is approximately
  - 5%–17% for women with a cervical cytology result interpreted as ASC[3]
  - 15%–30% for women with LSIL on cervical cytology[3]
  - 70%–75% for women with a cytologic diagnosis of HSIL[3]

1. Solomon D, Davey D, Kurman R, et al, for the Forum Group Members and the Bethesda 2001 Workshop. *JAMA*. 2002;287:2114–2119. 2. Bonnez W. In: Richman DD, Whitley RJ, Hayden FJ, eds. Washington, DC: American Society for Microbiology Press; 2002:557–596. 3. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ, for the ASCCP-Sponsored Consensus Congress. *JAMA*. 2002;287:2120–2129.

CIN as seen in Colposcopy

Colposcopy findings confirmed by histology[1]

- CIN 1: Mild dysplasia; includes condyloma (anogenital warts)[2]
- CIN 2: Moderate dysplasia[2]
- CIN 3: Severe dysplasia; cancer in situ (CIS); FIGO Stage 0[2,3]

CIN 1

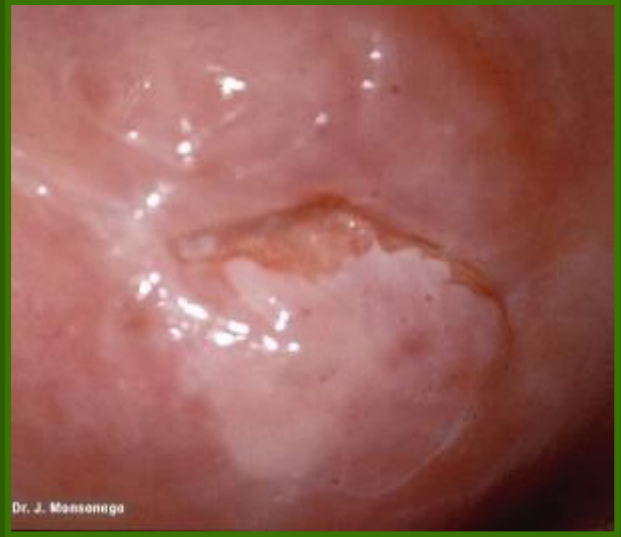


Photo courtesy of Dr. J. Monsonego

CIN 2

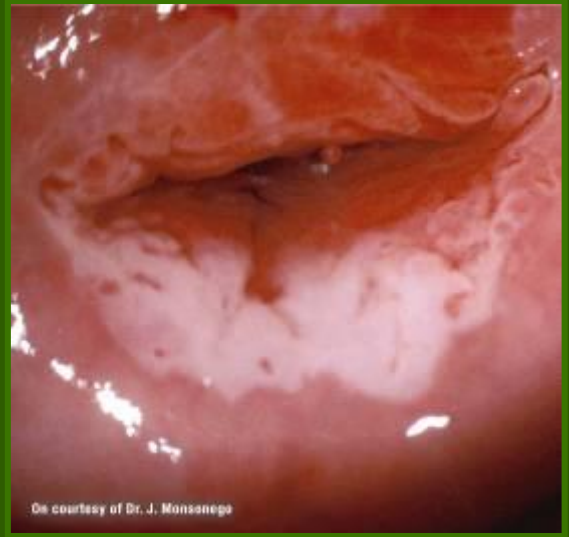
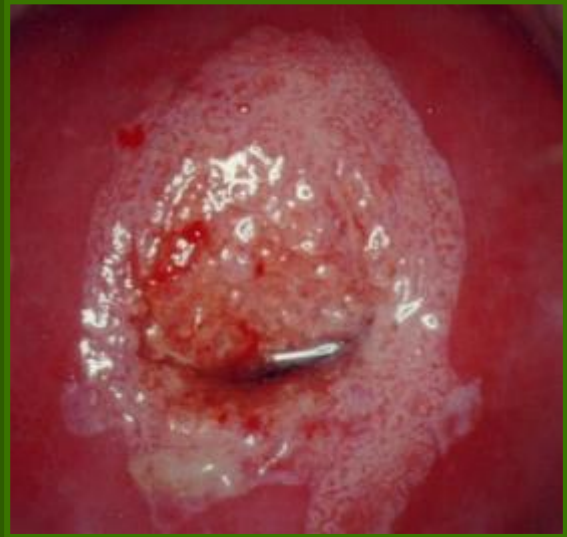


Photo courtesy of Dr. J. Monsonego

CIN 3



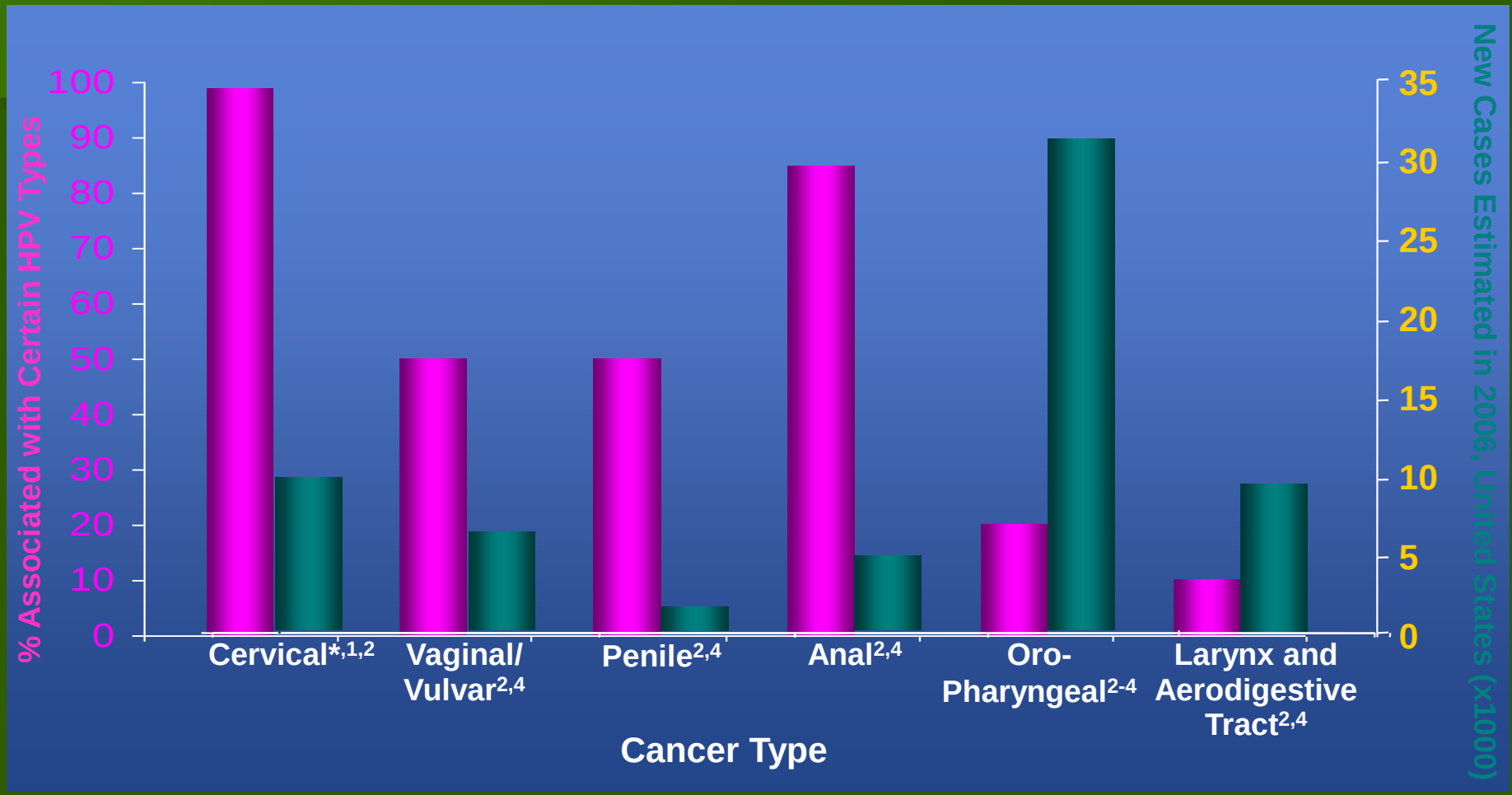
From IARC, 2003.[4]

1. Wright TC Jr, Cox JT, Massad LS, et al, for the ASCCP-Sponsored Consensus Congress. *JAMA*. 2002;287:2120–2129. 2. Bonnez W. In: Richman DD, Whitley RJ, Hayden FJ, eds. Washington, DC: American Society for Microbiology Press; 2002:557–596. 3. Canadian Cancer Society. Cervical Cancer: What you need to know. Available at: http://www.cancer.ca/vgn/images/portal/cit_86751114/63/40/151140772cw_library_wyntk_cervical_en.pdf. Accessed March 13, 2006. 4. Reprinted with permission from Sellors JW, Sankaranarayanan R, eds. Colposcopy and Treatment of Cervical Intraepithelial Neoplasia. A Beginner's Manual. Lyon, France: International Agency for Research on Cancer; 2003.

Biomarkers in cervical cancer

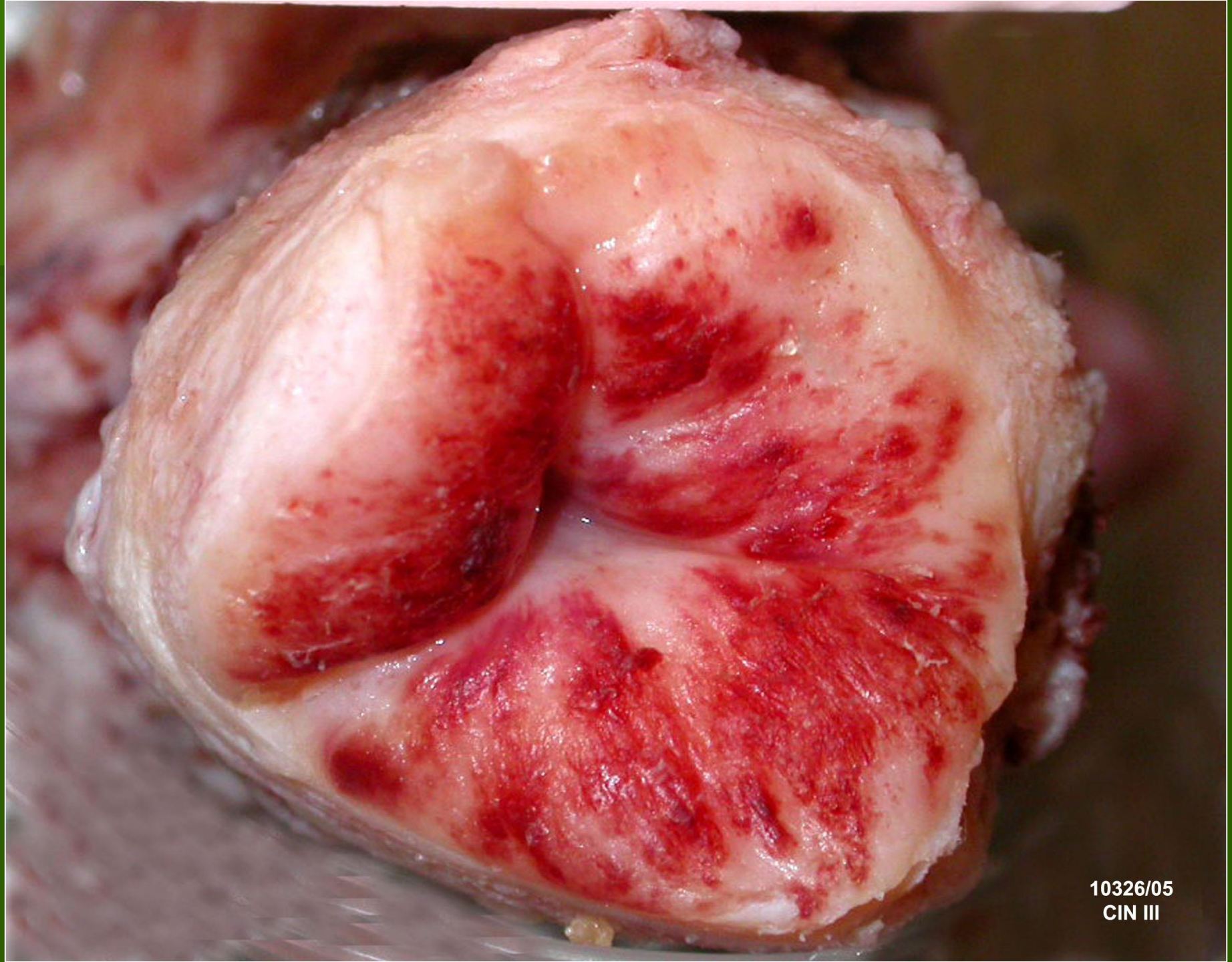
- Ki-67 (MIB1)
  - Correlates with proliferation
- Cyclin-dependent kinase 2A inhibitor: $p16^{ink4}$
  - Rb-dependent negative feedback loop regulates p16 expression, continuous inactivation of RB by hrHPV E7 results in increased p16 levels
  - Overexpression: diffuse strong cytoplasmic and nuclear immunostaining
- pRb
- p53

