Appropriate Use of Cytology and HPV Testing in the New Cervical Cancer Screening Guidelines

Tim Kremer, MD
Ralph Anderson, MD
Objectives

- Describe the natural history of HPV particularly as it relates to primary cervical cancer screening recommendations

- Determine appropriate age-specific cervical cancer screening recommendations, and appropriate management of women age 30 and older screened by co-testing with a Pap and HPV DNA test

- Choose the cervical cancer screening option, or options, most likely to benefit the patient

- Develop skills in counseling about HPV infection, the purpose of cervical cytology screening, and the reasons for specific screening recommendations for an individual patient based on age and history
Cancer of the Cervix

### Incidence

<table>
<thead>
<tr>
<th>2012</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>530,000</td>
<td>275,000</td>
</tr>
<tr>
<td>U.S.</td>
<td>12,170</td>
<td>4,220</td>
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<thead>
<tr>
<th>United States</th>
<th>1975</th>
<th>2008</th>
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<tr>
<td>Incidence cervical cancer (Per 100,000 women)</td>
<td>14.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Mortality cervical cancer (per 100,000 women)</td>
<td>5.55</td>
<td>2.38</td>
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Cancer of the Cervix

Etiology

- **Human papillomavirus**
  - HPV 16 – 55-60% of cancer cases
  - HPV 18 – 10-15% of cancer cases
  - 10 other HPV genotypes – 25-30% of cancer cases

- **Related factors**
  - Cigarette smoking
  - Immunosuppression
    - Patients with transplants
  - HIV Infection
  - Early onset of intercourse (age 13-16)
  - Multiple sexual partners (increased exposure)
  - High risk partners
    - Those with previous sexual partners who develop precancerous or cancerous diseases of the cervix
Infection with High Risk Oncogenic HPV Virus

- Infection with high risk “oncogenic” HPV is the cause of:

  - 100% of cancers of the cervix
  - 90% of anal cancers
  - 40% of vulvar cancers
  - 40% of vaginal cancers
  - 12% of oropharyngeal cancers
  - 3% of oral cancers
  - 3% of skin cancers
Human Papillomavirus (HPV) Infection

- Young women are more likely to be infected with HPV (90%) but the chance of it resolving is much higher. (>90%)

- Older women are less likely to be infected (70%) but the chance of it persisting is higher. (70%)

- Persistent infection is more common with
  - Older age
  - Infection with multiple HPV types
  - Coincident vulvar condyloma
Cancer of the Cervix

Continuum of Disease

Normal

Atypical

Cervical Intraepithelial Neoplasia (CIN)

CIN I
CIN2
CIN 3

Microinvasive Cancer of the Cervix

Invasive Cancer of the Cervix
## Natural History of CIN: A Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>Regress %</th>
<th>Persist %</th>
<th>Progress %</th>
<th>Progress to Invasive %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Lacking CIN</td>
<td>80</td>
<td>15</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>CIN 1</td>
<td>57</td>
<td>32</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43</td>
<td>35</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32</td>
<td>56</td>
<td>12</td>
<td>14</td>
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Recommendations For Screening For Cancer of the Cervix
## Screening Methods for Cervical Cancer

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<td>Follow age-specific recommendations (same as unvaccinated women)</td>
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Role of HPV Testing For Primary Screening
Role of HPV Testing For Primary Screening

An FDA advisory panel has unanimously supported expanding the approval of the Cobas Human Papillomovaratus Test (Roche) to include its use as a FIRST LINE PRIMARY CERVICAL CANCER SCREENING TEST to detect high-risk HPV, including genotyping for HPV 16 and 18 in women 25 year of age and older.
Role of HPV Testing For Primary Screening

HPV testing as primary screening for cancer of the cervix is NOT currently recommended.

Because of the higher sensitivity of HPV testing compared with Pap cytology, some have advocated the use of HPV testing as primary screening with cytology triage rather than the reverse (cytology with HPV triage).
Proposed Screening Algorithm For HPV Testing

HPV test age 25

Negative

Repeat 3 years

Positive

HPV 16 or HPV 18

Colposcopy

12 other Oncogenic strains

Pap Smear
Abnormal Cervical Cytology
Abnormal Cervical Testing

- Normal Pap Smear
  - Positive high risk HPV DNA

- Atypical squamous cells of undetermined significance (ASCUS)

- Atypical squamous cells – cannot rule out HSIL

- Low grade Squamous Intraepithelial Lesion (LSIL)
  - Generally associated with transient HPV infection
  - However, 28% of women with LSIL cytology results have CIN 2 or CIN 3 (2/3 identified by colposcopy)

- High grade Squamous Intraepithelial Lesion (HSIL)
  - Associated with persistent infection and cancer risk.

