HPV AND ATYPICAL PAP SMEARS

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BACKGROUND

- Family Practice @ Mount Carmel Medical Group Sedalia
- My practice interest is women's health, especially prevention of STIs, teenage pregnancy and gynecologic cancer
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IN ORDER TO REALIZE THE IMPORTANCE, LET'S PUT A FACE ON CERVICAL CANCER

Eva Peron

Henrietta Lacks

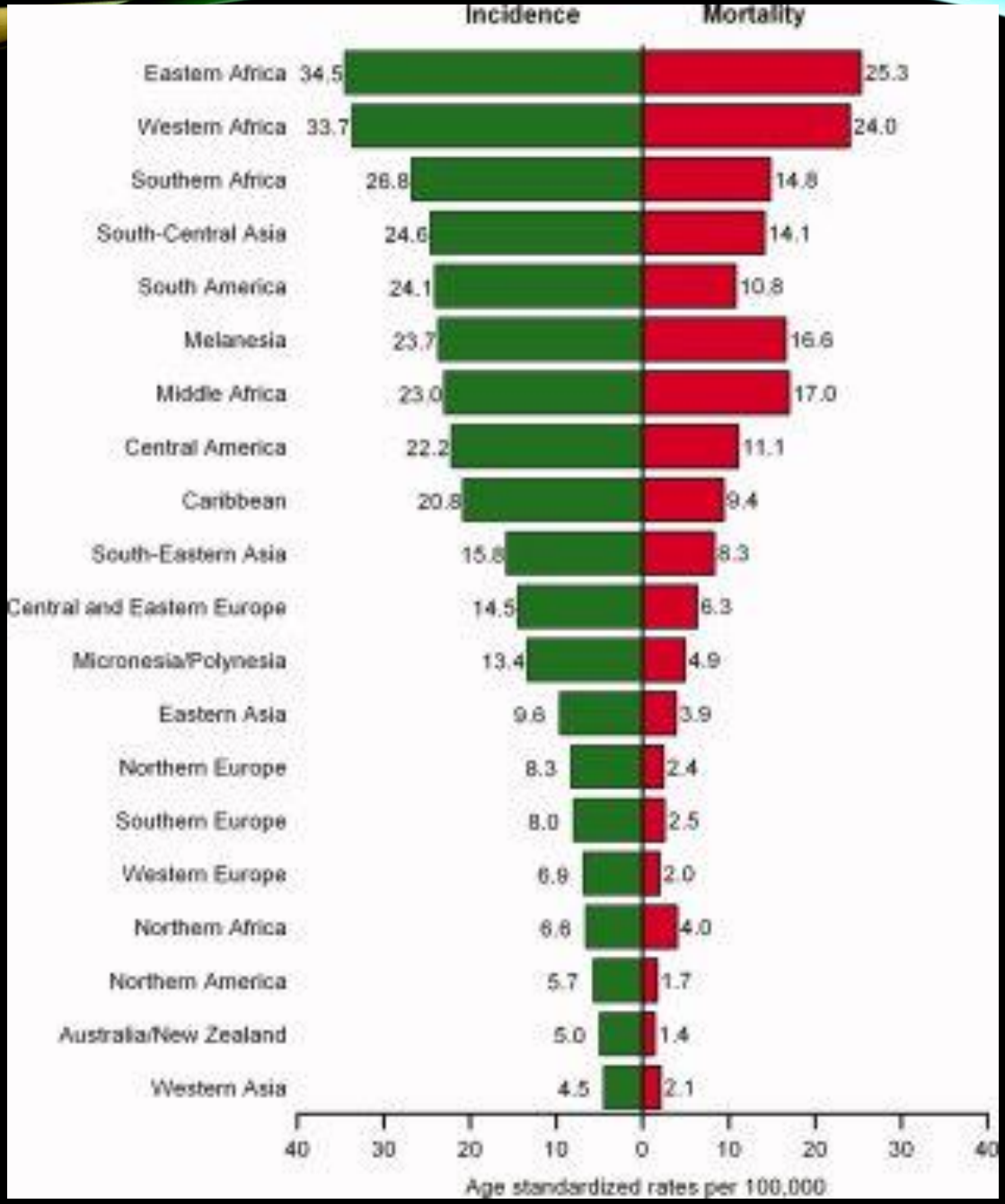
Jade Goody

CERVICAL CANCER

Worldwide incidence:

- Roughly 500,000 affected
- 250,000 deaths worldwide
- Ranked as 3rd most commonly diagnosed and 4th most common cause of cancer death worldwide
- Rates are significantly higher in developing countries, 80% of all cases
- India = over 25% of all deaths worldwide from cervical cancer (more than breast cancer)
- Significant loss of years of life

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E. and Forman, D. (2011), Global cancer statistics. CA: A Cancer Journal for Clinicians, 61: 69–90. doi: 10.3322/caac.20107

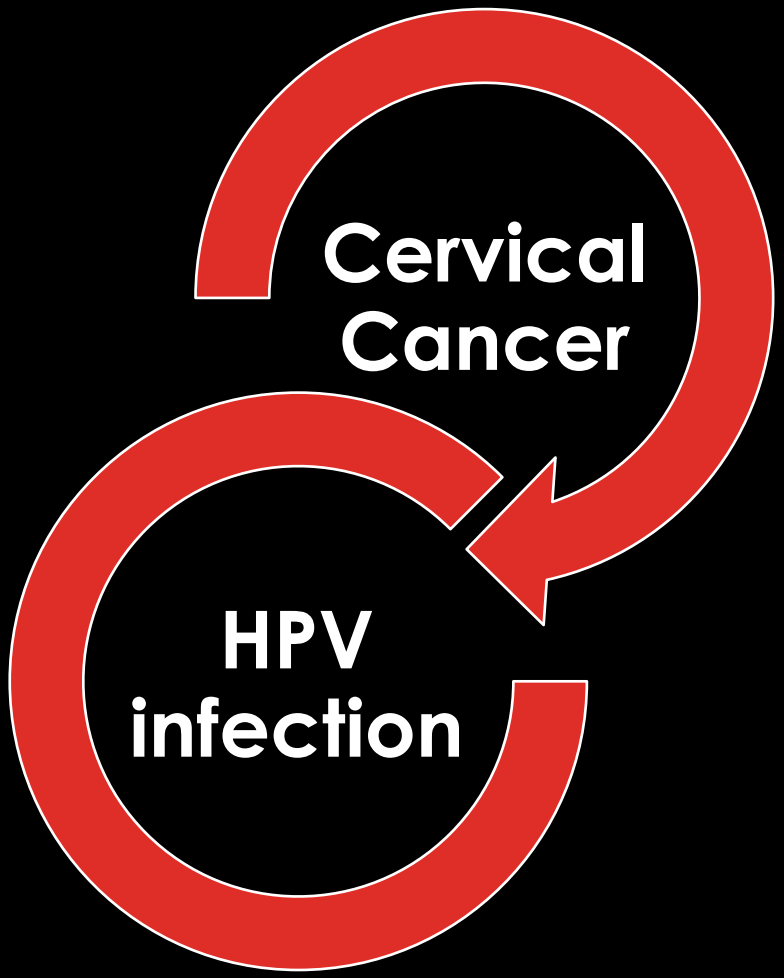


Source: GLOBOCAN 2008

Factors increasing cervical cancer rates in developing countries…

1. Lack of effective screening
2. Ability to obtain screening- only 19% of women in developing countries and 64% in industrialized nations
3. Higher HPV prevalence in East/West Africa, Latin America and South Asia and lower in West Asia and parts of Mediterranean
4. Lack of resources towards public education on condom use, prevention/screening, vaccination

Singh, Gopal K., Romuladus E. Azuine, and Mohammad Siahpush. "Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development." *International Journal of MCH and AIDS* 1.1 (2012): 17-30.