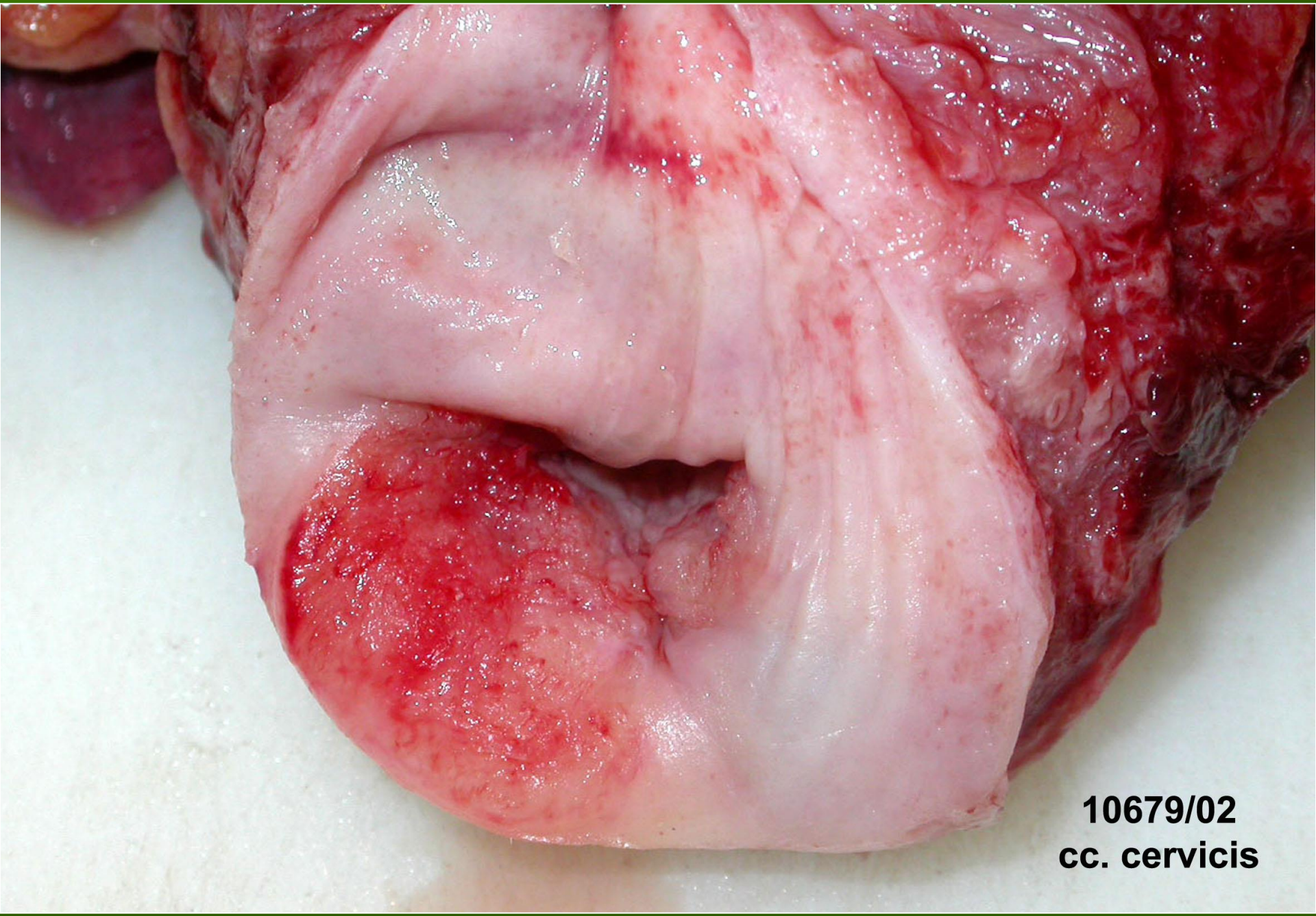
HPV and Cancer: A Broader Picture

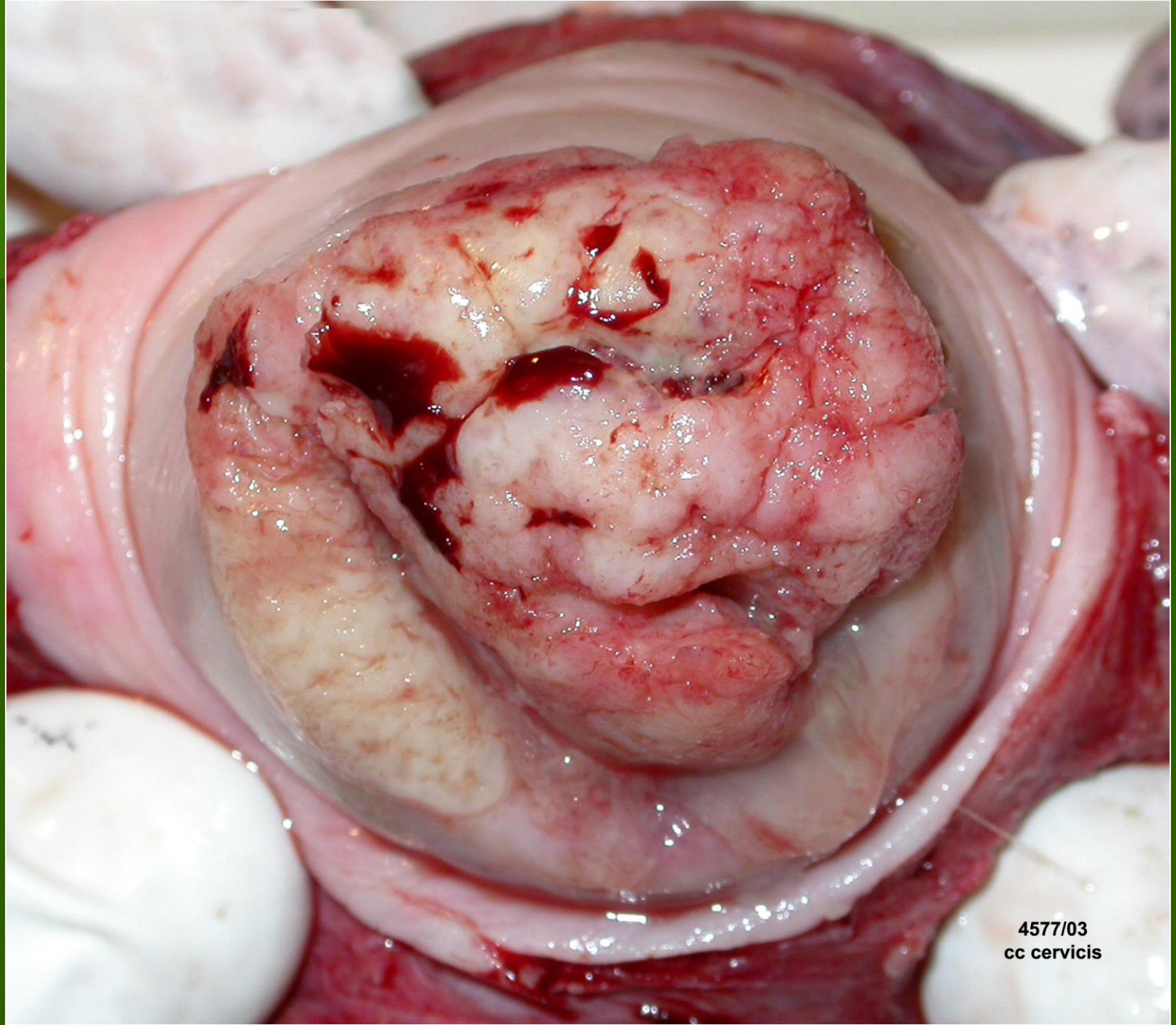


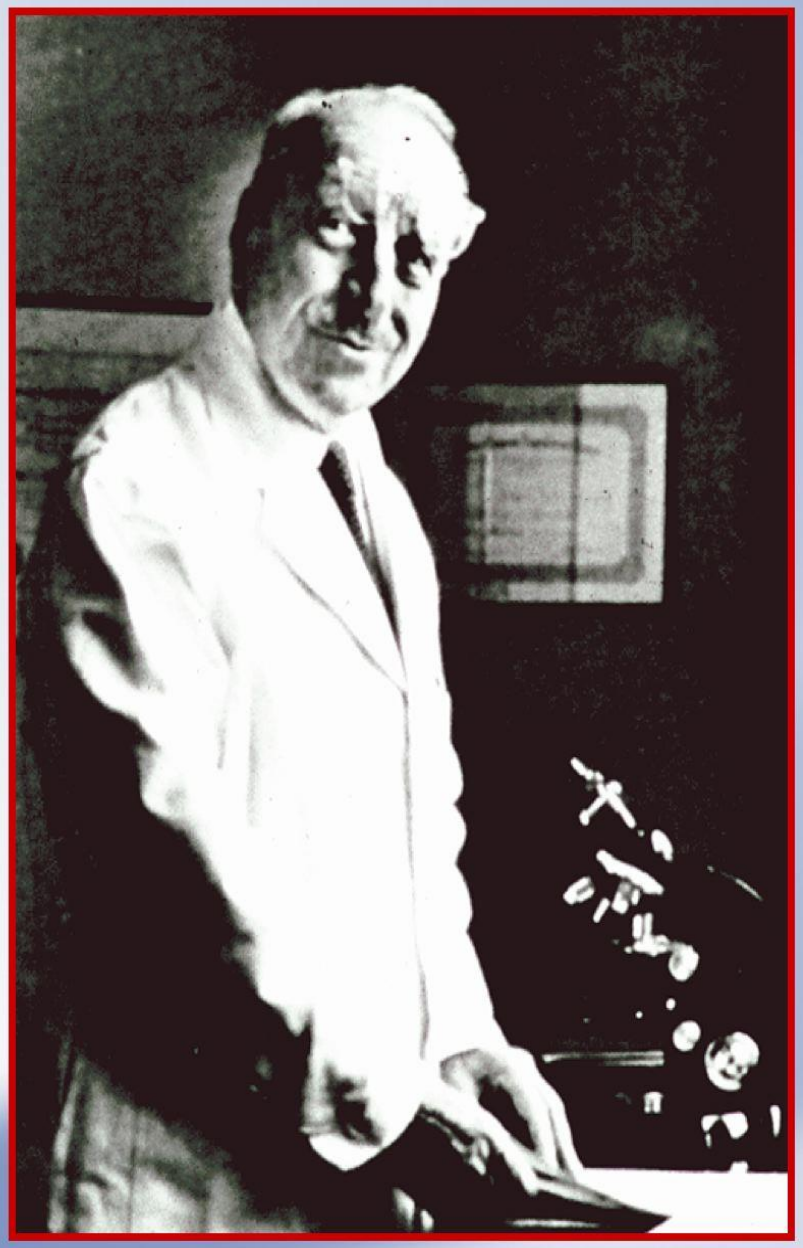
*Includes cancer and intraepithelial neoplasia

1. Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19. 2. American Cancer Society. Available at: http://www.cancer.org. Accessed March 30, 2006. 3. Herrero R, Castellsagué X, Pawlita M, et al. *J Natl Cancer Inst*. 2003;95:1772–1783. 4. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22.


