Preventing Anal Cancer

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Faculty Disclosure

- In the past 12 months…

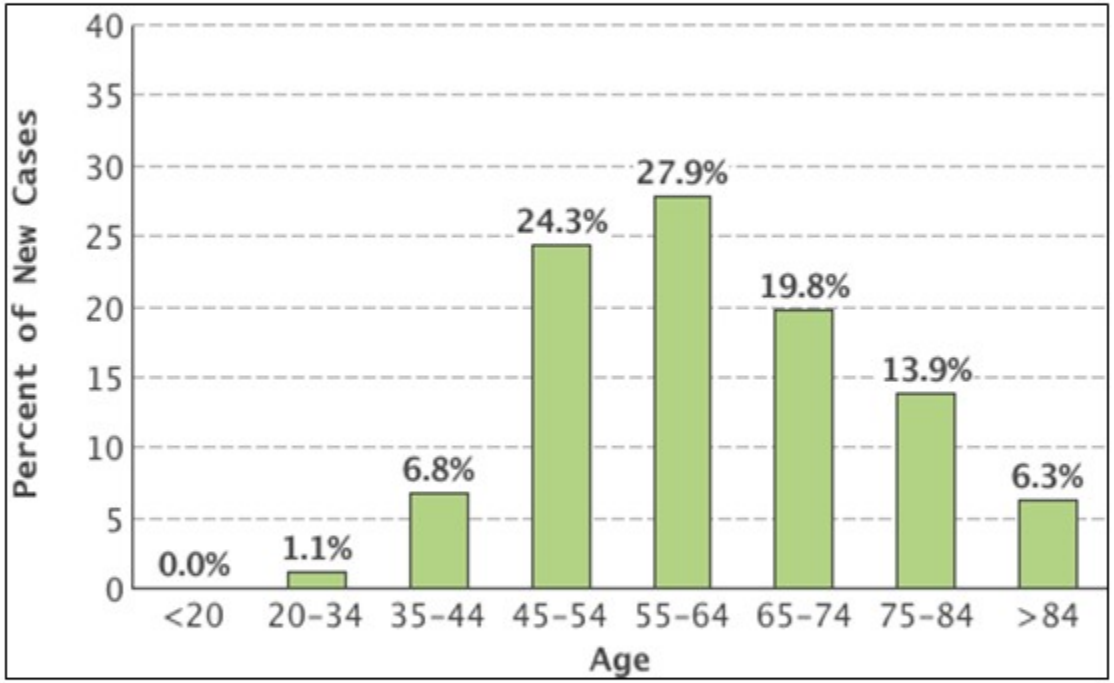
- Hologic: Research supplies for anal cytology
- Roche: Honorarium and travel expenses

Objectives

- Why screen?
- Who to screen?
- How to screen?
  - Anal Cytology & DARE
  - Anal HPV testing
  - High resolution anoscopy & biopsy

Anal Cancer Statistics, U.S.

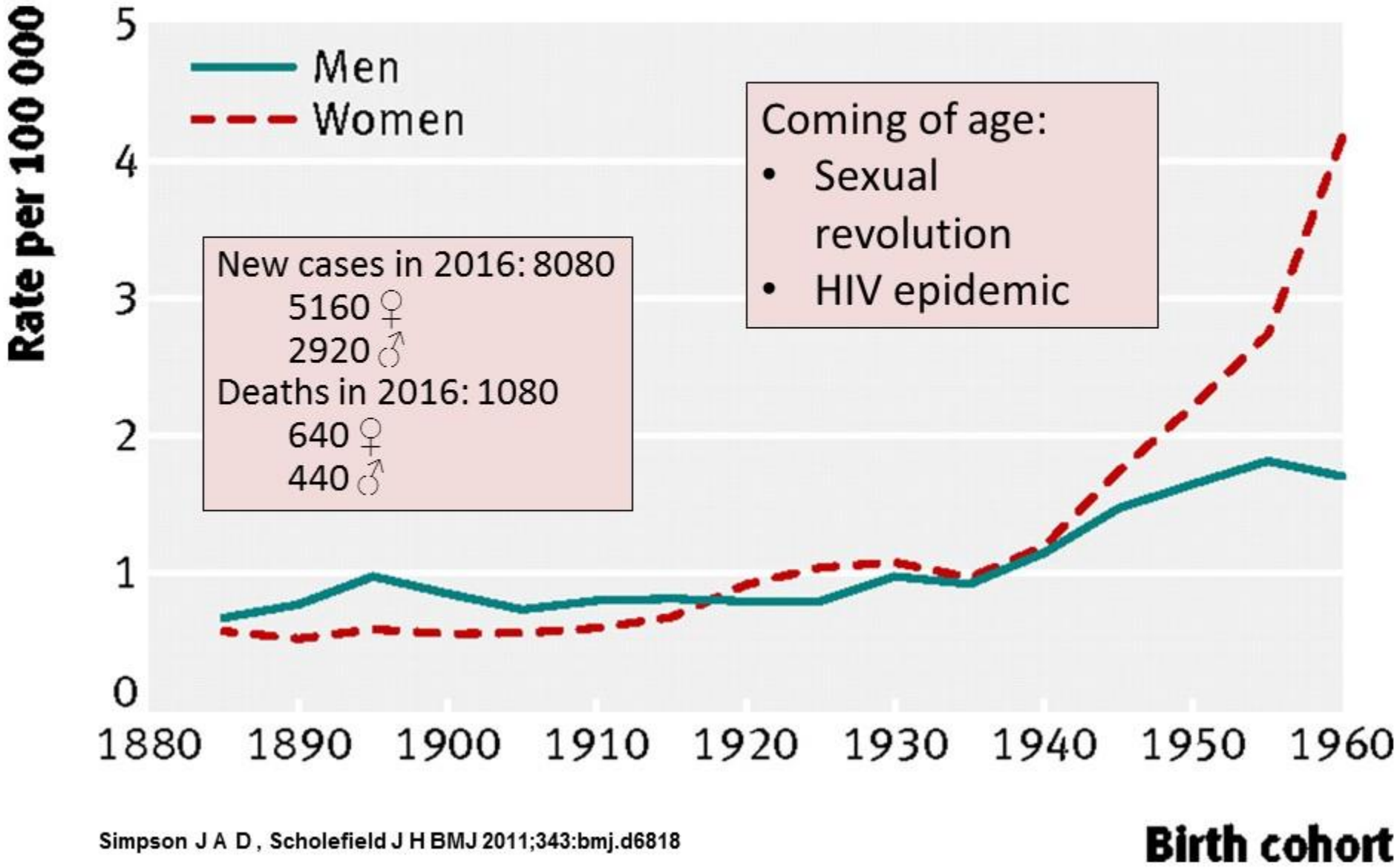
- Incidence rates:
  - Women: 1.8 / 100K
  - Men: 1.4 /100K
- Median age at diagnosis: 61 years
- 10+ years later than cervical cancer



1 in 500 people born today will be diagnosed with anal cancer

American Cancer Society: www.cancer.org SEER: http://seer.cancer.gov

Anal Cancer Rates by Birth Cohort



Simpson J A D , Scholefield J H BMJ 2011;343:bmj.d6818

HPV infection - attributable cancer in 2002: developed & developing countries

Site	Attributable to HPV (%)	Developed countries			Developing countries		
		Total cancers	Attributable to HPV	% all cancer	Total cancers	Attributable to HPV	% all cancer
Cervix	100	83,400	83,400	1.7	409,400	409,400	7
Penis	40	5200					0.1
Vulva, vagina	40	18,300					0.1
Anus	90	14,500	13,100	0.3	15,900	14,300	0.2
Mouth	3	91,200	2700	0.1	183,100	5500	0.1
Oro-pharynx	12	24,400	2900	0.1	27<,700	3300	0.1
All sites		5,016,100	111,500	2.2	5,827,500	449,600	7.7

Screening vs. No Screening

D. Maxwell Parkin , Freddie Bray. **Chapter 2: The burden of HPV-related cancers.** Vaccine, Volume 24, Supplement 3, 2006, S11 - S25. http://dx.doi.org/10.1016/j.vaccine.2006.05.111

Anal Cancer and Cervical Cancer

	Rates per 100,000
• Cervical cancer in US:	
– prior to Pap screening	• 40-50 / 100K
– currently	• 8 / 100K
• Anal cancer:	
– women, general pop.	• 1.8 / 100K
– HIV- MSM*	• 35 / 100K
– HIV+ MSM*	• 131 / 100K
– HIV+ women	• 30 / 100K

*MSM = men who have sex with men

Silverberg M et al. CID 2012; 54:1026-34

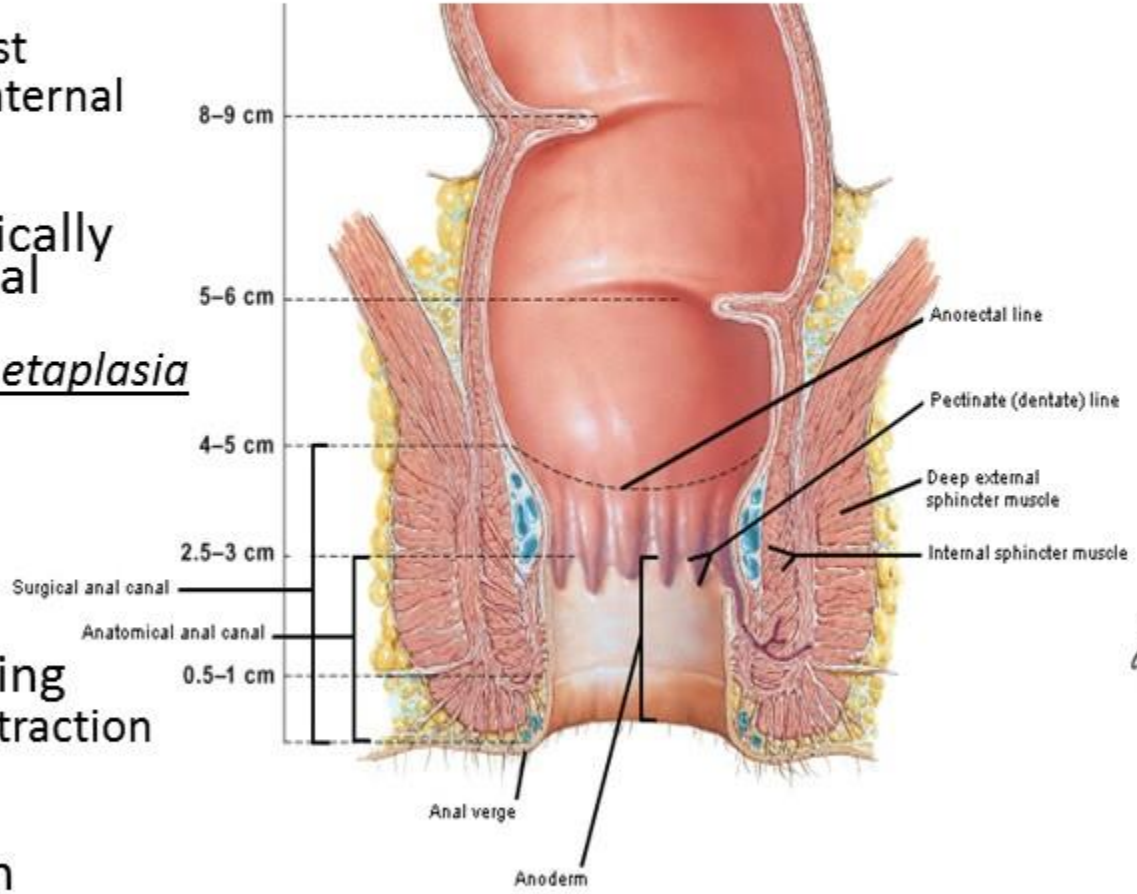
Anal Cancer and Cervical Cancer

- Common risk factors
  - Sexual intercourse
    - Vaginal
    - Anal
- HPV infection
  - High-risk HPV
  - HPV 16 and 18
- >90% of anal cancers
  - HPV-related
  - Especially HPV 16

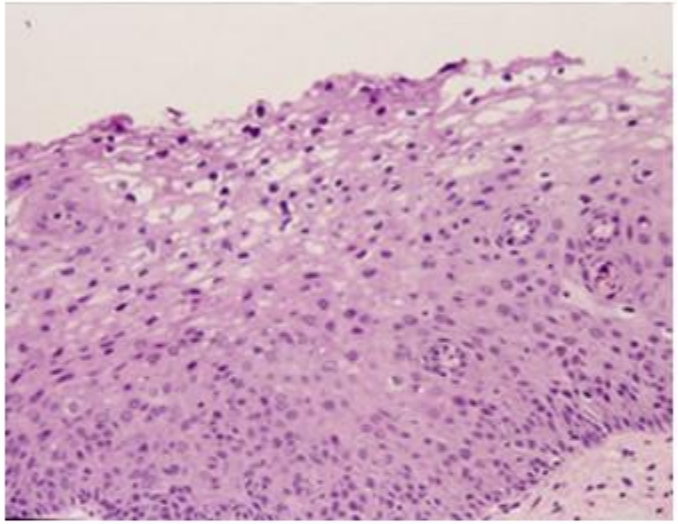
- Anatomic commonality:
  - Transformation zones
  - Regions of active squamous metaplasia
  - Vulnerable to high-risk HPV
- Morphologic similarity
  - Precursor lesions
    - HSIL and LSIL
    - CIN vs AIN
  - Cancer: Squamous cell carcinoma

