Pap Smears & HPV: What’s New & What’s Next?
Erin E. Stevens, MD
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September 2015

Oh Dear God, They are Going to Change the Guidelines Again!?
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Objectives
- Revisit the history of screening for cervical cancer and cancer precursors
- Review the changes in screening for cervical cancer and the consensus guidelines for management
- Explain the rationale for primary HPV triage
- Discuss the new interim clinical guidance document for use of primary HPV testing
Georgios Papanicolaou (1883-1962)

- 1923 Reported ability to see Malignant cells under the microscope
- "Non-invasive" method
- Screening has decreased cervical cancer incidence and mortality

Screening Test

Criteria for a Good Screening Test

- Disease
- Treatment
- Test

The 2 x 2 Table

- Sensitivity (A/A+C)
- Specificity (D/B+D)
- Positive Predictive Value (A/A+B)
- Negative Predictive Value (D/C+D)
Chlamydia: STD Clinic

- Prevalence of disease: 30%
- Sensitivity: 98%
- Specificity: 97%
- PPV: 93%
- NPV: 99%

<table>
<thead>
<tr>
<th>PCR Positive</th>
<th>PCR Negative</th>
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<tbody>
<tr>
<td>Chlamydia Positive</td>
<td>294</td>
</tr>
<tr>
<td>Chlamydia Negative</td>
<td>6</td>
</tr>
</tbody>
</table>

Chlamydia: Private Practice

- Prevalence of disease: 3%
- Sensitivity: 98%
- Specificity: 97%
- PPV: 50%
- NPV: 100%

<table>
<thead>
<tr>
<th>PCR Positive</th>
<th>PCR Negative</th>
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<tbody>
<tr>
<td>Chlamydia Positive</td>
<td>29</td>
</tr>
<tr>
<td>Chlamydia Negative</td>
<td>1</td>
</tr>
</tbody>
</table>

Cervical Cancer Incidence (SEER) and U.S. Death Rates, 1975-2005
Cervical Cancer

CDC Data from 2008:
- 12,410 women diagnosed in U.S.
- 11,967 (96.4%) are HPV related
- 4,008 women Died in U.S.

Estimates for 2012:
- 12,170 Diagnosed, 4,220 Deaths in U.S.

http://www.cdc.gov/cancer/cervical/statistics/

New End Point for Cytological Screening

CIN 3

Human Papilloma Virus

Timing of Screening

ASCCP Cervical Cancer Screening Recommendations, 2012

Harms and Benefits

- Harms
  - Anxiety
  - Stigma of STI
  - Discomfort with additional tests (Colposcopy)
  - Pregnancy Risks
Why Does it Matter?

- Brodersen & Siersma (2013)
- 272 women (false positive)
- 908 matched controls
- Followed for 3 years
- Statistically greater negative psycho-social outcomes lasting 3 years past false positive mammogram result


ACS, ASCCP, ASCP, Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

August 2012
(Adopted by ACOG Nov 2012)

2012 Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommended Screening</th>
<th>Key Points</th>
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</thead>
<tbody>
<tr>
<td>&lt; Age 21</td>
<td>No Screening</td>
<td>No Screening</td>
</tr>
<tr>
<td>Age 21-29</td>
<td>Cytology Alone Q3 years</td>
<td>HPV Reflex Testing ONLY</td>
</tr>
<tr>
<td>Age 30-65</td>
<td>HPV and Cytology Co-Testing Q5 years or Cytology Q2 Years</td>
<td>HPV Routine Testing; Genotype Testing For HPV 16/18</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>No Screening Following Adequate Negative Screening</td>
<td>If History of CIN2+ Continue x 20 years</td>
</tr>
<tr>
<td>After Hysterectomy</td>
<td>No Screening Unless History of CIN2+</td>
<td>If History of CIN2+ Continue x 20 years</td>
</tr>
<tr>
<td>After HPV Vaccination</td>
<td>Age Specific</td>
<td>Same as Unvaccinated Women</td>
</tr>
</tbody>
</table>

Screening Under 21

• 0.2% cervical cancers in women under age 21

• Only 24 women diagnosed each year in the ENTIRE U.S.


Prevalence of HPV

Why so far apart?

• Ages 21-29: Cytology Alone every 3 years
  • Lifetime risk of developing cancer:
    • 3 / 1000 in annual screening
    • 5-8 / 1000 in every 3 year screening
  • Dying from cancer
    • 3 / 100,000 in annual screening
    • 5 / 100,000 in every 3 year screening
Why So Far Apart?

• Ages 21-29: Cytology Alone every 3 years
  • Annual screening: 2000 colposcopies / 1000 women
  • Every 3 year screening: 760 colpos / 1000 women
  • 1240 less colposcopies
  • For what benefit?