10326/05
CIN III


10679/02
cc. cervicis


4577/03
cc cervicis



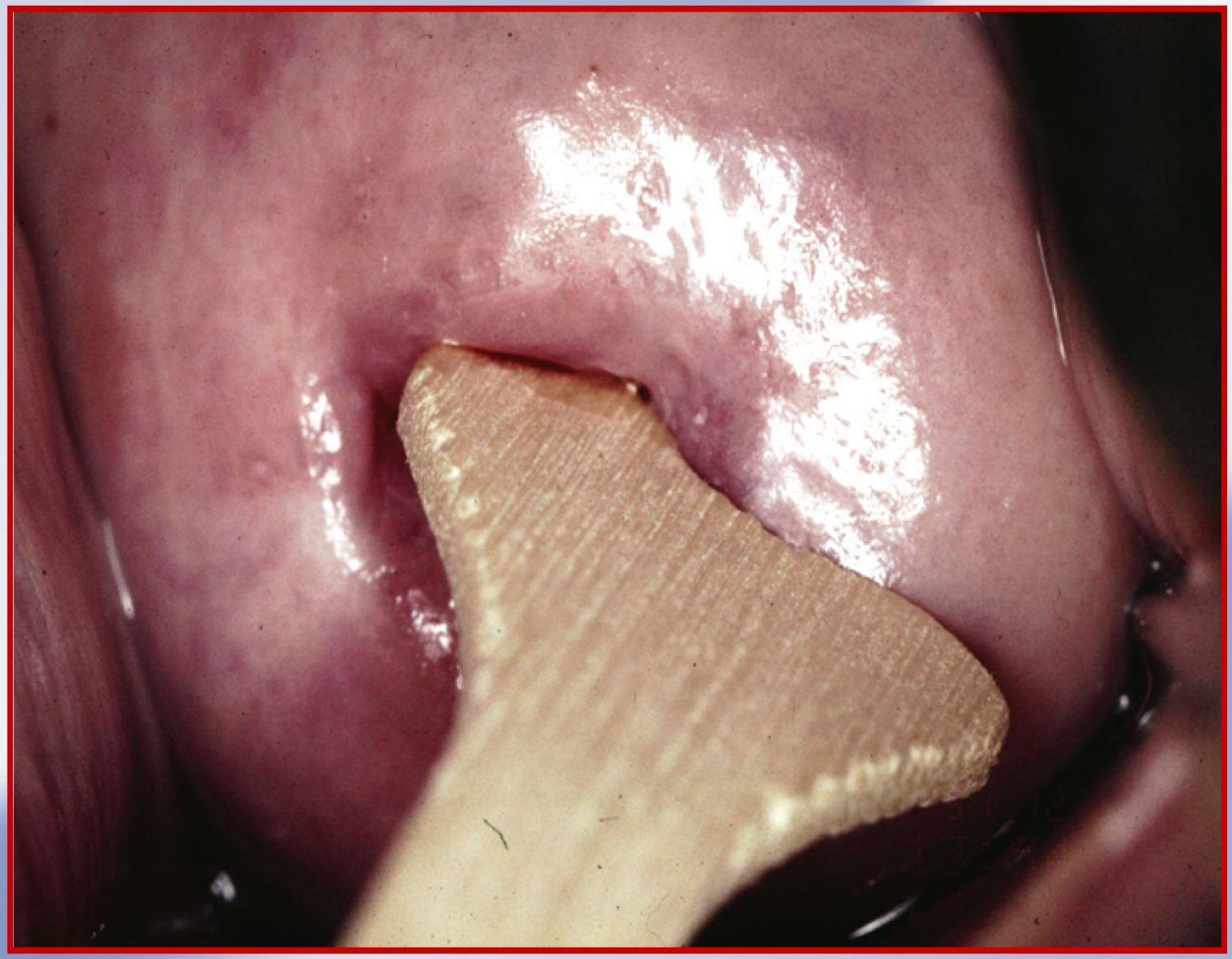
Conventional Pap Test

Introduced by Babes and Papanicolaou in 1920's

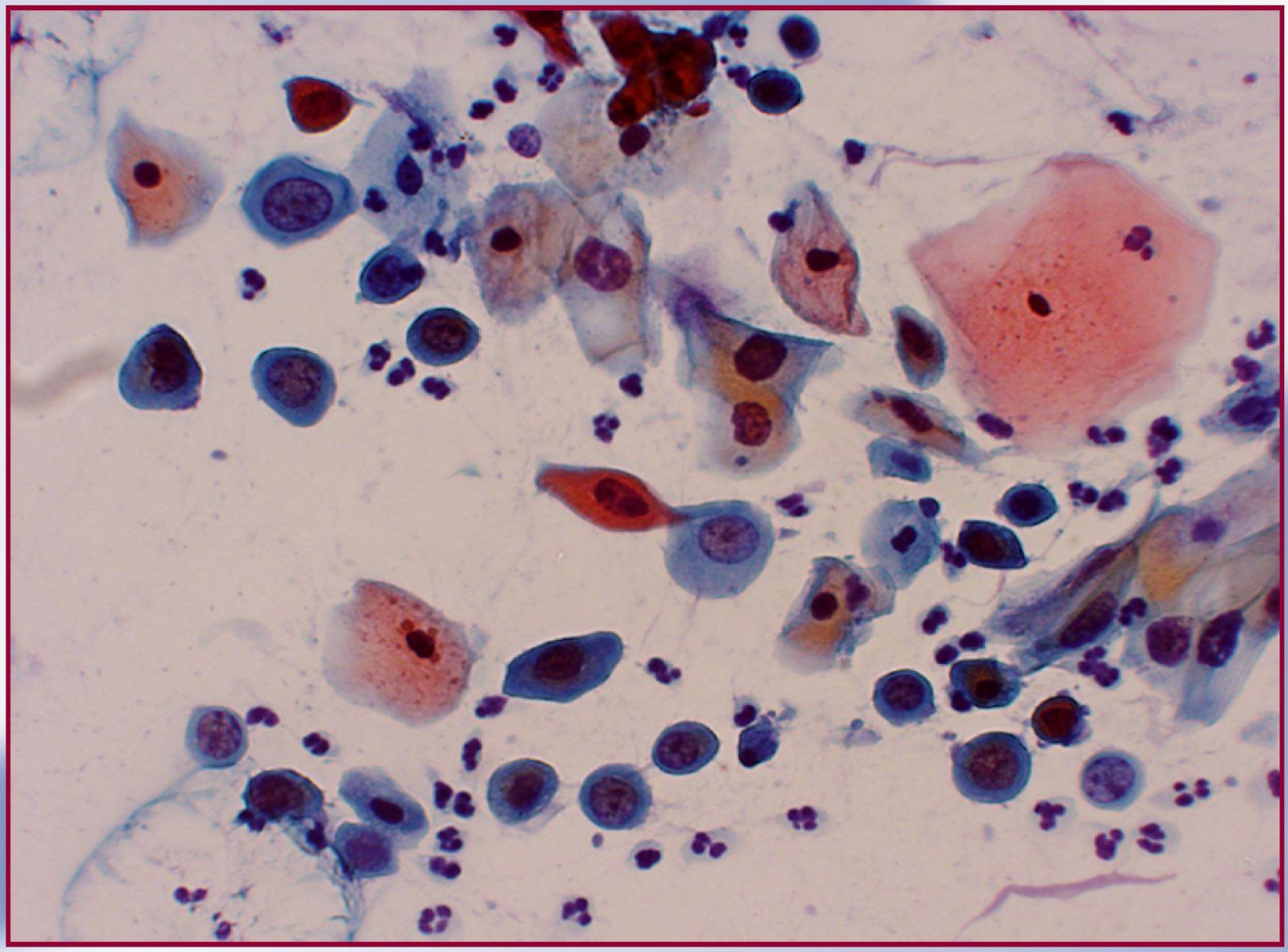
Became widely adopted in the US in the 1950's

Reduced cervical cancer dramatically

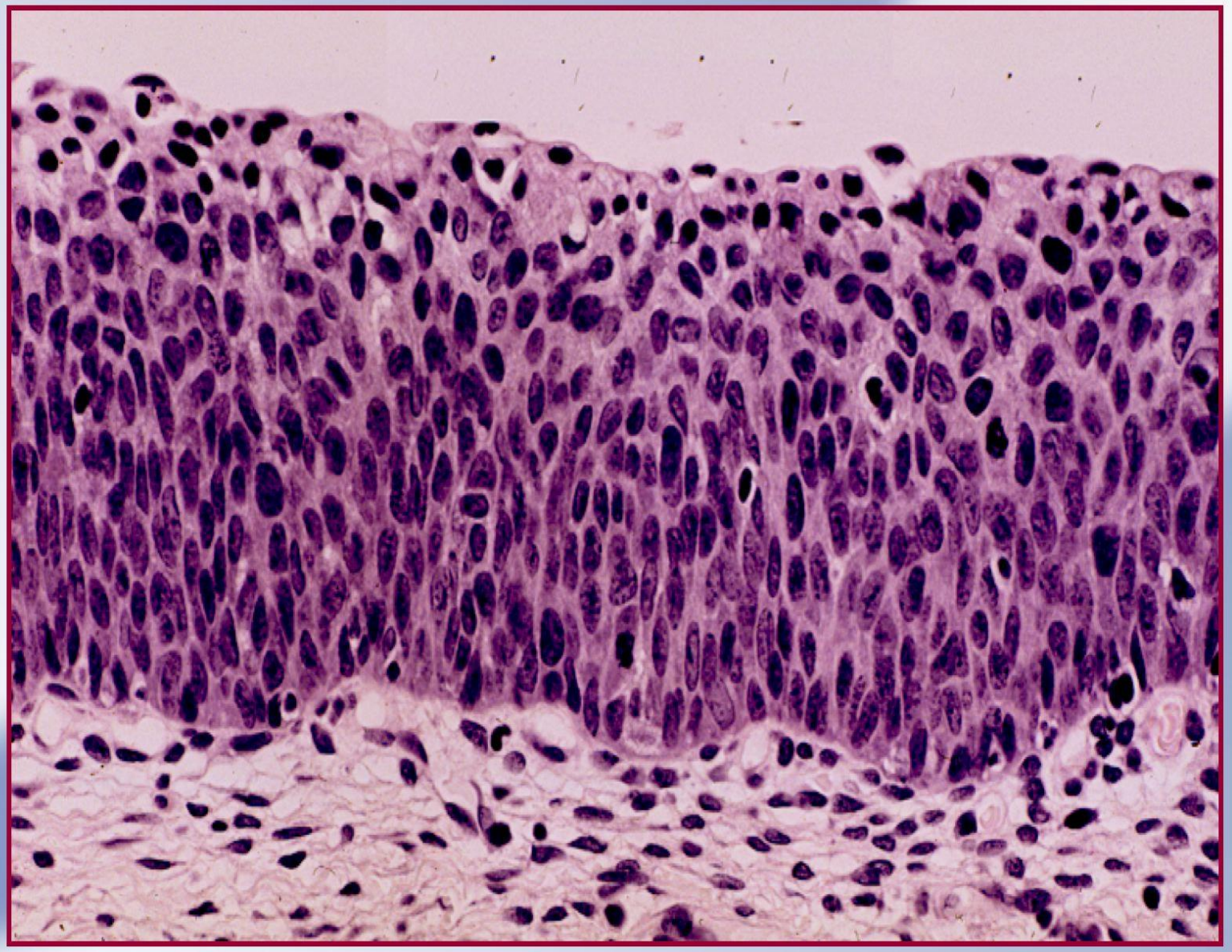
Dr. George M. Papanicolaou
1883-1962



Pap Test from Patient with CIN 2,3



High-grade Cancer Precursor (CIN 2,3)



Colposcopy

HPV

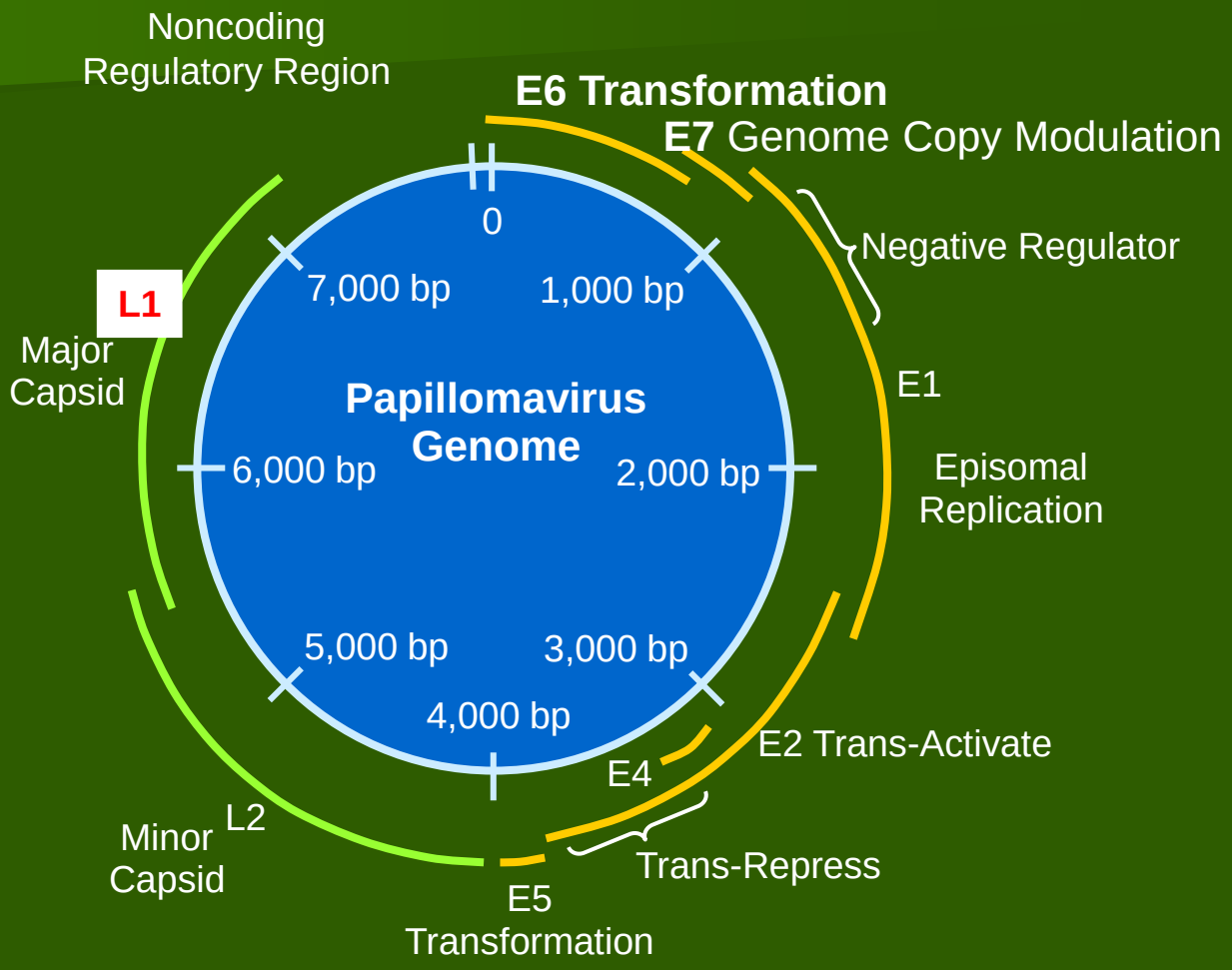
Nonenveloped double-stranded DNA virus[1]

Reprinted from Hagensee ME, Olson NH, Bakers TS, Galloway DA. *J Virol*. 1994;68:4503–4505, by permission of the American Society for Microbiology and Dr. Michael Hagensee.