- Abnormal glandular cells
Patient With Normal Cervical Cytology and Positive High Risk HPV DNA
A 32-year-old g2p2 female presents for her annual examination. Her last Pap Smear was at age 29 and was satisfactory and negative for any abnormal cells.

She has no complaints.

Pap Smear negative.

HPV DNA positive for high risk (oncogenic) HPV DNA.

The appropriate management is:

A. Repeat Pap Smear and HPV DNA in 6 months
B. Repeat Pap Smear and HPV DNA in 1 year
C. Repeat Pap Smear and HPV DNA in 3 years
D. Colposcopic examination
E. HPV genotype-specific testing for HPV 16 and HPV 18
Management of Patient Aged 30 or Older with Negative Cytology and Positive High Risk HPV

- Occurs in 3.7% of women older than 30 years
- Risk of significant pathology is low
- 12 month risk of CIN 3
  - 0.8 – 4.1%
  - 10% if HPV 16 or HPV 18 present
  - Follow-up with Pap smear and HPV DNA in 1 year is recommended
  - Colposcopy not recommended unless genotype testing reveals HPV 16 or HPV 18 when colposcopy is reasonable because risk of CIN 3 is 10%
Management of Patient Aged 30 or Older with Negative Cervical Cytology and Positive High-Risk HPV

1. Repeat co-testing in 12 months

   - HPV Positive Cytology
     - ● ASCUS or more
       - Colposcopy
   - HPV Negative Cytology
     - Cytology Negative
       - Repeat Cytology 3 years

2. HPV genotype-specific testing for HPV 16 alone or HPV 16-18

   - Positive
     - (Risk of CIN 3 with HPV 16 – 10%)
       - Colposcopy
   - Negative
     - Cotesting 12 months
Atypical Squamous Cells of Undetermined Significance
A 28-year-old g5p5, patient presents for her annual examination. Her Pap Smear reveals atypical squamous cells of undetermined significance.

The next step in the management is:

A. HPV DNA testing
B. Repeat Pap Smear at 12 months
C. Repeat Pap Smear in 6 months
D. Colposcopy
Management of Women with Atypical Squamous Cells of Undetermined Significance

- HPV DNA Testing
  - Preferred
  - (> 25 years of age)

  - HPV negative
    - Repeat co-testing
      - 3 years
  - HPV positive
    - Colposcopy

- Repeat Cytology
  - at 1 year
  - Acceptable

  - Negative
    - Routine Screening
  - >ASC
    - Colposcopy
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

**Repeat Cytology**
- @ 1 year
- Acceptable

**HPV Testing**
- Preferred

**HPV Positive**
- (managed the same as women with LSIL)

**HPV Negative**

- Repeat Cotesting @ 3 years

**Colposcopy**
- Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

**Manage per ASCCP Guideline**

*Management options may vary if the woman is pregnant or ages 21-24.
*Cytology at 3 year intervals

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Management of Women Aged 21-24 with Atypical Cells of Undetermined Significance (ASCUS) and Low Grade Squamous Intraepithelial Neoplasia (LSIL)
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

- Repeat Cytology @ 12 months Preferred
  - Negative, ASC-US or LSIL
    - Repeat Cytology @ 12 months
      - Negative x 2 ≥ ASC
      - Colposcopy
    - ASC-H, AGC, HSIL
      - Repeat Cytology @ 12 months
      - HPV Negative
        - Reflex HPV Testing Acceptable for ASC-US only
          - HPV Positive
            - Reflex HPV Testing Acceptable for ASC-US only

Routine Screening
Atypical Squamous Cells Cannot Exclude High-Grade SIL ASC-H
Management of Patient with ASC-H

- Colposcopy with directed biopsies
- Endocervical curettage
Atypical Squamous Cells

A cytologic result of Atypical Squamous Cells in the least reproducible of all cytologic categories.