Why So Far Apart?

• Ages 30-64
  • Cytology Alone every 3 years  OR
  • Co-Testing (Cytology plus HPV) every 5 years

Stop Screening > 65

• Adequate negative prior screening
  • 3 consecutive negative cytology
  • 2 consecutive negative co-tests
  • Within 10 years before ceasing screening, with the most recent test within the past 5 years
  • No history of CIN2+ within the last 20 years
Stopping Screening

• Why providers don’t stop screening:
  • I don’t know the pap history
  • My patient is “High Risk”
  • My patient has a new partner
  • I don’t believe in stopping

Who is High Risk?

• “High Risk” Patients
  • History of CIN2/3 or invasive cancer
  • History of DES exposure
  • Immun suppressed

TABLE 1
The latest cervical cancer screening guidelines

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<thead>
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<tbody>
<tr>
<td>Age 21-29</td>
<td>Every year</td>
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<td>Every year</td>
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<tr>
<td>Age 30-39</td>
<td>Every year</td>
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<td>Stop screening</td>
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<tr>
<td>After CIN2</td>
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<td>Stop screening</td>
<td>Stop screening</td>
<td>Stop screening</td>
</tr>
<tr>
<td>After CIN3</td>
<td>Stop screening</td>
<td>Stop screening</td>
<td>Stop screening</td>
<td>Stop screening</td>
</tr>
</tbody>
</table>

Notes:
- CIN = cervical intraepithelial neoplasia
- ACRP = American College of Radiology
- NCCN = National Comprehensive Cancer Network
- NCCN does not recommend screening for women with no history of CIN 2-3 or invasive cervical cancer.
Where are the Failures?

- 50% of the cancers diagnosed in the US are women never screened
- 10% of the cancers diagnosed are in women not screened within the past 5 years

ASCCP Cervical Cancer Screening Recommendations, 2012

Who are the Rarely and Never Screened?

<table>
<thead>
<tr>
<th>Descriptions</th>
<th>Where are the data?</th>
</tr>
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<tbody>
<tr>
<td>Minorities</td>
<td>US Census</td>
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<tr>
<td>Low SES*</td>
<td>NCHS Cervical cancer mortality</td>
</tr>
<tr>
<td>Foreign born</td>
<td>BRFSS&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Living in the US &lt; 10 years</td>
<td>NHIS&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>No usual source of health care</td>
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</table>

* Socio-economic status
<sup>5</sup> National Centre for Health Statistics, CDC
<sup>**</sup> National Health Interview Survey, CDC

ASCCP Cervical Cancer Screening Recommendations, 2012

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

Green Journal - April 2013
Update to 2006 Guidelines

- ASCCP Consensus Conference Sept 2012
- CIN1 on ECC
- Co-testing and Genotyping for HPV
- Changing Adolescent Criteria Age <25
- Unsatisfactory Paps, Missing Endocervical
- Return to Routine Screening

Box 1: Essential Changes from Prior Management Guidelines

- Cytology reported as negative but testing endocervical cells can be managed without early repeat.
- CIN 1 on endocervical cells should be managed as CIN 1, not as a positive ECC.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Genotyping typing HPV positive women with HPV type 18 or type 16 to earlier colposcopy if negative HPV testing; biopsies is indicated if positive HPV and ASC-US, regardless of genotyping result.
- For ASC-US cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, not 6 months and 12 months, and is if negative; cytoscopy every 3 years.
- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 25 years.
- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating co-testing and long-term follow-up.
- Management of LSIL is the same for women aged 25-65 years; the strategy is risk-based. Pap-only strategies are now limited to women younger than 30 years, but cervical is extended even to women younger than 30 years in some circumstances. Women aged 31-65 years are managed conservatively.

Finding the Guidelines

- asccp.org
- Journal of Lower Genital Tract Diseases
- Management paper and algorithms
- acog.org
- Screening: Practice Bulletin #131
- Management: Green Journal - April 2013
There's an App for That!

What's Next?
Primary HPV Testing
(ATHENA Trial)

How Common Is HPV?

- Most men and women who have had sex have been exposed to HPV at some point in their lifetime.

  Up to 80% of all sexually active women and men have been exposed to HPV by the age of 50.
HPV and Cervical Cancer

About 80% of Women will be infected with HPV in their lifetime.

About 7% of Women will have an abnormal Pap test.
HPV and Cervical Cancer

About 300,000 women (per year in the United States) will have a high grade precancerous lesion.