- >100 types identified[2]
- ~30–40 anogenital[2,3]
  - ~15–20 (high risk),[2,3]
    - HPV 16 and HPV 18 types account for the majority of worldwide cervical cancers.[4]
  - low risk types
    - HPV 6 and 11 are most often associated with external anogenital warts.[3]

1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229. 2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

Genome of Papillomaviruses*,[1]

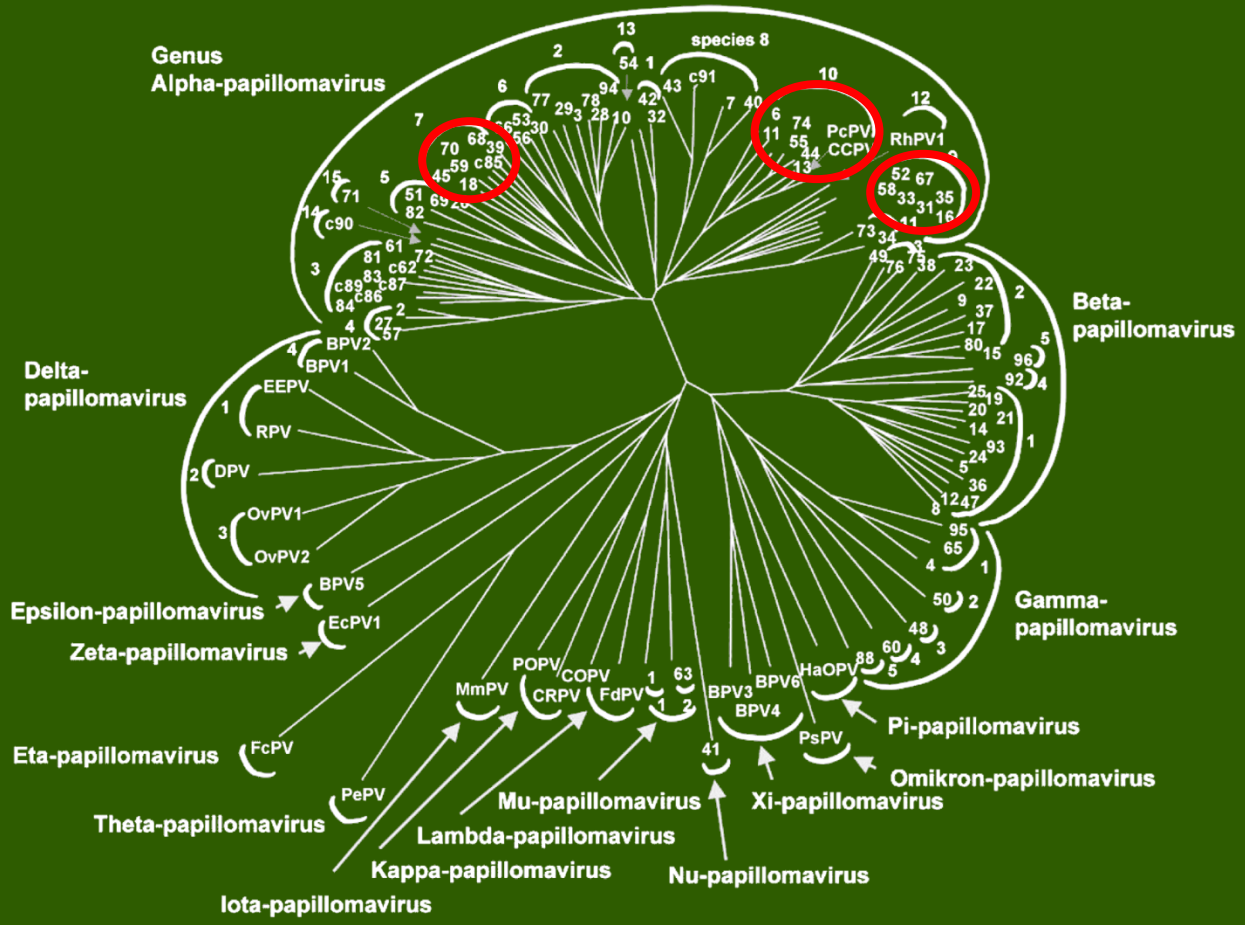


*Bars represent open reading frames. E = early region; L = late region; bp = base pair

1. Koutsky LA, Galloway DA, Holmes KK. *Epidemiol Rev.* 1988;10:122–163. Reprinted by permission of Oxford University Press.

Family Papillomaviridae – Genus Papillomavirus[1]

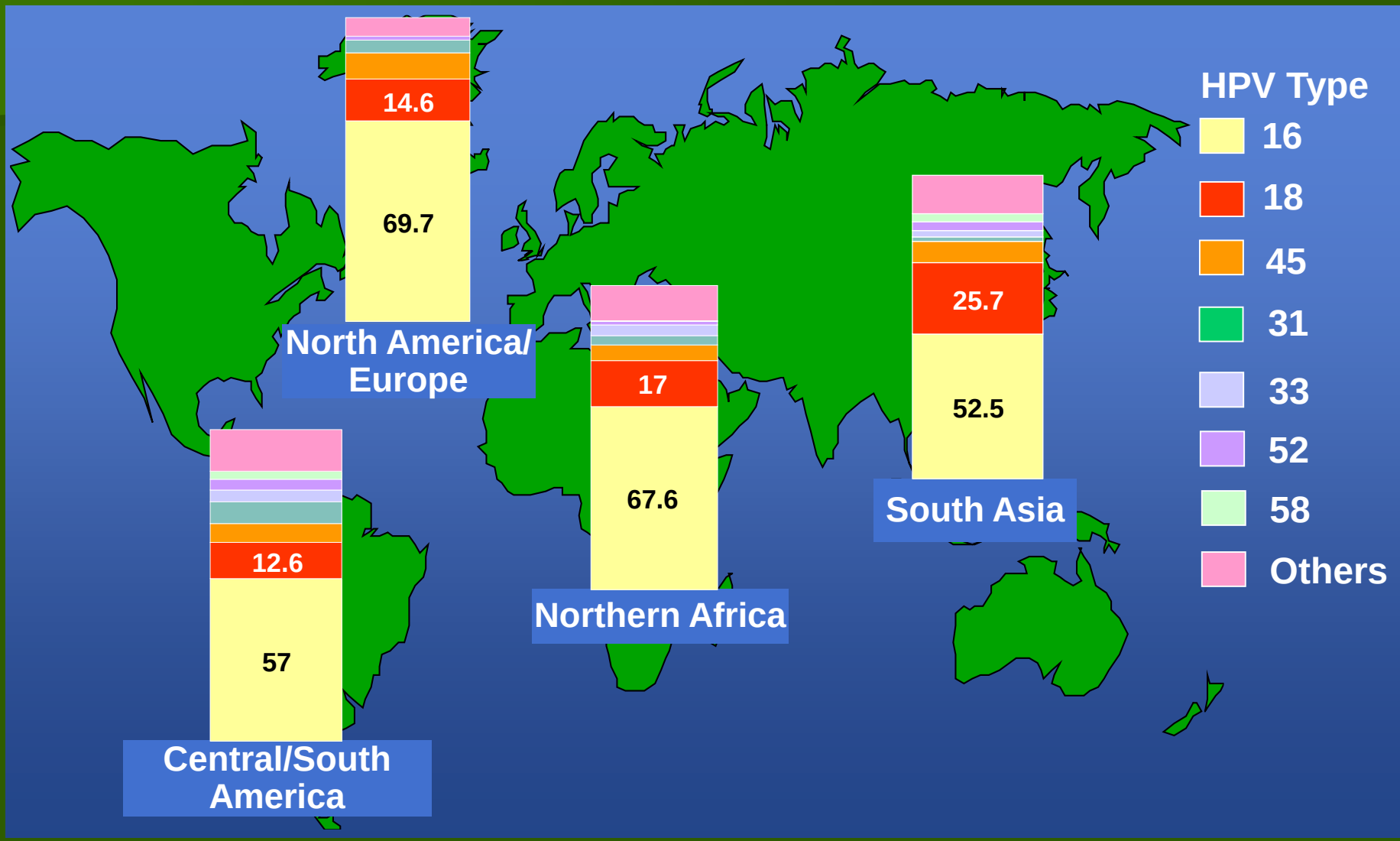
Human papillomavirus (HPV) types within a species are related:
Alpha 7 Species: HPV 18, 39, 45, 59, 68, 70, c85
Alpha 9 Species: HPV 16, 31, 33, 35, 52, 58, 67
Alpha 10 Species: HPV 6, 11, 13, 44, 55, 74, PcPV, CCPV



HPV types are organized into genera and species on the basis of homology in the sequence of the L1 (major capsid protein) gene.

De Villiers EM et al. *Virology*. 2004;324:17–27. Reprinted with permission from Elsevier.

Worldwide Prevalence of HPV Types in Cervical Cancer*,1



*A pooled analysis and multicenter case control study (N = 3607)

1. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

HPV types according to carcinogenic potential

Species	Types							
α5	26	51	69	82				
α6	30	53	56	66				
α7	18	39	45	59	68	70	85	97
α9	16	31	33	35	52	58	67	
α11	34	73						

Adapted from IARC [1].

Group 1 carcinogens.

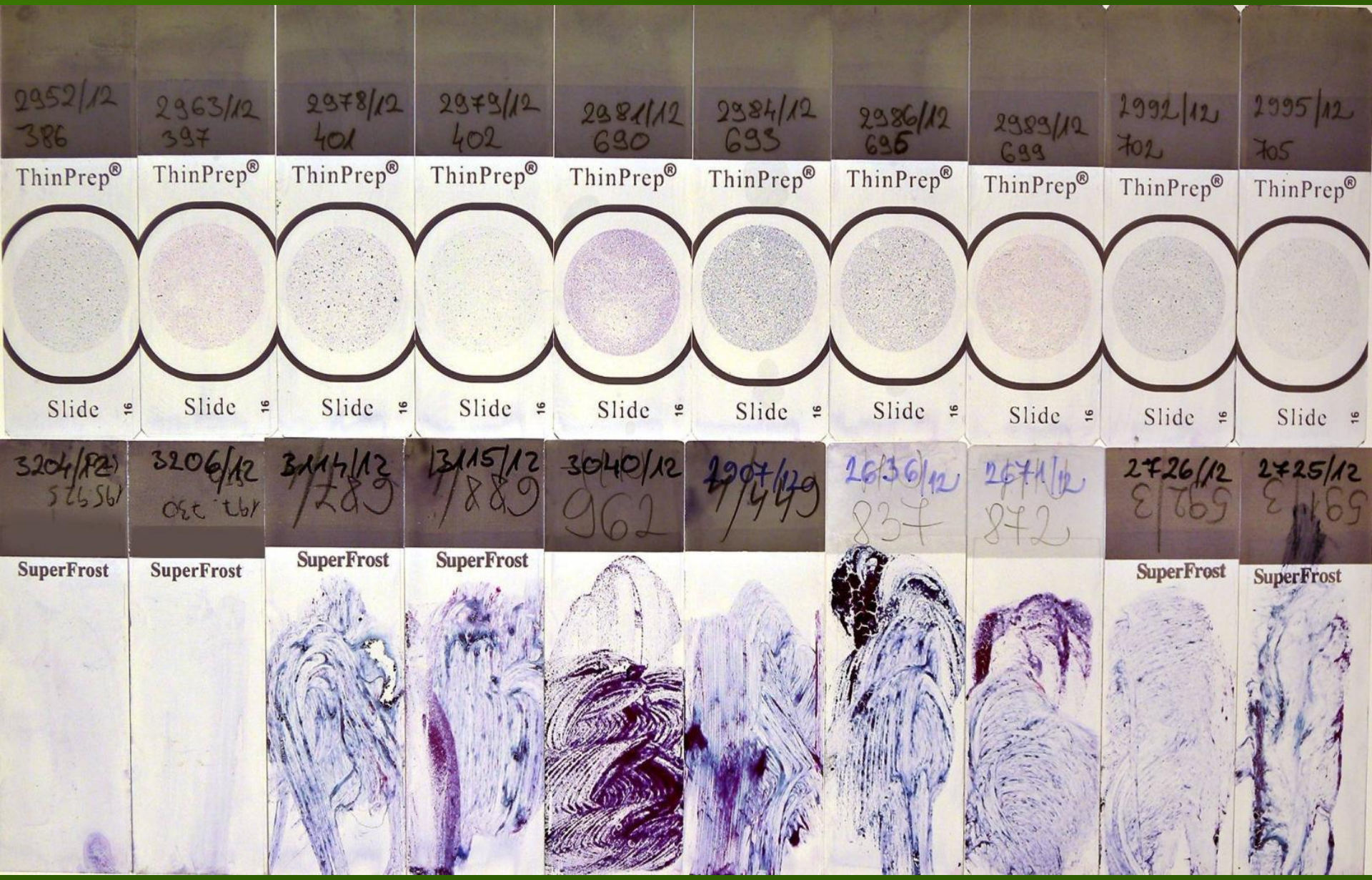
Group 2A carcinogens.

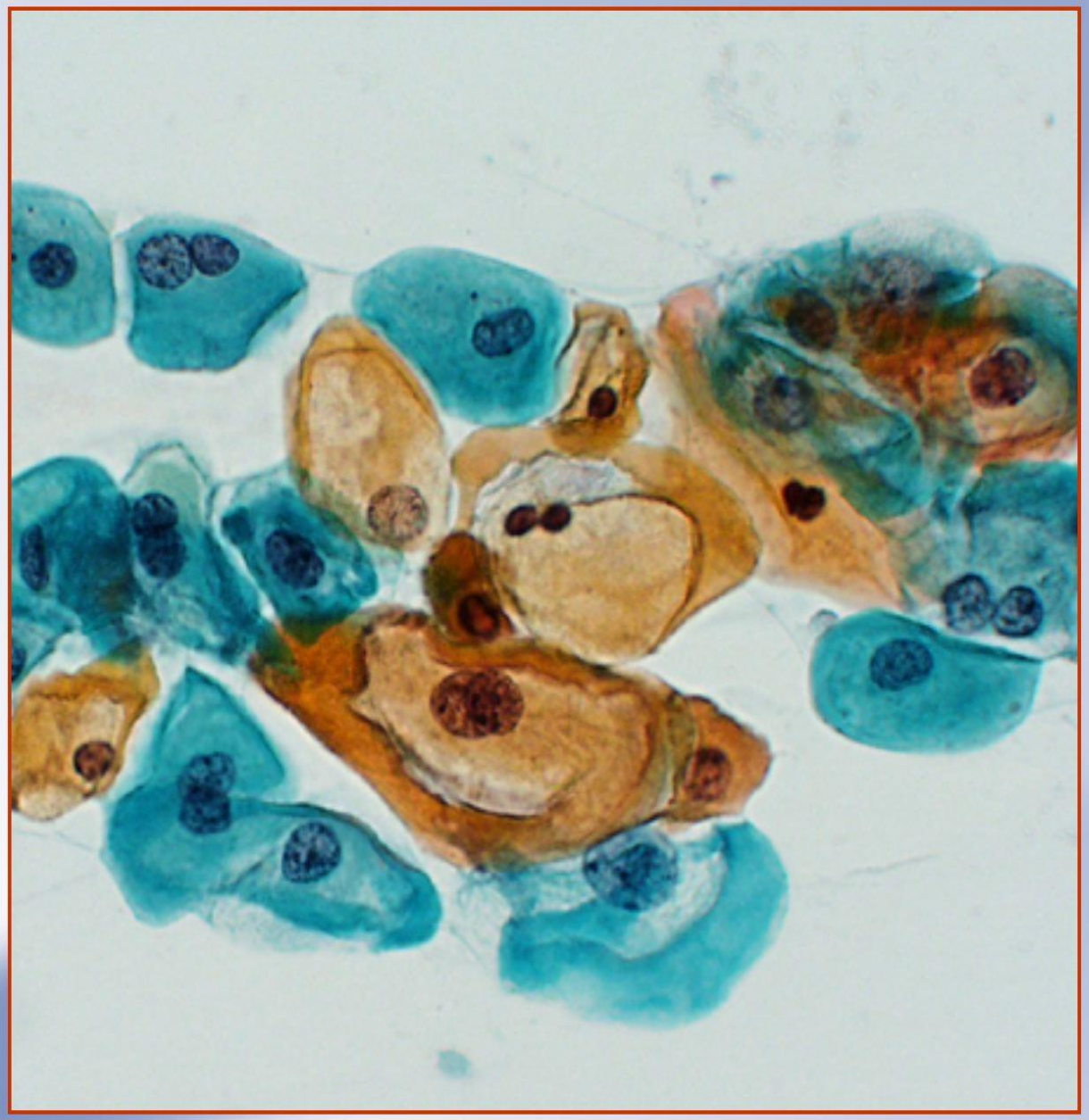
Group 2B carcinogens.