ASCUS – meta-analysis of 20 studies
- Biopsy – confirmed CIN 2-3 9.7%
- Invasive cancer 0.1 – 0.2%
- Management
  - ASCUS – Negative High Risk HPV – Screening according to age
  - ASCUS – Positive High Risk HPV
    - Colposcopy with directed biopsies
    - Repeat cytology at 1 year acceptable

ASC-H
- Biopsy confirmed CIN 2-3 50%
- ASC-H should be considered similar to HSIL
- Management
  - Colposcopy with biopsies
Low Grade Squamous Intraepithelial Lesion
Low Grade Squamous Intraepithelial Neoplasia (LSIL)

- Mean LSIL reporting rate is 2.9% for liquid-based specimens.
- A result of LSIL is a good indication of HPV infection.
- 77% of women with LSIL are HPV positive, making HPV triage inappropriate.
- 27.6% of women with LSIL have CIN 2 or CIN 3.
- The risk of CIN 2-3 is the same in women with LSIL and with ASCUS with positive high risk HPV DNA.

Management
- Colposcopy with directed biopsies.
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*

**LSIL with negative HPV test**
- Preferred
  - Repeat COTesting @ 1 year
    - Cytology Negative and HPV Negative
      - Repeat COTesting @ 3 years

**LSIL with no HPV test**
- Acceptable
  - Colposcopy
    - ≥ ASC
      - Non-pregnant and no lesion identified
        - Endocervical sampling "preferred"
      - Inadequate colposcopic examination
        - Adequate colposcopy and lesion identified
          - Endocervical sampling "preferred"
      - HPV positive
        - No CIN2,3
          - Manage per ASCCP Guideline
        - CIN2,3
          - Manage per ASCCP Guideline

**LSIL with positive HPV test**

* Management options may vary if the woman is ages 21-24 years (see text)
Management of Women Ages 21-24 Years With Atypical Squamous Cells of Undetermined Significance (ASC-US) and Low Grade Squamous Intraepithelial Lesion (LSIL)
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

- Repeat Cytology @ 12 months Preferred
  - Negative, ASC-US or LSIL
    - Repeat Cytology @ 12 months
      - Negative x 2 ≥ ASC → Colposcopy
  - ASC-H, AGC, HSIL
    - HPV Positive → Reflex HPV Testing Acceptable for ASC-US only
      - HPV Negative → Routine Screening

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Management of Women Aged 25 Years and Older with Cervical Cytology Test Results Reporting as HSIL
High Grade Squamous Intraepithelial Neoplasia

Mean reporting range in U.S. literature is 0.7%

A finding of HSIL carries a high risk for significant cervical disease.

- CIN 2-3 with colposcopy 53-66%
- CIN 2-3 and LEEP 84-97%
- Invasive cancer 2%

Management

- Colposcopy with directed biopsies
Management of Women Age 25 Years and Older with Cervical Cytology Test Results Reporting as HSIL

- Loop Electrosurgical Excision
- Colposcopy With biopsies ECC

or
Management of Women Age 21-24 Years with Cervical Test Results Reported as HSIL (or ASC-H)
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)

Colposcopy
(Immediate loop electrosurgical excision is unacceptable)

No CIN2,3

CIN2,3

Observation with colposcopy & cytology *
@ 6 month intervals for up to 2 years

High-grade colposcopic lesion or HSIL
Persist for 1 year

Biopsy

CIN2,3
Manage per ASCCP Guideline for young women with CIN2,3

HSIL
Persist for 24 months with no CIN2,3 identified

Diagnostic Excisional Procedure *

Other results

Routine Screening

Two Consecutive Cytology Negative Results and No High-grade Colposcopic Abnormality

*If colposcopy is adequate and endocervical sampling is negative. Otherwise a diagnostic excisional procedure is indicated.

*Not if patient is pregnant

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Management of Patient with Atypical Glandular Cells
Management of Patients with Atypical Glandular Cells

- Colposcopy with directed biopsies
- Endocervical curettage (ECC)
- Endometrial biopsy
  - In patients over 35
  - In patients with clinical conditions suggesting risk of endometrial neoplasia
    - Unexplained vaginal bleeding
    - Condition suggesting chronic anovulation
      - PCOS
      - Hypothyroidism
      - Renal failure
    - Obesity
Management of Cervical Intraepithelial Neoplasia
Management of Cervical Intraepithelial Neoplasia (CIN 1)

- Less than ½ of lesions diagnosed as CIN 1 by pathologists are classified as CIN 1 when reviewed by a panel of pathologists.

- CIN 1 is the histologic manifestation of HPV infection.

- High rate of spontaneous regression especially in adolescents (80-90%).

