Cervical Cancer Screening and Follow-up Guidelines

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Speaker Information

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- Medical Director, LifeServe Blood Center, Sioux City
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Today’s Agenda

• Review epidemiology and role of human papilloma virus (HPV) in development of cervical cancer
  o Discussion restricted to squamous abnormalities of cervix (excluding glandular pathologies - endocervical adenocarcinoma)

• Current tools for screening and treatment of cervical cancer and its precursors

• Discuss current terminology of cervical precancerous changes

• Discuss latest ASCCP recommendations for use of HPV testing alone for cervical cancer screening
Cervical Cancer Overview

- Cancer that develops in the cervix of the uterus
- Over 12,000 women in the US are diagnosed yearly
  - Lifetime risk of developing cervical cancer - 0.78%
  - More than 4,000 of women will die annually
- 4th most common cancer for women worldwide
- Deaths in the US decline by ~ 2 % a year due to screening with the PAP test
- Most women who have abnormal cervical cell changes that progress to cancer have never had a Pap test or have not had one during prior 3-5 years
Cervical Cancer: Worldwide Incidence and Death Rate

Estimated age-standardized rate per 100,000

Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012.
Cervical Anatomy

• Ectocervix: portion of the uterus that extends into the vagina usually pink color and covered with flat, thin cells called squamous cells.
• Endocervix: cervical canal lined by columnar cells.
• “Transformation zone” (T-zone): area where ectocervical squamous cells transition to endocervical columnar cells
• T-zone most likely location for abnormal or precancerous cells to develop.
Cervical Microscopic View
Human Papilloma Virus (HPV)

- Over 100 different genotypes of HPV exist
- Approximately 50% infect the genital tract
- Human papillomavirus (HPV) is found in about 90+% of cervical cancers
- Infections with different HPV genotypes have varying risk of cancer development
  - High-risk HPV types are classified as carcinogenic for humans
  - Probable high-risk types have some evidence of carcinogenicity
  - Low risk types occur infrequently in cervical carcinoma
- Over 65% of cervical cancer cases can be attributed to HPV-16 and HPV-18
Prevalence and Incidence of HPV Infection

- Approximately 20 million people are currently infected with HPV in the United States\(^1\)
- Annual incidence of sexually transmitted HPV infection is \(\sim 5.5\) million\(^1\)
  - \(\sim 1.4\) million (1\%) individuals currently have genital warts in the United States\(^2\)
  - \(\sim 15\%\) of adults have subclinical infection\(^2\)
- Overall, an estimated 75\% of sexually active men and women have been exposed to HPV at some point in their lives\(^2\)
- HPV incurs the highest direct medical costs of all STDs other than HIV, at $1.6 billion annually\(^3\)

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HPV = human papilloma virus; STDs = sexually transmitted diseases.

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>Risk Association for development of dysplasia or neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 &amp; 59</td>
<td>High Risk (HR)</td>
</tr>
<tr>
<td>HPV-26, 30, 34, 53, 66, 67, 68, 69, 70, 73, &amp; 82</td>
<td>Probable High Risk</td>
</tr>
<tr>
<td>HPV-6, 11, 32, 40, 42, 43, 44, 54, 57, 61, 62, 71, 72, 74, 77, 81, 83, 84 &amp; 89</td>
<td>Low Risk</td>
</tr>
<tr>
<td>All other types: i.e., 41, 49, ect</td>
<td>Insufficient epidemiological data to assign risk association</td>
</tr>
</tbody>
</table>
Transmission of HPV

- Genital HPV infection is transmitted by intimate sexual contact
- Risk factors:
  - Early age at first intercourse
  - Multiple sexual partners
  - Intercourse with a person who has external genital warts
  - Smoking also increases risk
  - Women who are immunocompromised (HIV infection, organ transplant recipients or those on immunosuppressive medication) are at higher risk for infection
    - Hormonal contraceptives
  - Women with genital herpes or chronic chlamydia infection may be at increased risk
HPV Infection in the United States*

25% - Genital warts
10% - Detected by colposcopy
4% - HPV DNA positive: Colposcopy negative
1% - Presence of antibodies (negative HPV test)
60% - Not currently infected