Phylogenetic analogy with carcinogenic types.

Abyn et al: Are 20 human papillomavirus types causing cervical cancer?, J. Pathol. 2014, 234:431-435

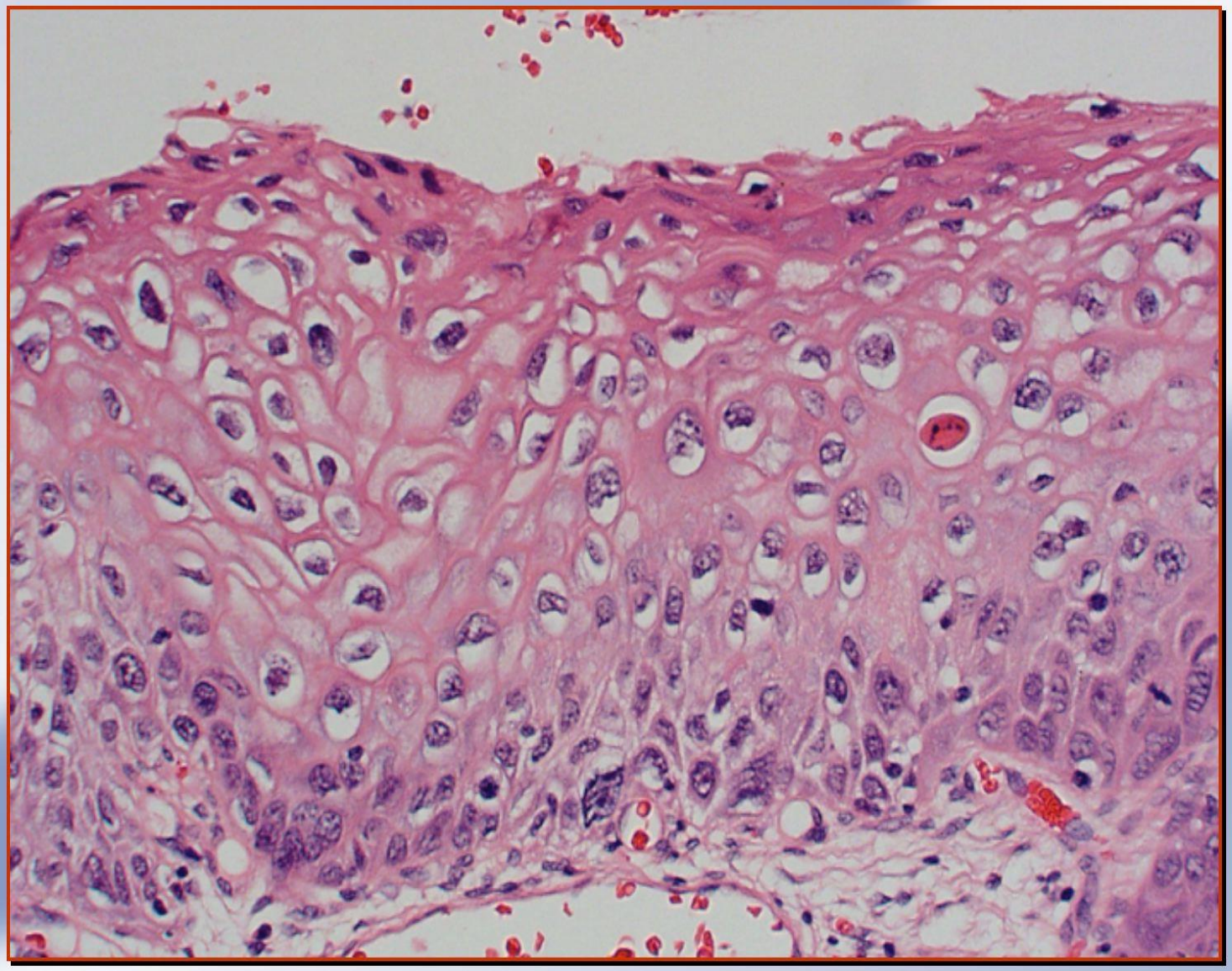
Cervical cytology: „conventional” and LBC





HPV Cytopathic Effects (LSIL)

HPV Productive Infection or CIN 1



Low and High Risk HPV

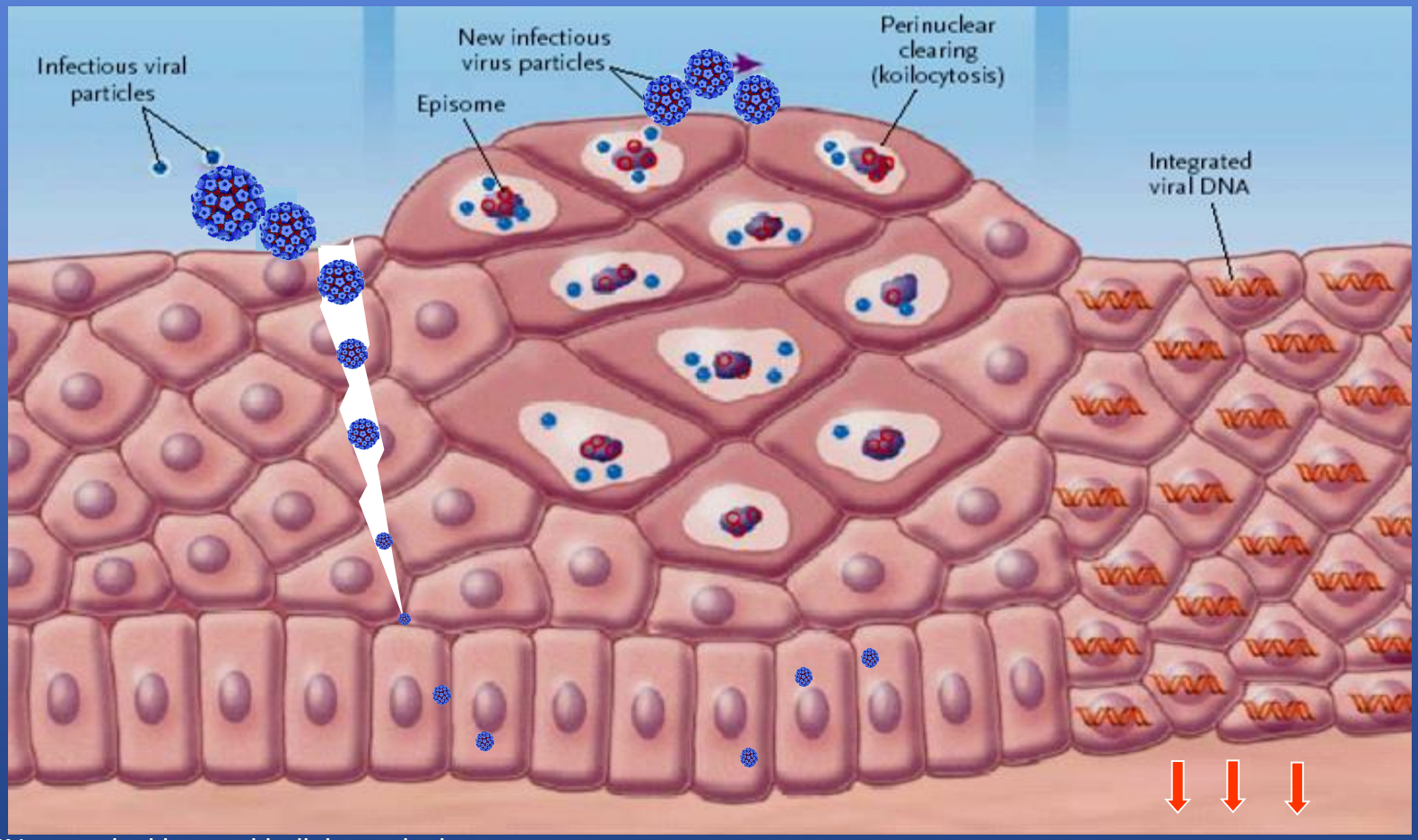
- HPV subtypes classified as low risk or high risk based on whether the genital tract lesions with which these HPVs are associated are at significant risk for malignant progression
  - High risk: 16, 18, 31, 33, 35 (15 types)
  - Intermediate: 26, 53, 66
  - Low risk: 6, 11, 40, 42

How Do Viruses like HPV and HBV Cause Cancer?

- Very small viruses
- Can integrate their viral DNA into host genome
- They code for viral proteins which block tumor suppressor proteins in cells

Spectrum of HPV induced cervical alterations

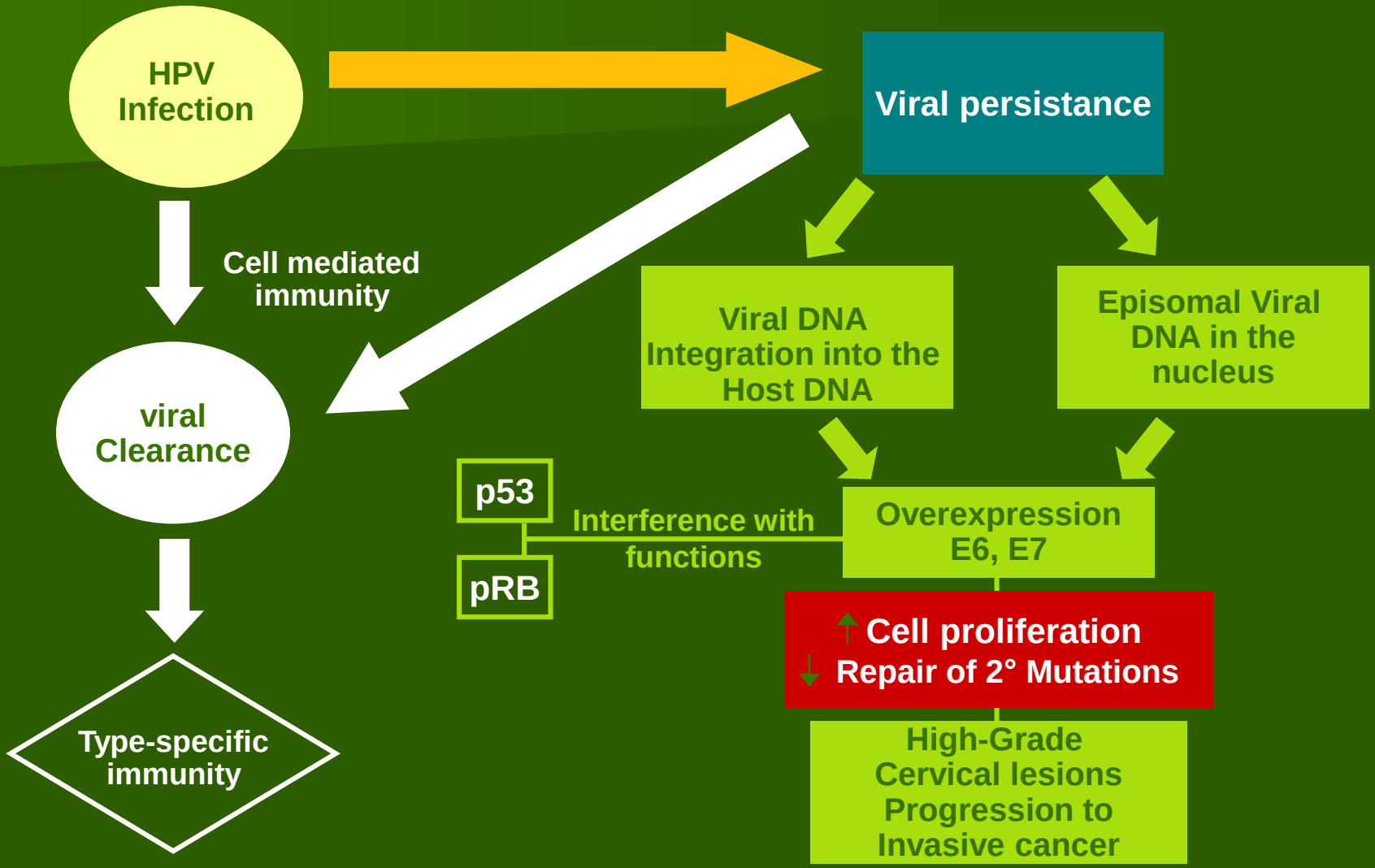
Normal Cervix | **HPV Infection / CIN* 1** | **CIN 2 / CIN 3 / Cervical Cancer**



*CIN = cervical intraepithelial neoplasia

1. Adapted from Goodman A, Wilbur DC. *N Engl J Med*. 2003;349:1555–1564. Copyright © 2003 Massachusetts Medical Society. All rights reserved. Adapted with permission.

