Disclosures

• Chief Medical Officer, ASCCP (paid)
• Editor in Chief, Journal of Lower Genital Tract Disease (paid)
• Adjunct Associate Professor, Emory University School of Medicine, Department of Gynecology and Obstetrics (volunteer)
• Industry – No relationship
Today’s Presentation Objectives

- Describe 2012 ACS/ASCCP/ASCP cervical cancer screening guidelines
- Compare the new guidelines to the 2012 USPSTF screening guidelines
- Introduce use of an FDA approved HPV test (2014) for primary cervical cancer screening
Objectives of Screening

- Prevent morbidity and mortality from cervical cancer
- Prevent overzealous management of precursor lesions that most likely will regress or disappear and for which the risks of management outweigh the benefits
Oh, crap! Was that TODAY?

Courtesy of Hallmark Shoebox Greetings, Hallmark, Inc.
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Natural History of Cervical Cancer

HPV infection → CIN 1 → HPV disappearance

 Avg. 6-24 mo

CIN 1 → CIN 2,3

 Avg. 10-13 yrs

Invasive CA

Avg. 6-12 mo.
Being rarely or never screened is the major contributing factor to most cervical cancer deaths today.
Who are the Rarely and Never Screened?

Descriptions

• Minorities
• Low SES*
• Foreign born
  • Living in the US < 10 years
• No usual source of health care

Where are the data?

• US Census
• NCHS§ Cervical cancer mortality
• BRFSSμ
• NHIS**

* Socio-economic status
§ National Center for Health Statistics, CDC
μ Behavioral Risk Factor Surveillance System, CDC
** National Health Interview Survey, CDC
System Failures Leading to Cervical Cancer Diagnosis

Health care providers do not screen women at visits

Women do not come in for screening

Colposcopy for abnormal screen not done

Patient gets cervical cancer

Patient does not get appropriate therapy

Courtesy of Connie Trimble, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Retrospective Study of Cervical Cancers Diagnosed at Kaiser Northern California

Cytology results 3-36 months prior to diagnosis

N=833

- Failure to screen
  No cytology: 464 (56%)

- Failure in detection
  1st cytology: 263 (32%)

- Failure to follow-up
  1st cytology abnormal: 106 (13%)

No visit: 19%
1-2 visits: 18%
>3 visits: 63%

Why isn’t “finding lesions” the objective of screening?

- Don’t know which lesions will progress.
- Need to place emphasis on:
  - *Persistent* HPV infections
  - *CIN3* (no margin for error)
  - *CIN2* in older women (no risk to pregnancies)
  - Persistent CIN2 and CIN2/3 in non-adolescent women
Consensus Conference
Sponsored by

- American Cancer Society (ACS)
- American Society for Colposcopy and Cervical Pathology (ASCCP)
- American Society for Clinical Pathology (ASCP)
ACS/ASCCP/ASCP Guidelines Development Process

• 2009-2011 – A steering committee from the 3 organizations created 6 working groups and a data group to direct the evidence evaluation

• Participating organizations:
  AHRQ, AAFP, ABOG, ACHA, ACOG, ASHA, ASC, ASCT, CAP, CDC, CMS, FDA, NCI, NCCN, NPWH, PPFA, SCC, SGO, SGOC, USPSTF, VHA
Guidelines Development
Evidence Review

- Used “Grading Recommendations Assessment, Development, and Evaluation” (GRADE) system (grade.org)
- Articles retrieved 1995 to mid-2011
- WGs reviewed and graded evidence as ‘critical,’ ‘important,’ and ‘nice to know’
- WGs developed recommendations --“strong” or “weak” depending on the quality of the evidence
ACS/ASCCP/ASCP Guidelines
Development Process

6 topic areas identified:
• Optimal screening intervals
• Screening women 30+
• Managing discordant cytology/HPV results
• Exiting women from screening
• Impact of HPV vaccination on screening
• Potential for primary HPV testing (no cytology)
Guidelines Development
Process Principles & Assumptions