Anal Anatomy: Landmarks

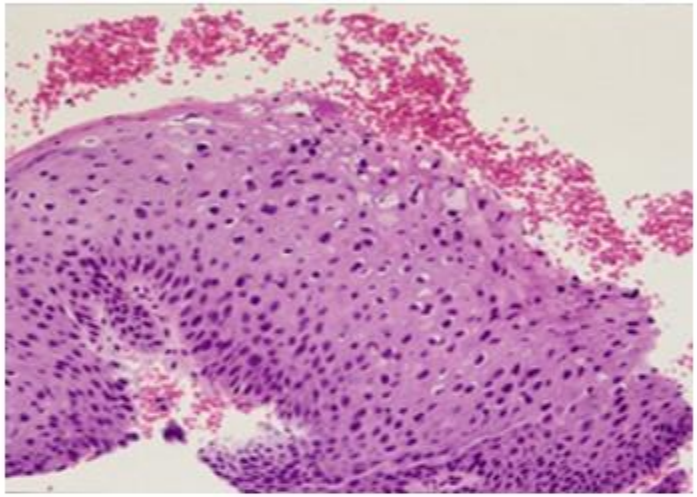
- Anal canal = Intra-anal
  - Mucosa opposed at rest
  - Tone of external and internal sphincters
- Anal t-zone morphologically analogous to the cervical transformation zone
  - Region of *squamous metaplasia*
  - Variable
- Dentate line
- Anal verge = Anal opening
  - Visualized by gentle retraction of the buttocks
- Peri-anus = Anal margin
  - Extend 5 cm from verge

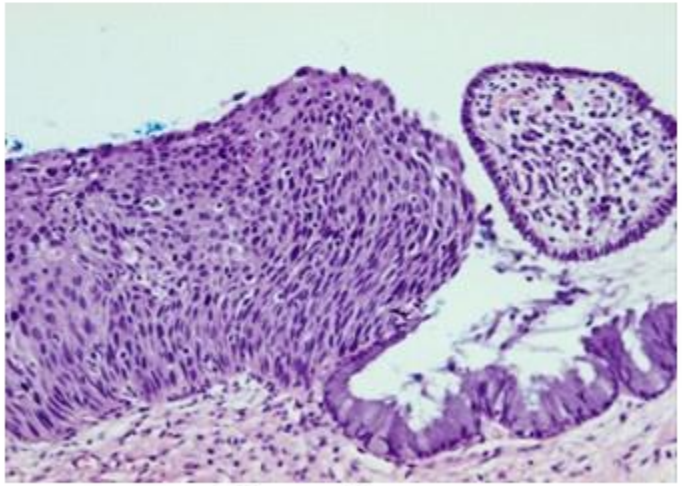


Cervix and Anus: Lesions morphologically similar

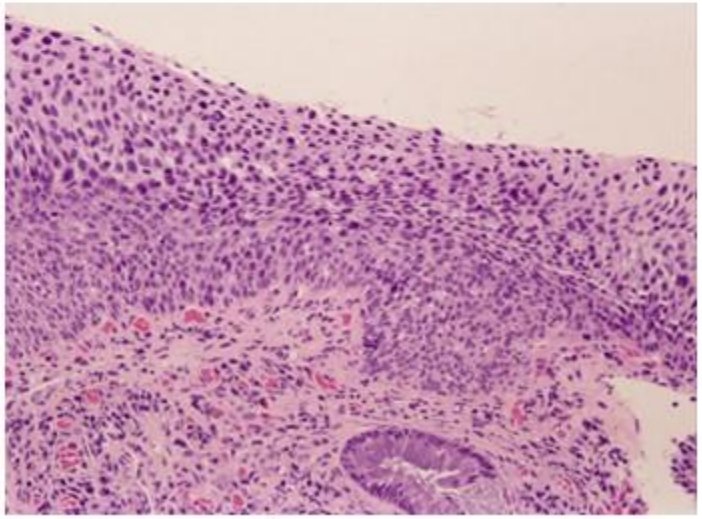


Low grade





High grade



Cervix

Anus

Anal Cancer: Who is at risk? Targeted screening

- Men who have sex with men (MSM)
- Patients with HIV disease
- Women with HSIL / cancer
  - Multifocal HPV-related disease
  - Vulvar / perianal > cervix
- Other causes of immunosuppression
  - Solid organ transplantation
  - ? Other causes of immunosuppression, e.g.
    - Autoimmune disease
    - Inflammatory bowel disease
    - Cancer chemotherapy

Anal Cancer: U.S. Screening Guidelines

- No national screening guidelines
- CDC: Acknowledges that some experts recommend anal cytologic screening for HIV+ men and women
- ACS: Anal cytology, sometimes called the anal Pap test, may be useful in early diagnosis of anal cancer and precancer (called *anal intraepithelial neoplasia* (AIN)...Some doctors already recommend this test for people at high risk for anal cancers, such as those who are HIV positive.
- New York State Department of Public Health AIDS Institute:
  - Clinicians should obtain anal cytology at baseline and annually in the following HIV-infected populations:
    - Men who have sex with men
    - Any patient with a history of anogenital condylomas
    - Women with abnormal cervical and/or vulvar histology

Journal of Lower Genital Tract Disease

SYSTEMATIC REVIEW, META-ANALYSIS, NARRATIVE REVIEW

Screening for Anal Cancer in Women

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Objective: The incidence of anal cancer is higher in women than men in the general population and has been increasing for several decades. Similar to cervical cancer, most anal cancers are associated with human papillomavirus (HPV), and it is believed that anal cancers are preceded by anal high-grade squamous intraepithelial lesions (HSIL). Our goals were to summarize the literature on anal cancer, HSIL, and HPV infection in women and to provide screening recommendations in women.

Methods: A group of experts convened by the American Society for Colposcopy and Cervical Pathology and the International Anal Neoplasia Society reviewed the literature on anal HPV infection, anal SIL, and anal cancer in women.

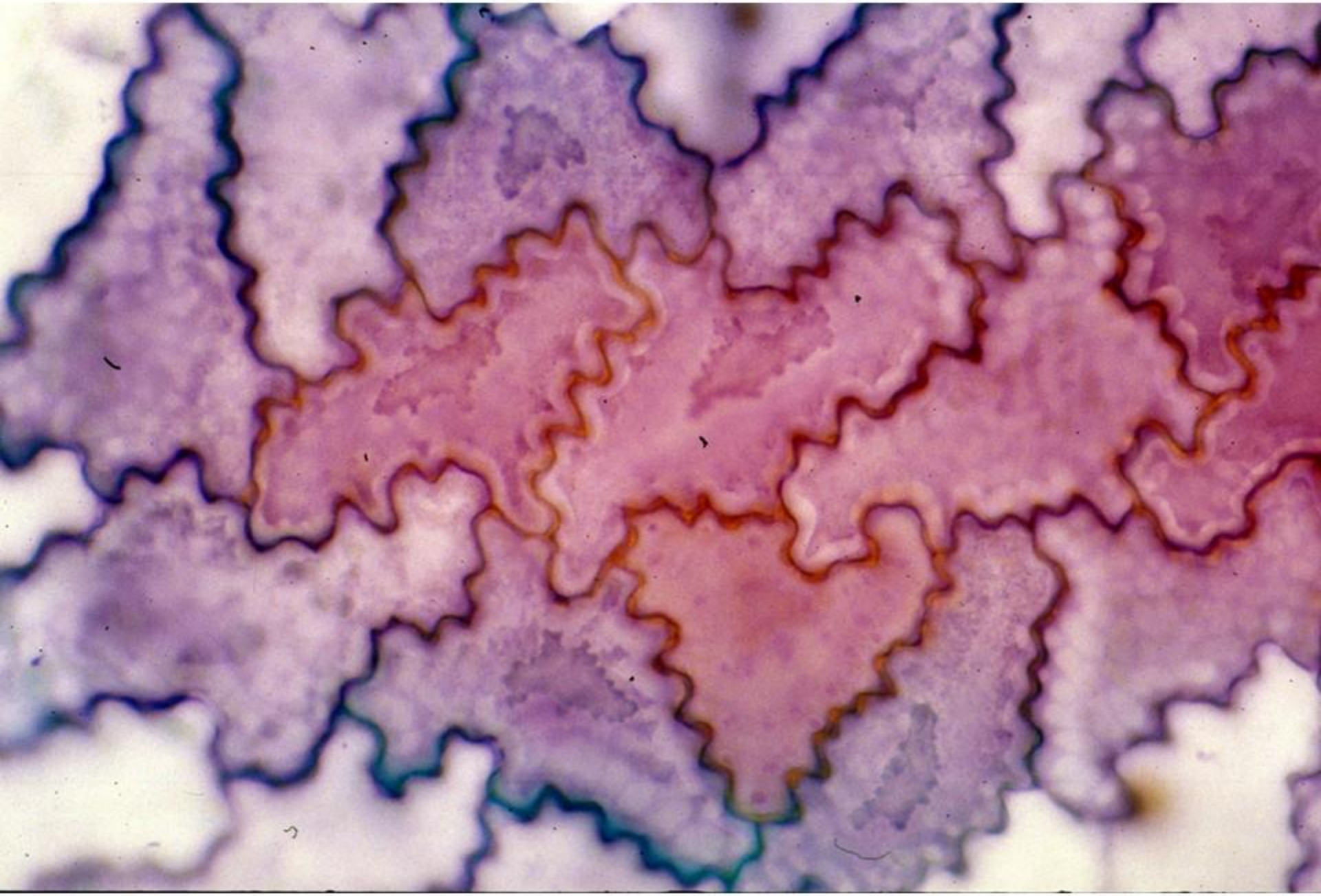
Results: Anal HPV infection is common in women but is relatively transient in most. The risk of anal HSIL and cancer varies considerably by risk group, with human immunodeficiency virus–infected women and those with a history of lower genital tract neoplasia at highest risk compared with the general population.

Conclusions: While there are no data yet to demonstrate that identification and treatment of anal HSIL leads to reduced risk of anal cancer, women in groups at the highest risk should be queried for anal cancer symptoms and required to have digital anorectal examinations to detect anal cancers. Human immunodeficiency virus–infected women and women with lower genital tract neoplasia may be considered for screening with anal cytology with triage to treatment if HSIL is diagnosed. Healthy women with no known risk factors or anal cancer symptoms do not need to be routinely screened for anal cancer or anal HSIL.

Key Words: anal cancer, HIV infection, women, lower genital tract neoplasia

(*J Lower Gen Tract Dis* 2015;19: S27–S42)

The overall objective of this report was to summarize current knowledge of anal cancer, anal squamous intraepithelial lesions (ASIL), and anal human papillomavirus (HPV) infection



Anal Cancer and AIN: Screening and Diagnosis

HPV-related lesions of the anal canal

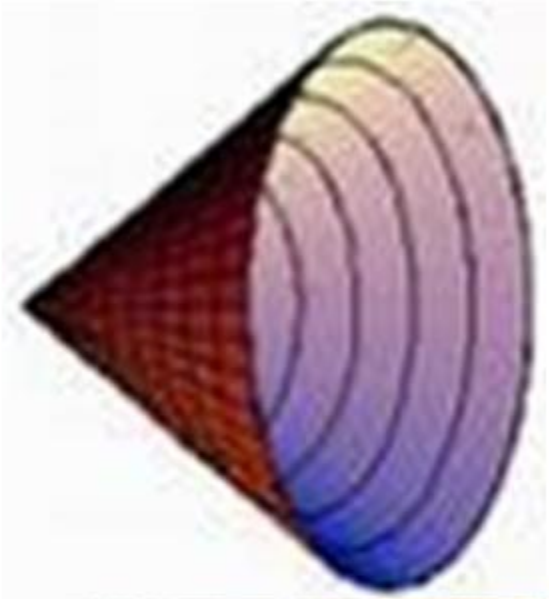
- Anal cytology
- ***Digital anal-rectal examination (DARE)***
- High resolution anoscopy (HRA)
- HRA-directed anal biopsy

- **Link screening to treatment!**

Digital Anorectal Exam (DARE)