Conservative Management

- HPV DNA testing every 12 months

OR

- Repeat Pap smear every 6-12 months.
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by "Lesser Abnormalities"*

Follow-up without Treatment

→ Cotesting at 12 months
  → HPV(-) and Cytology Negative
  → Age appropriate retesting 3 years later
  → Cytology negative +/- HPV(-)
  → Routine screening*

→ ≥ ASC or HPV(+)
  → Colposcopy

No CIN

→ Manage per ASCCP Guideline

CIN2,3

→ If persists for at least 2 years
  → Follow-up or Treatment

CIN1

* "Lesser abnormalities" include ASC-US or LSIL Cytology, HPV 16+ or 18+, and persistent HPV

** Management options may vary if the woman is pregnant or ages 21-24.

† Cytology if age <30 years, cotesting if age ≥30 years

‡ Either ablative or excisional methods. Excision preferred if colposcopy inadequate, positive ECC, or previously treated.
Management of CIN 2-3
Management of Patient with CIN 2-3

- LEEP (Loop Electrosurgical Excision Procedure)
- Laser vaporization
- Conization of cervix
  - Pap Smear reveals more than biopsy
  - Transformation zone not completely visualized
  - Suspicion of invasive cancer
Management of Young Women (<25 years) With Biopsy-Confirmed Cervical Intraepithelial Neoplasia (CIN 2 – CIN 3)
Management of Young Women (<25 Years) With Biopsy Confirmed Cervical Intraepithelial Neoplasia (CIN 2-CIN3)

Either treatment or observation is acceptable providing colposcopy is adequate.

- **CIN 2**
  - Observation

- **CIN 3**
  - Treatment preferred

Observation
Colposcopy or Cytology
@ 6 month intervals for 12 months

Treatment using Excision or Ablation of T-zone
Adenocarcinoma in Situ
Adenocarcinoma In Situ

- A diagnosis of Adenocarcinoma in Situ cannot be made without an excisional procedure.

- AIS frequently extends for a considerable distance into the endocervical canal making complete excision difficult.

- AIS is frequently multi-focal and frequently has “skip lesions” (lesions that are not contiguous). Thus negative margins on a diagnostic excisional specimen do not necessarily mean the lesion has been completely excised.

- Because of those considerations, hysterectomy is the treatment of choice for AIS in women who have completed child-bearing.
Adenocarcinoma In Situ

Excisional Procedure for Women to Maintain Their Fertility

- Failure rate after an excisional procedure (recurrent/persistent AIS or invasive adenocarcinoma) – 8%
  - Margin status and endocervical sampling at the time of excisional biopsy are predictors of residual disease.

- Some (highly suggestive but not conclusive) evidence that there is an increased recurrence rate as well as an increase in positive margins where a leep excision procedure as opposed to cold knife conization is used.

- Irrespective of conization method, it is important to note that the margin status and interpretability of the margins are important for future treatment planning and management.

An excisional biopsy is required in all women with AIS prior to making any subsequent management decisions.
Conclusions
# Screening Methods for Cervical Cancer

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## Management of Abnormal Pap Smears

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<th>Follow-up with Pap smear and HPV DNA in 1 year</th>
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<td>◦ In patients &gt; 35</td>
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Unexplained bleeding

Conditions suggesting chronic ovulation

PCOS, Hypothyroidism, Renal failure

Obesity
# Management of CIN

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<td><strong>CIN 1</strong></td>
<td>HPV DNA testing every 12 months or Repeat Pap smear every 6-12 months</td>
<td>Repeat Pap smear in 12 months</td>
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Endometrial Cells on Pap smear

- Found in 0.5-8% of Pap Smears in women over 40

  - Premenopausal
    - No further evaluation for asymptomatic premenopausal women with
      - Benign endometrial cells
      - Benign endometrial stromal cells
      - Histiocytes

  - Postmenopausal
    - Are associated with clinically important abnormalities in 5% of post-menopausal women
      - Endometrial biopsy

- Post Hysterectomy
  - No further evaluation
Negative Cytology and Absent Endocervical Components

- 21-29 Routine screening
- 30 +
  - HPV negative
    - Routine screening
      - Cytology every 3 years
      - Cytology HPV DNA every 5 years
Positive Margins on Leep or Conization Specimen

- Pap smear with ECC at 4-6 months after treatment (preferred)
- Diagnostic excisional procedure (acceptable)
- Hysterectomy acceptable if a repeat diagnostic procedure is not feasible (insufficient residual cervix)