~75% of population exposed to HPV

*Men and women ages 15-49.
Infection with HPV

- HPV is estimated to be the most common sexually transmitted infection in the US.
  - By age 50, estimated up to 80% of women have been infected with HPV
- The majority of women infected with the HPV virus do NOT develop cervical cancer.
- For most women the HPV infection does not last long
  - 70-75% of infections resolve on their own within 1 year; 90% within 2 years
- A small number of women (est 10-20%) do not clear the HPV virus and are considered to have “persistent infection.
- A woman with a persistent HPV infection is at greater risk of developing cervical cell abnormalities and cancer than a woman whose infection resolves on its own.
- HPV can also infect the vaginal lining, vulva and perianal area, oral and upper respiratory tract
Natural History of Cervical Carcinogenesis

Normal Cervix -> Infection -> HPV-Infected Cervix

HPV-Infected Cervix -> Progression -> Precancer

Precancer -> Invasion -> Cervical Cancer

Mild Cytologic and/or Histologic Abnormalities

Cervical Carcinogenesis

- Following inoculation (typically late teens, early 20s), infection enters latency period (1–8 months)
  - Most clear infection with no detectable HPV lesions
  - In some women, may last years to decades
- If immune system doesn’t suppress virus, active growth phase occurs (3–6 months) with detectable lesions (PAP)
  - Treatment during this time may be unsuccessful with regrowth at same or additional new sites
- If infection persistent, genetic damage occurs over time resulting in cancerous cells (carcinoma in situ, 8-9 years)
- Transition from carcinoma in situ to microinvasive cancer takes a long time (12 years, median age 41) with invasive carcinoma not for another 7 years after that.
Cervical Infection with HPV

- Abnormal areas on visible exam of cervix
  - Whitened areas (Acetowhite), warts, condylomas
- Abnormal cells in PAP smears
  - Atypical squamous cells of undetermined significance (ASCUS)
  - Abnormal cells (premalignant or malignant)
- Altered cell growth patterns in tissue biopsies
  - OR NO VISIBLE CHANGE
- Detectable viral DNA by molecular probes in cellular samples from infected tissue
  - More sensitive and reliable, hence recent recommendations
Grading of Cervical Pathology

• Three systems commonly used (interchangeably)
  • Dysplasia/Carcinoma system – surgical pathology
    o Mild, moderate, severe, carcinoma in situ (CIS)
    o Invasive squamous cell carcinoma
  • Cervical intraepithelial neoplasia (CIN) - culposcopy
    o CIN 1, CIN 2, CIN 3, CIS
  • Bethesda System (2001) - cytology
    o Low grade squamous intraepithelial lesion (LSIL)
    o High grade squamous intraepithelial lesion (HSIL)
    o NILM: Negative for intraepithelial lesions or malignancy
    o Carcinoma
# Cervical Dysplasia Terminology

<table>
<thead>
<tr>
<th>Graded Dysplasia</th>
<th>Cervical Intraepithelial Neoplasia (CIN)</th>
<th>The Bethesda System</th>
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</thead>
<tbody>
<tr>
<td>Mild dysplasia</td>
<td>CIN I</td>
<td>Low-Grade Squamous intraepithelial lesion</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>CIN II</td>
<td>High-Grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>Severe dysplasia/Carcinoma in-situ</td>
<td>CIN III</td>
<td></td>
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![Illustration of cervical dysplasia stages with images](image-url)
Cervical Manifestations of HPV

Subclinical condyloma
- Seen only after application of acetic acid

Clinically overt condyloma

Subclinical papillomavirus infection

Clinically overt warts
Cervical Dysplasia

- Normal
- Mild Dysplasia
- Moderate Dysplasia
- Severe Dysplasia
Cervical Intraepithelial Neoplasia
(AKA Dysplasia)
Liquid-Based PAP

Difficult to visualise: the conventional Pap test slide under a microscope

Clear and more effective: the ThinPrep® Pap test slide under a microscope

With a conventional Pap test, up to 80% of cells collected may not make it to the slide. And they can appear overlapped and crowded, making a correct diagnosis difficult.³
Diagnostic Procedures

