Screening for Cervical Cancer: Update on Guidelines
Holly B Fontenot, PhD, RN, WHNP-BC
DISCLOSURES

• There has been no commercial support or sponsorship for this program.
• The planners and presenters have declared that no conflicts of interest exist.
• The program co-sponsors do not endorse any products in conjunction with any educational activity.
Boston College Connell School of Nursing Continuing Education Program is accredited as a provider of continuing nursing education by the American Nurses Association Massachusetts, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.
SESSION OBJECTIVES

- Identify correct national guidelines and recommendations for cervical cancer screening for women.
- Describe the multi-strain nature of the HPV virus and its causal relationship with cancers in men and women, primarily cervical cancers in women.
- Recognize how emerging HPV science influences cervical cancer screening guidelines.
An update: HPV & Cervical Cancer Screening Guidelines

Holly B. Fontenot, PhD, RN, WHNP-BC
Assistant Professor, Boston College
Director, WHNP Program
Adjunct Faculty, The Fenway Institute
NP, Fenway Health/Sidney Borum Health Center
Outline:

• Updates on HPV
  • A Review, then...
  • Discussion of Latest and Emerging Science
  • How this impacts our cervical cancer screening practices

• Review of American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines
Papillomaviruses

- Papillomaviruses are small double-stranded DNA viruses that infects squamous epithelia
- They are species specific
  - Therefore Human Papillomavirus (HPV) only infects humans
- This virus is classified according to it’s issue tropism (mucosal or cutaneous) and oncogenic potential
Human Papillomavirus (HPV)

- HPV is a virus family with over 100 types
- 40 types infect human mucosal surfaces
  - These types discussed as sexually transmitted
- Certain types (13-25) are **oncogenic** (**high risk**) and persist to cause cancers
- Certain types are **Non oncogenic** (**low risk**) cause genital warts (condyloma) and rarely, juvenile-onset recurrent respiratory papillomatosis (RRP)
HPV mucosal types

- U.S. & Globally HPV is the **most common STI**
- 20 million Americans are currently infected, with 6 million new cases each year
- National prevalence data (documented rates):
  - Females as high as 53.8% (ages 20-24 yrs)
  - Males ranging from 52% to 69%
- 290 million women globally have HPV
- Disparities in STIs exist in the adolescent population—same is true for HPV
  - Approximately 50% of all new HPV infections are among youth ages 15-24

(CDC, 2013; WHO 2014; Dunne, 2011; Giuliano, 2009)
HPV Transmission

• Predominate route is via sexual contact
  ▫ Genital to genital contact
  ▫ Oral to genital (oral sex)
  ▫ Vaginal and anal intercourse
• Vertical transmission (far less common, but possible)
  ▫ Mother to child- not well understood
• Horizontal transmission and other route?
  ▫ Possible routes include: fingers and mouth, and skin contact outside of sexual contact
  ▫ ? Self inoculation to other sites
HPV Transmission

- Males and females may have HPV and transmit it without knowing
  - Transmission occurs without outward signs and symptoms
- Persons can still have HPV even if they have not had sexual contact for years
- It is possible to carry more than one type of HPV

- It is difficult to determine transmission, duration, and incubation—may take months or years for any abnormalities to appear
U.S. data

**HPV Cancers**

- In general overall incidence of CA in the U.S. has decreased for men and is stable for women
- However, rates have increased for 2 HPV associated CA: oropharyngeal and anal
- HPV associated CA accounts for
  - 3.3% of cancers in women (~21,700 cases)
  - 2% of cancers in men (~11,700)
- HPV related cancers for men are on the rise and affect younger men 3:1

**Condylomas**

- HPV caused anogenital and oral condylomas are pervasive
  - ~1 million new cases each year
### CDC: Number of HPV-Attributable Cancer Cases per Year