• Preventing all cervical cancer is unrealistic
• A reasonable risk strategy should be cytology alone at 2-3y intervals
• Screening strategies with similar outcomes are acceptable
• Women at similar risk for cancer should be managed the same
Guidelines Development Process Principles & Assumptions (2)

- Conventional and liquid-based cytology perform similarly
- Screening interval
  - Risk of developing invasive cancer before next screen should be unlikely
  - Earlier detection of CIN3+ is a benefit
- Even studies with less sensitive tests show similar CIN3 detection--no increased cancer risk during later screening rounds
Guidelines Development
Process Principles & Assumptions (3)

• Possible harms of screening
  ▪ Anxiety over a positive test
  ▪ Stigma of an STI
  ▪ Pain/bleeding from procedures
  ▪ Treatment-related pregnancy complications
• Number of colposcopies performed is a marker for harms
Treatment saves lives, but at what cost?

- Risk of unanticipated reproductive outcomes
- Risk rises with depth and number of LEEPs
- 2014 report suggests all women with CIN2+ have risk whether treated or not

Bruinsma et al BJOG 2007;114:70-80
Guidelines Development Evidence Review Process

- Recommendations posted to ASCCP website for public comment 10/19-11/9/11
  - Revisions made based on comments as needed
- Consensus conference held 11/17-18/2011
- Discussion of draft recommendations by attendees
- Recommendations approved by at least a 2/3 majority of delegates
2012 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines*

Guidelines do not apply to special populations – hx of cervical cancer, DES exposure, & immune-compromise

New ACS/ASCCP/ASCP Guidelines

When to begin screening

Cervical cancer screening should begin at age 21.

Women < 21 should not be screened regardless of age of sexual onset

Trends in Cervical Cancer Among Women < Age 40, SEER, United States, 1973-2008, by 5 Year Age Groups

## Cervical Cancer Incidence and Mortality Rates per 100,000 women, United States, 1999-2007

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
<th>US Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15 – 19</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>20 – 24</td>
<td>1.5</td>
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<td>25 – 29</td>
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<td>0.5</td>
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<tr>
<td>30 – 34</td>
<td>11.7</td>
<td>1.4</td>
</tr>
<tr>
<td>35 – 39</td>
<td>14.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Average annual count of 21 cases of invasive cervical cancer in 10-19 year olds.

Histopathology Dx For Women Ages < 40

- Carcinomas (n = 24,248)
  - 70% Squamous cell
  - 25% Glandular (adeno- and adeno-squamous)
  - 5% Other

- Non-carcinomas (n = 310)
  - 30% were childhood sarcomas
    - 100% diagnosed in 0-14 year olds
    - 80% diagnosed in 15-19 year olds

Adolescent Needs

- HPV, Tdap and Meningococcal vaccines,
- Care for contraception
- STI screening/treatment
  - STI testing can be done using urine
- No cervical cancer screening
- No speculum exam for asymptomatic women
Screening for ages 21-29*

- Cytology alone every 3 years
- HPV testing “should not be used to screen”
  - Not as a component of cotesting
  - Not as a primary stand-alone screen

*2012 ACS/ASCCP/ASCP screening guidelines; prior to FDA approval of cobas HPV for primary screening.
Rationale for Longer Cytology Screening Intervals

• Sensitivity of single Pap test 50-70%
  – Cancer risk 18mo after 3 neg Paps = 1.5/100,000
  – Cancer risk 36mo after 3 neg Paps = 4.7/100,000
  → 99,997 women screened unnecessarily to help 3
• Risk of HSIL/cancer <3 years after negative Pap not significantly higher than risk after 1 year
• Longer Pap screening intervals (e.g., 5y) inappropriate for mobile US population

Rationale for Longer Cytology Screening Intervals-2

- Screening harms: lifetime risk of colposcopy
  - Screening q3y: 760 colpos/1000 women
  - Screening q2y: 1080 colpos/1000 women
  - Screening annually: 2000 colpos/1000 women