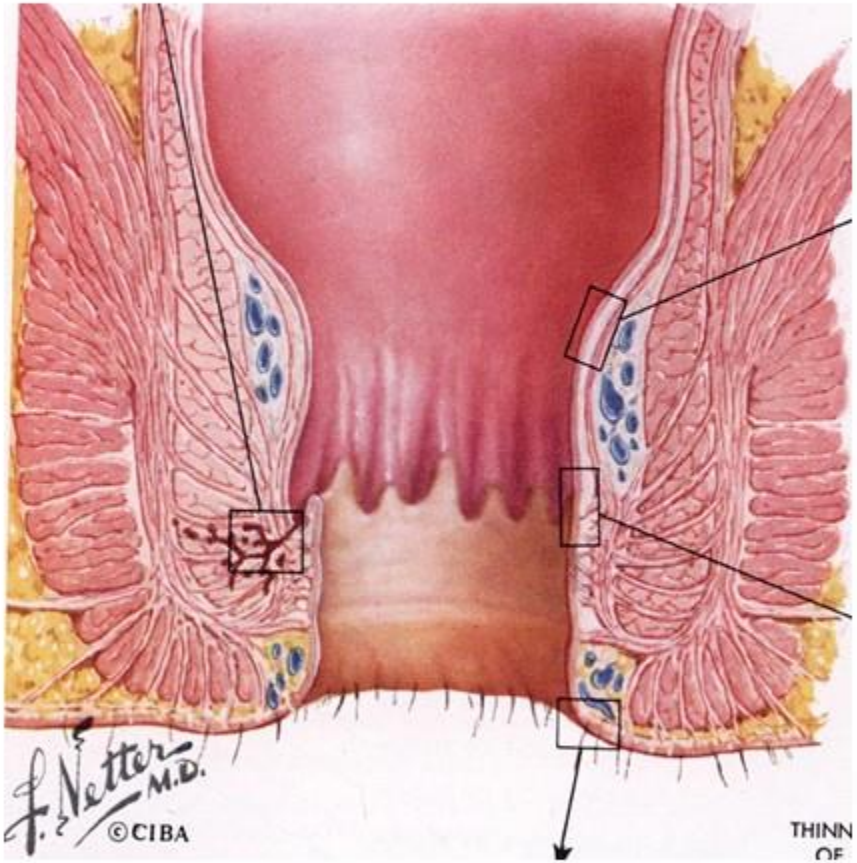
- Palpate for areas of:
  - Induration
  - Nodularity, etc
  - Pain
- This is the <u>cancer</u> screening test!
- Perform after anal cytology

Anal Cytology: Technique



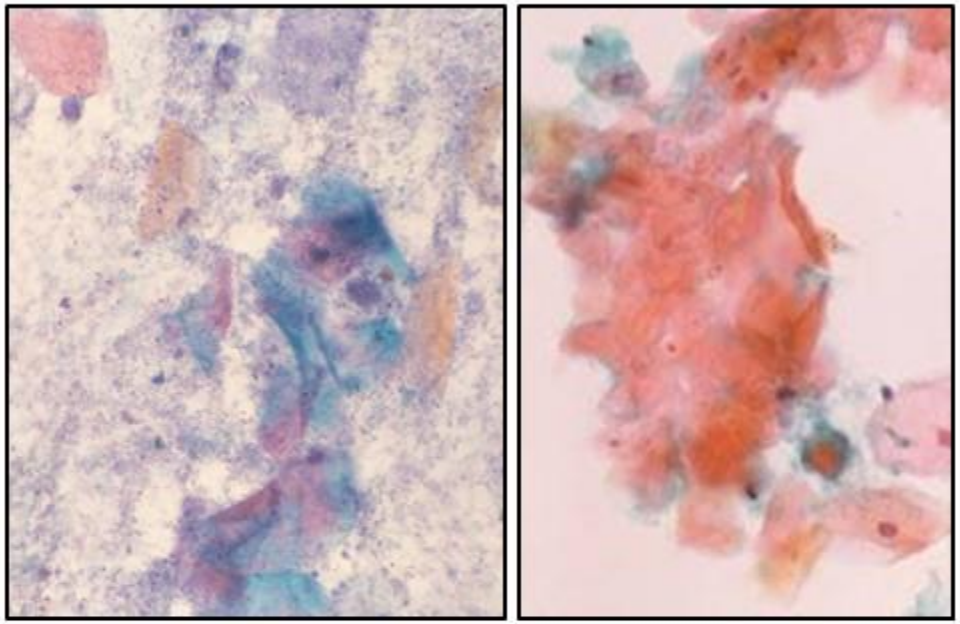
- Use moistened Dacron swab
  - Not on wood stick!
  - Do not use pre-scored swab!
- Insert into canal until resistance
  - Above anal verge to distal rectum
- Rotate / apply pressure to walls of canal while removing sampling device
- Liquid-based cytology or direct smear

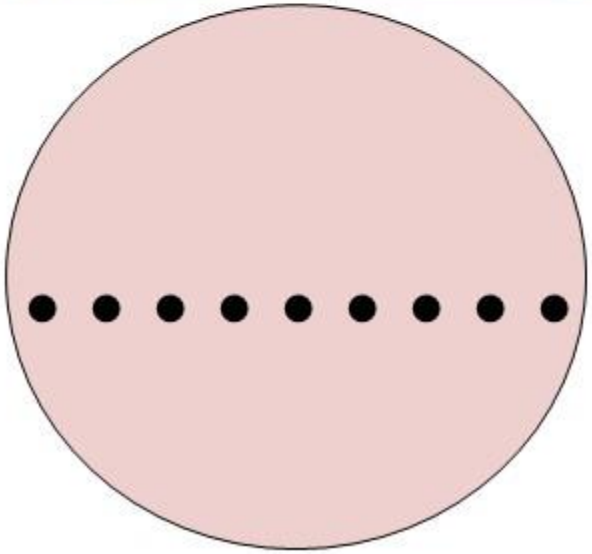
Anal Cytology: Goal



- Sample entire anal canal
- Anal transition zone
  - Analogous to cervical TZ
  - Squamous metaplasia
- Non-keratinized squamous mucosa
- Keratinized squamous mucosa

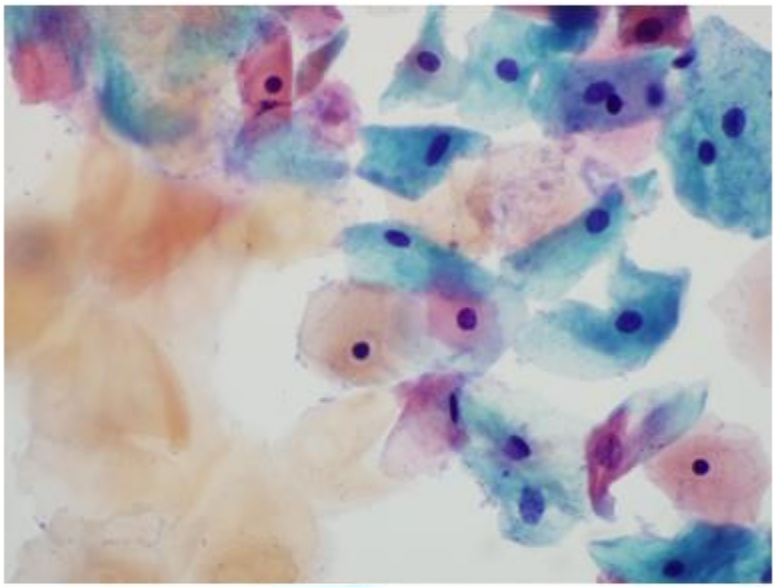
Anal Cytology: Specimen Adequacy



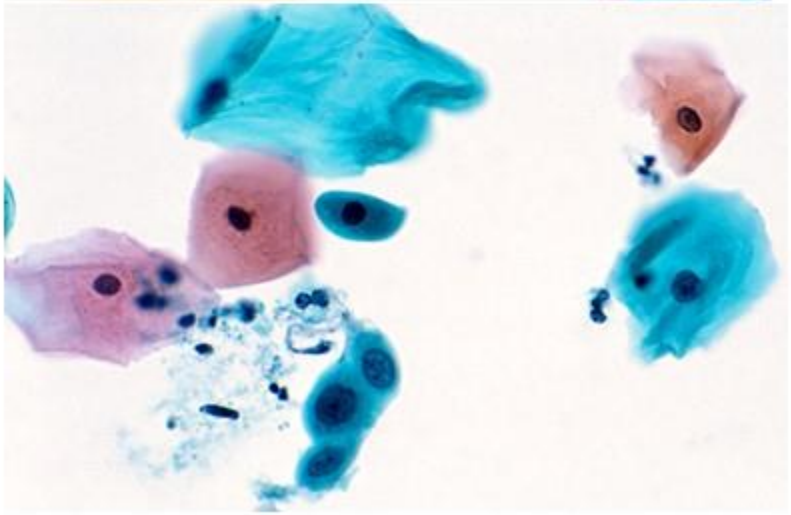


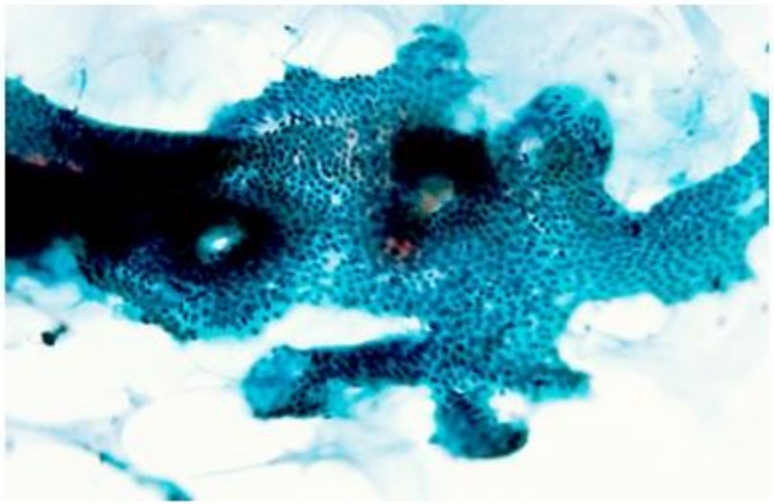
- Liquid vs conventional pap
  - Better cell preservation
  - ↑ Cellular harvest
  - ↓ Bacteria / fecal contamination
  - ↓ Mechanical / air-dry artifacts
- Minimum cellularity:
  - 2000-3000 nucleated squamous cells
- ThinPrep (20 mm):
  - 1 to 2 nucleated cells / hpf
- SurePath (13 mm):
  - 3 to 6 nucleated cells / hpf
  - > 6/hpf (Arain et al)

Anal Cytology: Normal Components

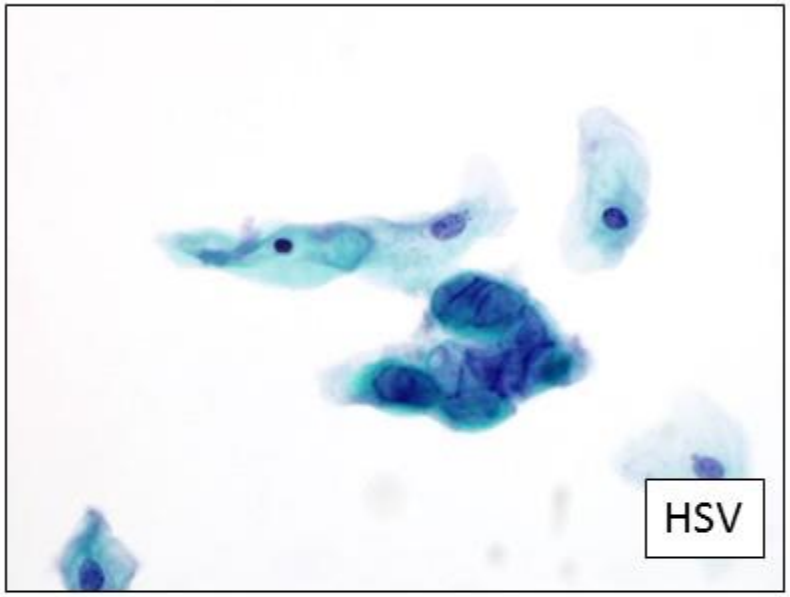


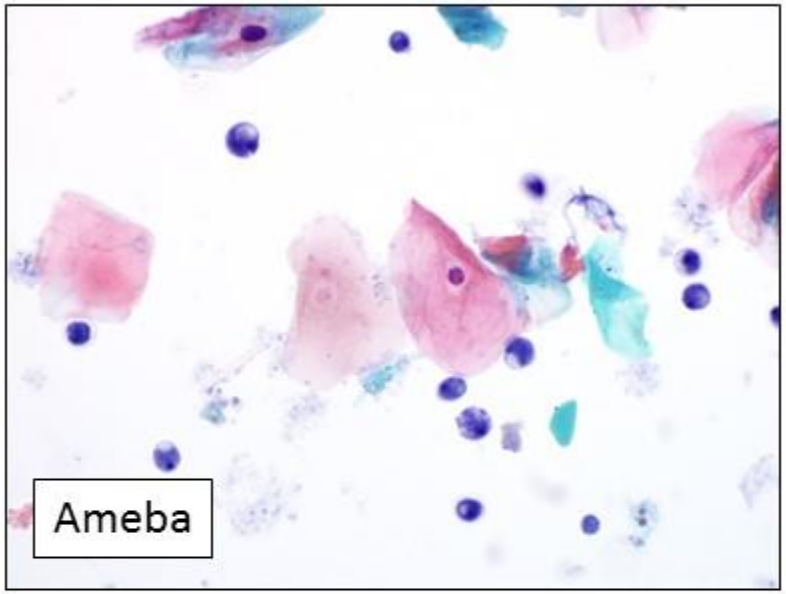
- **Transformation Zone components:**
  - **Rectal columnar cells**
  - **Squamous metaplasia**
- **Nucleated squamous cells**
- **Anucleate squames**