Cervical Cancer
HPV infection

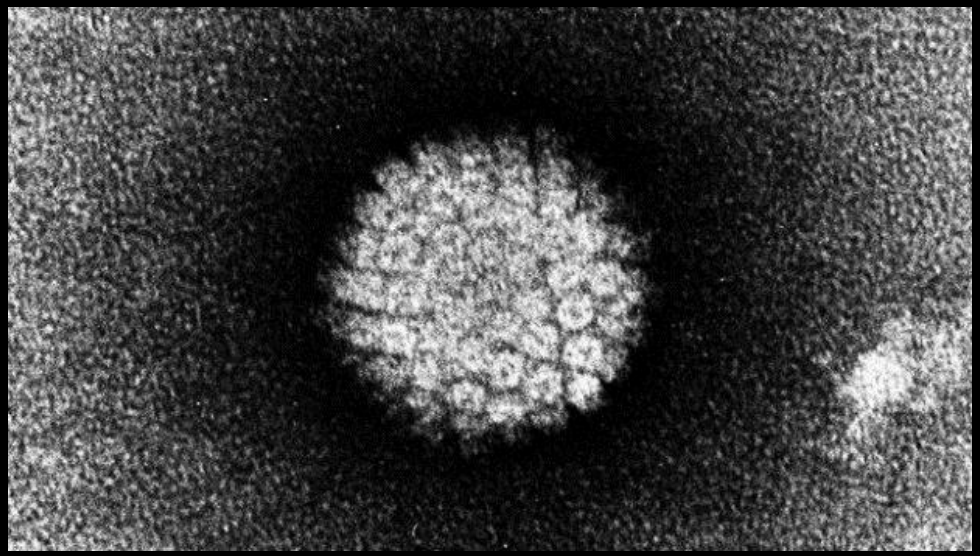
History of HPV discovery…

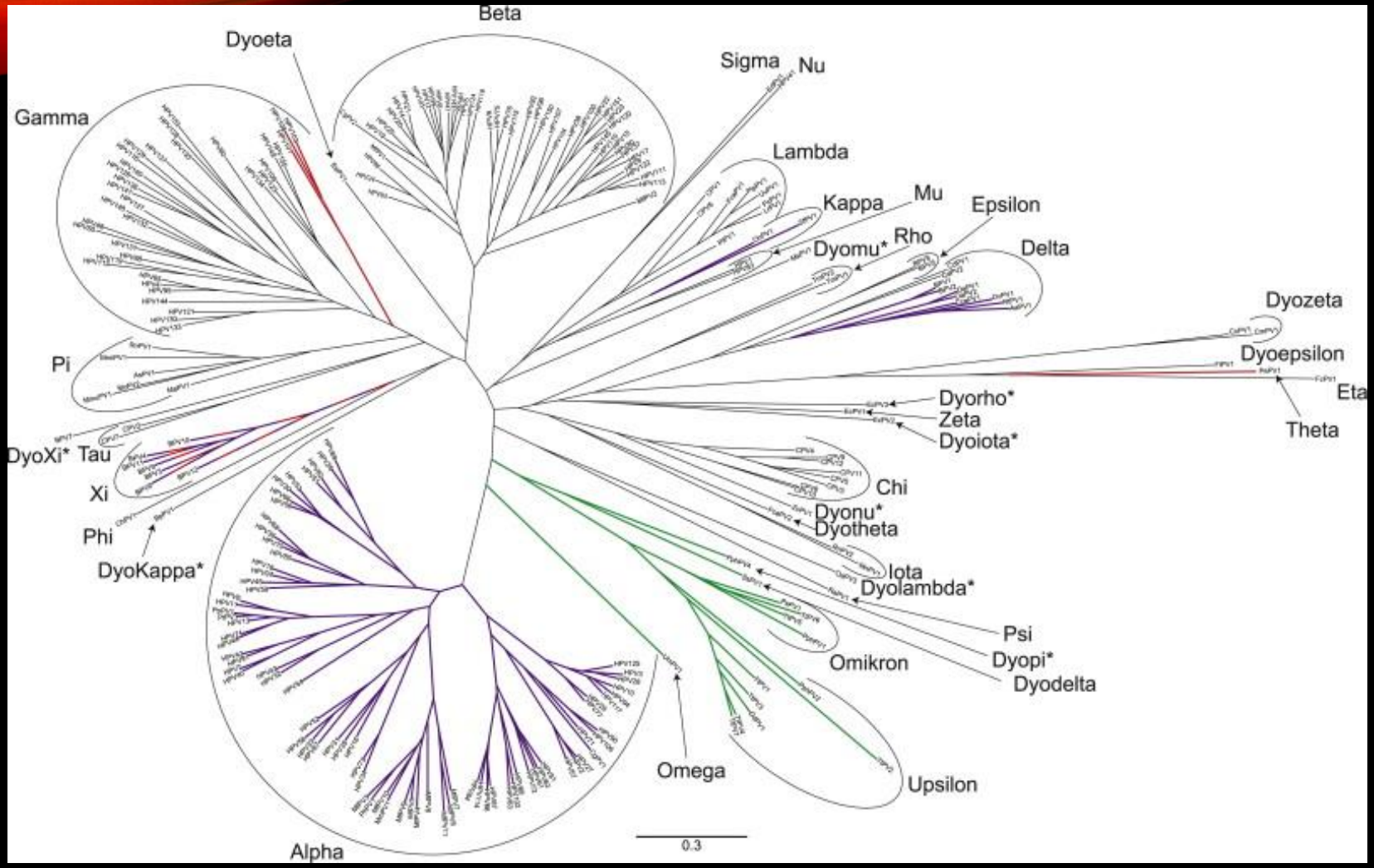
- 1842-Italian physician Rigoni-Stern postulated that cervical cancer did not occur as frequently in virgins and nuns based on analysis of death certificates at the time and showed increase in married women and prostitutes
- Late 1960s- theories that cervical cancer resulted from HSV2
- 1970s- Eventually, HPV began to be studied as to difference in antigens between genital and skin warts
- In 1980s and early 1990s, multiples studies demonstrated presence of HPV in anogenital cancers and in cervical intraepithelial lesions

Harald zur Hausen, Papillomaviruses in the casuation of cervical cancers- a brief, historical account, Virology, Volume 384, Issue 2, 20 February 2009, Pages 260-265.

HPV

- Member of Papillomaviridae family
- Approximately 200 types papillomaviruses identified so far.
- Sub-grouped based on ability to infect either skin or the mucosa of upper respiratory or genital tract





http://www.sciencedirect.com/science/article/pii/S0042682213002924

HPV linked to:

- Warts
- Anogenital carcinoma/dysplasia ****
- Laryngeal papillomatosis (HPV 6 and 11)
- Some oropharyngeal cancers

CDC.gov

According to CDC, in the U.S., HPV annually causes:

- 360,000 cases of genital warts
- 2,100 vulvar cancers
- 500 vaginal cancers
- 600 penile cancers
- 2,800 anal cancers in women
- 1,500 anal cancers in men
- 1,700 oropharyngeal cancers in women and 6,700 oropharyngeal cancers in men.*** (***of course, tobacco/ETOH use)

100%

Percentage of primary cervical cancers caused by HPV

Lifetime risk:

- Most sexually active adults will have been exposed to HPV in their lifetime
- Per CDC, 14 million new infections each year
- According to 2007 study in JAMA, the overall incidence of HPV in women age 14-59, the overall prevalence was 26.8%*
- Highest prevalence HPV infection age 20-24*
- 90% of HPV infections clear within 2 years*

*Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV Infection Among Females in the United States. *JAMA.* 2007;297(8):813-819. doi:10.1001/jama.297.8.813.

Risk factors for cervical cancer

- Early onset of sexual activity or multiple sexual partners
- Cigarette smoking
- Compromised immune system
- Low socioeconomic status
- Infection with a high risk HPV type

http://www.medscape.org/viewarticle/558452

HPV Genome

E1: DNA helicase/NTPase

E2: Transcriptional *trans*-modulator, replication control

E4: Cytokeratin disruption

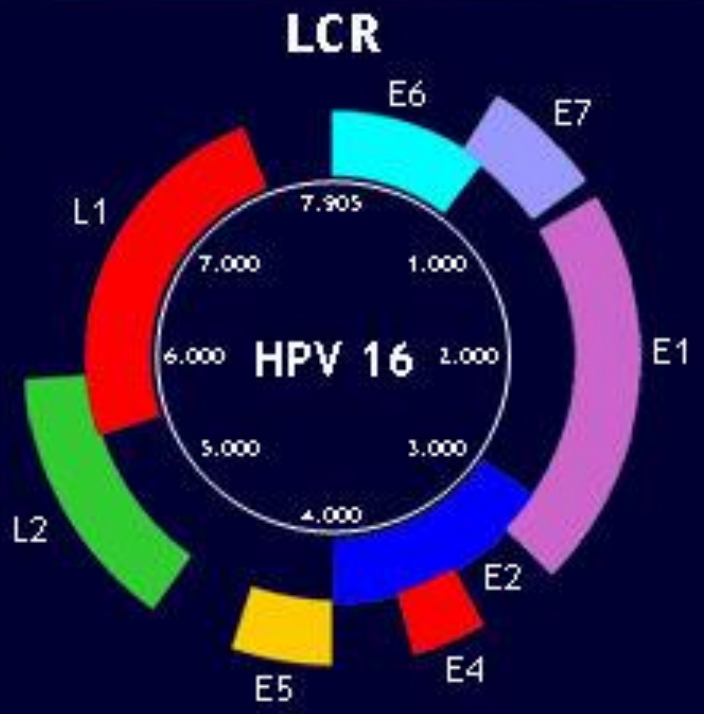
E5: Cell proliferation (binds PDGF receptor)

E6: Transforming protein (binds p53)

E7: Transforming protein (binds pRb)

L1: Major capsid protein

L2: Minor capsid protein



LCR=locus control region; NTPase=nucleoside 5'-triphosphatase; PDGF=platelet-derived growth factor.