Rationale for Avoiding HPV Tests Among Women Ages 21-29

- Prevalence of carcinogenic HPV approaches 20% in teens and early 20s
- Most carcinogenic HPV infections resolve without intervention
- Identifying carcinogenic HPV that will resolve leads to repeated call-back, anxiety, and interventions without benefit
Screening For Women Ages 30-64

- Cytology + HPV testing (cotesting) every 5 years is preferred

- Cytology alone every 3 years is acceptable
Rationale for Cotesting, Ages 30-64

- Increased detection of prevalent CIN3
- Decreased CIN3 in subsequent screening rounds
- Achieves risk of CIN3 equal to cytology alone @ 1-3 year intervals
- Enhances detection of adenocarcinoma/AIS
- Minimizes the increased number of colposcopies, thus reducing harms.
Why Not Annual Cotesting?

• High NPV of one cotest means most abnormal screens at 1-3y intervals are transient HPV infection, not precancer.
• Potential harms are amplified without benefit.
Rapid clearance of HPV in Women $\geq 30$

* Histological progression
Managing HPV+/Cytology- Cotests

“Women cotesting HPV positive and cytology negative should be followed with either:

1) Repeat cotesting in 12 months, or
2) Immediate HPV genotyping for HPV16 alone or HPV 16/18.

Direct referral to colposcopy is not indicated”
1) Repeat cotest in 12 months

- If either repeat test is positive, refer to colposcopy
- If both tests are negative, return to routine screening.
2) Immediate HPV genotyping

• If HPV 16 or HPV 16/18 positive, refer directly to colposcopy.

• If HPV 16 or HPV 16/18 negative, repeat cotest in 12 months and then...
  – If either repeat test is positive, refer to colposcopy
  – If both tests are negative, return to routine screening.
Managing HPV+/Cytology- Cotests

Rationale

• Consistent observational data indicate short term risk of CIN3 far below risk threshold of HPV+/ASC-US and LSIL used for colposcopy referral

• Evidence from cohort studies shows majority of transient infections clear by 12 months allowing most to return to routine screening without excessive risk.
When to Stop Screening

• Stop @ age 65 if adequate negative prior screening.
• No CIN2+ within the last 20 years.

Definition of adequate negative screening:
• 3 consecutive negative cytologies or
• 2 consecutive negative HPV tests
  (Tests within 10 years of stopping; most recent within 5 years.)
Stop screening at age 65

• Screening “should not resume for any reason, even if a woman reports having a new sexual partner.”
Rationale For Stopping at Age 65

- *CIN2+ is rare after age 65*
  - Most abnormal screens, even HPV+, are false + and do not reflect precancer
- HPV risk remains 5-10%
- Colposcopy/biopsy/treatment more difficult
  - Harms are magnified
- *Incident HPV infection unlikely to lead to cancer within remaining lifetime*

Chen HC et al. JNCI 2011;103:1387-96;
Rodrigues AC et al. JNCI 2009;101:721-8
When to stop screening - 2

- Stop after hysterectomy with removal of cervix and no history of CIN2+

- “Evidence of adequate negative prior screening is not required.”
Stopping Screening after Hysterectomy: Rationale

- Vaginal cancer rate = 7/million/year
- 663 vag. cuff cytologies needed per 1 VAIN
- 2,066 women followed after hysterectomy for average 89 months
  - 3% had VAIN, 0 had cancer
- Risk of cytology abnormality after hyst = 1%.
- Compare to risk of breast cancer in men for which screening is not recommended.

Pearce KF et al. NEJM 1996;335:1559-62;
Piscitelli JT et al. AJOG 1995;173:424-30
When **NOT** to stop at age 65

- If cotest result is ASC-US/HPV- *
- If history of CIN2, CIN3, or AIS (CIN2+)
  - Continue “routine screening” for at least 20 years, “even if this extends screening past age 65.”

