HPV Infection and Cervical Cancer Screening

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Faculty Disclosure

• I have no personal financial interests or affiliations to disclose
• The University of Arizona has contracts with pharmaceutical and molecular testing companies for the conduct of clinical trials, but I derive no direct benefit from these
Learning Objectives

• Apply knowledge of HPV transmission and carcinogenesis to inform clinical decisions and counsel patients
• Review recent changes in screening and terminology recommendations and how these apply to the clinical care setting
• Identify target populations who benefit the most from HPV vaccine
• Explain to the need for ongoing cervical cancer screening after HPV vaccination
Global Burden of HPV Related Disease

CA (600K)
HG SIL (10M)
Warts (30M)  LGSIL (30M)
HPV Infection/NILM (300M)

Cancer Risk
1/1
1/20
1/60
1/600
HPV Point Prevalence by Age Group

Infection From Time of First Sexual Intercourse (Winer 2003)

Cumulative Incidence of HPV Infection vs. Months Since First Intercourse
Prevalent HPV Infections Resolve Spontaneously and Rapidly in Young Women

![Graph showing the resolution of HPV infections over time for different HPV types. The x-axis represents time in months, ranging from 0 to 24. The y-axis represents the proportion of persistent infections, ranging from 0.0 to 1.0. Different types of HPV are indicated by various colors and line styles. The graph shows a rapid decline in the proportion of infections with time, indicating spontaneous resolution.](Plummer. JID 2007)
HPV Distribution in Cervical Cancer, CIN3, and Normal Cytology

Wheeler CM. JNCI 2010.
Proportional Impact of HPV 16/18 and Other Viral Types by Tumor Type

- Squamous CA
  - Other HR HPV: 70%
  - HPV 16/18: 30%
- Adeno CA
  - Other HR HPV: 80%
  - HPV 16/18: 20%

Source: deSanJose. Lancet Oncol 2010
Predictive Value of HPV Genotype

Kaiser – NCI follow-up study

- 20,817 women with adequate cytology at enrollment (1994-1996)
- Tested frozen cervical lavage samples for HPV using PCR assay
- Follow-up was with cytology and "standard workup" of abnormals
- Case-control of women with/without CIN

Kahn. JNCI 2005
Long Term Risk of CIN3+ in Women ≥30 with NILM Cyto at Baseline

Kahn. JNCI 2005
Predictive Value of HPV Genotype

Danish follow-up study

• Cohort of 8,656 women 20-29 yrs of age examined twice 2 years apart (1991-1995).
• Had gynecological exam, Pap test, HPV testing (and genotyping)
• Follow-up through nationwide Danish Pathology Data Bank for up to 13.5 years

Kjaer. JNCI 2010
Long-term CIN3+ Risk with Persistent HRHPV Infection

Kjaer. JNCI 2010
Sensitivity \textit{Pap v HPV} for $\geq$CIN 2: UPSTF Review

Average sensitivity increase of 65%

Whitlock Ann Intern Med 2011
Specificity $\text{Pap} \, \text{v. hrHPV} \geq \text{CIN} \, 2$: UPSTF Review

Whitlock Ann Intern Med 2011
• Infection with high risk HPV types is common occurring shortly after onset of sexual activity
• Resolves spontaneously in the immune competent host
• Cervical cancer is the very rare consequence of “persistent” type-specific HR HPV infection
• HPV type has important long term prognostic significance for the development of cancer, and has implications for screening
Screening Guidelines:
Cervical Cancer Screening Guidelines Development Process

- Process led by ACS, ASCCP, and ASCP between 2009 to 2011
- Convened expert panel to develop new screening recommendations based on a systematic review of evidence
- The process overseen by a Steering Committee, and supported by an independent Data Group.
- 6 topical working groups developed draft recommendations
- Draft recommendations and rationale posted for public comment
- Culminated in a Consensus Conference that finalized the recommendations
### 2012 ACS/ASCCP/ASCP Cvx Ca Screening Guidelines

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21</td>
<td>No screening</td>
</tr>
<tr>
<td>21-29</td>
<td>Cyto alone q 3 years, either liquid or conventional. Recommend AGAINST annual cyto</td>
</tr>
<tr>
<td>30-65</td>
<td>HPV/cyto “co-testing” combo q 5 years (<em>preferred</em>) OR q 3 years cyto alone (<em>acceptable</em>) Recommend AGAINST more frequent screening</td>
</tr>
<tr>
<td>&gt;65</td>
<td>Discontinue if 3 neg cytos OR 2 neg HPV tests in last 10 years, and most recent screen ≤ 5 years</td>
</tr>
<tr>
<td>Post-Hyst</td>
<td>Discontinue if for benign indication</td>
</tr>
<tr>
<td>Post Vaccine</td>
<td>Follow age-appropriate recommendations</td>
</tr>
</tbody>
</table>
| HPV neg, ASC-US | Cyto/HPV combo in 5 years *(preferred)*  
|                 | OR  
|                 | Cyto only in 3 years *(acceptable)* |
| HPV pos, cyto neg | 12-month follow-up with cyto/HPV combo  
|                  | OR  
|                  | HPV16 /18 genotype test  
|                  | If pos refer to colpo  
|                  | If neg cyto/HPV at 12-months |
Other Recommendations