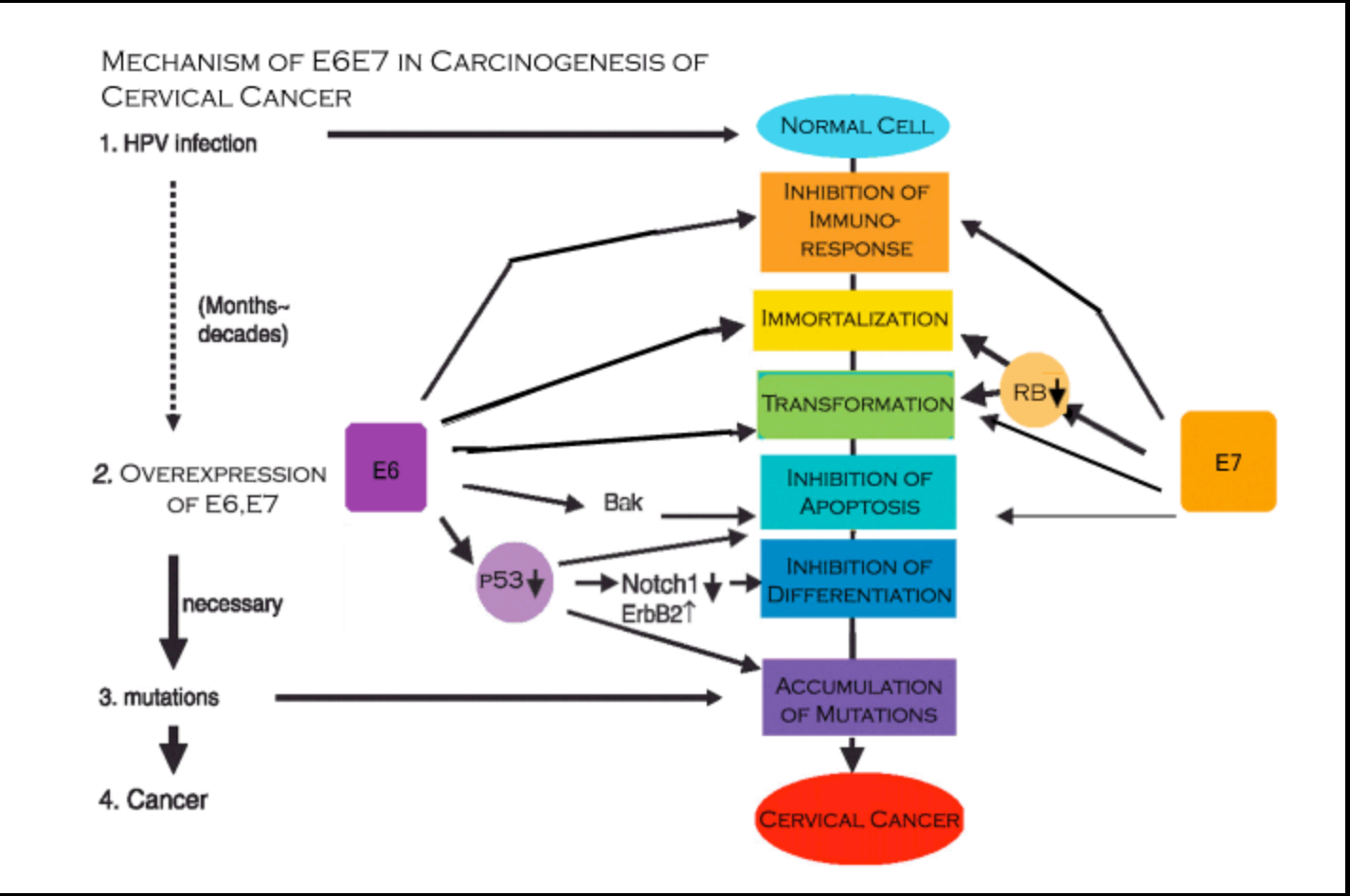
Doorbar J. *Clin Sci (Lond)*. 2006;110:525-541.

http://www.medscape.org/viewarticle/558452

HPV viral genes E6 and E7 contribute to high grade lesions and cancers in multiple ways including…

- E6 ➡ Inactivation of tumor suppressor p53 which is responsible for arresting cell growth after any damage to cell DNA
- E7 ➡ Inactivation of retinoblastoma protein, which prevents DNA damaged cells from progressing along in their cell cycle
- End result is that HPV induces and maintains cellular transformation by interfering with cell cycle control and cell death.

Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Role of E6 and E7 proteins" Narisawa-Saito and Kiyono, Cancer Sci 2007; 98:1505-1511.)



Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Role of E6 and E7 proteins" Narisawa-Saito and Kiyono, Cancer Sci 2007; 98:1505-1511.)

HPV

Oncogenic or high-risk types =

16, 18, 31, 33, 35, 39, 45, 51, 52, and 58

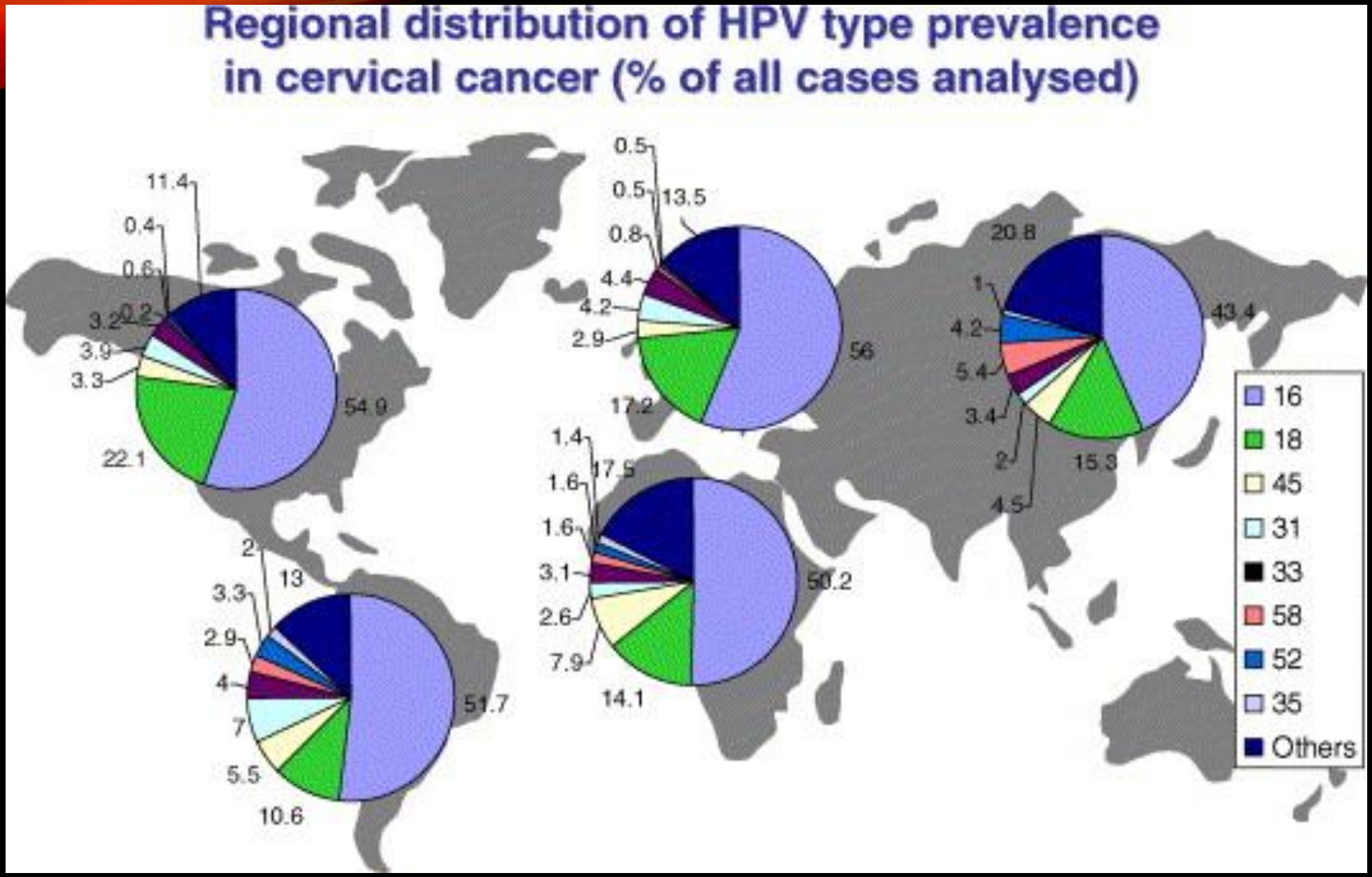
➡ cervical, vulvar, vaginal, and anal cancers

