Cervical Cancer Screening

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Director, Division of Women's Reproductive Healthcare

Learning Objectives

– Describe the etiology, natural history, and usage of the human papillomavirus (HPV) in cervical cancer screening
– Discuss the rationale for the currently available cervical cancer screening modalities
– Give examples of the management of abnormalities identified during cervical cancer screening

Disclosures

– I have no financial interest or other conflict of interest in relation to this program/presentation.
Cervical Cancer Screening

**Top 5 Cervical Cancer Screening Take Home Messages**

1. “Most cases of cervical cancer occur in women who were either never screened or screened inadequately”


2. “Liquid-based and conventional methods of cervical cytology specimen collection are acceptable for screening”

3. “Infection with oncogenic HPV is a necessary but not sufficient factor for the development of squamous cervical neoplasia.”


Cervical Cancer Screening

4. “The shift from cytology to HPV testing will be a significant change—from an oncologic screening paradigm to a communicable disease paradigm”


Cervical Cancer Screening

5. Screening and management algorithms are too complicated to remember...GET THE APP!
HUMAN PAPILLOMAVIRUS (HPV)
HARALD ZUR HAUSEN – ISOLATED HPV 16 IN 1983

HPV

• HPV Transmission
  – Almost exclusively acquired from sexual exposure
  – Concordance among partners varies from 40-60%
  – HPV detected from multiple sites: cervix, anus, penis, hands, scrotum, vulva, and oropharynx
  – Vertical transmission occurs in 20-30% of patients
  • Majority of neonatal infections are cleared by the first year of life


HPV Prevalence

HPV

• Natural History of Infection
  – “The majority of HPV infections are cleared and only a minority persist and progress to CIN or invasive cancer”
  – Young women are more likely to clear infections than older women
  – Low risk HPV infections clear more quickly than high-risk HPV infections
  – Men have higher rates of HPV clearance

HPV Clearance vs. Progression

<table>
<thead>
<tr>
<th>Gender</th>
<th>Time Frame</th>
<th>Clearance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1 year</td>
<td>40-70%</td>
</tr>
<tr>
<td></td>
<td>2-5 year</td>
<td>70-100%</td>
</tr>
<tr>
<td>Men</td>
<td>1 year</td>
<td>75%</td>
</tr>
</tbody>
</table>

Among Women Who Do Not Clear Their Infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2-3</td>
<td>8-28%</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>3-5%</td>
</tr>
</tbody>
</table>
Natural History of HPV

HPV Testing

• Indications for HPV Testing
  – Women > 21 with an ASCUS Pap smear
  – Co-testing with cytology in women > 30
  – Follow-up after excisional procedures or ablation of CIN2,3
  – Management of postmenopausal women with LSIL
  – Management of women with AGC
  – Follow-up of CIN 1 when it was preceded by LSIL, ASCUS, and ASC-H


(Quinn et al., BMJ 1999; 318: 9048)
Cervical Cytology (Pap)

- Why did we move away from cytology alone?
  - Very subjective
  - Low reproducibility rate
  - Not as sensitive for CIN2, 3 as previously thought
  - Identifies women with lesions; not those at risk for developing lesions

Variability of Cervical Cytology

<table>
<thead>
<tr>
<th></th>
<th>LAB A</th>
<th>LAB B</th>
<th>LAB C</th>
<th>LAB D</th>
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<tbody>
<tr>
<td>Number</td>
<td>12,294</td>
<td>4,218</td>
<td>16,979</td>
<td>12,442</td>
</tr>
<tr>
<td>Median Age</td>
<td>40.9</td>
<td>37.9</td>
<td>39.3</td>
<td>40.1</td>
</tr>
<tr>
<td>≥ASCUS</td>
<td>3.8%</td>
<td>5.2%</td>
<td>8.1%</td>
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Very Subjective with Low Reproducibility

In Athena Trial, 53.5% of women with CIN 3 or >, had NORMAL liquid based cytology
### Comparative Sensitivity Cross Sectional Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>#</th>
<th>Endpt</th>
<th>Pap</th>
<th>HPV</th>
<th>Cotest</th>
</tr>
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<tr>
<td>Petry</td>
<td>2003</td>
<td>8466</td>
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<td></td>
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<tr>
<td>Ronco</td>
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<tr>
<td>Sensitivity of cytology</td>
<td>42.0%</td>
<td>51.0%</td>
<td>60.5%</td>
<td>73.0%</td>
</tr>
<tr>
<td>Sensitivity of HPV</td>
<td>90.1%</td>
<td>88.2%</td>
<td>88.4%</td>
<td>88.9%</td>
</tr>
</tbody>
</table>


Cervical Cytology Co-Testing

- More sensitive for CIN2, 3 than cytology alone
- Allows interval extension to 5 years
- Using HPV allows us to identify women at-risk for cervical disease in the future
- Identifies a higher rate of adenocarcinoma
Primary HPV Screening

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<td>75%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Cervical Cancer Screening

![Graph showing cumulative incidence of CIN3+ per 10,000 patients]

Primary HPV Screening

![Diagram showing diagnosis and treatment pathways]

## HPV Screening

### HPV Type Matters

<table>
<thead>
<tr>
<th>HPV Results</th>
<th>10-Year Risk of CIN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16+</td>
<td>17%</td>
</tr>
<tr>
<td>HPV 18+</td>
<td>14%</td>
</tr>
<tr>
<td>Other hrHPV (+)</td>
<td>3%</td>
</tr>
<tr>
<td>hrHPV (-)</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

"HPV Persistence is perhaps the most important risk factor for cervical cancer".

