HPV Spectrum Update 2014:
Cervical, Oropharyngeal, Anal Cancer in Women

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Onset, Massachusetts

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• FNP for 35 years specializing in Women's Health
• Newton Wellesley ObGyn, Massachusetts
• Doctoral student, Rocky Mountain University, Provo, Utah
• Certified North American Menopause Practitioner (CNMP)
• 2013 Lifetime Achievement Award, Mass Coalition of NPs
• Co-author 2012, “Fast Facts About The Gyn Exam for NPs”
• Co-author, 2010, “Advanced Health Assessment of Women; Skills & Procedures” both by Springer publishing
• Visiting Scholar - Boston College
• Fellow in AANP, American Assoc. of Nurse Practitioners
• Owned practice for 12 years in Cambridge, Mass (1984-1995)
• Worked in Bethel, Alaska for 7 years (1992-1999)

Mimi Secor, MS, M.Ed, FNP-BC, FAANP
Disclosure

Speaker- Genpath, Shionogi
Objectives (No pharm credits)

- Discuss current epidemiology of cervical cancer. 15 minutes
- Describe updated cancer screening guidelines and rationale for these guidelines, anal and oral cancer too 45 minutes
- Explain new 2013 ASCCP follow-up guidelines for abnormal Pap smear findings. 30 minutes
HPV 2014 Update: What’s New?

- Vaccine Update:
- Cervical Cancer Screening Guidelines: New 2012
- F/u of Abnormal Pap Guidelines: New 2013
- External Genital Warts:
  - May harbor high grade lesions
- Anal Cancer Screening: Controversial
- Oral Cancer Association: The New STI
Estimated Prevalence of STDs in the US
20 Million New Infections a Year!

Genital Herpes
50 Million+

Chlamydia
3 Million

Hepatitis B
1.25 Million

HIV/AIDS
1.2 Million

Human Papillomavirus
20 Million

References:

Trends in oral cavity, pharyngeal, oesophageal and gastric cancer mortality rates in Spain, 1952-2006:

- Together, oral cavity and pharyngeal cancers ranked 8th in number of NEW cancer cases & DEATHS


A Little Coitus Never “Hoitus”

Teens “hooking up”
Friends with “benefits”

Married men, having sex with men
living on the “down low”
HPV: Introduction

- Most common STI in US
- Cause of cervical cancer
- Associated with external genital warts, and cancer of the penis, vagina, vulva, anus & oropharynx!


HPV Associated Cancers – US 2007
American Cancer Society

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Cancers</th>
<th># Cases Attributable to HPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,150</td>
<td>11,150 (100%)</td>
</tr>
<tr>
<td>Penis</td>
<td>1,280</td>
<td>512 (40%)</td>
</tr>
<tr>
<td>Vulva/Vagina</td>
<td>5,630</td>
<td>2,252 (40%)</td>
</tr>
<tr>
<td>Anus</td>
<td>4,650</td>
<td>4,185 (90%)</td>
</tr>
<tr>
<td>Airway</td>
<td>24,540</td>
<td>9,380 (38%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>47,250</td>
<td>24,479 (12%)</td>
</tr>
</tbody>
</table>

HPV Vaccine Update: Girls & Boys
Ages 9-26; Three Doses @ 0, 2, 6 months

Girls, Women: 2 doses may provide protection, ? duration
- Quadrivalent (Gardasil): FDA approved 2006
  HPV Vaccine 6, 11, 16, 18, by Merck
- Bivalent (Cervarix): FDA approved 2009
  HPV Vaccine 16, 18, by Glaxo Smith Kline

Boys, Men:
- Quadrivalent (Gardasil) for MEN: Ages 9-26 years
  - FDA approved 2009
  - Prevents Genital Warts, MAY prevent “Anal Cancer”!

Recommendations by CDC & ACIP
Advisory Committee on Immunization Practices of CDC

New: 9-Valent HPV Vaccine by Merck

- Containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58
- Under investigation


Flasher Pumpkin
NEW- March, April 2012: Cervical Cancer Screening Guidelines

Citations:

2012: NEW Cervical Cancer Screening Guidelines

- **Ages 21-29**
  - 1st Pap at age 21
  - Repeat every 3 years*
- **Age >30 years:** *if low risk
  - Pap and HPV = Primary screening
  - If both negative, repeat every 5 years
  - Pap ONLY = every 3 years
- **Age 65 years:** MAY STOP (if negative history)