- HPV 16 is the most oncogenic: 50 % of cervical cancers
- HPV 16 and 18 =70% of cervical cancers

Low-risk types =

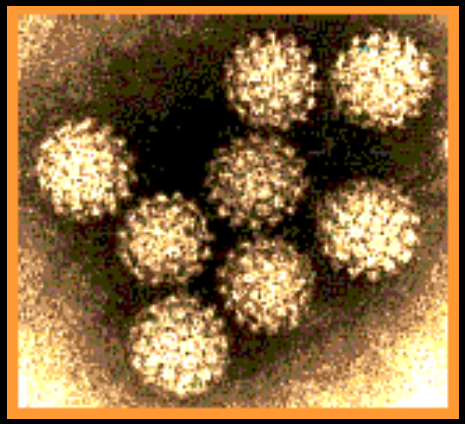
6, 11, 40, 42, 43, 44, and 54 ➡ genital warts.

- HPV 6 and 11 are the most common strains associated = 90% of genital warts.



Pagliusi, S., and M. Aguado. "Efficacy and Other Milestones for Human Papillomavirus Vaccine Introduction." Vaccine 23.5 (2004): 569-78.

- Infection with high-risk HPV is associated with cervical dysplasia or cervical intraepithelial neoplasia.
- Persistent infection leads to mild and moderate dysplasia = low levels of E6 and E7 expression
- Severe dysplasia and invasive cancer = high expression of E6 and E7 and integration of HPV into genome of the host



Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Role of E6 and E7 proteins" Narisawa-Saito and Kiyono, Cancer Sci 2007; 98:1505-1511.)

HPV VACCINES

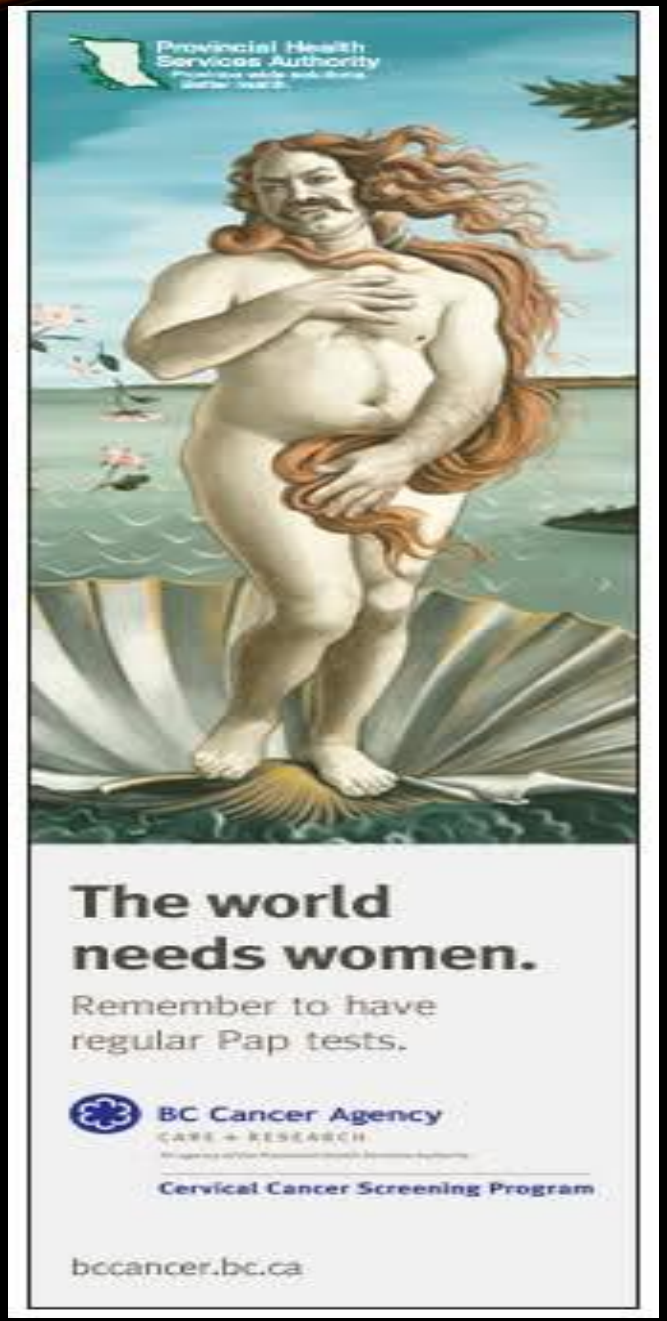
- Gardasil™- quadrivalent vaccine containing virus-like particles derived from HPV types 6,11,16 and 18
- Three dose regimen: IM injection @ initial, 2 months, 6 months later
- Indications: prevention of cervical, vulvar and vaginal cancers, precancerous lesions, genital warts
- Ages indicated: 9-26, men and women

FDA.gov

Cervarix™

- Virus like particles (VLPs) from HPV 16 and 18
- Three dose regimen: Initial, 1 month, 6 months
- Prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ, and cervical intraepithelial neoplasia (CIN) grade 1
- Indications for females 9-25 only – obviously.

FDA.gov


Provincial Health Services Authority
The world needs women.
Remember to have regular Pap tests.
BC Cancer Agency
CARE + RESEARCH
Cervical Cancer Screening Program
bccancer.bc.ca

GEORGE PAPANICOLAUO, M.D.

- Began work at Cornell University in the Department of Anatomy in 1914.
- He studied the use of vaginal smears to study sex cycle of guinea pigs, and eventually focused on humans to monitor the changes that occurred with ovarian and uterine pathology.
- His wife was his first and frequent test subject!
- In 1928, he published paper titled “New Cancer Diagnosis” which involved his findings of uterine cancer through vaginal smears.
- 1943- Published “Diagnosis of Uterine Cancer by the Vaginal Smear”
- 1945- American Cancer Society formed and began training physicians to perform pap smears