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Male</th>
<th>Female</th>
<th>Both Sexes</th>
<th>Percentage probably caused by HPV</th>
<th>Number probably caused by HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Anus</td>
<td>1,549</td>
<td>2,821</td>
<td>4,370</td>
<td>91%</td>
<td>1,400</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>11,422</td>
<td>11,422</td>
<td>91%</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>9,974</td>
<td>2,443</td>
<td>12,417</td>
<td>72%</td>
<td>7,200</td>
</tr>
<tr>
<td>Penis</td>
<td>1,048</td>
<td>0</td>
<td>1,048</td>
<td>63%</td>
<td>700</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>735</td>
<td>735</td>
<td>75%</td>
<td>0</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>3,168</td>
<td>3,168</td>
<td>69%</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>12,571</strong></td>
<td><strong>20,589</strong></td>
<td><strong>33,160</strong></td>
<td></td>
<td><strong>9,300</strong></td>
</tr>
</tbody>
</table>

*Individual cells may not sum to total due to rounding.*
HPV associated cancers

Total (N = 34,788)
- Oropharynx: 32.7% (n = 11,388)
- Anus: 2.1% (n = 734)
- Cervix: 9.3% (n = 3,242)
- Vagina: 2.9% (n = 1,001)
- Vulva: 15.6% (n = 5,434)
- Penis: 37.3% (n = 12,989)

Men (N = 13,446)
- Oropharynx: 14.4% (n = 1,934)
- Anus: 7.4% (n = 1,001)
- Cervix: 37.3% (n = 12,989)
- Vagina: 37.3% (n = 12,989)
- Vulva: 15.6% (n = 2,101)
- Penis: 5.3% (n = 711)

Women (N = 21,342)
- Oropharynx: 11.6% (n = 2,478)
- Anus: 16.4% (n = 3,500)
- Cervix: 78.2% (n = 10,511)
- Vagina: 53.4% (n = 11,388)
- Vulva: 15.2% (n = 3,242)
- Penis: 3.4% (n = 734)
Vaccination has been established as the primary preventative strategy to reduce HPV related diseases.

“HPV vaccination, one of the most remarkable discoveries of the past decade, is currently implanted all around the world and is expected to prevent a substantial proportion of cervical and other HPV-related cancers in the future”

(Trottier, 2011)
HPV Vaccines

• Bivalent Vaccine (Cervarix®)(HPV2)
  ▫ HPV 16 and 18
    • HPV related pre-cancers and cancers

• Quadrivalent Vaccine (Gardasil®)(HPV4)
  ▫ HPV 6, 11, 16 and 18
    • HPV related pre-cancers and cancer
    • Genital warts in women and men

• Nanovalent Vaccine (Gardasil 9®)(HPV9)
  ▫ HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
    • HPV related pre-cancers and cancer
    • Genital warts in men and women
    • Now 90% coverage for cervical cancers
Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Cancers Worldwide

Type Attribution by Cancer Site, US

- HPV 16/18
- HPV 31/33/45/52/58
- Other HPV
- HPV Negative

Saraiya et al, February 2014, ACIP
Vaccine Safety

• According to the National Cancer Institute there has not been any serious side effects and the most common problems have been brief soreness and/or local symptoms at the injection site.

• The most common adverse events have been reported as (rate per 100,000 doses):
  ▫ Syncope (8.2), local site reactions/pain (7.5), dizziness (6.8), nausea (5.0), headache (4.1), hypersensitivity (3.1), itching (2.6)
  ▫ These events not greater than any other vaccine

• More than 46 million does of vaccine have been distributed in the US as of June 2012 (primarily Gardasil®)
HPV vaccines are effective

- HPV4 and HPV2 available ~ 10 years

- Largest multinational trials of efficacy:
  - Women ≥ 1 dose, 100% efficacy against cervical precancers (16&18) and 93% efficacy against all precancers irrespective of type
  - Males 90.4% efficacy to external genital lesions and nearly 80% efficacy against anal intraepithelial neoplasia

- In a large international clinical trial of Gardasil9, reported efficacy for the 5 additional HPV types was documented at 96.7%
On the horizon... changes in dosing?

- Current dosing HPV4 and HPV9- IM- 3 doses (0, 2, 6 month schedule)
- World Health Organization (WHO) (2014) now recommend a 2-dose schedule (0 and 6 months)
  - This recommendation was following the results of a systematic review of 3 randomized studies reporting non-inferior immunogenicity among females ages 9-14 years
  - WHO’s new recommendation is: 2-dose schedule for females and males ages 9 to 13 years and 3-dose schedule for those ≥ 14 years
- The 2-dose alternative is currently being discussed and evaluated by the ACIP
- The FDA has not currently approved a 2-dose schedule; however a 2 verses 3 dose trial of HPV9 has been initiated
Vaccine uptake in U.S.