*2013 ASCCP Management Guidelines*
Screening a Vaccinated Cohort

- "Recommended screening practices should not change on the basis of HPV vaccination."

- Vaccination against HPV 16/18
  - Reduces CIN3+ by 17-33%
  - Reduces colposcopy by 10%
  - Reduces treatment by 25%

- But who is vaccinated?
  - Recall? Completed series? HPV naïve?

HPV as a Primary Screening Test*

- Strong NPV of HPV test suggests it might replace cotesting, but test specificity lacking
  - Follow-up to HPV+ test remains unclear
    - Pap? Repeat HPV in 1y? Genotyping? Colpo?
    - Knowing HPV status biases cytology reports to abnormal
  - Harms undefined
  - No US prospective trials published to date
- "In most clinical settings, women ages 30-65 should not be screened with HPV testing alone."

*2012 ACS/ASCCP/ASCP Consensus conference for cervical cancer screening.
### Comparison of ACS/ASCCP/ASCP, ACOG and USPSTF Guidelines, 2012

<table>
<thead>
<tr>
<th>Age to start</th>
<th>ACS, ACOG, 2012</th>
<th>USPSTF, 2012</th>
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<tbody>
<tr>
<td>Age to start</td>
<td>Age 21</td>
<td>Age 21</td>
</tr>
<tr>
<td>Women 21-29</td>
<td>Cytology every 3 years</td>
<td>Cytology every 3 years</td>
</tr>
<tr>
<td>Women 30-65</td>
<td>Cotesting every 5 years (preferred) or Every 3 years with Pap alone</td>
<td>Cotesting every 5 years or Every 3 years with Pap alone</td>
</tr>
<tr>
<td>Women &gt;65</td>
<td>Discontinue after age 65 years with adequate negative screening</td>
<td>Discontinue after age 65 years with adequate negative screening</td>
</tr>
<tr>
<td>Post-Hysterectomy</td>
<td>Discontinue if for benign reason</td>
<td>Discontinue if for benign reason</td>
</tr>
</tbody>
</table>

HPV Primary Screening for Cervical Cancer

- FDA approval of cobas HPV test, April, 2014
- Athena end of trial results pending.
  - >40,000 participants ≥ age 25
  - Followed up in 3 years if HPV test negative
  - Colposcopy if HPV 16+ or 18+
  - Cytology if HPV 16 neg. or 18 neg.
- Interim recommendations developed by ASCCP/SGO to be published soon
- Downstream management currently uncertain as few long term data exist.
HPV as the Initial Screening Test

Screen with hrHPV (>25 years)

hrHPV (-)

- Rescreen in 3 yrs

hrHPV (+)

Triage Test Performed (cytology / genotyping / p16)

- (-)
  - Rescreen at some interval

- (+)
  - Colpo
Current Screening Dilemma

- Can we integrate the 2 screening systems?
- At what age should cotesting or 1\(^{\circ}\) HPV screening begin?
- What is a reasonable screening interval for a negative HPV test?
- What about screening intervals if vaccine uptake is sufficient?
- Is there additional benefit to cotesting vs. 1\(^{\circ}\) HPV testing alone?
- Will other approved HPV products be available soon?
- Will the community revolt and regress to 3 year screening?
Conclusions

• “The biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among women rarely or never screened. . .

• Clinicians, hospitals, health plans, and public health officials should seek to identify and screen these women.”

• ACA Health Plans expected to cover cytology and HPV testing without copayment per screening recommendations.

ACS, 2002, 2012
Caveats

• Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view recommendations as dictates. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients.

• Users of guidelines may reasonably conclude that following some strong recommendations based on high-quality evidence will be a mistake for some patients. No clinical practice guideline or recommendation can take into account all of the often compelling unique features of individual patients and clinical circumstances. Thus, nobody charged with evaluating clinician’s actions, should attempt to apply recommendations in rote or blanket fashion.