Source: cornell.edu

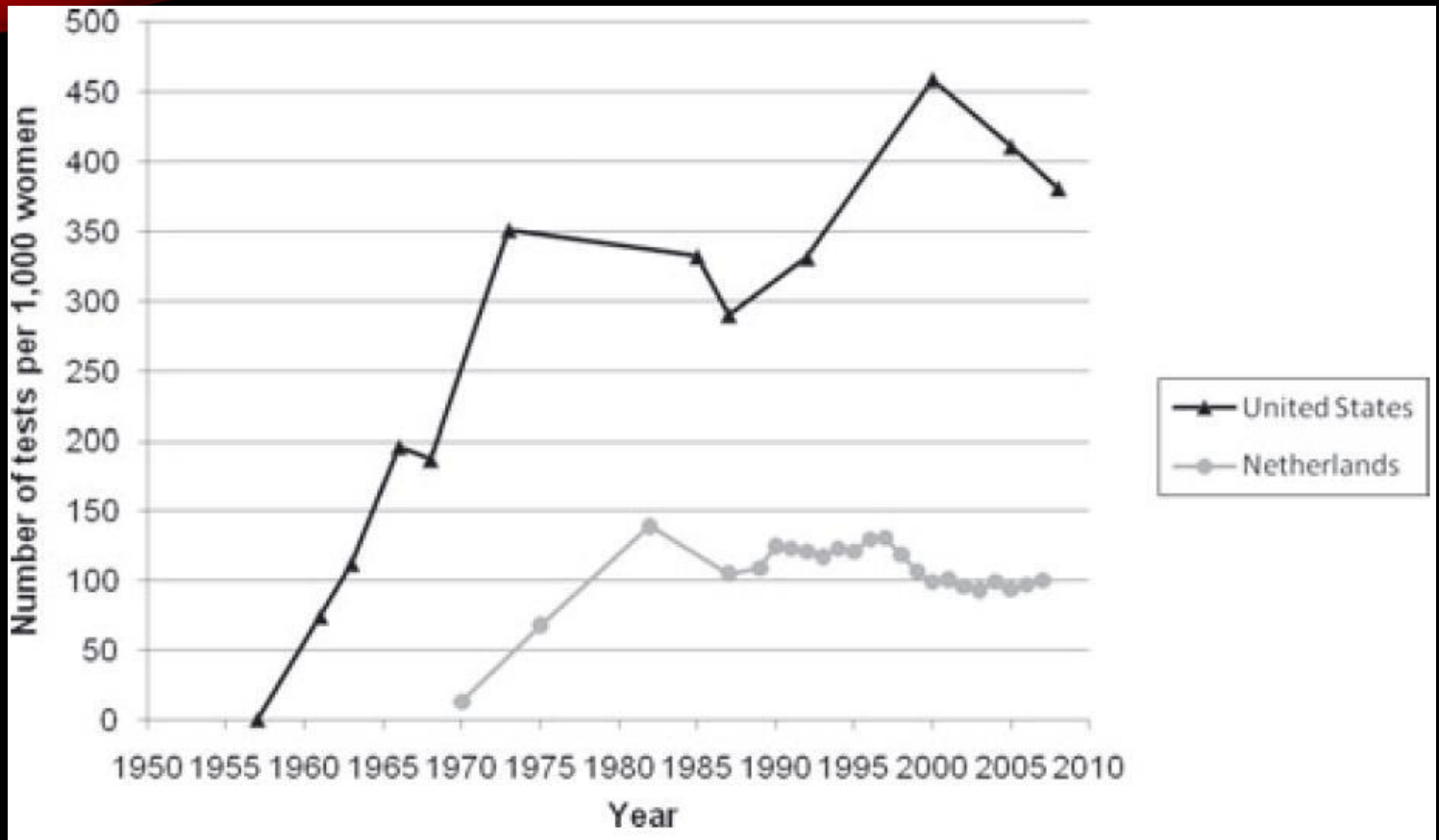


FIGURE 1. Number of Pap smears per 1,000 Women per year in the United States and the Netherlands, Age Standardized to the U.S. 2000 Population
Sources: United States: NHIS, see Gardner and Lyon 1977; National Center for Health Statistics 2011a, 2011b; Swan et al. 2010. Netherlands: PALGA, see Casparie et al. 2007; Habbema et al. 1988.

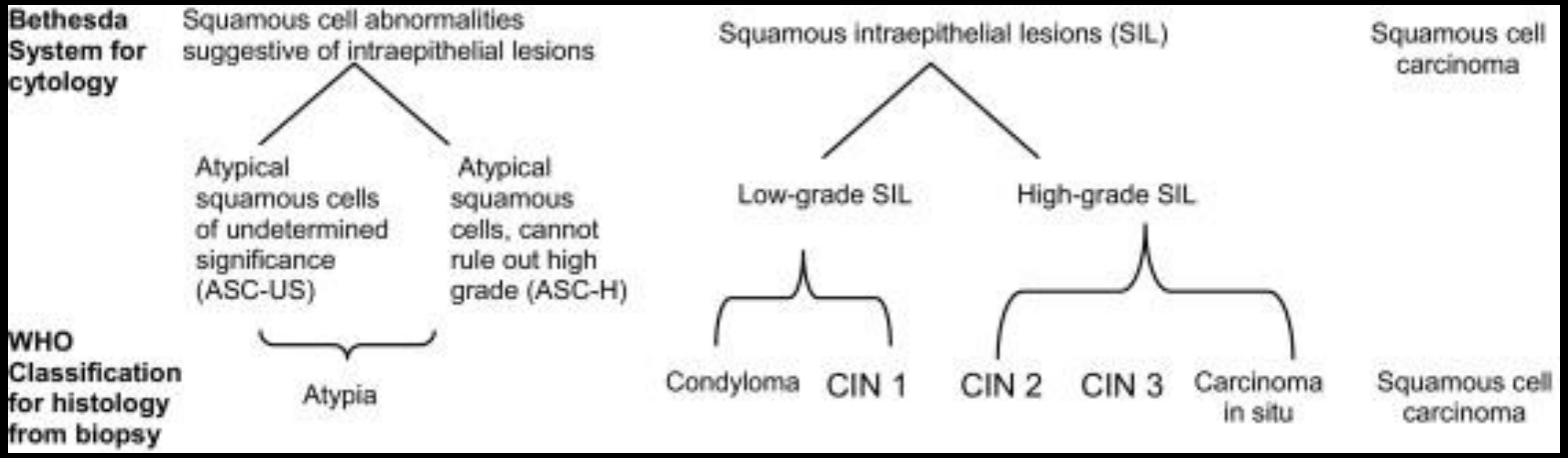
1940s: Cervical cancer #1 cause of cancer in women and leading cause of cancer death in U.S.

2013: Ranked 14th in frequency in the United States with approx.12,000 cases per year

Source: cdc.gov

Pap smear results:

- Reporting of pap smear results standardized by the Bethesda System in 1988 and revised in 1991, 2001
- Bethesda system worked to eliminate confusion of pap results.



The 2001 Bethesda System terminology.
Barbara S. Apgar, Lauren Zoschnick, Thomas C. Wright, Jr
Am Fam Physician. 2003 November 15; 68(10):

Includes

1. Specimen type (conventional, liquid based pap)
2. Specimen adequacy (satisfactory or unsatisfactory)
3. Interpretation of results
   a. Presence of organisms (candida, BV, trichomonads)
   b. Epithelial cell abnormalities
   c. Other nonneoplastic findings (inflammation, atrophy)

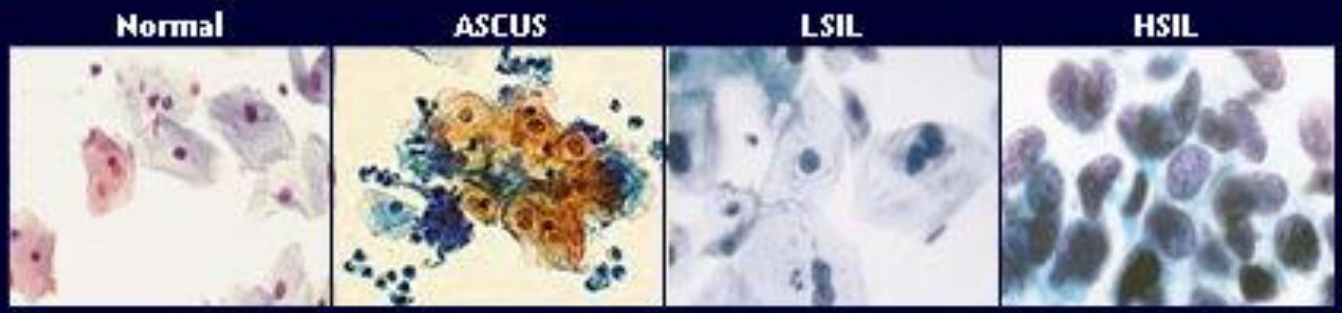
The 2001 Bethesda System terminology.
Barbara S. Apgar, Lauren Zoschnick, Thomas C. Wright, Jr
Am Fam Physician. 2003 November 15; 68(10):

HPV related atypical pap findings

1. ASCUS: Atypical Squamous cells of undetermined significance
2. ASC-H: Atypical Squamous cells, cannot exclude high grade squamous lesion
3. LGSIL: Low grade squamous intraepithelial lesion
4. HGSIL: High grade squamous intraepithelial lesion

Terminology for Cervical Cytology and Histopathology

Bethesda classification (Cytology)	Normal	ASCUS	LSIL		HSIL		Invasive cancer
WHO classification (Histopathology)	Normal	Condyloma	CIN 1 Mild dysplasia		CIN 2 Moderate dysplasia	CIN 3 Severe dysplasia/ carcinoma *in situ*	Invasive cancer