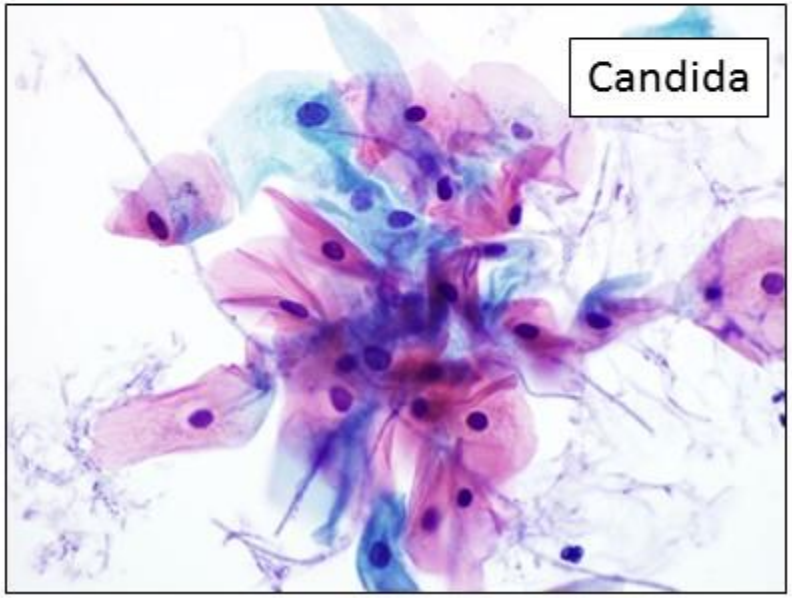


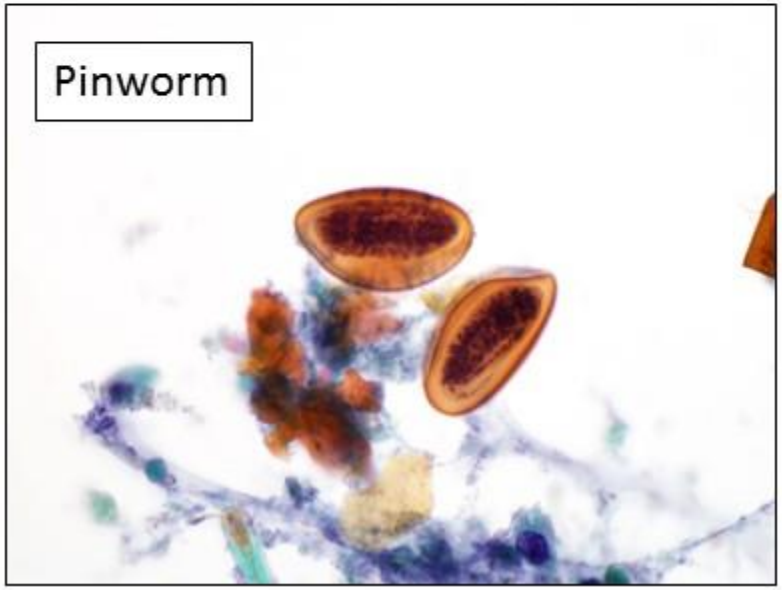


Anal Cytology: Organisms









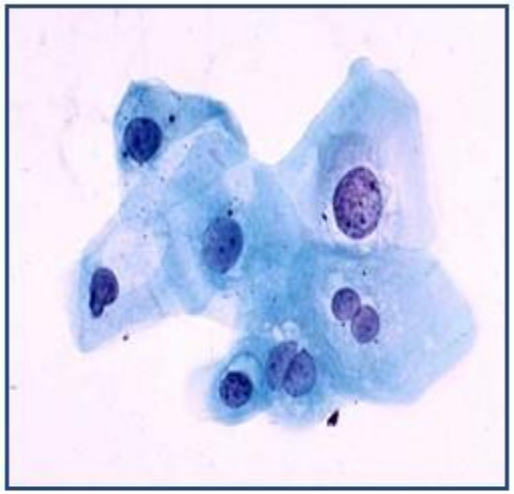
2001 Bethesda System: Epithelial Cell Abnormalities

- Squamous cell abnormalities
  - Atypical squamous cells
    - of undetermined significance (ASC-US)
    - Cannot exclude HSIL (ASC-H)
  - Low grade SIL (LSIL)
  - High grade SIL (HSIL)
  - Squamous cell carcinoma
- (Glandular cell abnormalities)

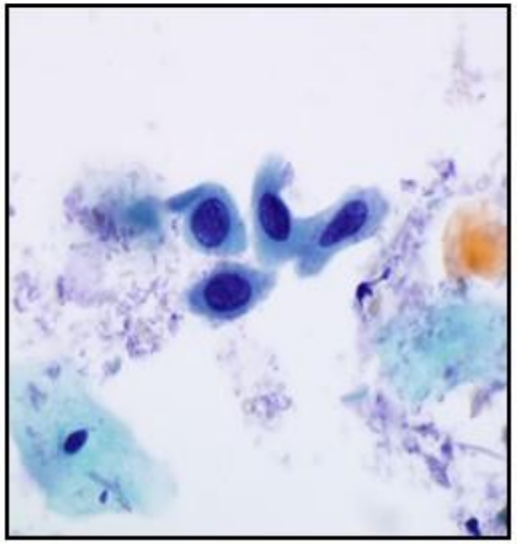
Anal Cytology: Squamous Atypia

- Atypical squamous cells that quantitatively or qualitatively are not sufficiently atypical to warrant an interpretation of LSIL or HSIL

- ASC-US
  - Suggestive of low grade SIL
- ASC-H
  - Cannot exclude high grade SIL