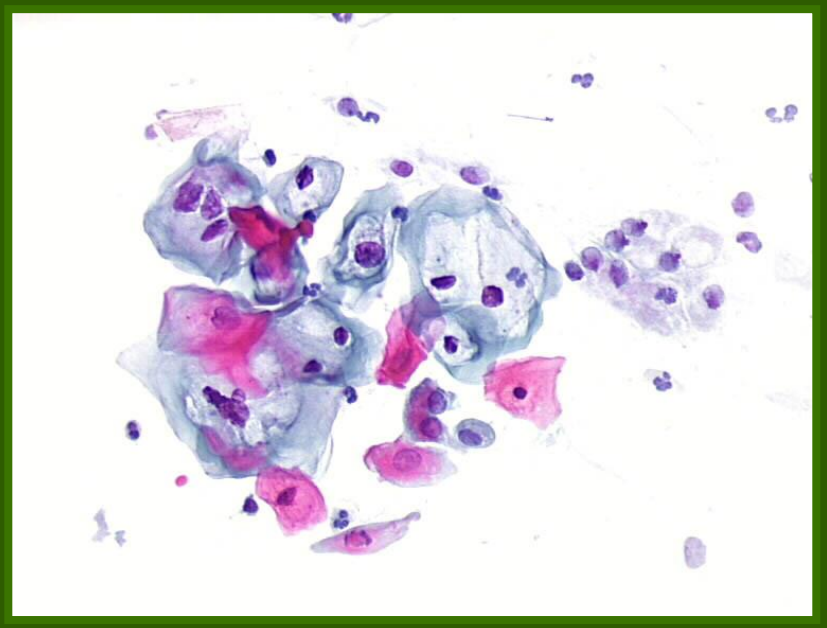
Mechanism of HPV carcinogenesis



1. Castle PE. *J Low Genital Tract Dis.*2004;8:224–230. **2.** Frazer IH. *Nature Rev Immunol*. 2004;4:46–54. **3.** Doorbar J. *J Clin Virol*. 2005;32(suppl):S7–S15. **4.** Münger K, Basile JR, Duensing S, et al. *Oncogene*. 2001;20:7888–7898. **5.** Furumoto H, Irahara M. *J Med Invest*. 2002;49:124–133.

Physiology of HPV Transmission

- The keratinocyte is the target cell for HPV.[1]
- Desquamated cornified cells are continuously shed from the stratum corneum and serve as vehicles for transmission.[1]
- Koilocytosis is the morphologic manifestation of productive HPV infection.[2]
- Each koilocyte contains approximately 50–100 HPV virions.[1,3]



From IARC, 2004.[4]

1. Bryan JT, Brown DR. *Virology*. 2001;281:35–42. 2. Bonnez W. In: Richman DD, Whitley RJ, Hayden FJ, eds. Washington, DC: American Society for Microbiology Press; 2002:557–596. 3. Meyers C, Bromberg-White JL, Zhang J, et al. *J Virol*. 2002;76:4723–4733. 4. Reprinted with permission from Frappart, et al. Histopathology and Cytopathology of the Uterine Cervix. Digital Atlas, Lyon, France: IARC *Press*, 2004.

Several Factors May Minimize/Prevent HPV Exposure to the Immune System

- No blood-borne phase of infection[1]
  - No viremia
- Limited and delayed expression of late viral capsid proteins[1,2]
- HPV does not lyse keratinocytes.[1]
  - No release of pro-inflammatory cytokines[1]
  - Little tissue destruction associated with HPV
- E6 and E7 suppress interferon signaling necessary for cell-mediated immune response.[1]
- No activation of antigen-presenting cells (APCs)[1]

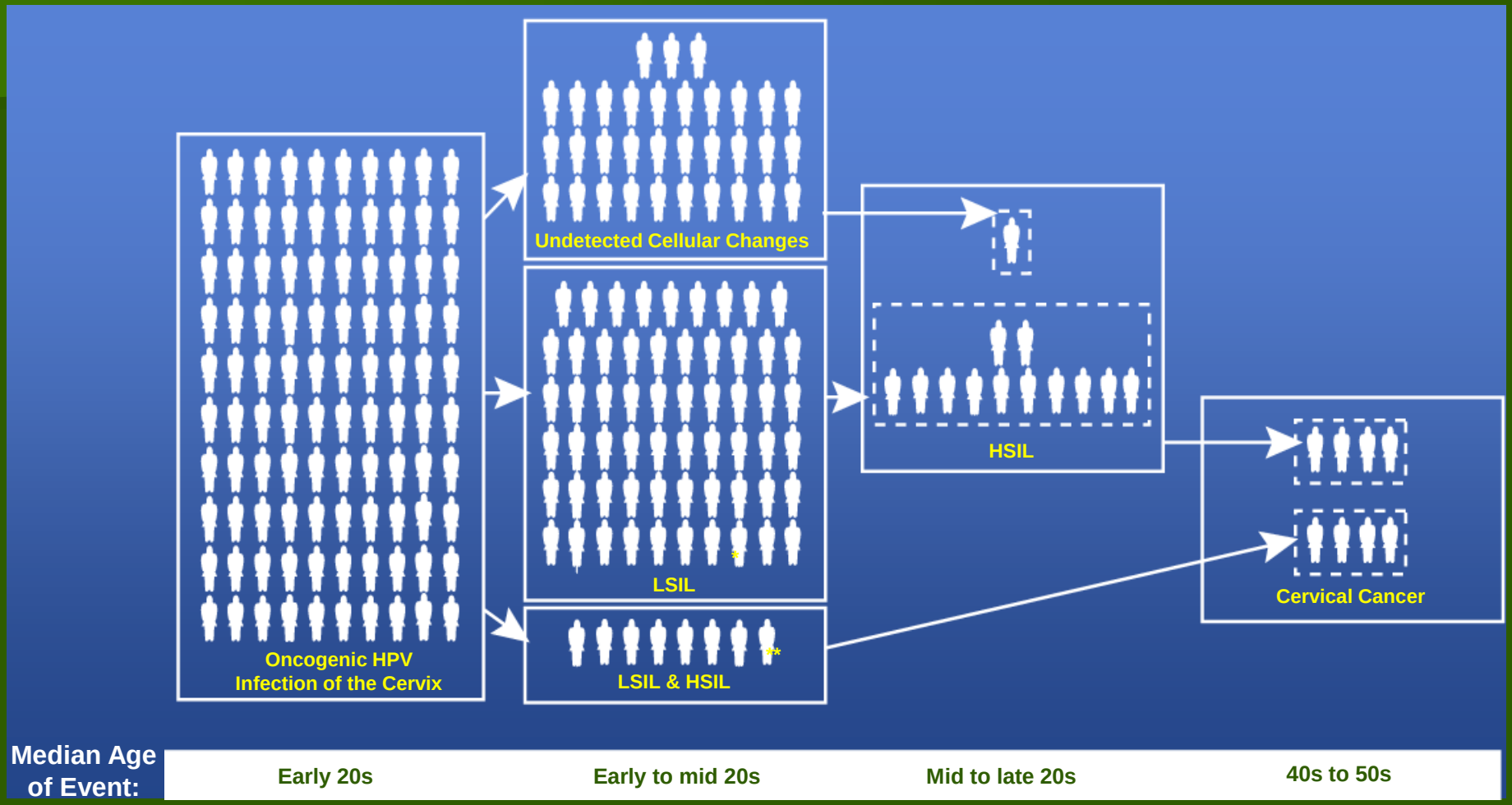
1. Tindle RW. *Nat Rev Cancer*. 2002;2:1–7. 2. Scott M, Nakagawa M, Moscicki A-B. *Clin Diagn Lab Immunol*. 2001;8:209–220. 3. Frazer IH. *Nature Rev Immunol*. 2004;4:46–54.

Detectable Serum Antibodies to HPV: Limitations as Marker of Infection or Natural Immunity

- Antibody responses to HPV infection slow and weak[1]
- Antibody responses vary with HPV type.[1]
- Antibody levels are inconsistently found in cervical cancer patients.[2]

1. Carter JJ, Koutsky LA, Hughes JP, et al. *J Infect Dis*. 2000;181:1911–1999. 2. Carter JJ, Madeleine MM, Shera K, et al. *Cancer Res*. 2001;61:1934–1940.

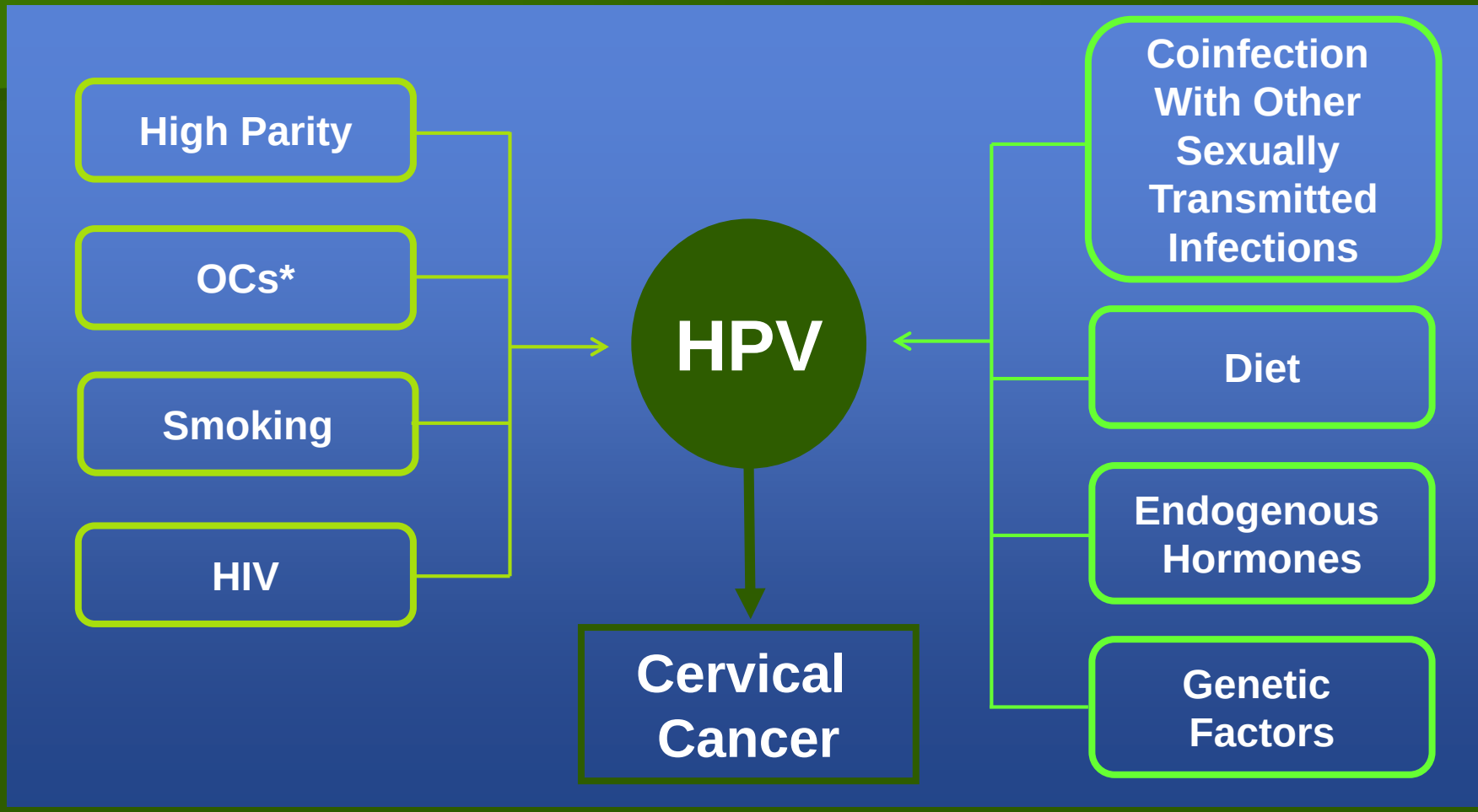
Natural History from HPV Infection to Cervical Cancer[1]



*LSIL = low-grade squamous intraepithelial lesion
**HSIL = high-grade squamous intraepithelial lesion

1. Adapted from Baseman JG, Koutsky LA. *J Clin Virol.* 2005;32S:S16-S24, with permission from Elsevier.

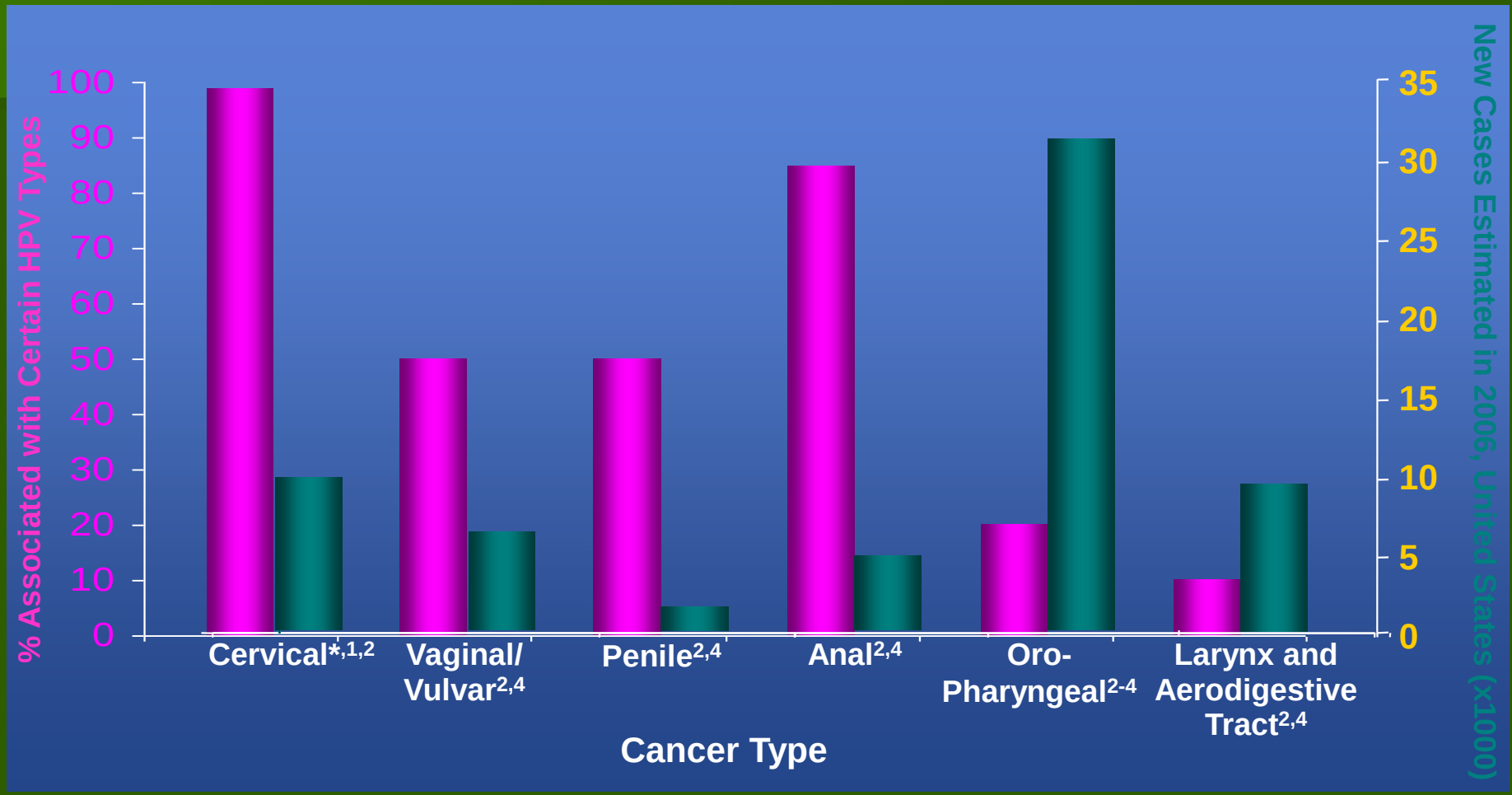
Established and Potential Cofactors Involved in HPV Carcinogenesis[1]