- CDC’s Advisory Committee on Immunization Practices (ACIP) is concerned about current rate of vaccination
- Not on target to meet Health People 2020 goals—80%
  - ~37% females 13-17 ≥ 3 doses; 57% ≥ 1 dose
  - ~14% males ≥ 3 doses; 34% ≥ 1 dose
- Coverage lowest in South (where cervical CA rates are the highest and recent pap test is the lowest)
Note: Australia has achieved over 80% coverage.
Lessons learned from Australia

• 90% of Australian adults view vaccines as positive
• Broad national school based vaccine programs are effective
• Australia has achieved 83% vaccine coverage in females ages 12-13 having ≥ 1 dose
• This has lead to near elimination of HPV 6 & 11 and 75% decreased incidence of 16 & 18
• Current 2014 national incidence of genital warts for those <21 = 0%; previous rates at 25%
The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination program (2011)

*Sexually Transmitted Infection*
Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study

*The Lancet, 2011*

Figure 2: Incidence of high-grade cervical abnormalities, by age group
Lessons learned

- Herd immunity is important
- Need high levels of vaccination to achieve effect, predicted to need at least 50-70% rates of vaccination to reduce or nearly eliminate genital warts
- Need higher levels to achieve significant reductions in cervical, oral, and anal cancers (70% vaccinated)
- Potentially even higher to achieve effect for MSM
- Early impact data in U.S. is emerging, showing a decline in 6, 11, 16, & 18 of 56% among females after vaccine introduction
Screening for cervical cancer

ASCCP Guidelines*
Cervical Cancer

- In U.S. cervical cancer death rate has decreased by 74% (1955-1992) due to Pap screening for cervical cancers
- Continues to decline due to impact of HPV vaccines
- Disparities exist in the U.S. (socioeconomic, region, racial/ethnic)

- Disparities even more evident globally:
  - Developing countries- Access to screening is low
  - 2nd/3rd most common cancer diagnosis
  - 4th leading cancer causing death
Goals of screening

- Prevent morbidity and mortality from cervical cancer
- **Prevent overzealous management** of precursor lesions that will most likely regress
  - Where risk of management outweigh the benefits

- Being rarely or never screened is the major contributing factor to most cervical cancer deaths today
Bethesda System terminology

• Uniform system to provide clear guidance for clinical management
• Specimen adequacy; general categorization; interpretation/result

1) **Negative for intraepithelial lesion or malignancy**
   • Organisms (Trich; candida; BV); reactive cellular changes (inflam, IUD); atrophy

2) **Epithelial Cell Abnormalities**

3) **Other**
   • Endometrial cells in a woman >40 yrs
Epithelial Cell Abnormalities

Squamous cell
- Atypical squamous cells (ASC)
  of undetermined significance (ASC-US)
  cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
  encompassing: human papillomavirus/mild dysplasia/cervical
  intraepithelial neoplasia (CIN) 1
- High-grade squamous intraepithelial lesion (HSIL)
  encompassing: moderate and severe dysplasia, carcinoma in situ;
  CIN 2 and CIN 3
- Squamous cell carcinoma

Glandular cell
- Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)
- Atypical glandular cells, favor neoplastic (specify endocervical
  or not otherwise specified)
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma
More terminology

- **Colposcopy** - examination of cervix, vagina, vulva, with colposcope after applying 3-5% acetic acid solution coupled with obtaining directed biopsies of suspected lesions (neoplasia)

- **Endocervical sampling** - specimen using endocervical curette (histopathologic eval) or using cytobrush (cytological eval)

- **Diagnostic excisional procedure** - specimen from transformation zone and endocervical canal for histopathological evaluation
  - LEEP - loop electrosurgical excision procedure
  - Laser conization
  - Cold-knife conization
  - Loop electrosurgical conization