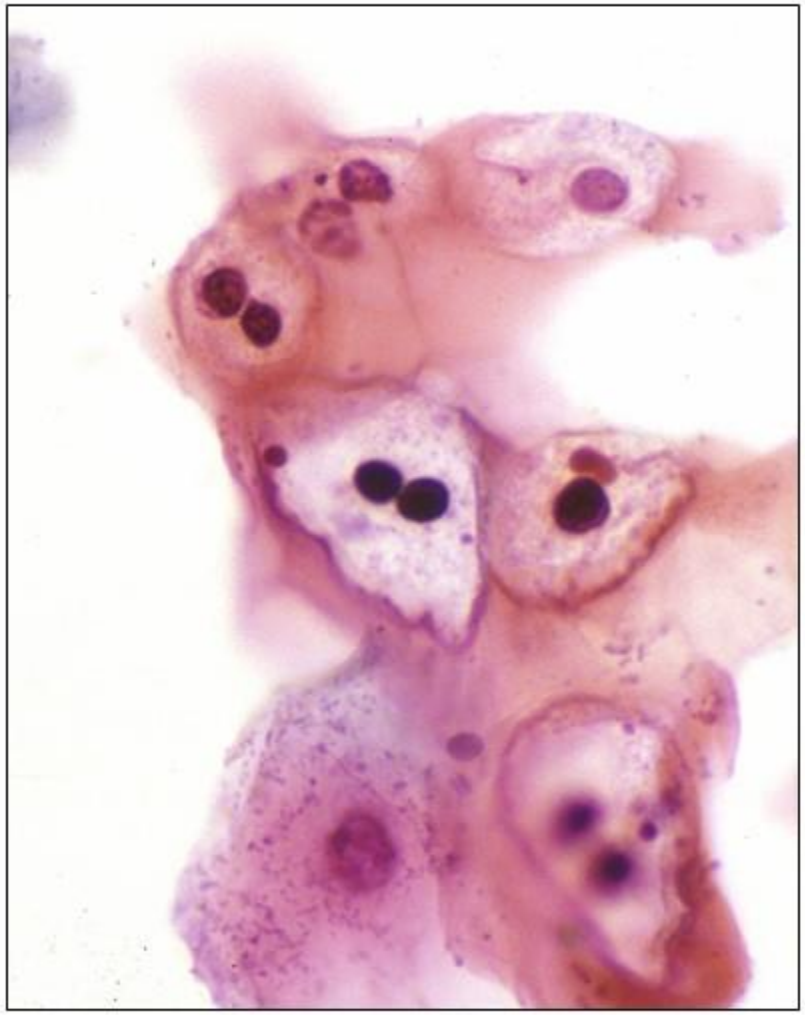


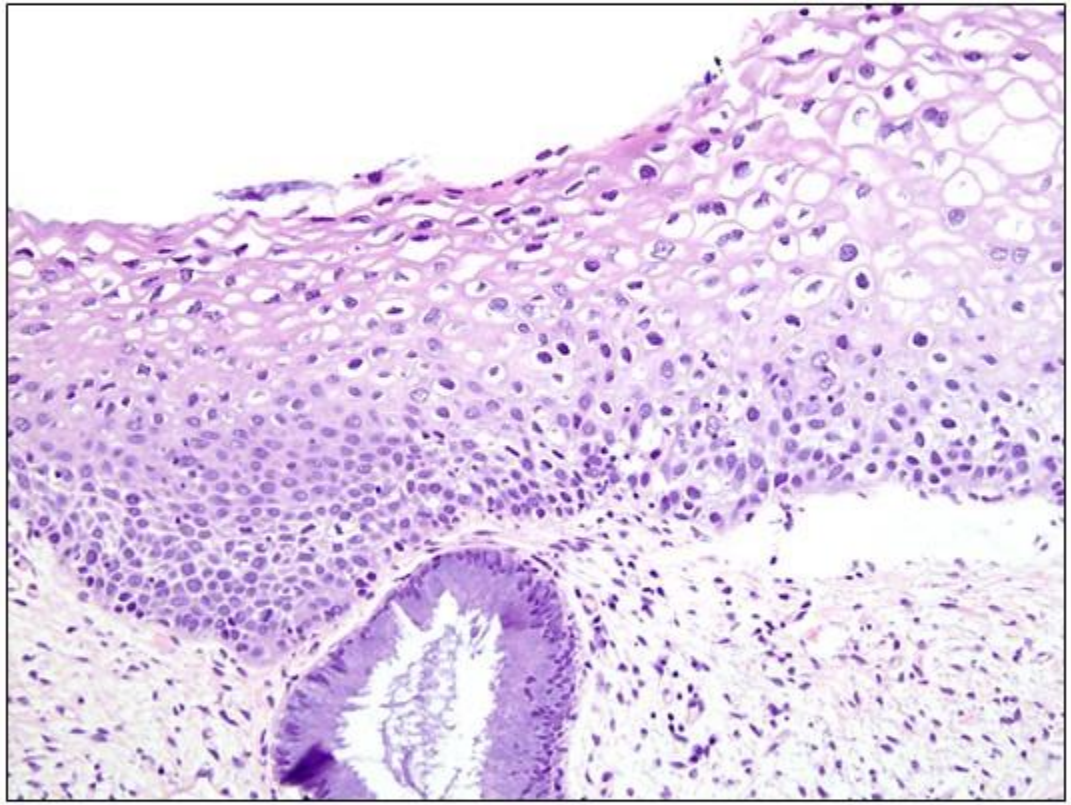
- ASC-US



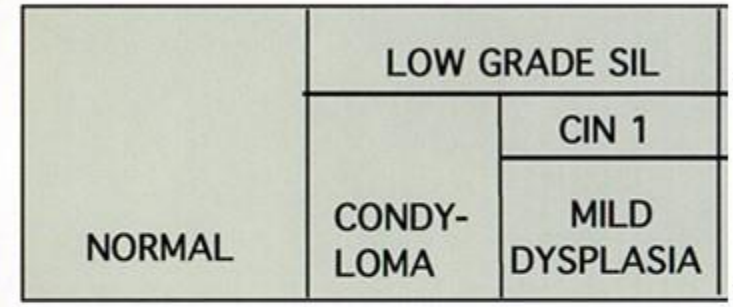
- ASC-H

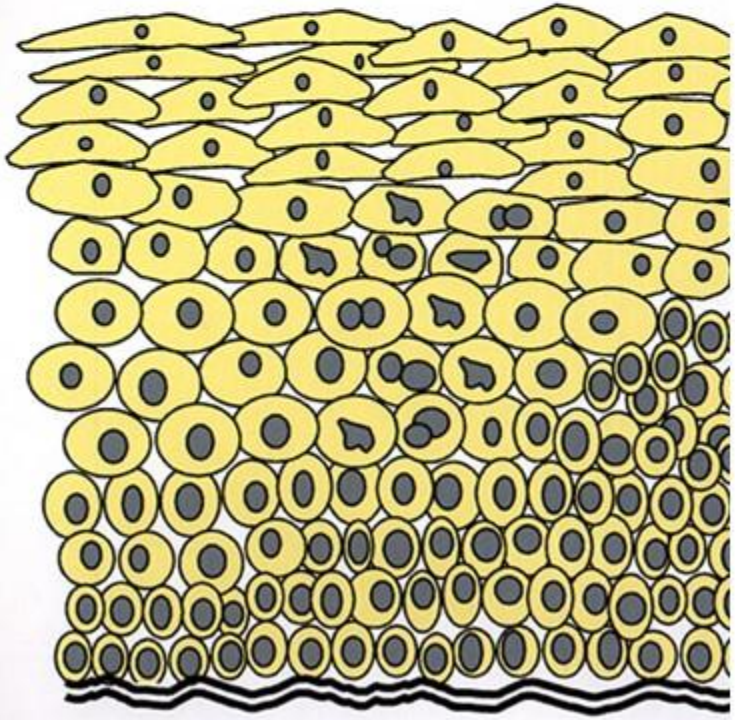
Anal LSIL





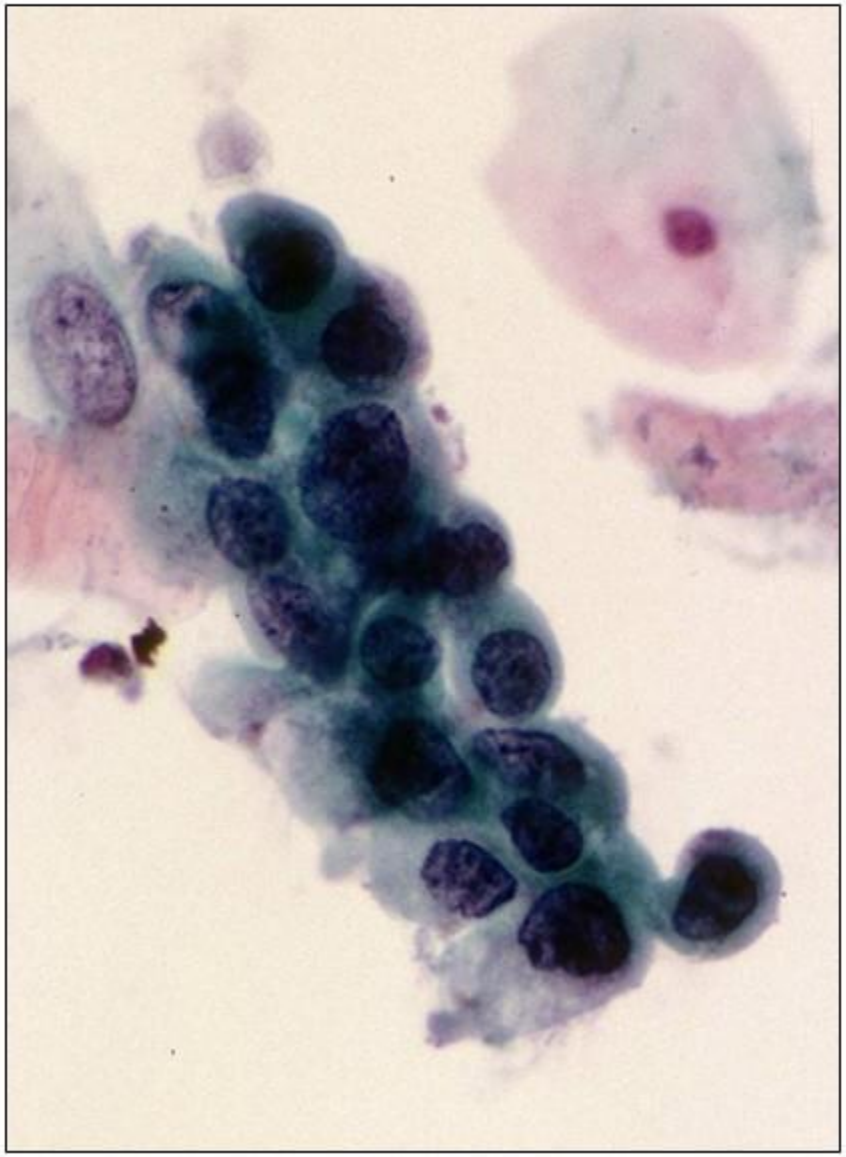
Low Grade Lesions

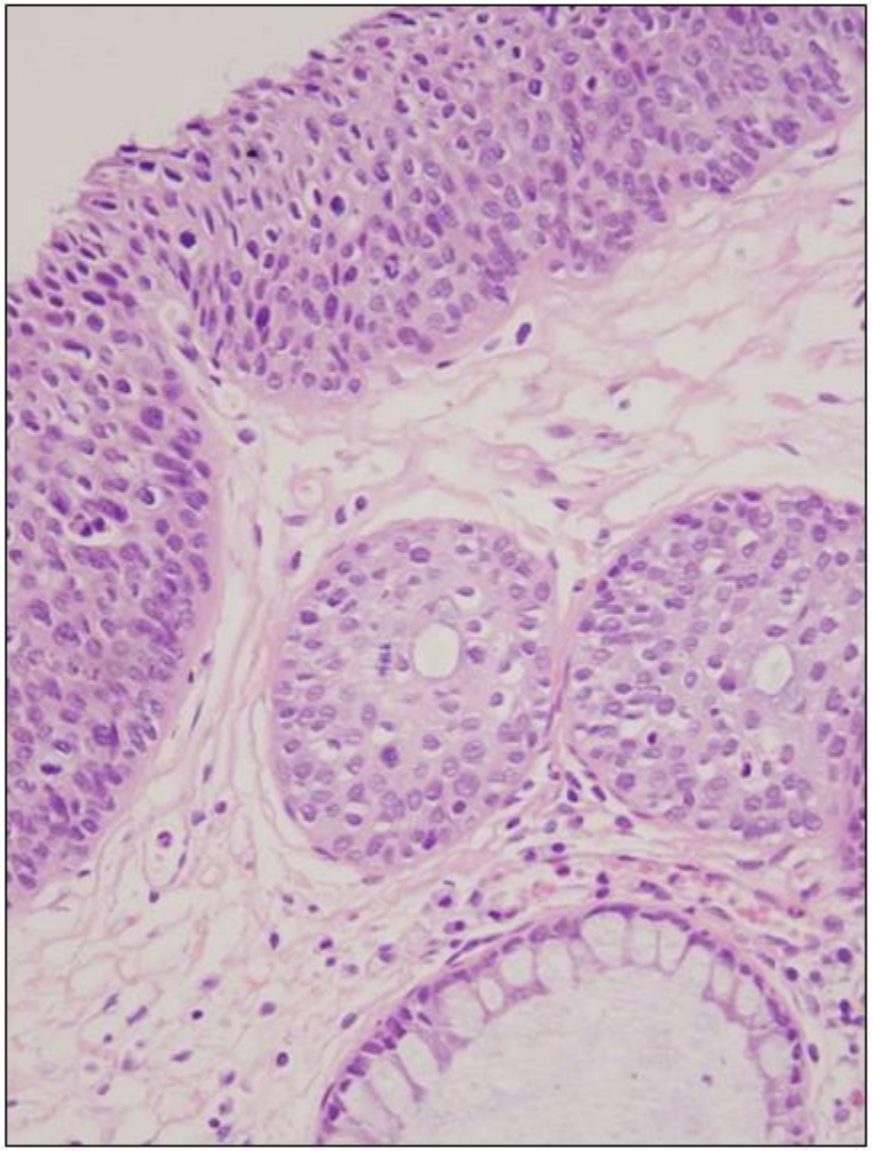




- Caused by <u>both</u> high-risk and low-risk viral types
- Most of these will *spontaneously regress,* if immunocompetent
- <u>*Productive*</u> HPV infections
- In general, close clinical observation <u>without</u> treatment is recommended

