An Update on HPV and Cervical Cancer Prevention

Nancy R. Berman MSN, ANP-BC, NCMP, FAANP
Adult Nurse Practitioner/Colposcopist
Certified Menopause Practitioner (NAMS)
Millennium Affiliated Physicians
Division of Michigan Healthcare Professionals
Farmington Hills, Michigan
Clinical Instructor
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Detroit, Michigan
Disclosures

Advisory Board: Hologic
Advisory Board: LabCorp
Objectives

At the end of this session, the attendee will:

1. Describe the role of persistent oncogenic HPV in the development of pre-cancer and cancer of the cervix
2. List the current Advisory Committee on Immunization Practice (ACIP) recommendations for appropriate use of 2 or 3 doses of 9vHPV Vaccine
3. Describe the use of HPV testing as co-testing along with the Pap in cervical cancer screening in women 30 and older
4. Describe the use of HPV primary screening in women 25 and older
The Burden of HPV Disease
High Lifetime Risk of HPV Infection

• 6.2 million new infections
• Approximately 20 million people in US currently are infected with HPV
• By age 50, 80% of sexually active women will have acquired genital HPV infection

Most people will never know that they have been infected!

HPV and Non-Cervical Cancers

• HPV 16
  ▪ Evidence of causal role in cancer of vagina, vulva, penis, anus, oral cavity, oropharynx; limited evidence for carcinogenicity in the larynx

• HPV 18
  ▪ Limited evidence of carcinogenicity in vagina, vulva, penis, anus, oral cavity, larynx

• HPV 6 and 11
  ▪ Limited evidence of carcinogenicity in vulva, penis, anus, larynx

## Cancers Caused by HPV: U.S.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Male</th>
<th>Female</th>
<th>Both Sexes</th>
<th>Percentage per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anus</td>
<td>1,400</td>
<td>2,600</td>
<td>4,000</td>
<td>91%</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>10,400</td>
<td>10,400</td>
<td>91%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>7,200</td>
<td>1,800</td>
<td>9,000</td>
<td>72%</td>
</tr>
<tr>
<td>Penis</td>
<td>700</td>
<td>0</td>
<td>700</td>
<td>63%</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>600</td>
<td>600</td>
<td>75%</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>2,200</td>
<td>2,200</td>
<td>69%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>9,300</strong></td>
<td><strong>17,600</strong></td>
<td><strong>26,900</strong></td>
<td></td>
</tr>
</tbody>
</table>

You Are the Key to HPV Cancer Prevention, CDC

CDC, United States Cancer Statistics (USCS), 2006-2010
HPV and Cervical Cancer

Virtually all cervical cancers are associated with persistent infection with high-risk HPV types

- Data from a variety of studies have confirmed that certain HPV types are associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Others are probably associated: 26, 53, 66, 68, 73, 82

Oncogenic HPV is a necessary cause of cervical cancer!

Role of Persistent Infection

- Persistent infection with high-risk types of HPV is necessary for the progression of high-grade lesions to invasive cancer.
- Average episode lasts 4-20 months.
- <50% of women have same type 1 year later.
- Type 16 has a greater risk of persistence.

Risk Factors for *Persistent* HPV Infection and/or Neoplastic Progression

- Smoking
- HPV type
- Increasing age
- Lack of condom use
- Immunodeficiency (eg, HIV)
- Possibly OC use
- Possibly other STIs, such as chlamydia

HPV and Cervical Cancer
Putting Risk Into Perspective

• Risk (odds) of cervical cancer with HPV 16 compared with HPV (−) is 455.

• Risk of lung cancer in U.S. white male smoker compared with nonsmoker is only 8.

• Risk of breast cancer with hormone replacement therapy is only 1.8.
Natural History of HPV & Cervical Cancer

Persistence

Normal Cervix

Infection

Clearance

HPV Infection

Progression

Regression

Pre-cancer

Invasion

Cancer

Courtesy of M. Schiffman, National Cancer Institute.
Why Is the Cervix At Risk

Understanding Transformation Zones
Transformation Zones and HPV Infection

- Area where one type of epithelium contacts and gradually replaces another through process of metaplasia
- Present in cervix, anus, tonsils
- Areas of HPV-related carcinogenesis

Moscicki AB. *Vaccine*. 2006.
Cervical Transformation Zone

HPV Vaccines
Adolescent Vaccination Coverage
United States, 2006-2013

You Are the Key to HPV Cancer Prevention, CDC
HPV Vaccine Comparison

<table>
<thead>
<tr>
<th>HPV Types Included in Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