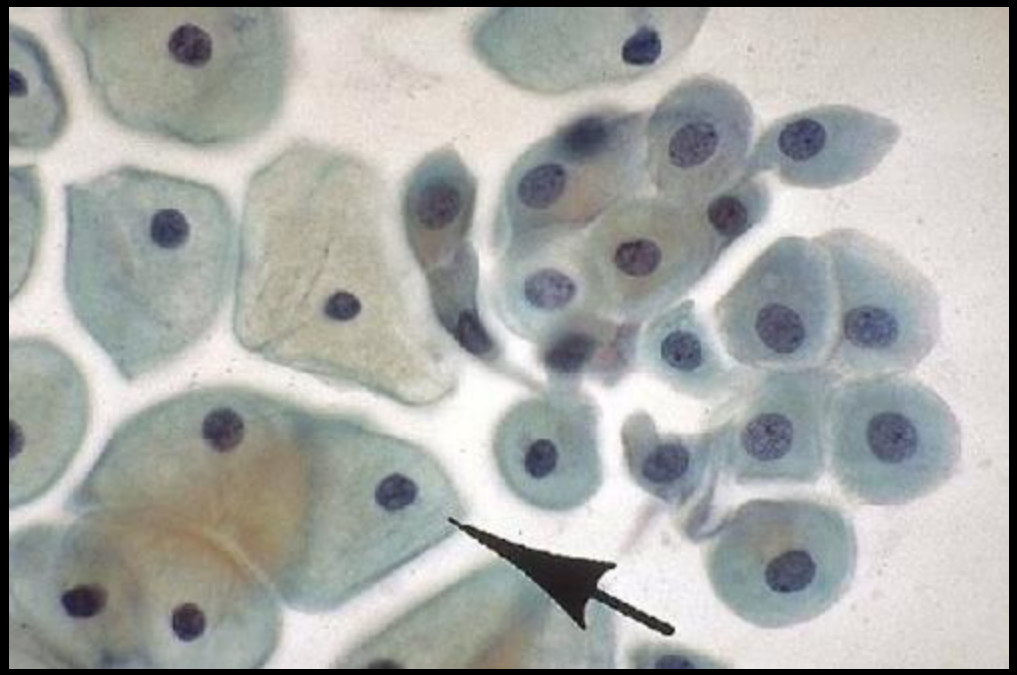


ASCUS=atypical squamous cells of undetermined significance; CIN=cervical intraepithelial neoplasia; HSIL=high-grade squamous intraepithelial lesion; LSIL=low-grade squamous intraepithelial lesion; WHO=World Health Organization.

Solomon D, Nayar R, eds. *The Bethesda System for Reporting Cervical Cytology*. 2nd ed. New York: Springer-Verlag; 2004; Frappart L et al. *Histopathology and Cytopathology of the Uterine Cervix*-Digital Atlas [CD-ROM]. Lyon, France: International Agency for Research on Cancer; 2004.

http://www.medscape.org/viewarticle/558452

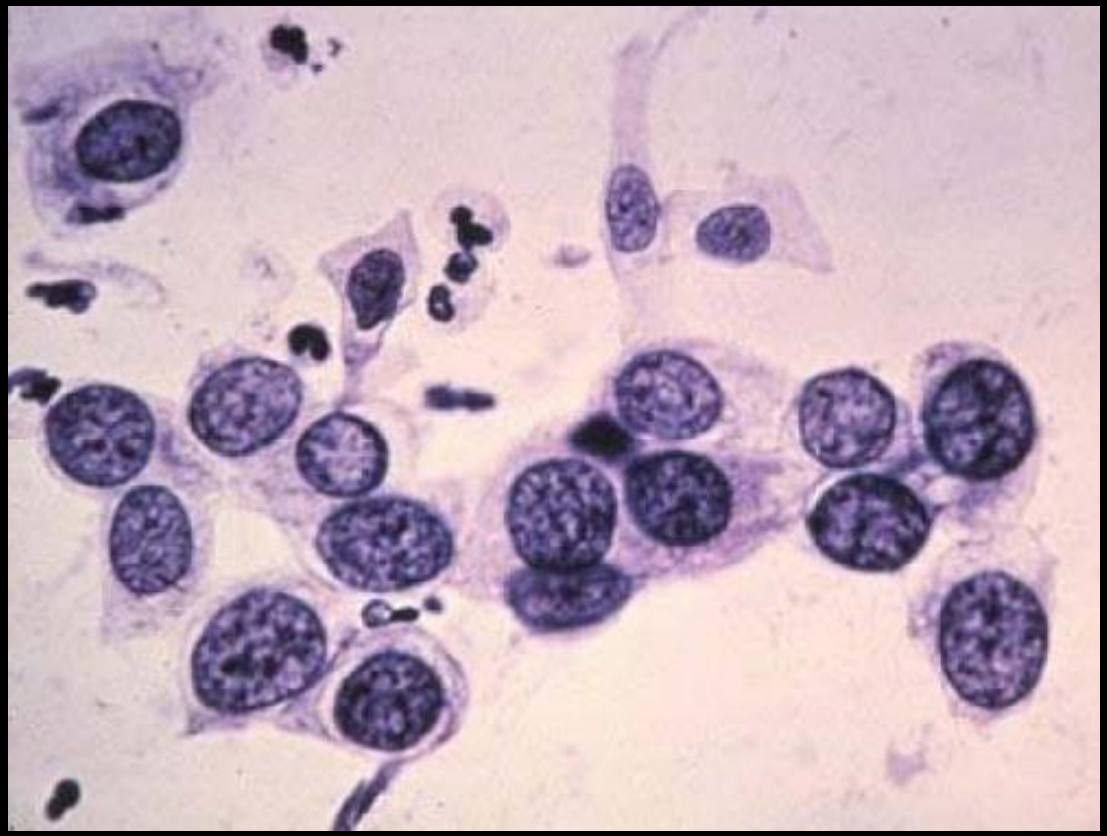
Normal pap smear



- Nucleus small
- Nucleus/cytoplasm ratio small

http://pathwiki.pbworks.com/w/page/14674115/Mod04Slide0405

Abnormal pap smear



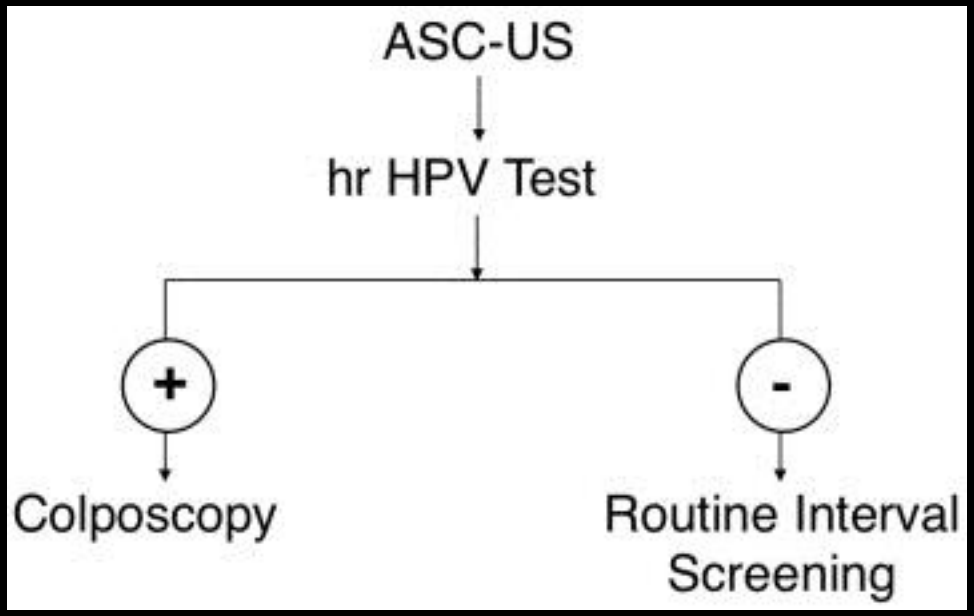
- Nucleus large
- Nucleus/cytoplasm ratio increased

http://pathwiki.pbworks.com/w/page/14674115/Mod04Slide0405

ASCUS pap smear

- Most common cervical cytology abnormality
- Considered lower risk, as 1/3 to 2/3 not associated with HPV infection
- Equivocal or borderline abnormal findings on pap
- Should not be ignored as can progress to higher grade dysplasia on follow up paps

ASCUS pap smear treatment guidelines



- If HPV test not available, reasonable to repeat pap in one year
- High risk HPV test = 13 HR HPV types

In a study of over 1 million paps done by Kaiser Permanente of women age 30-64:

5 year risk of developing premalignant or malignant disease:

HPV-positive:

CIN 2+ (18 percent)

CIN 3+ (6.8 percent)

cervical cancer (0.41 percent)

HPV-negative:

CIN 2+ (1.1 percent)

CIN 3+ (0.43 percent)

No cases of cervical cancer found

Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women with HPV testing of ASC-US Pap results. J Low Genit Tract Dis 2013; 17:S36.