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## Primary HPV Screening

### Primary HPV Screening

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>53%</td>
<td>96%</td>
</tr>
<tr>
<td>Primary HPV</td>
<td>96%</td>
<td>90%</td>
</tr>
</tbody>
</table>

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### Comparison of Strategies in Women > 25

<table>
<thead>
<tr>
<th>Strategy</th>
<th># Tests</th>
<th>CIN3 Baseline</th>
<th>CIN3+ Yrs 1-3</th>
<th>CIN3+ Missed</th>
<th>Colpos</th>
<th>Colpos Per CIN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>45,166</td>
<td>143</td>
<td>36</td>
<td>168</td>
<td>1934</td>
<td>10.8</td>
</tr>
<tr>
<td>Cotesting</td>
<td>82994</td>
<td>143</td>
<td>97</td>
<td>107</td>
<td>3097</td>
<td>12.4</td>
</tr>
<tr>
<td>HPV only</td>
<td>52651</td>
<td>197</td>
<td>97</td>
<td>53</td>
<td>3769</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Tradeoff between CIN3 detected and number of colposcopy procedures.
Cervical Cancer Screening

USPSTF Draft Recommendations for Cervical Cancer Screening

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-29</td>
<td>Cytology alone every 3 years</td>
</tr>
<tr>
<td>30-65</td>
<td>Cytology alone every 3 years OR HPV-testing alone every 5 years</td>
</tr>
</tbody>
</table>

Screening Guidelines

Benefits

Harms

Cervical Cancer Screening

Adolescent (< 21 Years of Age)
Cervical Cancer Prevention

- Safe sexual practices to limit exposure to sexually transmitted infections
- HPV vaccination
- Initiation of reproductive health care should not be predicated on screening

Cervical Cancer Screening

**Cancer screening should begin at age 21**
- Why?
  - 1-2 cases of cervical cancer per year per 1,000,000 females aged 15-19
  - Screening younger women has not decreased the rate of cervical cancer
  - Nearly all cases of HPV are cleared by the immune system within 1-2 years without producing neoplastic change

**Exception**
- Women who are infected with HIV or who are otherwise immunocompromised should be screened
Women aged 21-29 years should be tested with cervical cytology alone. Screening should be performed every 3 years. HPV co-testing should **NOT** be performed.

- Very high prevalence of high risk HPV infection
- Low incidence of cervical cancer in this population
- Transient infection without carcinogenic potential

### Comparison of Cervical Cancer Screening

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Cancer Detected</th>
<th># of Colpo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Years</td>
<td>37/100,000</td>
<td>176/100,000</td>
</tr>
<tr>
<td>3 Years</td>
<td>39/100,000</td>
<td>134/100,000</td>
</tr>
</tbody>
</table>

Kulasingam et al. AHRQ 2011

Why only screen every 3 years?
Cervical Cancer Screening
30 - 65 years

• Women aged 30 – 65
  – Preferred: Co-testing with cytology and HPV testing
  – Acceptable: Cytology alone every 3 years

<table>
<thead>
<tr>
<th>Screening Results</th>
<th>5-Year Risk of CIN 3 or &gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative cytology alone</td>
<td>0.26%</td>
</tr>
<tr>
<td>Negative co-testing</td>
<td>0.08%</td>
</tr>
</tbody>
</table>

Cervical Cancer Screening
Women > 65

Cervical Cancer Screening

• Women aged > 65
  — Screening should be discontinued in women with:
    • Evidence of adequate negative prior screening test results
    • No history of CIN 2 or higher
  — What is adequate negative screening?
    • 3 consecutive negative cytology results or
    • 2 consecutive negative co-testing results within the previous 10 years.


Cervical Cancer Screening

• Women aged > 65
  — Represent 14.3% of the population but account for 19.6% of the new cases of cervical cancer
  — Why do we stop screening?
    • Most cases occur in unscreened women
    • Cervical cancer occurs 15-25 years after HPV infection
    • Screening between 65 and 90 every 3 years would prevent 1.6/1000 cases of cancer
    • Increased false positive cytology results due to atrophy


Cervical Cancer Screening

• Women with a previous hysterectomy
  — If they have never had a h/o CIN2 or >, routine screening should be discontinued and not restarted for any reason
  — For those with a history of CIN2 or >, screen with cytology alone every 3 years for 20 years

MANAGEMENT OF CERVICAL CANCER SCREENING RESULTS

Absent Endocervical Cells

Cytology NILM* but EC/TZ Absent/fraudulent

- Ages 21-29:
  - HPV negative
  - HPV unknown

- Ages ≥30:
  - HPV testing (Preferred)
  - Repeat cytology in 3 years (Acceptable)

Repeat cytology in 3 years (Acceptable)

Cytology + HPV test in 1 year

Manage per ASCCP Guidelines

**Neglects for intraepithelial lesion or malignancy**

HPV testing is unacceptable for screening women ages 21-29 year

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Cytology Negative/HPV Positive

Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- Repeat Cytology @ 1 year Acceptable
- HPV DNA Typing Acceptable

- HPV Negative
- HPV positive

- HPV -16 or 18 Positive
- HPV 16 and 18 Negative

- Repeat Cytology @ 1 year

Manage per ASCCP Guidelines

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"Repeat cotesting in 1-year allows most women with transient infection and no carcinogenic risk sufficient time for the HPV infection to clear and identifies a smaller group at risk of precancerous lesions to undergo colposcopy."

"Women aged 30-65 with ASCUS-HPV (-) cytology results should have follow-up co-testing in 3 years rather than in 5 years."

Atypical Glandular Cells Results

Cervical Cancer Screening