- **Bivalent**
  - Genital warts
  - ~66% of Cervical Cancers

- **Quadrivalent**
  - Genital warts
  - ~15% of Cervical Cancers

- **9-valent**

These HPV Types Cause: Genital warts, ~66% of Cervical Cancers, ~15% of Cervical Cancers
Advisory Committee on Immunization Practice (ACIP)

Recommendations

**Current Recommendations: Advisory Committee on Immunization Practice (ACIP)**

Updated Recommendations of the Advisory Committee on Immunization Practices

- Routine and catch-up age groups
  - Can be started at age 9
  - Females through age 26
  - Males through age 21 who were not adequately vaccinated previous
  - Males age 22 through 26 may be vaccinated

*The number of recommended doses is based on age at administration of the first dose*

- Before age 15: 2 injections
- After age 15: 3 injections

HPV Vaccine Safety
• Ongoing safety monitoring has shown most reports are non-serious
• Among the 7.6% of reports coded as “serious,” most frequently cited possible side effects are headache, nausea, vomiting, and fever
• Syncope (fainting) continues to be reported following vaccination among adolescents
• Adherence to a 15-minute observation period after vaccination is encouraged
• More injection-site reactions expected among those who receive 9vHPV
#1 Reason That a Parent Doesn’t Vaccinate Their Child

“My Healthcare provider didn’t recommend it. I didn’t know it was so important.”

Newitt V, HPV Vaccination, Advance for Nurse Practitioners, July/August, 2015
Make a Strong Recommendation

Evidence shows that:

A health care provider recommendation to get vaccinated, is the single most influential factor in determining whether a parent gets an immunization for their child!

Frieden, MD, MPH, CDC Director, Morbidity and Mortality Weekly Report, 7/25/13
Cervical Cancer Prevention

Pap and HPV Testing
Goal of Cervical Cancer Screening

• Prevent morbidity and mortality from cervical cancer by:
  ▪ Identifying and treating high-grade cervical cancer precursors
  ▪ Avoiding unnecessary and potentially hazardous evaluations and treatment
  ▪ Minimizing costs to healthcare system

*Increase benefit and decrease harm!

Being rarely or never screened is the major contributing factor to most cervical cancer deaths today.
Guidelines: Age to Start Cervical Cancer Screening

ACS/ASCCP/ASCP, ACOG, USPSTF agree:

• Start at age 21 regardless of age of sexual debut

## Cervical Cancer Incidence by Age Group, USCS*, 1998-2002

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>0.1</td>
</tr>
<tr>
<td>20-29</td>
<td>4.5</td>
</tr>
<tr>
<td>30-39</td>
<td>13.9</td>
</tr>
<tr>
<td>40-49</td>
<td>16.5</td>
</tr>
<tr>
<td>50-64</td>
<td>15.4</td>
</tr>
<tr>
<td>65+</td>
<td>14.6</td>
</tr>
<tr>
<td>All ages</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Guidelines: Cervical Cancer Screening Interval

ACS/ASCCP/ASCP and ACOG

- Pap testing every 3 years for women ages 21-29
- Preferred for women 30 and older: Cotesting with Pap and HPV test every 5 years
- Acceptable for women 30 and older: Pap testing alone every 3 years

Guidelines: Cervical Cancer Screening Interval (Continued)

• USPSTF
  - Pap testing every 3 years for women ages 21-65
  - For women ages 30-65, may have Pap test plus HPV test every 5 years to extend screening interval

Moyer VA on behalf of the USPSTF. *Ann Intern Med.* 2012.
Factors Indicating Need for More Frequent Screening

• HIV infection
• Immunosuppression
• DES exposure in utero
• Previous treatment for CIN 2, CIN 3, or cancer

Guidelines: Age to Stop Cervical Cancer Screening

- ACS, ASCCP, ASCP, and ACOG
  - Can stop screening in women older than age 65 with no history of CIN2 within the past 20 years and with evidence of adequate negative screening*

- USPSTF
  - Can stop at age 65 if adequate recent screening with normal Pap tests and are not at high risk for cervical cancer

* defined as 3 consecutive normal Pap tests or 2 consecutive negative cotests within preceding 10 years, with the most recent test occurring within the past 5 years.

Guidelines: Screening Post-Hysterectomy

ACS/ASCCP/ASCP, ACOG, USPSTF Guidelines

• Recommend against routine screening if hysterectomy performed for benign disease and no history of high-grade precancer or greater

HPV Testing
Why Test for HPV?