ASC-H pap smear

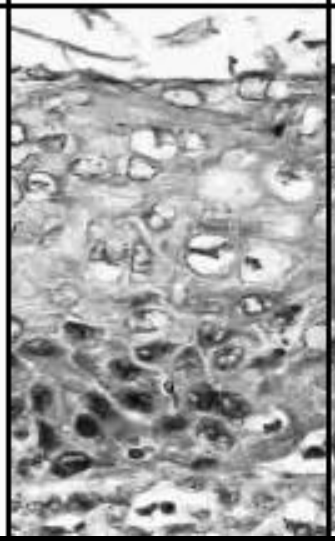
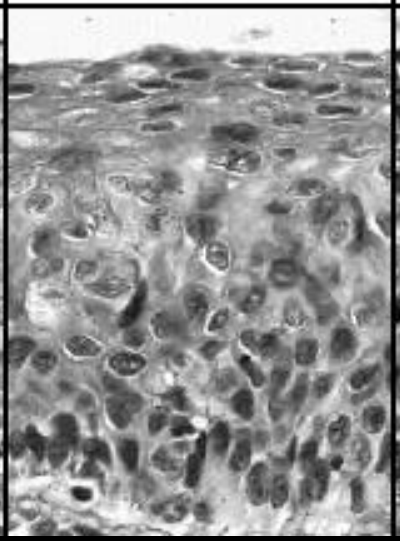
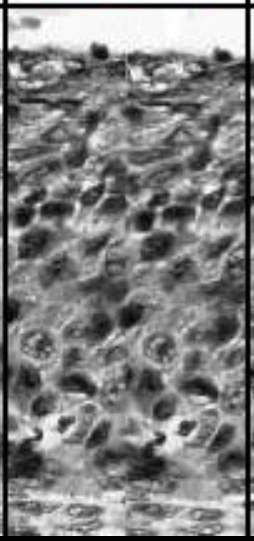
Atypical **S**quamous **C**ells-cannot exclude
High grade squamous intraepithelial lesion

Colposcopy

ASC-H pap smear results:

- HPV testing not required
- High rate of HPV in these paps ~ 71% in one study
- Up to 80% of these paps will go on to demonstrate a high grade lesion

Barreth, Drew, et al. "Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H): a result not to be ignored." *JOGC-TORONTO-* 28.12 (2006): 1095.

LAST System[1]	Cytology	LSIL	HSIL		
	Histology	LSIL	p16 staining should be performed*	HSIL	
Bethesda Classification System[2]	Cytology	LSIL	HSIL		
	Histology	CIN 1	CIN 2	CIN 3	
Previous terminology		Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in-situ
Histologic images					

1. Darragh TM, et al. Int J Gynecol Pathol 2012; 32:76.
2. Solomon D, et al. JAMA 2002; 287:2114.

*p16 is a marker for squamous dysplasia

LGSIL pap

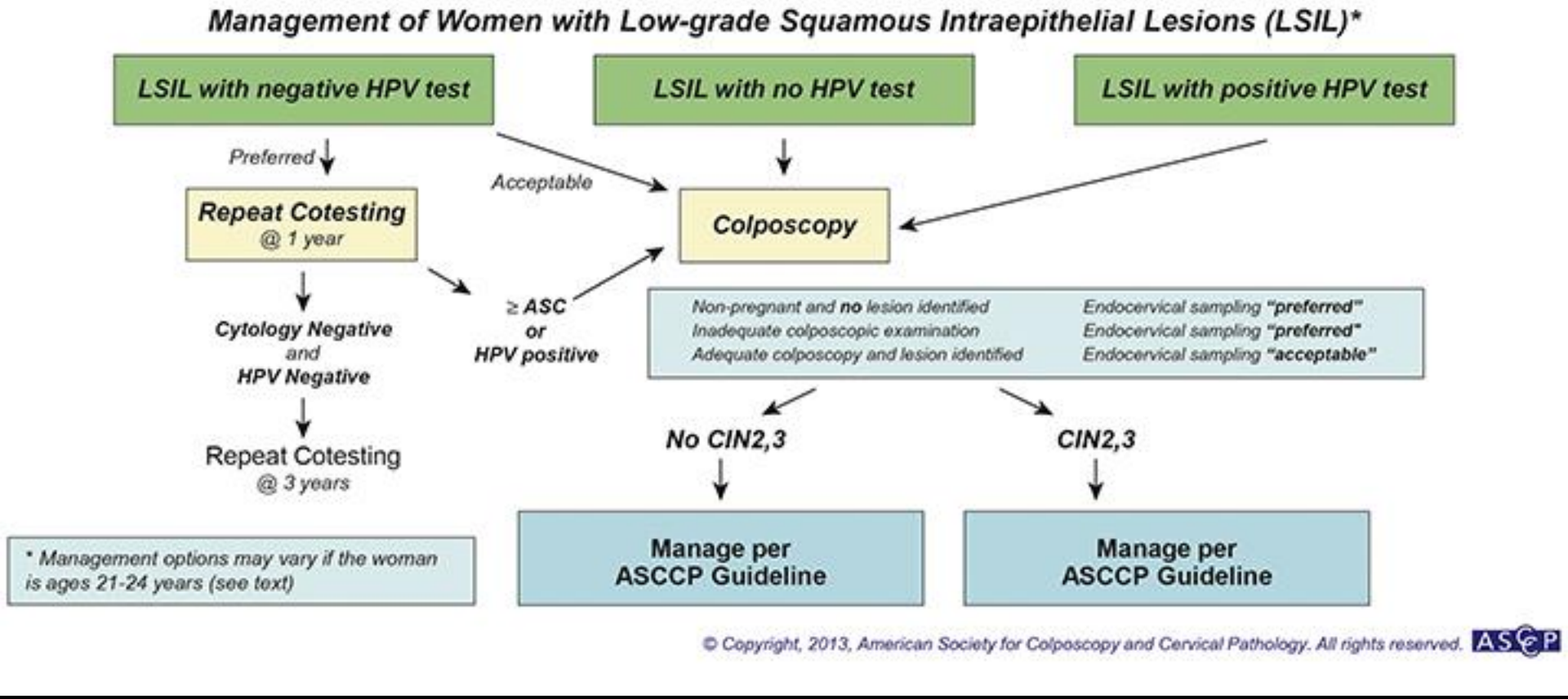
- Second most common cytologic abnormality found on paps
- In Kaiser Permanente study from 2003-2010, study of 965,360 paps, incidence was roughly 1%*
- Risk of finding invasive cervical cancer is low
- Strongly associated with HPV
- In ALTS trial, 82.9% of LGSIL paps were HPV +

*Katki HA, Schiffman M, Castle PE, et al. Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis 2013; 17:S28.

5 year risk of pre-malignant or malignant disease:

LGSIL cytology:
CIN 2: 16 percent
CIN 3: 5.2 percent
Cervical cancer: 0.16 percent

Katki HA, Schiffman M, Castle PE, et al. Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis 2013; 17:S28.