Foundation for Women’s Cancer, Vaccines to Prevent HPV-Associated Diseases (2013)

ATHENA Trial

ATHENA: Addressing THE Need for Advanced HPV Diagnostics

- Large prospective clinical trial
- Looking at Normal Cytology (NILM), ASC-US Cytology and Overall population trend
- Ultimate goal: HPV as first line test
ATHENA: Objectives

ATHENA HPV trial objectives

Objectives in the ASC-US and NILM populations

- To evaluate the performance of the together® HPV test (detection of 14 high-risk types) for identifying high-grade cervical disease (CIN2, CIN3, cervical cancer, or adenocarcinoma in situ [AIS]).
- To compare the rates of high-grade cervical disease between women with a positive and those with a negative together® HPV test result.

Analysis population: Subjects ≥18 years with an ASC-US cervical cytology.

Objectives in the NILM (women with normal cytology) population

- Compare the risk of having CIN2 among the following groups of women with normal cytology aged 30 years or more:
  - Positive vs. negative together® HPV test result (14 high-risk genotypes).
  - Positive result for HPV genotype 16 or 18 vs. negative result for all 14 high-risk genotypes.
  - Positive result for HPV genotype 16 or 18 vs. positive result for one of the other 12 genotypes.

Analysis population: Subjects ≥18 years with normal cytology.

ASC-US and CIN2+ Risk

Absolute risk of ≥CIN2 stratified by hrHPV status in the ATHENA ASC-US population.
**ASC-US and CIN3+ Risk**

Absolute risk of 2CIN3 stratified by hrHPV status in the ATHENA ASC-US population.

- ASC-US: 2.9
- hrHPV: 4.3
- hrHPV+: 8.4
- 12 other hrHPV+: 4.4
- HPV 16+: 20.0
- HPV 18+: 4.3

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**Conclusions: ASCUS**

- ASC-US
- hrHPV- 87.4%
- hrHPV+ 21.4%
- HPV 16+ 2.9%
- HPV 18+ 8.2%
- >CIN2
  - 1 in 133
  - 1 in 22
  - 1 in 33
  - 1 in 5

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**What about Normal Pap?**

Absolute risk of 2CIN2 stratified by hrHPV status in the ATHENA NILM population.

- NILM: 1.2
- hrHPV- 6.8
- hrHPV+ 6.1
- 12 hrHPV+: 4.6
- HPV 16+: 13.6
- HPV 18+: 7.0
Conclusions: Normal Pap

- Nearly 1 in 7 women with normal cytology that were HPV 16+ had CIN2+.
- Nearly 1 in 8 women with normal cytology that were HPV 16+ had CIN3+.
- HPV testing picked up more than cytology alone.

It’s still not perfect…
So what if we did HPV testing as primary screening?

Cytology with reflex HPV

- Current standard of care - Low sensitivity for detection of CIN3+

HPV with Reflex Cytology

- Identified a similar amount of disease (56% to 52%) but required less colposcopies to find CIN3+
HPV 16/18 and Reflex Cytology

- Detects 1.3 times more CIN3+ than current standard of care.

HPV Screening Alone

- Most sensitive screening - Found more disease but required a large number of colposcopies to find a single case of CIN3+

Primary HPV Testing
Assumptions

• No cancer screening test has the ability to detect all cases of prevalent or incipient cervical cancer

• Higher detection of CIN3+ at baseline and reduced detection of CIN3+ in subsequent screening rounds are considered benefits

• Increased numbers of colposcopies is considered a surrogate for harms of screening.

Is hrHPV testing as safe and effective as cytology based screening?

• Yes

• A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result.
Clinical Trials to date

<table>
<thead>
<tr>
<th>Referee</th>
<th>First names</th>
<th>Age</th>
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<tr>
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</tbody>
</table>

Can primary hrHPV be considered an alternative to cytology?

- Yes.

  - Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to current US cytology based cervical cancer screening methods. Cytology alone and cotesting remain screening options specifically recommended in major guidelines.

How should one manage a positive hrHPV result?

- Triage of hrHPV positive women using a combination of genotyping for HPV 16/18 and reflex cytology for women positive for the other 12 hrHPV genotypes appears to be a reasonable approach to managing hrHPV positive women.
Primary HPV Screening

What is optimal interval for primary hrHPV screening?

• Rescreening should occur no sooner than every three years.

At what age should primary hrHPV screening be started?

• Primary hrHPV screening should not be initiated prior to age 25.
Conclusions

- There is good evidence and sound rationale for why the screening and management guidelines have changed – and should be followed.
- There is a new endpoint for the pap smear: CIN3.
- There is now an interim clinical guidance for using hrHPV testing as primary screening.
- Vaccinations are needed as primary prevention!

Any questions?
Thank you!