*If Low Risk = NO history of CIN 2, CIN 3, HIV+, immunocompromised, DES


Age to START Screening for Cervical Cancer

Age 21

Age to Start Cervical Cancer Screening Factors to Consider

- HPV infections are common in young women
- AND frequently result in abnormal Pap results

- Evaluation of minor cytological abnormalities:
  - Is expensive
  - Anxiety producing
  - Can lead to unnecessary treatments: LEEP's, etc.
  - Can cause infertility, preterm labor


Clinical Uses of HPV Testing High-risk types: NEW 2012

- ASC-US management in women age ≥21 years old
- Pap plus HPV for screening women ≥ 30 years
  Primary Screening, Co-testing
- HPV testing ALONE is NOT recommended

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Guidelines: Screening Post-Hysterectomy

ACS, ACOG, USPSTF Guidelines

- Recommend against routine screening if hysterectomy performed for benign disease
- AND who have no history of high-grade CIN

Guidelines: Age may Stop Cervical Cancer Screening

- 65 years old*

* If no history of abnormal Paps


2013 ASCCP: Essential Changes

- More strategies incorporate "co-testing" to reduce follow-up visits.
- "Pap-only" strategies are now limited to women younger than 30 years.
- BUT co-testing is expanded even to women younger than 30 years in some circumstances.
- Women aged 21-24 yr are managed conservatively!
ASCCP 2013: Essential Changes

- HPV-negative & ASC-US should be followed with co-testing at 3 years rather than 5 years.

- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating HPV co-testing.

Cytology “Negative”, BUT Endocervical Cells Transformation Zone (ECC, TZ) Absent, Insufficient:

- 21-29 years = Routine Screening,
- > 30 years = HPV Testing Preferred (WHY?)

Unsatisfactory Cytology: NO READING
Repeat Cytology 2-4 months
HPV + Positive = Colpo or Repeat Pap
LSIL: Pregnant Women
Colpo Preferred

Management of Pregnant Women with Low-grade Squamous Intraepithelial Lesion (LSIL)

Pregnant Women with LSIL

- Colposcopy Preferred
- Rule Out HSIL (colposcopic, histologic, or cytologically suspected CIN2 or cancer)
- Pregnant women with no cytologic, histologic, or colposcopically suspected CIN2 or cancer

Postpartum follow-up

ASC-H, Cannot Rule Out HSIL:
(High Grade Squamous Intraepithelial Lesion)
Ages 21-24, Colpo for ALL

Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

- Two consecutive cytology negative results
- No high grade dysplasia/abnormality
- Biopsy results
- HSIL

Other findings

- CIN2
- CIN3

- Management per ASCCP Guidelines
- Management per ASCCP Guidelines

- HSIL

- CIN2
- CIN3

- No CIN2

- CIN3

- CIN1

- No CIN1

- Atypical squamous cells, cannot rule out HSIL

- Rule out HSIL
ASC-H, Cannot Exclude High Grade SIL: Ages 25-65+ years, Colpo for ALL

Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)*

- CIN2,3
  - No CIN2,3
  - CIN2,3

- Manage per ASCCP Guideline

*Management options may vary if the woman is pregnant or ages 21-29 years.

HSIL: All Ages, Colpo or LEEP
High-grade Squamous Intraepithelial Lesion

Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)*

- Immediate Loop Electrosurgical Excision
- Colposcopy

- CIN2,3
  - No CIN2,3
  - CIN2,3

- Manage per ASCCP Guideline

Atypical Glandular Cells, AGC: Clinical Significance

- Uncommon abnormality (0.4% in 2003)
- More common in “Older” women > 40 years
- Up to 17% have invasive cancer including:
  - Adenocarcinomas of cervix, endometrium, ovary & fallopian tube!
- Thorough workup required per ASCCP
Atypical Glandular Cells: AGC

Initial Workup of Women with Atypical Glandular Cells (AGC)

All subcategories include atypical glandular cells

- Cervical biopsy
- Endometrial biopsy

* Includes abnormal vaginal bleeding or cervical irritation suggestive of cervical infection.

Young Women w Biopsy-confirmed CIN 2, 3 in Special Circumstances (21-24 yrs) NEW CIN 2 = Observe, CIN 3 = Treat

Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances

- Observation — Cervical & Cytology
- Treatment using Excision or Ablation of Tissue

Young Women with CIN2

- Cervical negative
- Normal Cytology
- CIN 2: Cervical biopsy
- Treatment recommendation

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Biopsy-confirmed CIN- Grade 2, 3: Cervical Intraepithelial Neoplasia ≥24 yrs

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2 and 3 (CIN2,3)†

Best Follow-up after Treatment of CIN? Pap alone or Pap AND HPV?