Anal HSIL

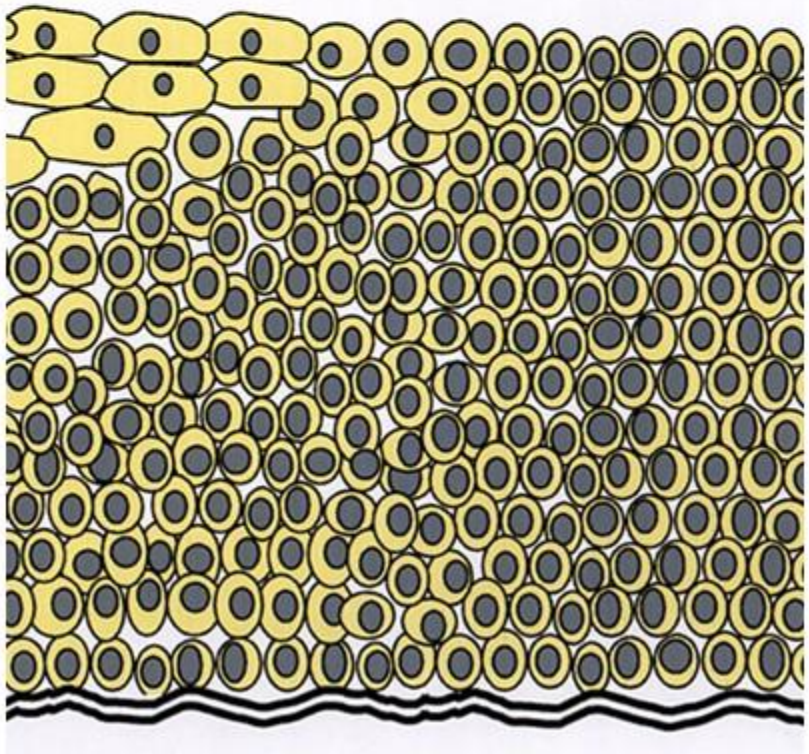




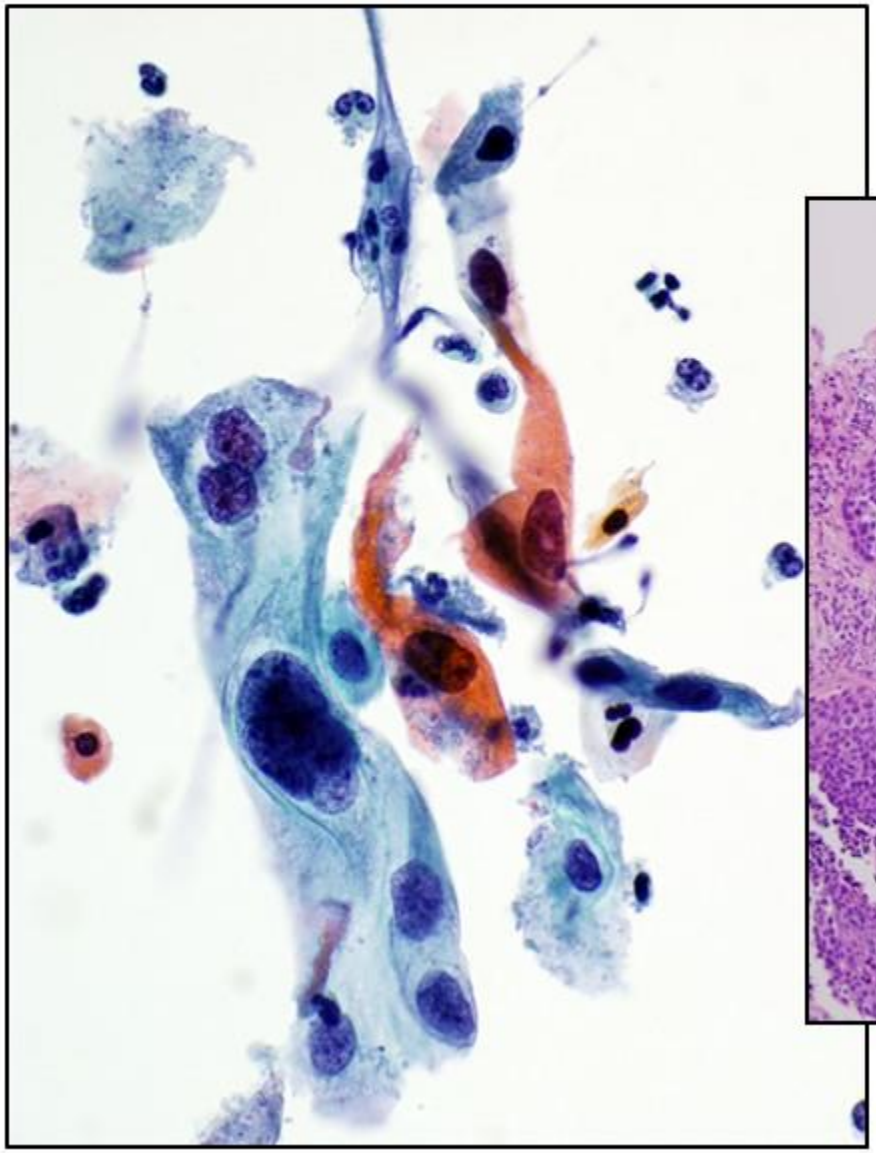
High Grade Lesions

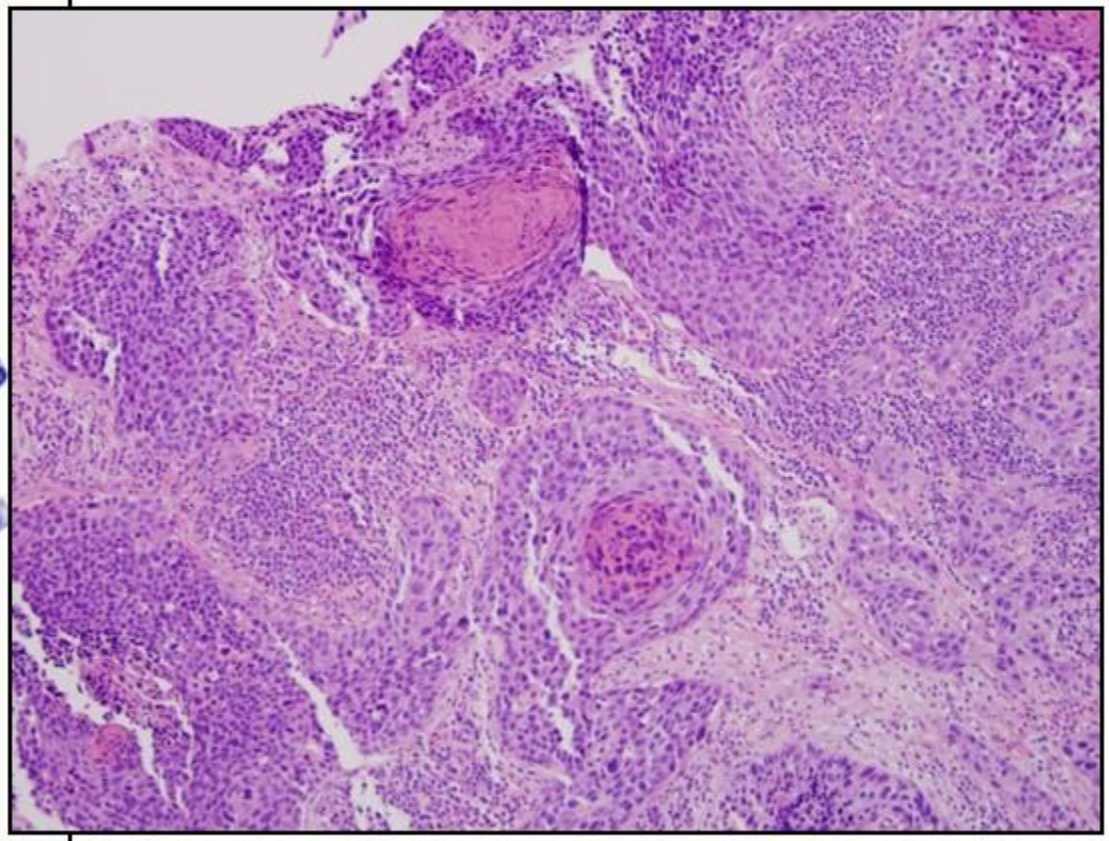
- Caused by high-risk viral types
- Most will *persist or progress*
- With time, become *integrated* HPV infections
- Goal: Treat precancer before it has the opportunity to develop into cancer

HIGH GRADE SIL		
CIN 2	CIN 3	
MODERATE DYSPLASIA	SEVERE DYSPLASIA	IN SITU CARCINOMA



Squamous cell carcinoma



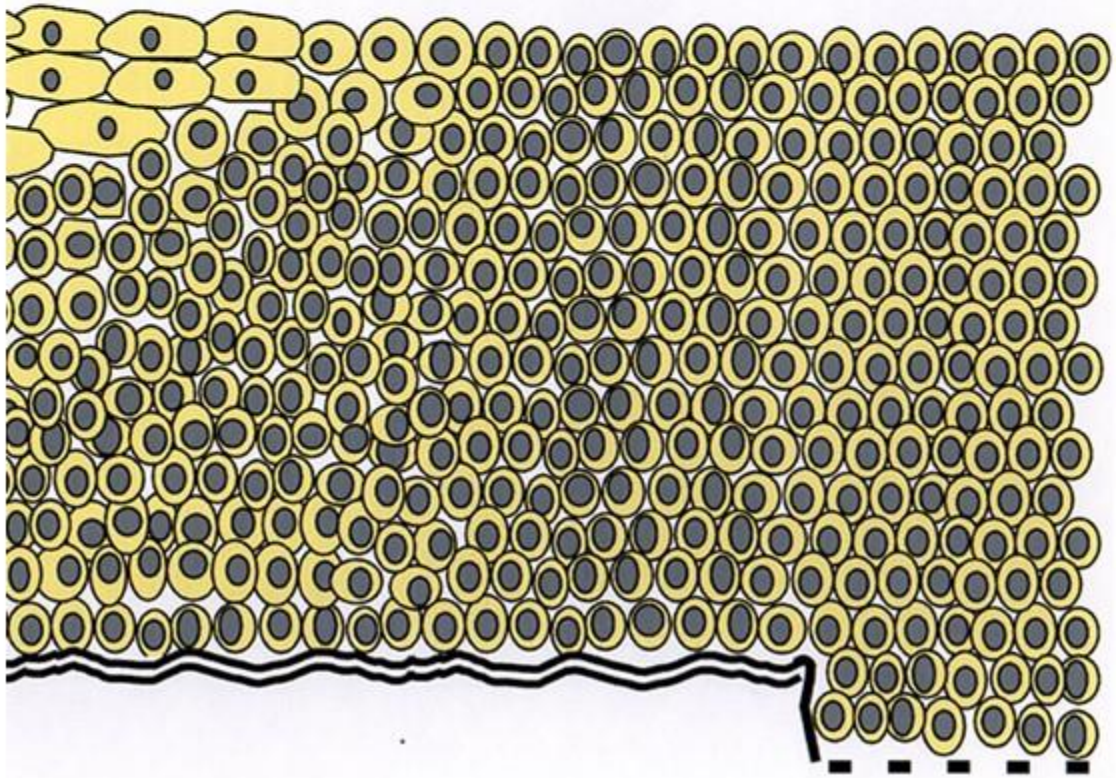


Anal Squamous Cell Carcinoma

- Invasive cancer
- Associated with high grade lesions

- No defined counterpart to cervical microinvasion
- T1 = 2 cm or less
- Not subdivided

HIGH GRADE SIL			
CIN 2	CIN 3		
MODERATE DYSPLASIA	SEVERE DYSPLASIA	IN SITU CARCINOMA	INVASIVE CANCER



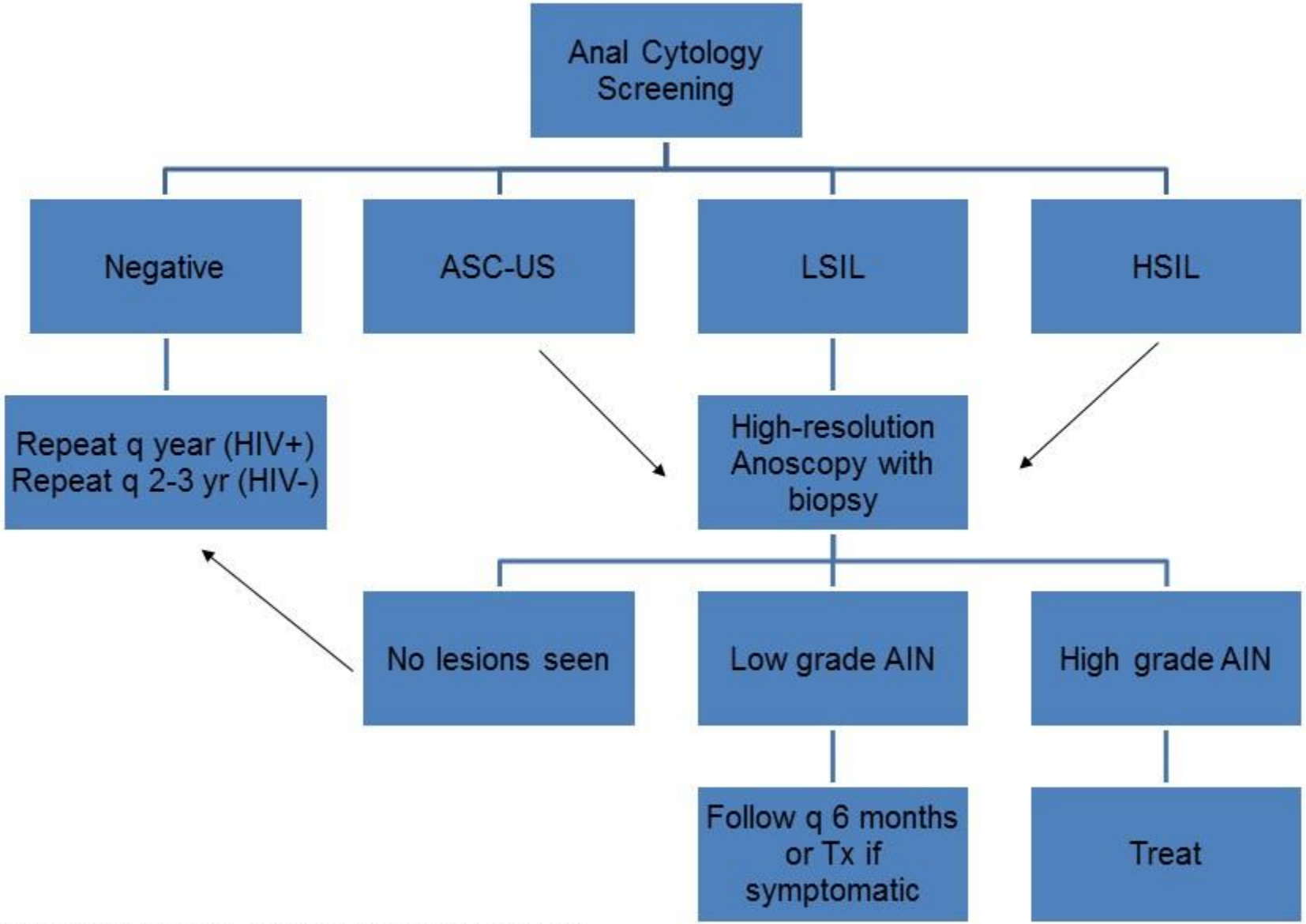
Anal Cytology: Sensitivity and Specificity

	Sensitivity*	Specificity*
HIV+	81%	63%
HIV-	50%	92%

*Includes ASCUS, Conventional smears

Palefsky et al, J AIDS & Hum Retrovir 1997, 14:415-22.

Screening for Anal SIL



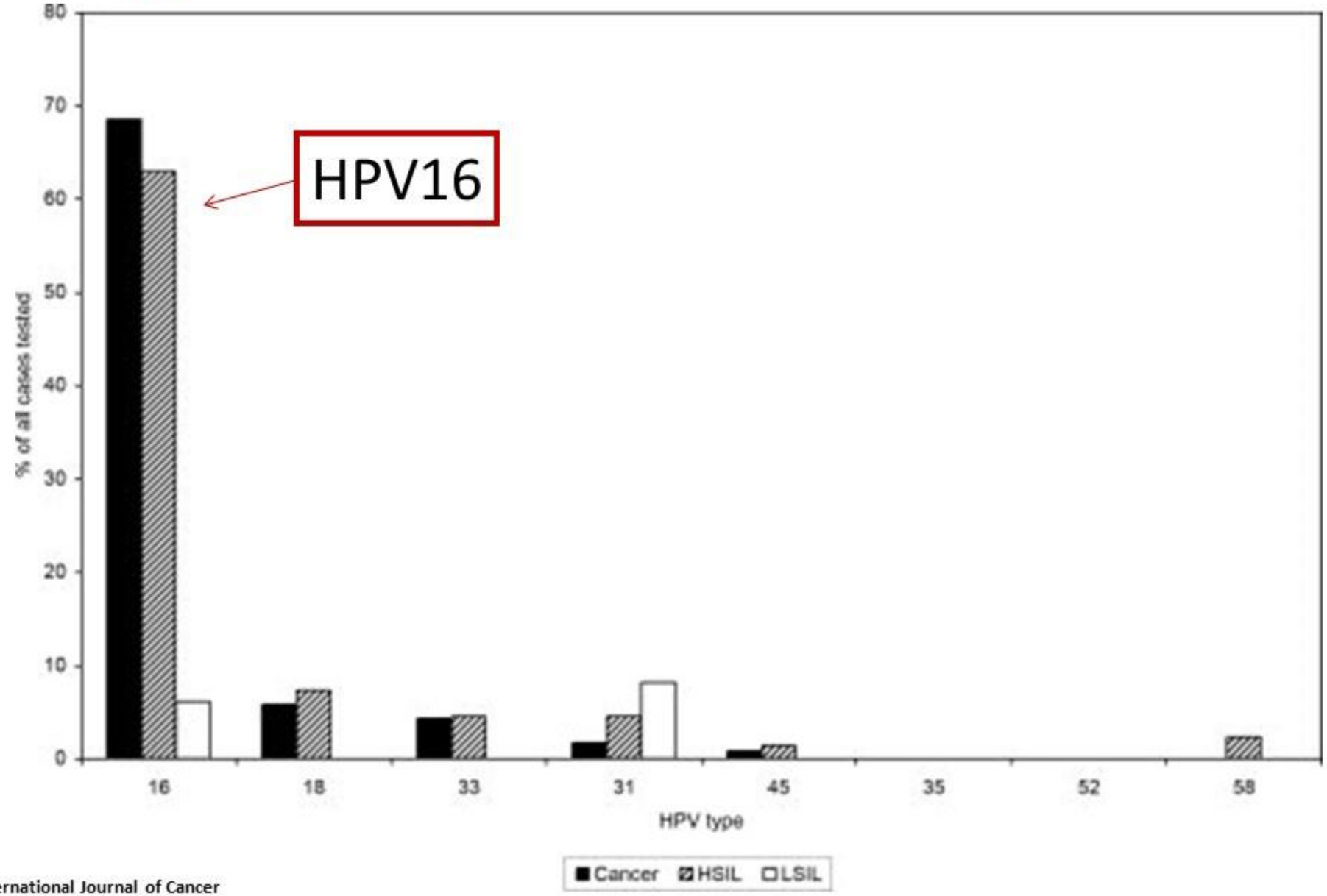
Chin-Hong and Palefsky. HIV/AIDS 2002;35:1127-1134

Anal HPV Testing?