*OCs = oral contraceptives

1. Castellsagué X, Muñoz N. *J Natl Cancer Inst Monogr*. 2003;31:20–28.

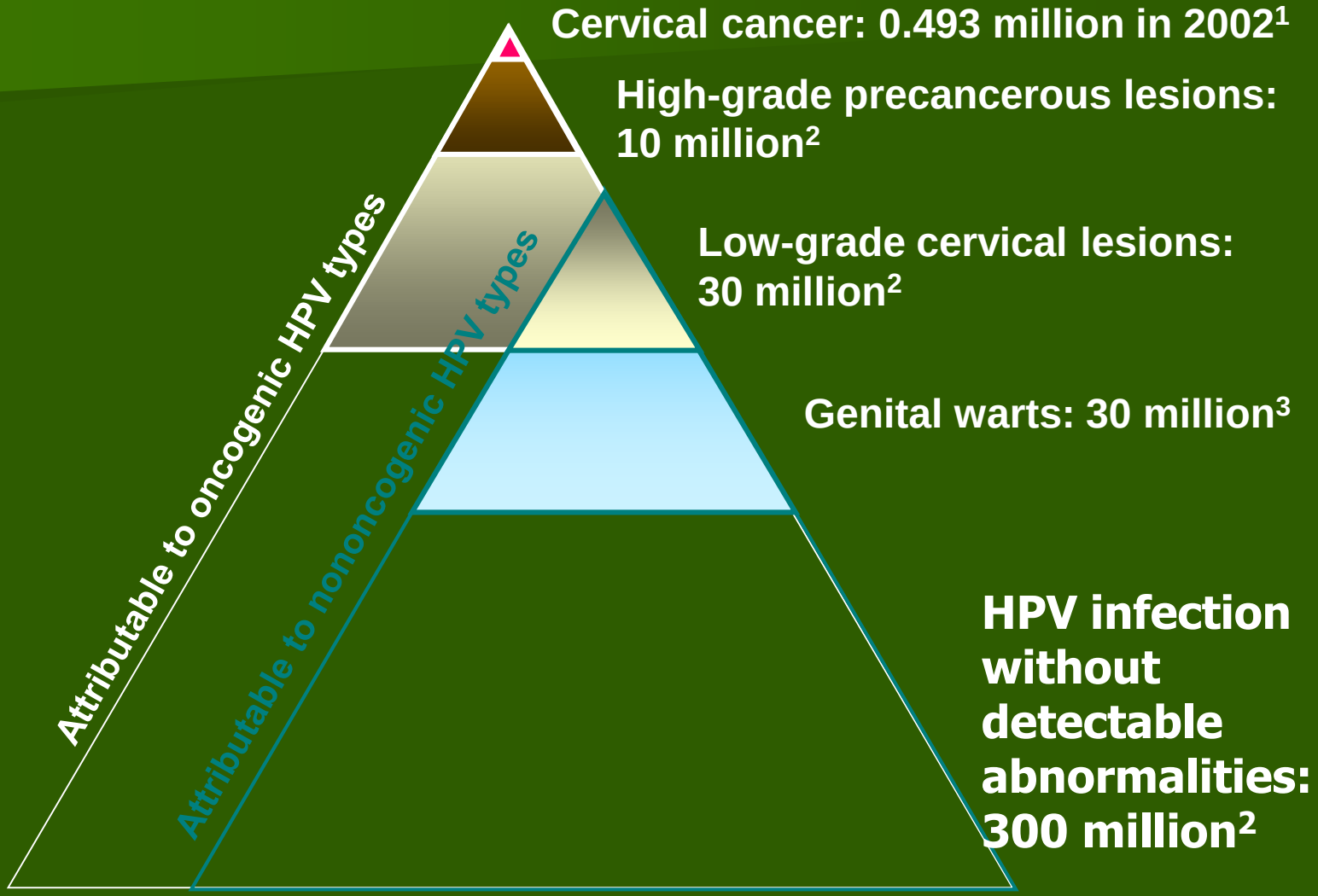
HPV and Cancer: A Broader Picture



*Includes cancer and intraepithelial neoplasia

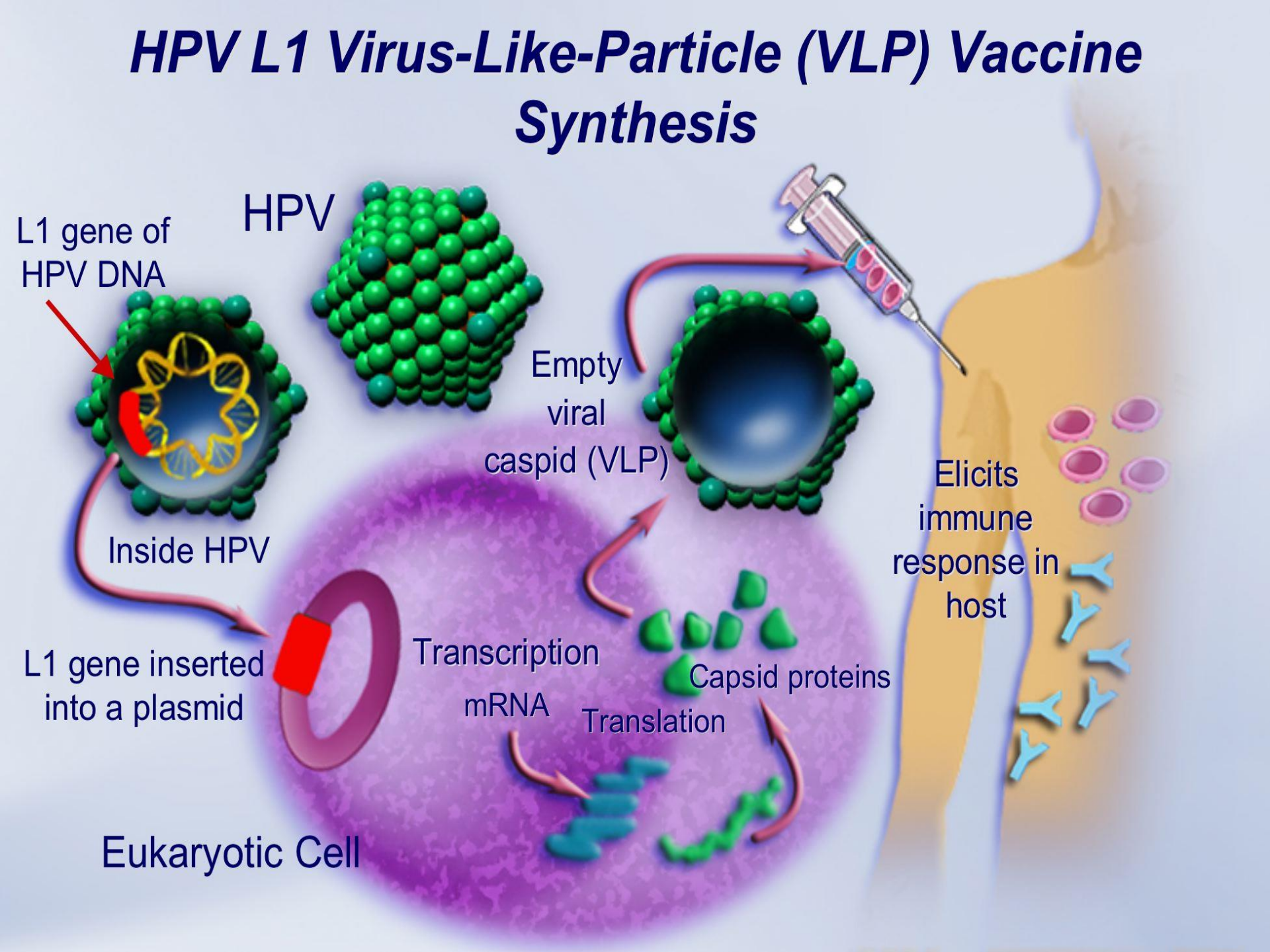
1. Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19. 2. American Cancer Society. Available at: http://www.cancer.org. Accessed March 30, 2006. 3. Herrero R, Castellsagué X, Pawlita M, et al. *J Natl Cancer Inst*. 2003;95:1772–1783. 4. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22.

Estimated World Burden of HPV-Related Diagnoses Focus on Cervical Disease and Genital Warts



1. Parkin DM, Bray F, Ferlay J, Pisani P. *CA Cancer J Clin*. 2005;55:74–108. 2. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 3. World Health Organization. WHO Office of Information. *WHO Features*. 1990;152:1–6.

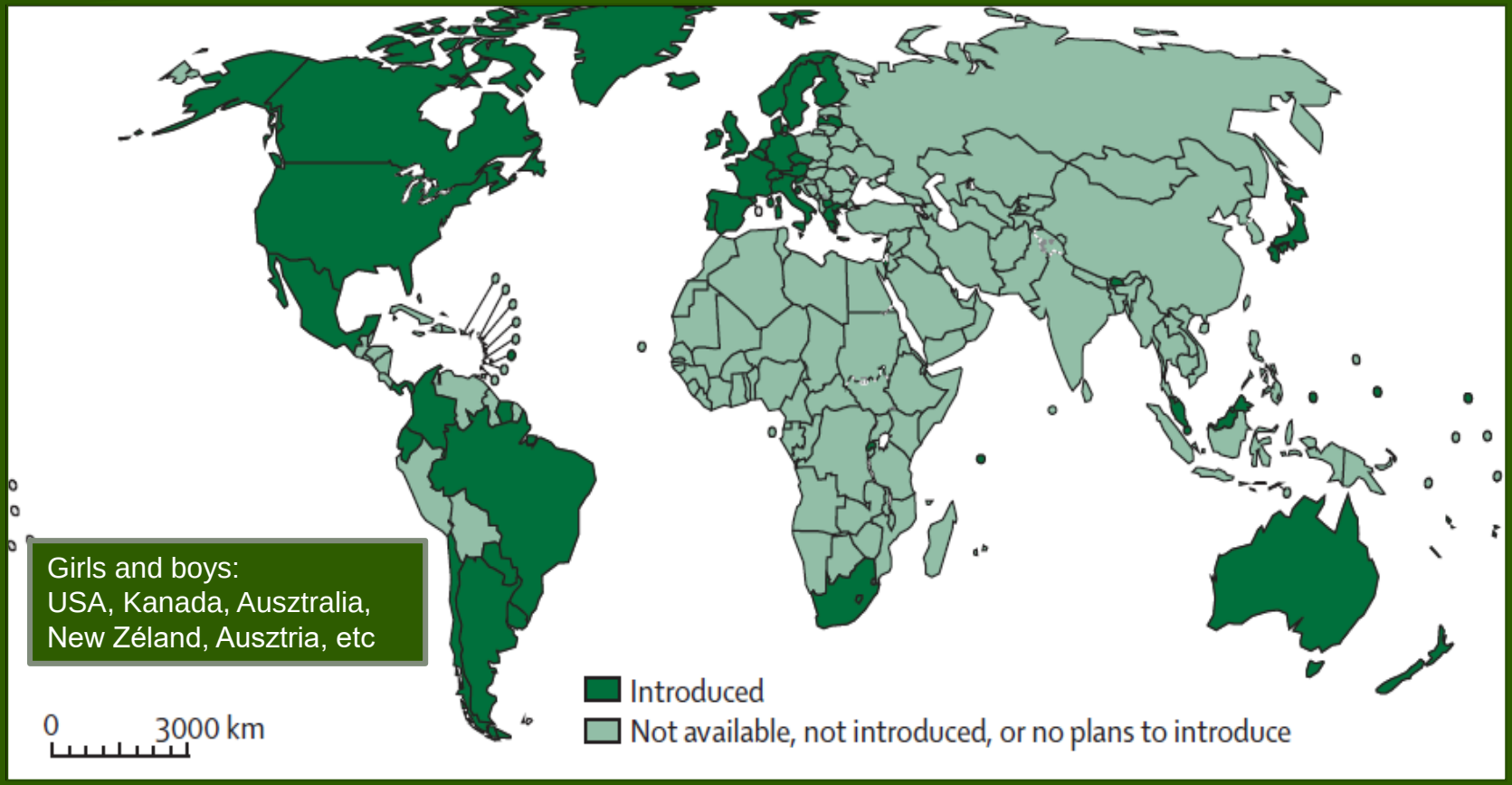
HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis



HPV vaccines

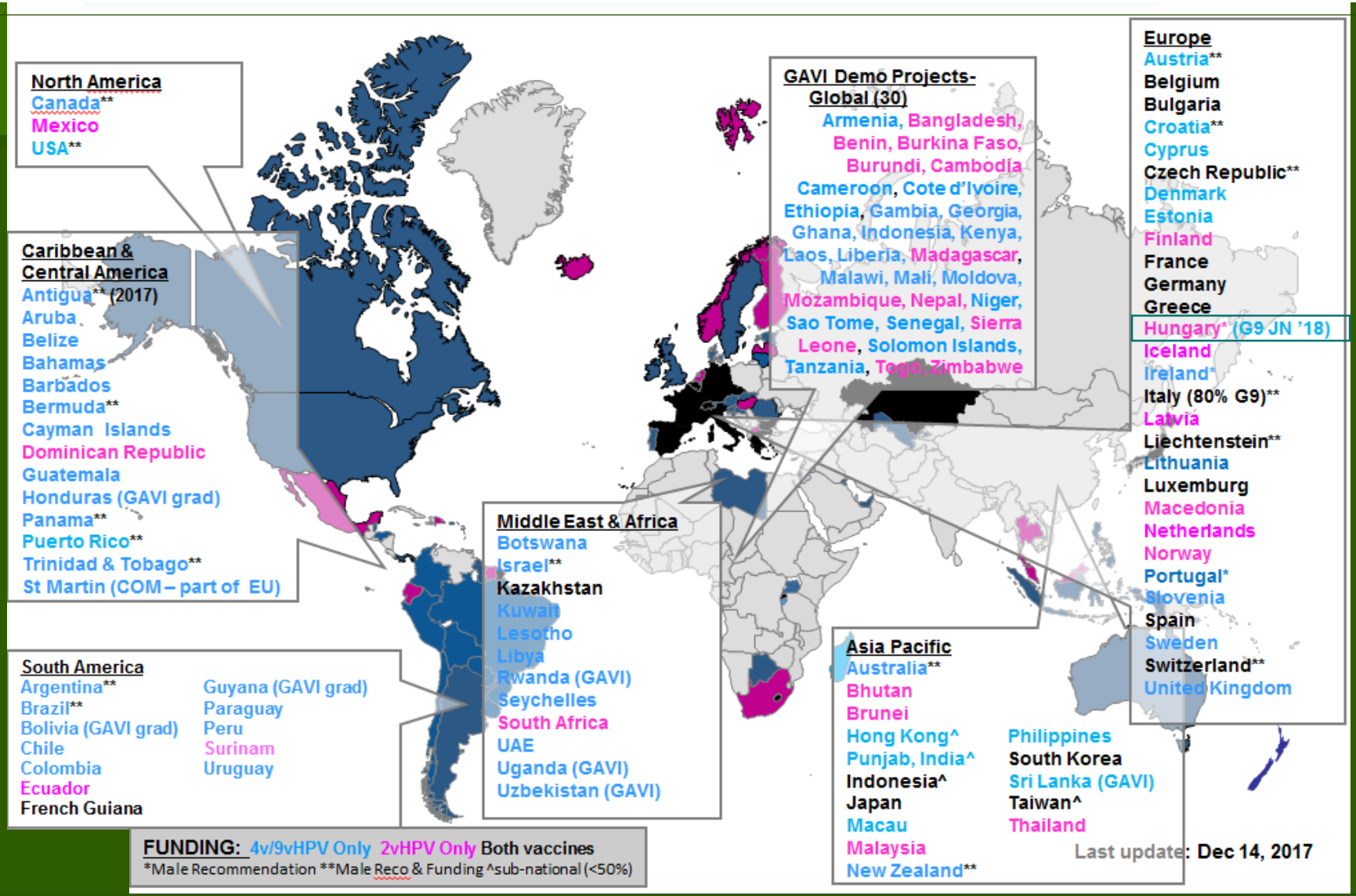
2v HPV, Cervarix GlaxoSmithKline Biologicals s.a.	4vHPV, Silgard (Gardasil) MSD	9vHPV, Gardasil 9 MSD
• **HPV 16, HPV 18**	• **HPV 16, HPV 18** • **HPV 6, HPV 11**	• **HPV 16, HPV 18** • **HPV 31, HPV 33, HPV 45, HPV 52, HPV 58** • **HPV 6, HPV 11**
1. generation	1. generation	2. generation
Intramuscular: 2 doses: 0., 5-13. month (9-14 év) 3 doses: 0., 1., 6.month (15 yr)	Intramuscular: 2 doses: 0., 6. month (9-13 év) 3 doses: 0., 2., 6. month (14 yr)	Intramuscular: 2 doses: 0., 5-13. month (9-14 yr) 3 doses: 0., 2., 6. hónap (15 yr)

HPV vaccination



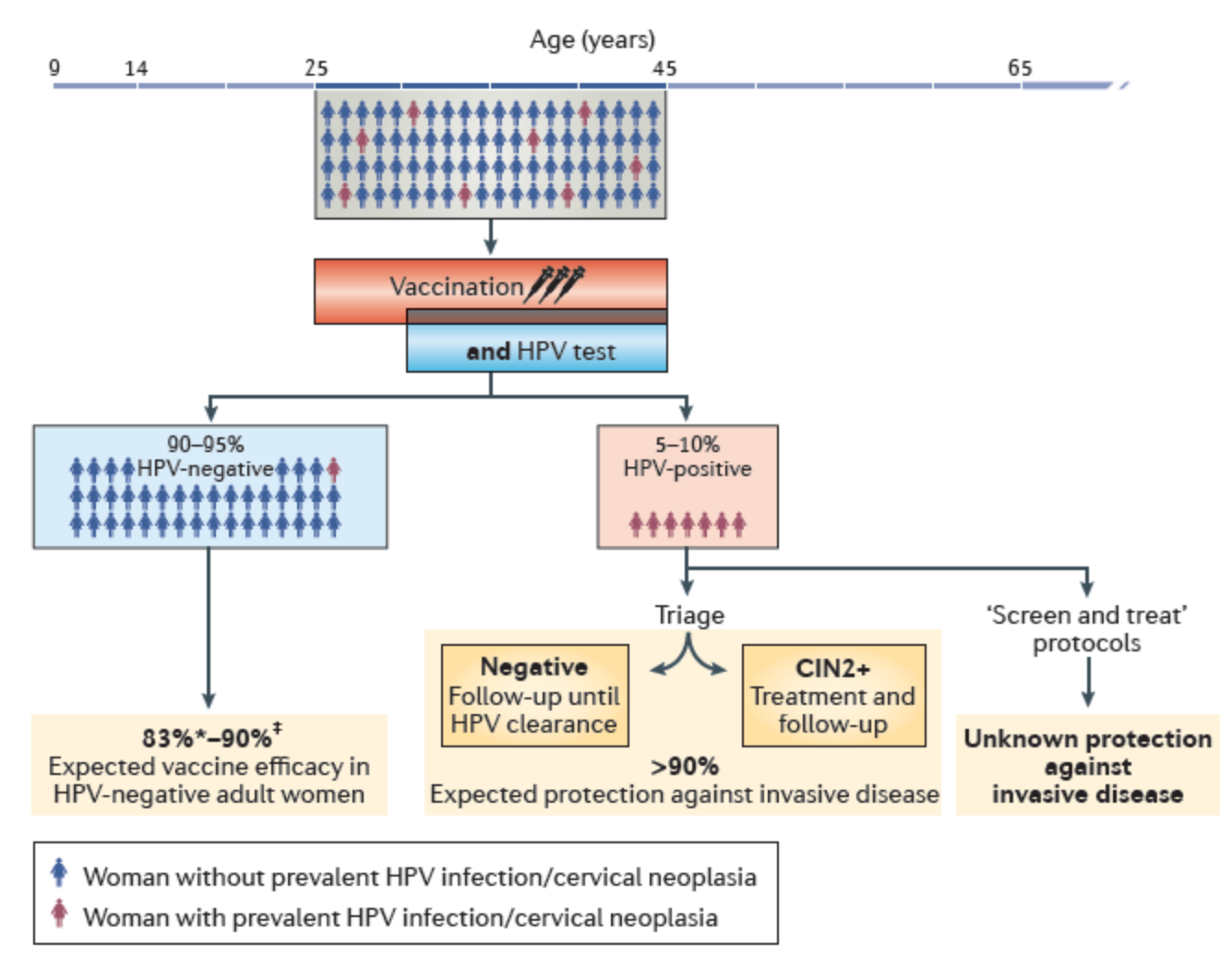
WHO's Immunization, Vaccines and Biologicals database (accessed Sept 29, 2014); Brotherton R et al, Future Virol. (2015) 10(8), 999–1009; Norwegian Folkehelseinstituttet anbefaler HPV-vaksine til gutter, http://www.fhi.no/artikler/?id=117699; Croatina Ministry of Health, (https://zdravlje.gov.hr/izvjesce-o-provedenom-savjetovanju-o-nacrtu-prijedloga-programa-imunizacije-seroprofilakse-i-kemoprofilakse-za-posebne-skupine-stanovnistva-i-pojedince-pod-povecanim-rizikom-od-tuberkuloze-hepatitisa/2476

HPV vaccination programs
Girls: 68, both sex: 17 countries



Combination of primary and secondary prevention

The HPV-FASTER core concept
combined HPV screening and vaccination of women up to 45–50 years of age



Bosch XF et a. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nature Reviews Clinical Oncology. 2016 Feb;13(2):119-32.

WHO position paper, 2017

- **Achieving high vaccination coverage in girls (>80%) reduces the risk of HPV infection for boys.**

- **Vaccination targeting multiple age cohorts of girls aged between 9 and 18 years at the time of HPV vaccine introduction would result in faster and greater population impact than vaccination of single age cohorts**, due to the estimated increase in direct protection and herd immunity.

World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. Vaccine. 2017 Oct 13;35(43):5753-5755.

The Nobel Prize in Physiology or Medicine 2008

"for his discovery of human papilloma viruses causing cervical cancer"

"for their discovery of human immunodeficiency virus"

© Klaus Rüschhoff, Springer Medizin Verlag

Harald zur Hausen

◑ 1/2 of the prize

Germany

German Cancer Research Centre
Heidelberg, Germany

Photo: Sakutin/SCANPIX

Françoise Barré-Sinoussi

◔ 1/4 of the prize

France

Regulation of Retroviral Infections Unit, Virology Department, Institut Pasteur
Paris, France

Photo: Magunia/SCANPIX

Luc Montagnier

◔ 1/4 of the prize

France

World Foundation for AIDS Research and Prevention
Paris, France

TNM and FIGO stages

- TNM:
  - Tis, T1,
    - T1a, (a1, a2,) T1b, (ba, b2,)
  - T2,
    - (2a, 2b,)
  - T3,
    - 3a, 3b,
  - T4,
  - M1
- FIGO (Fed.Intern. Gynec.Obst):
  - 0, I (Ia,Ia1, a2)
  - II (IIa, IIb)
  - III (IIIa, IIIb)
  - IV (IVa, IVab)

Biomarkers in cervical cancer

- Goal
  - To distinguish productive infection from transforming infection
- Mehtods
  - Immunohistochemistry (IH)
  - Immunocytochemistry (IC)
  - Methylation test, hrHPV infection, etc

Biomarkerek/tesztek a méhnyakrák diagnosztikájában

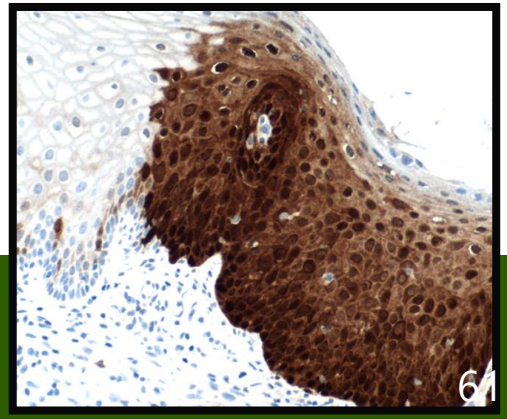
- $P16^{INK4a}$
- Ki67 (Mib1)
- $P16^{INK4a}$+Ki67 (CINtec Plus, Roch)
- ProExC (Beckton Dickinson)
- HPV E6/E7 mRNA teszt (Aptima, PreTec HPV-Proofer)
- BioCX biomarker teszt (CellCall)
- Telomerase (TERC)
- Sejtfelszíni markerek (Claudin1 etc)
- microRNS-ek
- Egyéb

CINtec® p16 Histology: CE / IVD

CINtec® p16 Histology immunhisztokémiai eljárás a **$p16^{INK4a}$ protein** detektálására, formalin fixált, paraffinba ágyazott metszeteken.

Ajánlott, hogy **H&E-festett metszetekkel együtt vizsgálják a diagnosztikus pontosság emelése.**

A módszert gyakorlott patológusnak célszerű végeznie, a megfelelő klinikai információk birtokában.



CINtec Plus
(Roch)

- $p16^{INK4a}$ és Ki67 fehérjék egyidejű, kvalitatív detektálása citológiai anyagban és szövetmetszetekben
- Két lépésben immunreakció
  - 2 primer monoclonalis antitest

Questions

- Bartholin cyst?
- Condyloma acuminatum?
- What is VIN? VAIN?
- What is CIN 1, 2, 3
- Characteristics of HPV
- What are the koilocytes?
- HR-HPV types
- LR-HPV types
- Diseases associated with HPV infection
- Geographic regions with high and low incidence and mortatlity of cervical cancer
- What is the mean age for cervical cancer in developed countries?
- Histology type of cervical cancer
- What is the Bethesda classification for cervical lesions? What the abbreviations are for? (ASCUS, HSIL, LSIL, AGUS)
- What is the Pappanicolaou classification for cervical smears? (P0-P5)
- What is the FIGO classification (stage)?