- F/u for 20 years after High-Grade CIN Treatment?
- "Short term monitoring post-treatment of women with combined HPV testing AND cytology at 6 months and 24 months seems to be sufficient to detect post-treatment cervical disease." Pap AND HPV !!!

Diagnosed w Adenocarcinoma in-situ AIS: during Diagnostic Excisional Procedure

Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure
"The Bean" as a Pelvic Model?

Anal Cancer Screening
New and Controversial

In memory of Farrah Fawcett

HPV-Associated Anal Lesions
High-grade precursor lesions = Anal intraepithelial neoplasia (AIN)

- 80% associated with high-risk HPV 16, 18
- 4,650 estimated cases in US 2007
  ~ Annual mortality: 260 men die, 430 women die

- Men Having Sex with Men/MSM
  ~ Cancer rate 35 per 100,000
  ~ Equal to cervical cancer rate before Paps!
**Anal Cancer: Risk Factors**

- Men having sex with men/MSM
- HIV infection
- IV Drug use
- > 15 lifetime sexual partners
- Receptive anal intercourse, unprotected
- History of CIN, Cervical Intraepithelial Neoplasia
- Cigarette smoking


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**Anal Dysplasia Risk Factors in Women with Cervical Dysplasia: NEW STUDY**

N= 64 Women with Anal Epithelial Dysplasia
N= 327 with Genital Dysplasia
- 74% Vulvar dysplasia
- 22% Cervical dysplasia
- 15% Vaginal dysplasia

Risk factors:
- Immunosuppression
- Vulvar intraepithelial neoplasia
- Anal sex


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**HPV Vaccine Effective Against Oral HPV 16/18**

Vaccination to prevent cervical cancer may also lower risk for HPV-associated oropharyngeal cancers!

4 years after receipt of vaccine:
- 15/2924 Control-vaccinated women
- 1/2010 HPV-vaccinated women had oral HPV 16 infections,
- Yielding a vaccine efficacy of 93%!!!

Specific to the HPV type included in the vaccine.

Herrero et al. (2013, Jul 17). Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. http://dx.doi.org/10.1371/journal.pone.0063325
Anal Screening Recommendations
No Universal Guidelines

- NOT recommended by CDC, USPSTF, ACS, or ISDA or the National Guidelines Clearinghouse

- Yearly: per New York Dept. of Health
  - HIV positive: Every 6 months 1st year screened
  - Men having Sex with Men/MSM
  - History of genital warts
  - History of CIN 2,3, Cervical intraepithelial Neoplasia


Anal Pap Procedure:
Position Patient on Side, or in Gyn Stirrups

- Use Dacron swab (+/- May use cytobrush)
  - Pre-moistened with tap water

- Insert 5 cm (about 2”)
  - Spiral motion, firm pressure, rotate 360 degrees
  - Circling 1 direction, DON’T reverse

- Gradually withdrawn over 10 sec (rotating)

- Agitate in liquid fixative for 15 seconds

- No reflex HPV testing available

http://www.analcancerinfo.ucsf.edu/
http://www.aids.about.com/cs/conditions/a/anapaps.htm
Differential Diagnosis of Genital Warts: Biopsy When in Doubt!

- Biopsy any atypical lesion: Before treatment
  - Immunosuppressed patients
  - Unresponsive to treatment
- Neoplastic lesions include:
  - Bowenoid papulosis, Bowen’s disease
  - Squamous cell carcinoma
  - Vulvar intraepithelial neoplasia (VIN)
  - Anal intraepithelial neoplasia (AIN)
  - Giant condyloma (Buschke-Löwenstein tumor)
  - Dysplastic nevi


Anal Condylomata: 2010
How Often Do Anal Warts Harbor High-Grade Neoplasia?

- Retrospective cohort, n = 319
- Among Men having Sex with Men, MSM
  - 50% HIV+, 50% HIV-
- High-grade lesions were frequently present within Anal Condylomata
  - If HIV positive = 47%
  - If HIV negative = 26%
- Appear benign on exam!
- Refer for: Anoscopy, Biopsy

Schlecht et al. Clin Infect Dis 2010 Jul 1;51:101

Imiquimod, (Zyclara) 3.5% cream: FDA Approved for Genital Warts

- Applied daily x 8 weeks
- Complete clearance 43.8% (statistically significant) versus placebo 22.7%
- Efficacy greater in Women than Men
- Side effects:
  - itching 2.5%, burning 5.8%, pain 6.8%
  - 31% needed rest periods due to side effects
- www.ZyclaraCream.com