- **Endometrial sampling** - specimen for histopathological evaluation using endometrial aspiration or biopsy device
<table>
<thead>
<tr>
<th>Cervical CA screening- Average Risk Woman**</th>
<th>ACS/ASCCP/ ASCP 2012 guide**</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>Age 21</td>
</tr>
<tr>
<td>Statement re: annual screening (reminder: average risk woman)</td>
<td>Women should not be screened annually by any screening method</td>
</tr>
<tr>
<td>Screening method and interval</td>
<td></td>
</tr>
<tr>
<td>Cytology: 21-65 yrs</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>HPV co-testing: 21-29 yrs</td>
<td>No HPV co-testing if &lt; 30 yrs</td>
</tr>
<tr>
<td>30-65 yrs</td>
<td>Every 5 yrs- preferred method</td>
</tr>
<tr>
<td>Primary HPV testing: 30-65 yrs</td>
<td>Screening by HPV testing along is not recommended in <em>most clinical settings</em>**</td>
</tr>
<tr>
<td>When to stop screening</td>
<td>Age &gt;65 yrs with adequate screening history</td>
</tr>
<tr>
<td>Screening post hysterectomy</td>
<td>If cervix is intact continue screening</td>
</tr>
</tbody>
</table>
OK... so what do you do if your Cytology Results are **not** NORMAL?
Cytology NILM* but EC/TZ Absent/Insufficient

Ages 21-29†
- HPV Negative
  - HPV Testing Preferred
  - Routine Screening

Age ≥ 30
- HPV Unknown
  - Repeat Cytology @ 3 years Acceptable
  - HPV Positive
    - Cytology & HPV Test @1 year
    - Genotyping
  - Manage per ASCCP Guideline

* Negative for intraepithelial lesion or malignancy
† HPV testing is unacceptable for screening women ages 21-29 years
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting @ 1 year Acceptable**
  - Cytology Negative and HPV Negative
    - Repeat Cotesting @ 3 years
  - ≥ ASC
    - HPV DNA Typing Acceptable
      - HPV 16 or 18 Positive
        - Colposcopy
          - Manage per ASCCP Guideline
      - HPV 16 and 18 Negative
        - Repeat Cotesting @ 1 year
          - Manage per ASCCP Guideline
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

**Repeat Cytology**  
@ 1 year  
Acceptable

- **Negative**
- **≥ ASC**

**HPV Testing**  
Preferred

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

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

**Manage per ASCCP Guideline**

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved. ASCP

* Management options may vary if the woman is pregnant or ages 21-24
† Cytology at 3 year intervals
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

**Repeat Cytology @ 12 months Preferred**
- Negative, ASC-US or LSIL → Repeat Cytology @ 12 months
- ASC-H, AGC, HSIL → Colposcopy

**HPV Positive**
- Reflex HPV Testing Acceptable for ASC-US only → HPV Negative
  - Routine Screening

**Routine Screening**
- Negative x 2
- ≥ ASC → Colposcopy
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*

**LSIL with negative HPV test among women ≥ 30 with cotesting**
- Preferred
  - Repeat Cotesting @ 1 year
    - Cytology Negative and HPV Negative
      - Repeat Cotesting @ 3 years

**LSIL with no HPV test**
- Acceptable
  - ≥ ASC or HPV positive
    - Colposcopy
      - Non-pregnant and no lesion identified
        - Endocervical sampling “preferred”
      - Inadequate colposcopic examination
        - Endocervical sampling “preferred”
      - Adequate colposcopy and lesion identified
        - Endocervical sampling “acceptable”
      - 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 pregnant or ages 21-24 years
† Management women ages 25-29 as having LSIL with no HPV test

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved. ASCCP
Additional management

- **LSIL** and pregnant → Colpo
- Atypical Squamous Cells (ASC), can not r/o **ASC-H** → Colpo
- **HGSIL** (ages 21-24) → Colpo
- **HGSIL** → Colpo or Immediate Loop Electrosurgical Excision procedure (LEEP)
- Atypical Glandular Cells (AGC) → Colpo with endocervical sampling and endometrial sampling (if ≥ 35 or at risk for endometrial neoplasia)
- Atypical Endometrial Cells → Endometrial and endocervical sampling (if no endo pathology then Colpo)
CIN 1

- CIN 1 is the histologic manifestation of HPV
  - Still commonly regresses especially in younger women
  - Progression to CIN2 is uncommon
- Risk of CIN3+ is substantially higher after history of HSIL, ASC-H, and AGC (15% 5 yr risk)
  - Relatively low rate of CIN3+ when CIN1 was diagnosed after ASCUS or LSIL (3.8% 5 yr risk)
- Management of CIN1 in endocervical samples needs special attention (? dx excisional procedure)
CIN 2 or 3