• Persistent high risk HPV is necessary for the development of cervical cancer

• An obvious corollary is that the absence of HPV means that the risk of cervical cancer is negligible

The negative predictive value for combined HPV Testing and the Pap has been shown to be 99.21% for CIN3.

HPV Testing for Screening: Stratifies Risk

• Allows for less frequent testing
• Identifies women who need increased surveillance

## FDA Approved HPV Tests

<table>
<thead>
<tr>
<th>Available Tests</th>
<th>HPV Types Detected</th>
<th>Identifies HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hybrid Capture 2</td>
<td>High and low risk panels (request high risk only)</td>
<td>No</td>
</tr>
<tr>
<td>Cervista HPV HR</td>
<td>High risk</td>
<td>No (add on test for 16 and 18)</td>
</tr>
<tr>
<td>cobas HPV Test</td>
<td>High risk</td>
<td>Yes for 16 and 18</td>
</tr>
<tr>
<td>APTIMA HPV mRNA assay</td>
<td>High risk</td>
<td>No (add on test for 16, 18, and 45)</td>
</tr>
<tr>
<td>Onclarity</td>
<td>High risk</td>
<td>Yes for 16,18, 45</td>
</tr>
</tbody>
</table>

ASFCCP. *Educate the Educators: HPV and the HPV Vaccines.* 2018
Screening Interval for Combined Pap and HPV Testing in Women 30 and Older: Co-Testing

<table>
<thead>
<tr>
<th>HPV Result</th>
<th>Cytology</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Cotest in 5 years</td>
</tr>
<tr>
<td>Negative</td>
<td>ASC-US</td>
<td>Cotest in 3 years</td>
</tr>
<tr>
<td>Positive</td>
<td>ASC-US</td>
<td>Colposcopy</td>
</tr>
<tr>
<td>Negative</td>
<td>LSIL</td>
<td>Repeat cotesting in 1 year preferred; colposcopy acceptable</td>
</tr>
<tr>
<td>Positive</td>
<td>Pap &gt; LSIL</td>
<td>Colposcopy</td>
</tr>
<tr>
<td>Any</td>
<td>HSIL</td>
<td>Colposcopy or immediate loop electrosurgical excision</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Option 1: Cotest in 12 months Option 2: Reflex to genotyping for HPV 16/18. If positive, colposcopy. If negative, cotest in 12 months</td>
</tr>
</tbody>
</table>

Genotyping to Triage Women ≥30 with Pap-/HPV+ Results

Genotyping

Positive for 16 or 18 → Immediate colposcopy

Negative for 16 and 18 → Co-testing in 12 months
## Management of Repeat Testing After HPV +, Cytology - Results

<table>
<thead>
<tr>
<th>HPV Result</th>
<th>Cytology</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Repeat cotesting in 3 years</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Perform colposcopy</td>
</tr>
<tr>
<td>Any</td>
<td>Pap &gt; ASC-US</td>
<td>Perform colposcopy</td>
</tr>
</tbody>
</table>

Primary HPV Testing for Cervical Cancer Screening

Stand-alone HPV test
2014 FDA Approval for Primary HPV Testing for Cervical Cancer Screening

Rationale

• More sensitive and reproducible than cytology
• Assesses current and future risk
• More cost-effective for large-volume screening
• May be more useful in women vaccinated against HPV
FDA Approved Tests for Primary HPV Screening (Stand Alone Testing)

• cobas HPV Test
  ▪ Provides genotyping for HPV 16 and 18 concurrently with testing for the presence of 12 other “high-risk” HPV types

• Onclarity Test
  ▪ Provides genotyping for HPV 16, 18, 45 and concurrently with testing for the presence of 11 other “high risk” types
Women with HPV16 and HPV18 infections are more likely to develop high-grade disease

Interim Clinical Guidance

Primary hrHPV screening should not be initiated before 25 years of age

- In Athena, 30% of CIN3+ cases were found in women between 25 and 29 years of age
- More than half of women from 25-29 with CIN3+ had normal cytology
- Primary hrHPV screening can be considered as an alternative to current U.S. cytology alone or co-testing
The HPV primary screening algorithm

Countries Implementing HPV Primary Screening

- **Netherlands**: Minister of Health approved HPV primary screening beginning in 2016
- **Australia**: National Health Service adopted screening with HV 16/18 genotyping starting at age 25 y at 5-yr intervals up to age 70-74
- **United Kingdom**: Evaluating in large national pilot study at 6 National Health Service screening sites including London, Liverpool, and Manchester.
- **Italy**: A number of regions have adopted primary screening
USPSTF: Current Draft Guidelines

• Pap every 3 years age 21 and older
• HPV testing alone every 5 years starting at age 30
• Co-testing with Pap and HPV no longer recommended
Algorithms Are Available!