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Head and Neck Cancer
New HPV Risk Confirmed in 2007

Our Daughter, Katherine with Neighbor Who Died from Oropharyngeal Cancer 2009

HPV and Oral Carcinoma New Risk Confirmed in 2007: 7% positive

- 35,000 cases per year in US (Men 25,000: Women 10,000)
- Up to 15,000 New cases per year HPV related!
- Up to 60% HPV related
  - ~ 47,000 oral cancer cases from 1973 to 2004
  - ~ 17,500 cases HPV related

Oropharyngeal Cancer

HPV 16 infection increases risk 50 fold!

- Major Risk Factors:
  - Tobacco, Alcohol, etc.
  - HPV HR types: 7% of US population infected!
    - Oral sex
    - Only takes 1 partner
    - Not a cancer of promiscuity
    - Number of lifetime sex partners
    - Age of 1st coitus, 50% HPV+ within 3 years

- Younger age than non-HPV cancers < 60 years

Oropharyngeal Cancer Symptoms

No Diagnostic Algorithm

History
- Unilateral persistent sore throat > 2 weeks
- Ear pain
- Speech changes
- Tongue numbness
- Lymph node in neck, unexplained

Exam:
- White leukoplakia, white patch along gum line
- Erythroplasia; flat patch, subtle, high risk
- Ulcers

Presentation: White Lesion

Oral Cancer

Presentation: White Patch
Moderate Dysplasia

Presentation: Erythroplasia
Carcinoma in situ

Presentation: Ulcer
Squamous cell carcinoma
Potential Screening Techniques for Oral Cancer

Current
- Annual
- Clinical exam with visual inspection
- Refer for tissue biopsy

Future
- Oral cytology (Pap smear)
- Oral HPV testing (ongoing research)
- Brush biopsy
- Visual assistance devices

Improving oral HPV detection using toothbrush sampling in HIV positive men who have sex with men (MSM)

Pre, post-abrasion oral rinse samples (ORS) & toothbrush sample detected HPV DNA in at least 1 sample among 45 (26%) of 173 HIV-positive MSM. Moderate agreement between HPV genotype detection pre-abrasion and post-abrasion ORS (κ=0.49, 95% CI:0.37-0.61). Good agreement between post-abrasion ORS and toothbrush (κ=0.70, 95% CI:0.60-0.80). Sensitivities for HPV genotypes detected were 80% (95% CI:69-88) for pre-abrasion ORS, 65% (95% CI:54-76) for post-abrasion ORS & 75% (95% CI:63-84) for toothbrush.


American Cancer Society Guidelines

“...the cancer-related check-up should include examination for cancers of the thyroid, testicles, cervix, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling...”

Smith RA. CA Cancer J Clin. 2003
2013 Bib: New Pap/HPV Guidelines


Resources and Bibliography
See addendum section

www.USPSTF.org
www.ASCCP.org
www.acs.org
www.cdc.gov/ stds
www.acog.org
Summary (No pharm credits)

- Discuss current epidemiology of cervical cancer. 15 minutes
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Acknowledgement

- ASCCP slides used with permission
Thank You and Good Luck!

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www.MimiSecor.com

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Bibliography and Resources

- www.cdc.gov/std/treatment (new 2006 guidelines)
cdc.gov/std/hpv (Gardasil pt education)
Herpesdiagnostics.com (Herpes-Select serology)
Asccp.org, ACS.org, Digene.com (Pap guidelines)
Asha.org (great patient education materials)

Bibliography

*clinicalslides*
- www.cdc.gov/stds/treatment
Addendum Slides: ASCCP Guidelines 2013

No Lesion or Biopsy-confirmed CIN 1 Preceded by “Lesser Abnormalities”

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN 1) Preceded by “Lesser Abnormalities”

Follow-up without Treatment
- 2 ASC or HPV(+) 
- Cytology negative
- Age appropriate/interval screening
- Cytology negative
- HPV(-)
- Manage per ASCCP Guidelines
- 2 periods for at least 1 year

No Lesion, or Biopsy-confirmed CIN-Grade 1: Preceded by ASC-H, or HSIL Pap

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN 1) Preceded by ASC-H or HSIL Cytology

Follow-up without Treatment
- Cervical Negative
- HPV(-)
- Manage per ASCCP Guidelines
- 2 periods for at least 1 year

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No Lesion, or Biopsy-confirmed CIN-1
Grade 1: Ages 21-24