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

Anal Cancer Rates by Birth Cohort

Rate per 100,000

Men
Women

Coming of age:
- Sexual revolution
- HIV epidemic

New cases in 2016: 8080
  5160 ♀
  2920 ♂
Deaths in 2016: 1080
  640 ♀
  440 ♂

Simpson J A D, Scholefield J H BMJ 2011;343:bmj.d6818
### HPV infection - attributable cancer in 2002: developed & developing countries

<table>
<thead>
<tr>
<th>Site</th>
<th>Attributable to HPV (%)</th>
<th>Developed countries</th>
<th>Developing countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total cancers</td>
<td>Attributable to HPV</td>
</tr>
<tr>
<td>Cervix</td>
<td>100</td>
<td>83,400</td>
<td>83,400</td>
</tr>
<tr>
<td>Penis</td>
<td>40</td>
<td>5200</td>
<td></td>
</tr>
<tr>
<td>Vulva, vagina</td>
<td>40</td>
<td>18,300</td>
<td></td>
</tr>
<tr>
<td>Anus</td>
<td>90</td>
<td>14,500</td>
<td>13,100</td>
</tr>
<tr>
<td>Mouth</td>
<td>3</td>
<td>91,200</td>
<td>2700</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>12</td>
<td>24,400</td>
<td>2900</td>
</tr>
<tr>
<td>All sites</td>
<td></td>
<td>5,016,100</td>
<td>111,500</td>
</tr>
</tbody>
</table>

**Screening vs. No Screening**
# Anal Cancer and Cervical Cancer

- **Cervical cancer in US:**
  - prior to Pap screening
  - currently

- **Anal cancer:**
  - women, general pop.
  - HIV- MSM*
  - HIV+ MSM*
  - HIV+ women

<table>
<thead>
<tr>
<th>Rates per 100,000</th>
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<tbody>
<tr>
<td>40-50 / 100K</td>
<td></td>
</tr>
<tr>
<td>8 / 100K</td>
<td></td>
</tr>
<tr>
<td>1.8 / 100K</td>
<td></td>
</tr>
<tr>
<td>35 / 100K</td>
<td></td>
</tr>
<tr>
<td>131 / 100K</td>
<td></td>
</tr>
<tr>
<td>30 / 100K</td>
<td></td>
</tr>
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</table>

*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
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)
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 cancer 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

- HSV
- Ameba
- Candida
- Pinworm
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
Low Grade Lesions

- Caused by both high-risk and low-risk viral types
- Most of these will *spontaneously regress*, if immunocompetent
- *Productive* HPV infections
- In general, close clinical observation without 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
Squamous cell carcinoma
Anal Squamous Cell Carcinoma

- Invasive cancer
- Associated with high grade lesions

<table>
<thead>
<tr>
<th>HIGH GRADE SIL</th>
<th>CIN 2</th>
<th>CIN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE DYSPLASIA</td>
<td>SEVERE DYSPLASIA</td>
<td>IN SITU CARCINOMA</td>
</tr>
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</table>

- No defined counterpart to cervical microinvasion
- T1 = 2 cm or less
- Not subdivided
### Anal Cytology: Sensitivity and Specificity

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity*</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>81%</td>
<td>63%</td>
</tr>
<tr>
<td>HIV-</td>
<td>50%</td>
<td>92%</td>
</tr>
</tbody>
</table>

*Includes ASCUS, Conventional smears

Screening for Anal SIL

Anal Cytology Screening

- Negative
  - Repeat q year (HIV+)
  - Repeat q 2-3 yr (HIV-)
- ASC-US
- LSIL
  - High-resolution anoscopy with biopsy
  - No lesions seen
- HSIL
  - Low grade AIN
  - High grade AIN
  - Follow q 6 months or Tx if symptomatic
  - Treat

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

HPV16
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

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage Distribution</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site)</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>12%</td>
<td>30%</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>9%</td>
<td>56%</td>
</tr>
</tbody>
</table>
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)

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