Colposcopy

Cervical biopsy ("punch"): small tissue samples are taken from the cervix and examined for disease or other problems.
Cervical Cancer Screening Guidelines

- Guidelines developed by American Society of Colposcopy and Cervical Pathology (ASCCP) and consortium of national OB/GYNs
- Included more age-specific guidelines
  - Don't start testing until age 21, regardless of behavior, risk factors, and age at first sex.
  - For women aged 21-29, cytology screen only every 3 years and do not conduct HPV testing.
  - Age 30 through 65, co-test every 5 years with both cytology and HPV testing. A high-risk HPV DNA test is the preferred recommendation, but cytology alone every 3 years is also acceptable. HPV testing alone is not.
  - After age 65, future screening recommendations depend on past screening results. If previous tests have been negative, no more screenings needed. Negative [in this case] means 3 consecutive negative cytology results or 2 consecutive co-testing results in the past 5 years.
  - Women with a history of CIN2, CIN-3, or adenocarcinoma can't stop screening at age 65. They must continue screening.
2012 Guideline Changes (cont)

- Cytology reported as negative but lacking endocervical cells could be managed without early repeat.
- CIN 1 on endocervical curettage should be managed as CIN 1, not as a positive ECC.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Genotyping triages HPV-positive women with HPV type 16 or type 18 to earlier colposcopy only after negative cytology.
- Colposcopy is indicated for all women with HPV and ASC-US, regardless of genotyping result.
2012 Guideline Changes (cont)

- For ASCUS cytology, immediate colposcopy is not an option.
- Serial cytology option for ASC-US incorporates cytology at 12 months, not 6 months and 12 months, and then if negative, cytology 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 65 years.
- The pathway to long-term follow-up of treated and untreated CIN 2+ more clearly defined by incorporating co-testing.
- 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 years are managed conservatively.
Example ASCCP algorithm

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

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

Routine Screening

Observation with Colposcopy & Cytology*
@ 6 month intervals for up to 2 years

Other Results

High-grade colposcopic lesion or HSIL Persists for 1 year

HSIL Persists for 24 months with no CIN2,3 identified

Biopsy

CIN2,3

Manage per ASCCP Guideline for Young Women with CIN2,3

Diagnostic Excisional Procedure†

(If no CIN2,3, continue observation)

* 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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ASCCP Interim Clinical Guidance: Primary hrHPV Cervical Cancer Screening (Aug’14)

• Use of hrHPV testing alone for primary cervical cancer screening in women can be considered an alternative to current cytology-based screening methods
  o Cytology alone and cotesting are still recommended approach
  o Prompted by recent FDA approval of HPV DNA test for primary cervical cancer screening (no cytology co-testing)
  o Overwhelming evidence that HPV testing is more reproducible than PAP testing
  o HPV testing identifies more precancerous lesions

• Rescreening after a negative hrHPV should not occur sooner than every 3 years

• Primary hrHPV screening shouldn’t be initiated prior to 25 years of age.

"Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance."  
Gynecologic Oncology DOI: 10.1016/j.ygyno.2014.12.022
Suggested hrHPV Screening Protocol

Diagram:
- **Primary HPV Screening**
  - 12 other hrHPV +
    - Cytology
      - ≥ASC-US
      - NILM
        - Follow up in 12 months
      - Negative
        - Routine Screening
    - Type 16/18 Positive
      - Colposcopy
Challenges of Cervical Cancer Screening and Prevention

• Extended PAP/HPV screening intervals creates wrong impression for women that other essential health screening activities (pelvic exam, breast exam, DM and BP screening etc.) don’t need to be done annually
• Occurrence of HSIL/CIS late teens and early 20’s
• Possible lab requirement to utilize FDA approved hrHPV test methodology vs. custom in-house validated lab methods (LDTs)
• Completion of follow-up testing and treatment within program standards (90 days)
• Improving HPV vaccination rates
  o 90+% cancers thought to be preventable by vaccination
• See Test and Treat programs (College of American Pathologists)
Questions?