2012 American Society for Colposcopy and Cervical Pathology (ASCCP) Guidelines

www.asccp.org
Download Algorithms

Mobile App: iPhone and Android
Anal Cancer

HPV
Anal Cancer

• Incidence relatively low compared with cervical cancer
• Incidence is increasing in both men and women by about 2% a year
• Reason for the increase is not well understood
• Men who have sex with men (MSM) shown to be one the populations at highest risk
• Anal receptive intercourse is a risk factor but is not necessary for anal cancer to develop

Anal Cancer

- History of HPV associated lesions at genital sites other than the anus are associated with anal cancer
- Immunosuppression is an important risk factor for anal cancer
- Solid organ transplant recipients of heart, kidney and lungs
- HIV- associated immunosuppression
- Anal cancer is associated with high-risk types of HPV (16 and 18 are identified in about 80%)

Anal Cancer Screening

- Anal screening
- Cytologic screening
- High resolution anoscopy (HRA)
- HRA directed biopsy
- Treatment of high grade anal intraepithelial neoplasia (HGAIN) aims to prevent invasive anal squamous cell cancer

Current Status of Screening Recommendations

- Routine anal cytology screening is NOT recommended by CDC, USPSTF, ACS, or ISDA
- National Guidelines Clearinghouse has no guidelines for anal cytology screening
- However New York State Department of Health now recommends anal cytology for HIV-infected individuals who: 1) are MSM, 2) have had genital warts or 3) have had CIN

Head and Neck Cancer

HPV
## Incidence in United States

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>11,710</td>
<td>28,540</td>
<td>40,250</td>
</tr>
<tr>
<td>Larynx</td>
<td>2,520</td>
<td>9,840</td>
<td>12,360</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14,230</td>
<td>38,380</td>
<td>52,610</td>
</tr>
</tbody>
</table>

HPV as a Risk Factor

- Incidence of HPV-positive oropharyngeal cancers increased by 225% from 1998 to 2004 (0.8 per 100,000 to 2.6 per 100,000)

- Incidence of HPV-negative cancers declined by 50% (2.0 per 100,000 to 1.0 per 100,000)

- If trends continue, incidence of HPV-positive oropharyngeal cancers will be greater than incidence of cervical cancers by 2020.

## Differences

<table>
<thead>
<tr>
<th></th>
<th>HPV positive</th>
<th>HPV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Tonsil, base of tongue</td>
<td>Various sites</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>Sexual behavior</td>
<td>Tobacco, alcohol</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>Better</td>
<td>Worse</td>
</tr>
</tbody>
</table>

Survival probability: HPV-negative vs. HPV-positive tumors

• Only HPV-positive oropharyngeal cancer patients showed significantly better survival when compared with all head and neck patients

• Best survival from oropharyngeal cancer:
  ▪ HPV-positive with no history of smoking

• Worst survival from oropharyngeal cancer:
  ▪ HPV-negative with a history of smoking

Oropharyngeal Cancer

Located in middle of the throat: base of the tongue, tonsils, soft palate, walls of the pharynx.

- No precursor lesions or biomarkers
- Data does not support the role of saliva tests
- Often presents as lymphadenopathy with the cancer deep in the tonsillar crypts
- Oral HPV or cancer in monogamous couples: no current recommendation to change behavior

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.

Release Date: November 2013

American Cancer Society Guidelines

“...the cancer-related check-up should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling...”

Counseling Patients with HPV

Remind your patient that:
• Most people will have HPV at some point.
• There is no way of knowing how long HPV has been present.
• Having HPV is not a sign of infidelity or promiscuity.
• Most women who have HPV do not develop abnormal cells or cancer.
• Most HPV infections will go away on their own in a relatively short time.
Summary

• HPV Vaccine is a cancer prevention vaccine
• Your recommendation is the most significant factor in whether age appropriate young men and women are vaccinated
• HPV vaccination is underutilized in the U.S.
Summary

The 2012 Guidelines for cervical cancer prevention

• Identifies low risk women (HPV and Pap negative) and reassures them about safety of longer screening interval
• Identifies truly at-risk women with persistent HPV … Follow them diligently
• FDA approval of HPV testing as a primary screen, April 2014

Never has education of patients and practitioners been more important!
Summary

- Majority of cervical cancer in U.S. occurs in women who have not been screened or infrequently screened

_Improving access to screening for these women will have a great impact on the prevention of cervical cancer!_
References