- No FDA-approved HPV test for anus
- Laboratories need to validate for this site

- Screening and triage?
  - Mixed reports of usefulness
  - High prevalence of HPV in at-risk populations
  - High negative predictive value
    - May be useful in post-HRA and post-treatment management
  - HPV 16 genotyping?

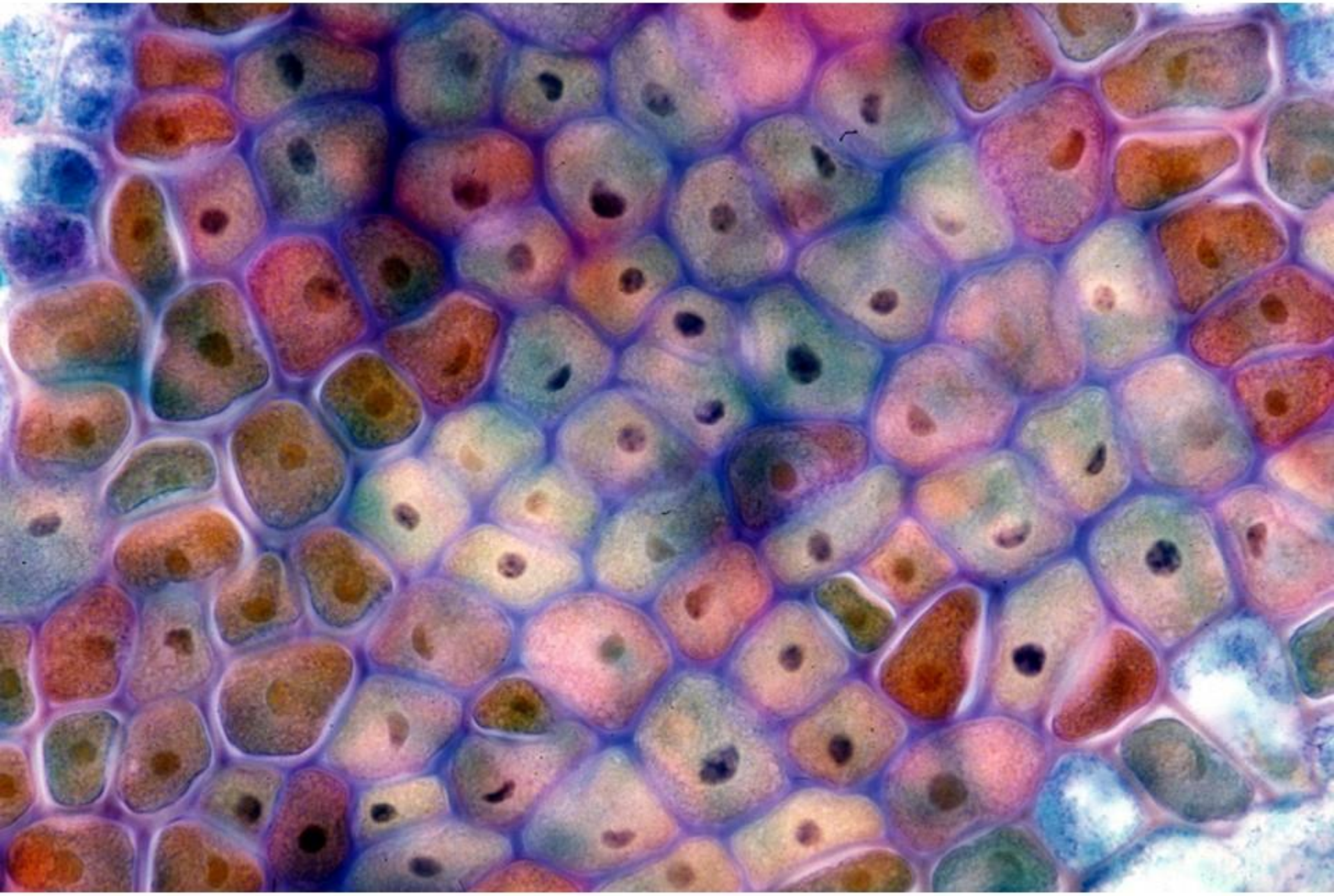
HPV type distribution in Anal Cancer and Precancer



International Journal of Cancer
Volume 124, Issue 10, pages 2375-2383, 15 DEC 2008 DOI: 10.1002/ijc.24215 http://onlinelibrary.wiley.com/doi/10.1002/ijc.24215/full#fig3

Anal Cytology / Histology

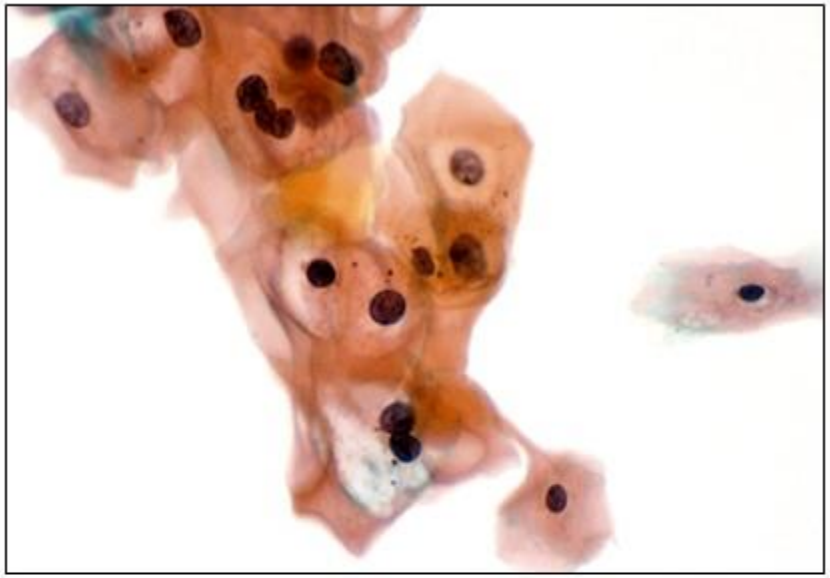
- Anal cytology used as screening test!
- Anal cytology often under-represents grade of disease
- Positive predictive value of HSIL is very good
- Anal cytology is complimentary to:
  - HRA and
  - Histology and
  - *Digital examination*
- "Gold Standard": HRA-guided biopsy

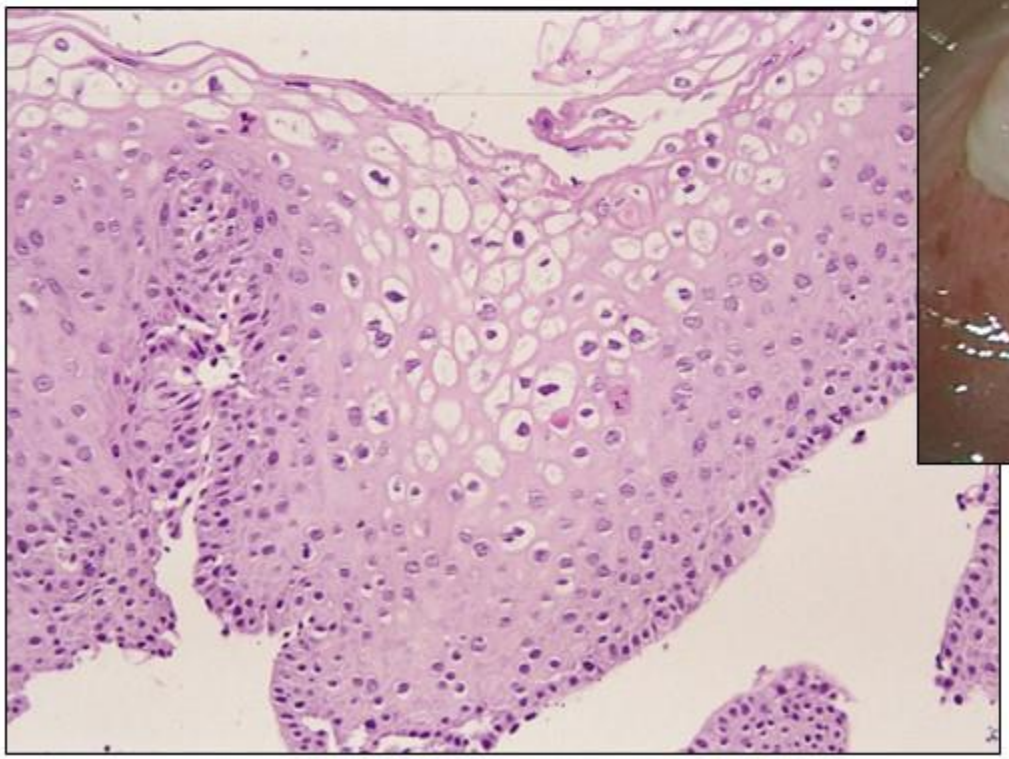


High-resolution Anoscopy

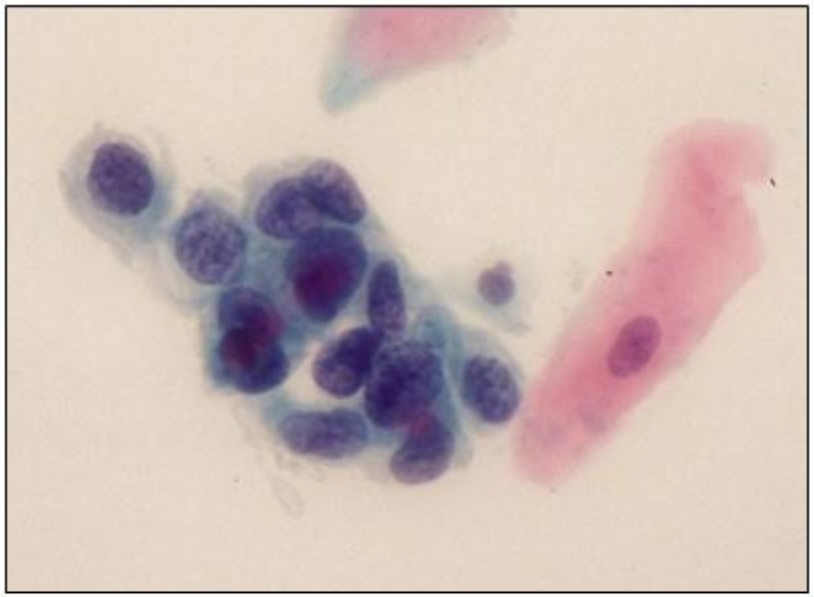
- Acetowhite lesions
- Contour changes
- Vascular changes