- With adequate colpo → excisional procedure, then cotesting every 12 months x 2 negative results then repeat in 3 years
- With inadequate colpo or recurrent CIN 2, 3 or endocervical sampling CIN2, 3 → excisional procedure, then cotesting every 12 months x 2, if any test is abnormal then colpo with endocervical sampling again
- For women ages 21-24 again be more conservative (either excision or... observation with colpo and cytology every 6 months... if continues to improve next step is to follow every 1 year x 2, etc...)
Adenocarcinoma in Situ (AIS)

- Incidence of AIS is low but rising
- Management is controversial
- AIS frequently extends into the endocervical canal making depths difficult to determine
- Invasive cancer can not be excluded without diagnostic excisional procedure
- Total hysterectomy remains treatment of choice for women who have completed childbearing
- Observation maybe an option with good margin status, but follow closely
- Knife conization maybe favored over loop
For further management/ reference

• Full range of algorithms

• Special populations (young women and pregnant women)

• [http://www.asccp.org/Portals/9/docs/ASCCP%20Management%20Guidelines_August%202014.pdf](http://www.asccp.org/Portals/9/docs/ASCCP%20Management%20Guidelines_August%202014.pdf)
The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, M.D., Terence J. Colgan, M.D., J. Thomas Cox, M.D., Debra S. Heller, M.D., Michael R. Henry, M.D., Ronald D. Luff, M.D., Timothy McCallmon, M.D., Ritu Nayar, M.D., Joel M. Palefsky, M.D., Mark H. Stoler, M.D., Edward J. Wilkinson, M.D., Richard J. Zaino, M.D., David C. Wilbur, M.D., and For Members of the LAST Project Work Groups

Interim Guidance for Managing Reports using the Lower Anogenital Squamous Terminology (LAST) Histopathology Diagnoses

FIG. 20. Pathology diagnoses using p16 and potential clinical management options for cervical biopsies. A. Use of p16 to evaluate the differential diagnosis of HSIL versus a mimic, such as immature squamous metaplasia and atrophy. B. Use of p16 to evaluate morphologic CIN2. The choice of clinical management for HSIL depends on the entire clinical scenario including patient’s age, colposcopic findings, and biopsy diagnosis. Management options include excisional therapy (cold knife cone, LEEP), ablative therapy (cryotherapy, laser vaporization) and close observation, as during pregnancy. Modified with permission. Courtesy of Philip E. Castel.
Latest Science

Clinical Commentary

Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance

Warner K. Huh a,*, Kevin A. Ault b, David Chelmow c, Diane D. Davey d, Robert A. Goulart e, Francisco A.R. Garcia f, Walter K. Kinney g, L. Stewart Massad h, Edward J. Mayeaux i, Debbie Saslow j, Mark Schiffman k,1, Nicolas Wentzensen k,1, Herschel W. Lawson l, Mark H. Einstein m

Article provides guidance for the clinical use of primary hrHPV screening
HPV Primary Screening

- Growing body of evidence to support HPV primary screening
  1. A negative hrHPV test provides greater reassurance of low CIN3+ risk than negative cytology alone
  2. Because of equivalent or superior effectiveness, hrHPV screening can be considered an alternative
  3. Triage of hrHPV positive women using combination of genotyping for HPV 16&18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears reasonable
  4. Rescreening after negative hrHPV screen should occur no sooner than every 3 yrs
  5. Primary hrHPV screening should not be initiated prior to age 25 yrs
Clinical Commentary

Primary HPV Screening → 12 other hrHPV + → Cytology

Type 16/18 Positive → Colposcopy

≥ASC-US → Follow up in 12 months

NILM

Negative → Routine Screening

Fig. 1. Recommended primary HPV screening algorithm.
Conclusion and things to come...

- Currently there is only one assay for HPV primary screening
  - More will be coming soon
- Important to monitor for updates to ASCCP guidelines
- As HPV vaccination rates continue to rise you will continue to see changes in cervical cancer screening guidelines to reflect herd immunity