*Age 21-24-colpo only if recurrent/severe. Repeat cytology 12 months in age 21-24 LGSIL

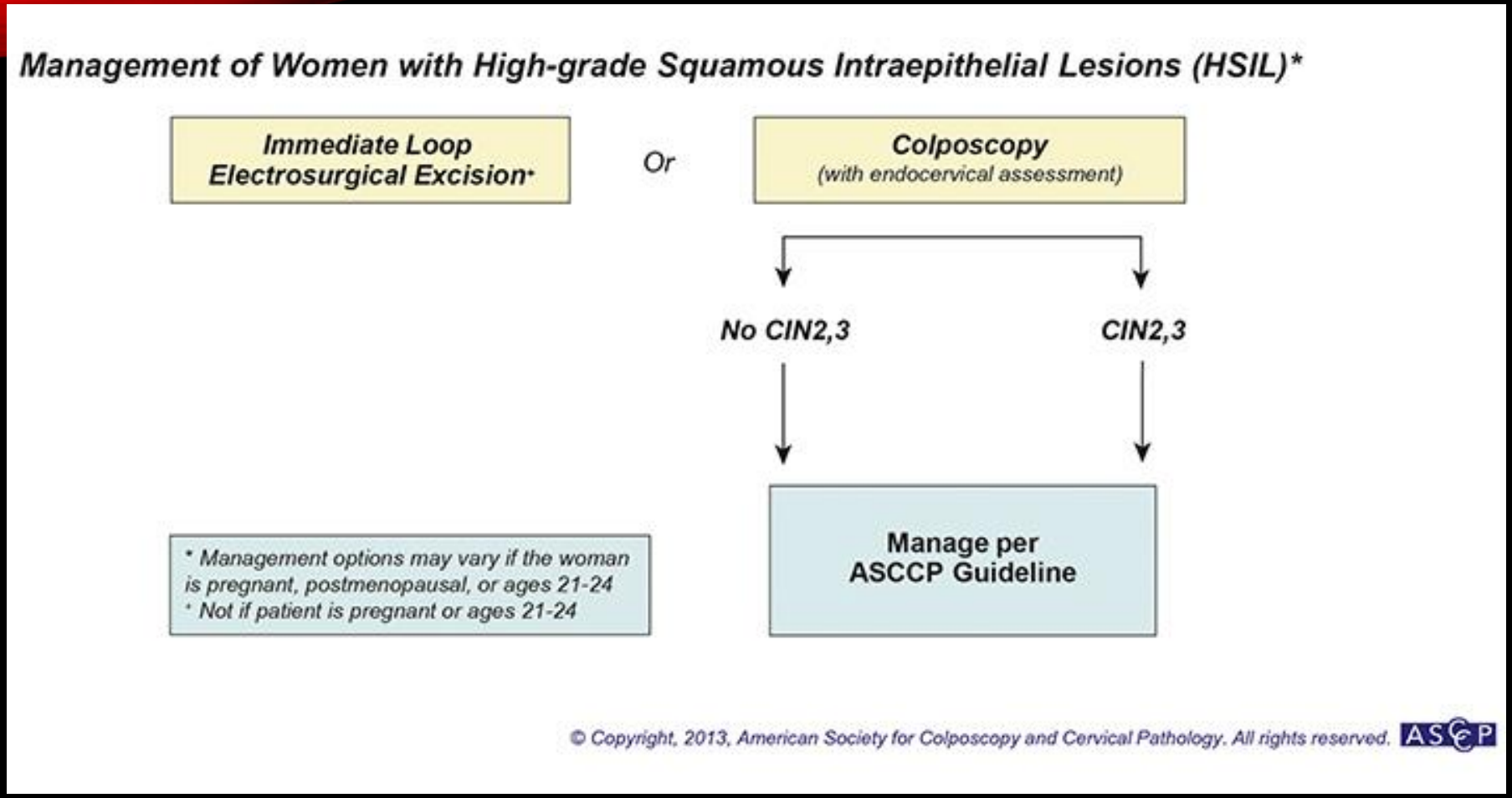
HGSIL pap

- SUBSTANTIAL RISK OF DEVELOPING INTO CERVICAL CANCER
- HIGH PREVALENCE OF HPV ~ 90%

5 year risk of pre-malignant or malignant disease:

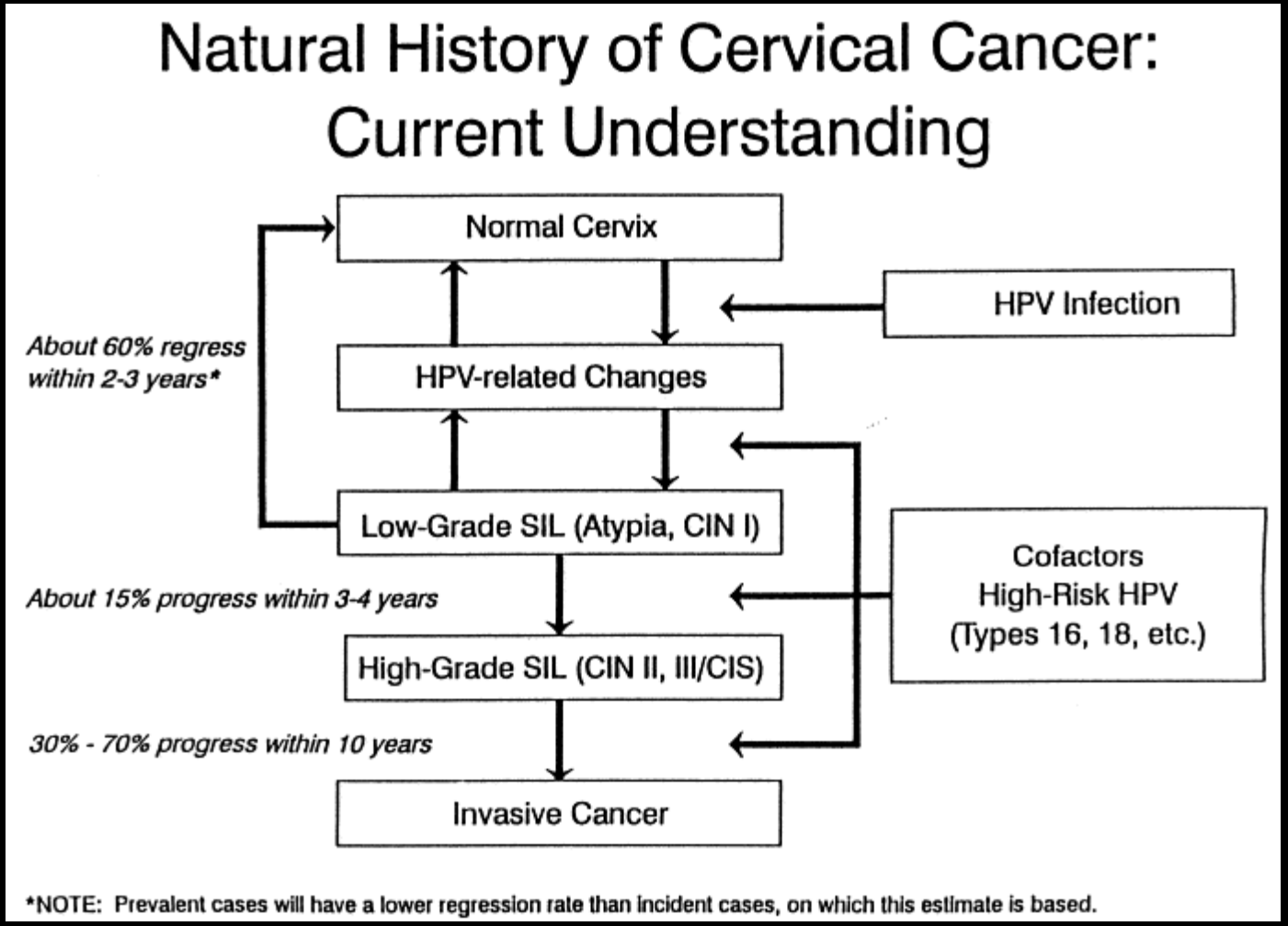
HGSIL cytology:
CIN 2: 69 percent
CIN 3: 47 percent
Cervical cancer: 7 percent

Katki HA, Schiffman M, Castle PE, et al. Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis 2013; 17:S28.



Women ages 21-24: manage with colposcopy first, LEEP not acceptable as initial management

Natural History of Cervical Cancer: Current Understanding



Maria Elena Soler, Lynne Gaffikin, Paul D Blumenthal, Cervical cancer screening in developing countries, Primary Care Update for OB/GYNS, Volume 7, Issue 3, May–June 2000

Public financial health burden of HPV

- Estimated $3-4 billion is spent annually on HPV related diseases and cervical cancer treatment
- HPV second most expensive STI after HIV
- In 2000, the estimated cost for treatment of genital warts alone was $167 million.
- Unable to measure productivity/work loss, let alone the emotional toll

Soper, David. "Reducing the Health Burden of HPV Infection Through Vaccination." Infectious Diseases in Obstetrics and Gynecology (2006): 1-5. Gale. Web. 13 Sept. 2013.

Becky Ryder