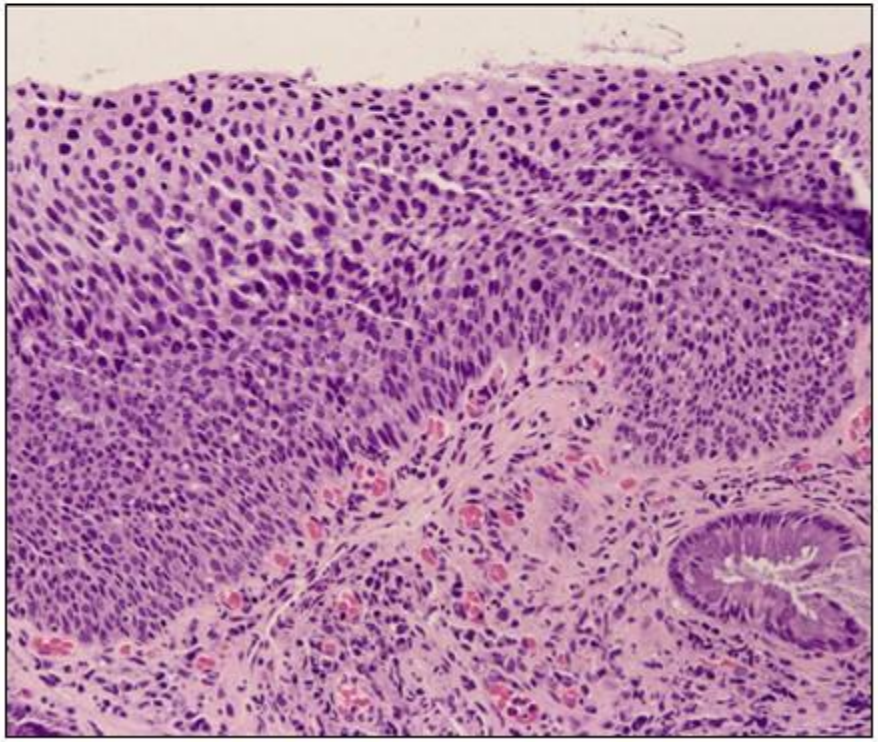
Low Grade

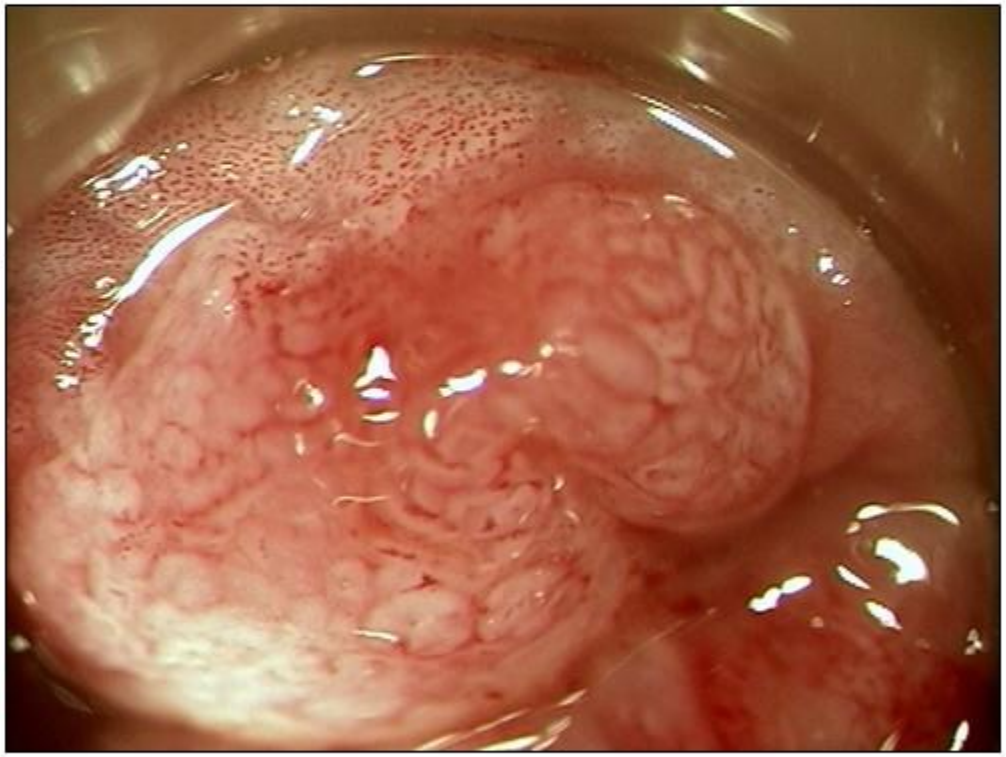




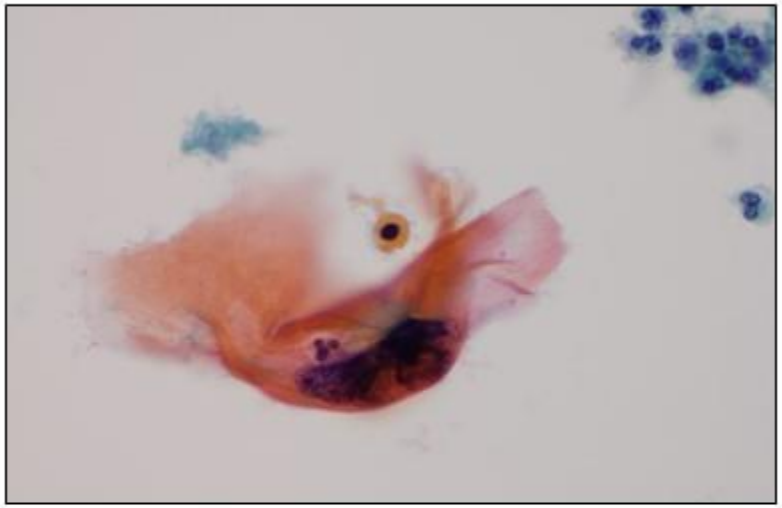
High Grade

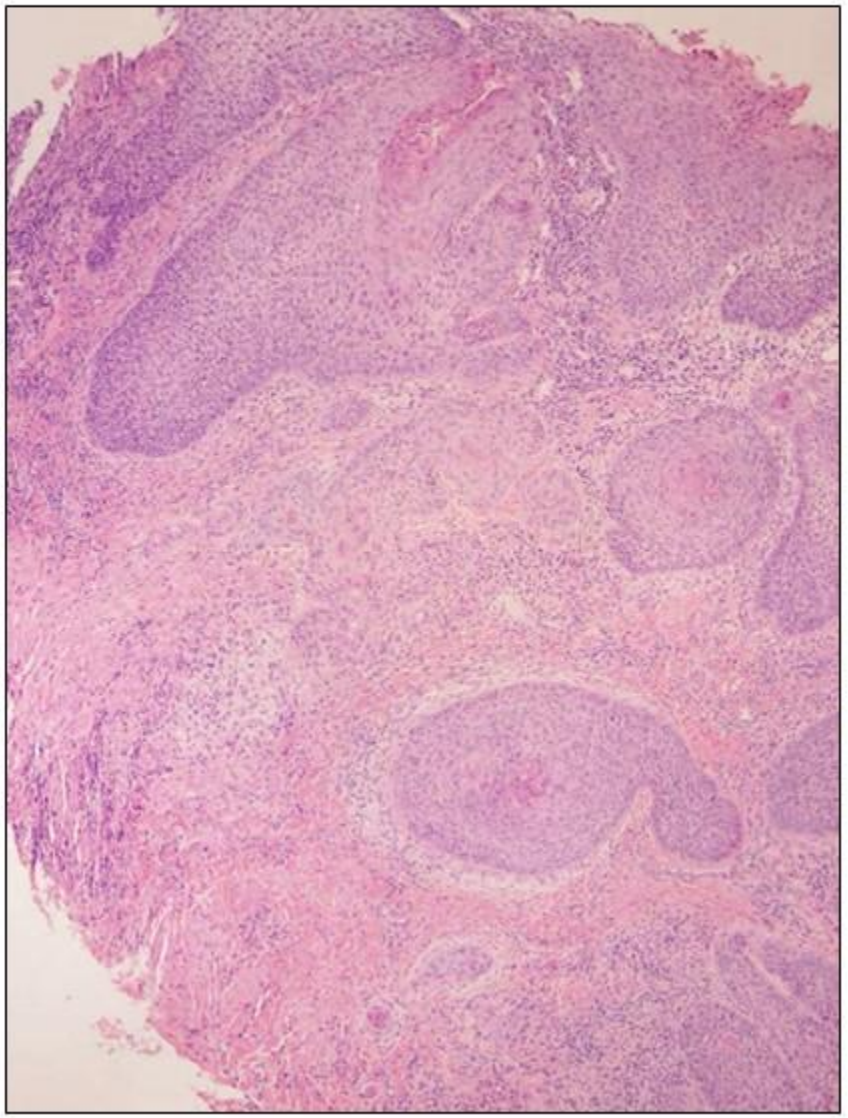






Anal Squamous Cell Carcinoma





Anal Cancer

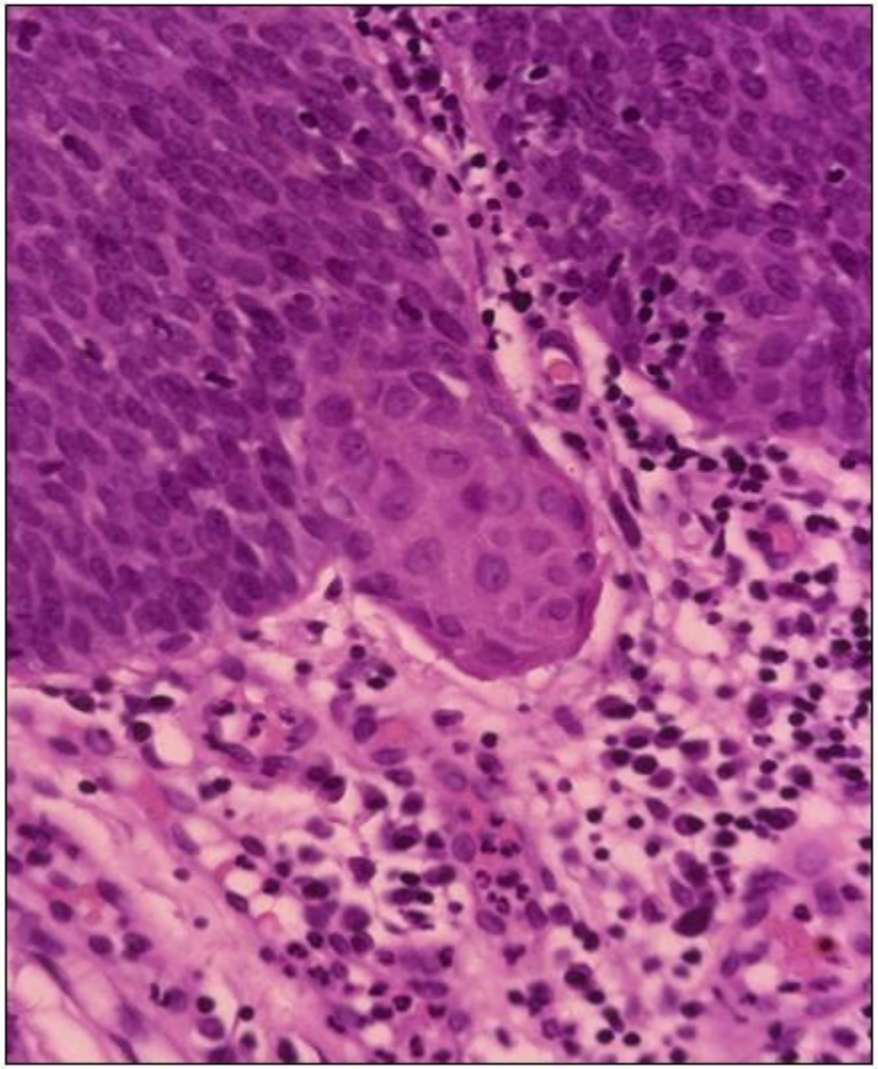
- Early detection makes a difference!
- Standard of care = Combined modality therapy

Stage at Diagnosis	Stage Distribution	5-year Survival
Localized (confined to primary site)	50%	80%
Regional (spread to regional lymph nodes)	29%	60%
Distant (cancer has metastasized	12%	30%
Unknown (unstaged)	*9%*	*56%*

Seer.cancer.gov

Superficially Invasive Anal SCC

- No defined counterpart to cervical micro-invasion
- CAP-ASCCP LAST Project
- SISCCA = superficially invasive squamous cell carcinoma
- ? Potentially amenable to conservative surgical therapy



Estimates of Anal Cancer Progression

- In HIV-infected patients with HSIL anal cytology, there is an estimated five year progression rate to invasive anal cancer of 1.7%.

- Machalek et al. calculated the theoretical progression rate to be 1 in 377 per year in HIV-infected MSM (compared with 1 in 4196 per year in HIV-uninfected MSM)

Cachay E, Agmas W, Mathews C. *HIV medicine.* Sep 6 2014.
Machalek DA, Poynten M, Jin F et al. Lancet Oncol 2012; 13: 487–500.

Current Unknowns

- Is effective treatment of anal HSIL possible?
- Will anal screening and treatment of anal HSIL lower the incidence of anal cancer?
- ANCHOR: Large multisite trial in U.S.
  - HIV-infected men and women
  - Biopsy proven anal HSIL
  - Treatment vs. non-treatment (active monitoring) arms

The Bad News

- The incidence of AIN and anal cancer is high among HIV-seropositive women and MSM (both HIV- and HIV+)
- HAART has limited positive effect on HPV-related neoplasia
- Evidence is mounting that the incidence of anal cancer will continue to rise among HIV-positive MSM

The Good News

- At-risk men and women should be considered for screening and treatment of anal HSIL
  - Treatment is improving!
- At-risk men and women should be screened for anal cancer with a digital rectal exam
  - Early detection of anal cancer has real benefits
- **HPV vaccines** have the potential to prevent anal HPV infection and ultimately, anal cancer

Photo by Alan Waxman, MD