• Women at any age should NOT be screened annually.
• HPV testing should NOT be used for screening women <30 years.
• Screening by HPV testing alone is not recommended for most clinical settings.
• Women with history of ≥CIN2 diagnosis should continue screening at least 20 years.
• NOT addressed: 1) history of cervical cancer, 2) in utero to diethylstilbestrol, or 3) immune-compromised, e.g. HIV+.
## Comparison of Guidelines

<table>
<thead>
<tr>
<th>Start Age</th>
<th>ACS-ASCCP-ASCP 2012</th>
<th>ACOG 2009</th>
<th>USPSTF 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 21-29</td>
<td>Cyto every 3 years (liquid/conventional)</td>
<td>Cyto every 2 years (liquid/conventional)</td>
<td>Cyto every 3 years (liquid/conventional)</td>
</tr>
<tr>
<td></td>
<td>AGAINST annual Pap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 30-65</td>
<td>Cotest every 5 years (preferred) or Every 3 years with cyto alone (acceptable)</td>
<td>Cotest every 3 years or Every 3 years with Cyto alone</td>
<td>Cotest every 5 years or Every 3 years with cyto alone</td>
</tr>
<tr>
<td></td>
<td>AGAINST more frequent screening</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Comparison of Guidelines

<table>
<thead>
<tr>
<th></th>
<th>ACS-ASCCP-ASCP 2012</th>
<th>ACOG 2009</th>
<th>USPSTF 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ages &gt;65</strong></td>
<td>Discontinue after age 65 if 3 negative Pap tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years</td>
<td>Discontinue at age 65-70 after 3 negative tests in last 10 years</td>
<td>Discontinue after age 65 if adequate prior screening</td>
</tr>
<tr>
<td><strong>Post-Hyst</strong></td>
<td>Discontinue, benign indication</td>
<td>Discontinue, benign indication</td>
<td>Discontinue, benign indication</td>
</tr>
<tr>
<td><strong>Screening after vaccination</strong></td>
<td>Same as for unvaccinated</td>
<td>Same as for unvaccinated</td>
<td>Same as for unvaccinated</td>
</tr>
</tbody>
</table>
Lower Anogenital Squamous Terminology Project

- CAP Pathology & Laboratory Quality Center & ASCCP, 2011/2012
- Convened a steering committee and 5 WGs
- Expert surgical pathologists, gynecologic pathologists, dermato-pathologists, and medical/surgical specialists including gynecologists, gynecologic oncologists, dermatologists, infectious disease specialists, and surgeons
LAST Project: Two Basic HPV Related Lesions

1. Infected sq epithelium supports viral production, resulting in transient (low-grade) lesions

2. Disrupted control of viral gene expression and epi differentiation; oncogene over-expression drives cell prolif/clonal expansion of undiff cells characterized clinically by persistent viral detection, and a substantial risk of malignant transformation (high-grade)

Indistinguishable by routine histology regardless of site of the lesion or sex of patient.

T Darragh, L Gen Tract 2101
LAST – General principles

- There is unified epithelial biology to HPV-related squamous disease.
- Each cytologic/histologic sample is a statistical representation of true biology.
- More samples/data points available, more accurate assessment of the true biology.
- True biology represents risk for cancer at that time and, to a lesser extent over time.
- Diagnostic variation improves: Aligning dx terms with bio relevant categories and use of biologic markers.
LAST Recommendation Summary

- Two-tiered terminology for HPV related lesions: HSIL & LSIL
- Establishes the term Superficially Invasive Squamous Cell Carcinoma: For CVX
  - lesion not grossly visible AND
  - invasion $\leq$ 3 mm from basement membrane AND
  - $\leq$ 7 mm max horizontal spread AND
  - Lesion completely excised
- P16 recommended for differentiation of equivocal lesions
Role of p16 & Impact on Diagnosis & Management
Prophylactic Vaccination
Timeline of Prophylactic Vaccines

- 2006, Merck quadrivalent HPV 6, 11, 16, 18 vaccine approved by FDA
- Recommended ACIP and included in VFC program
- 2009, GSK bivalent HPV 16, 18 vaccine approved by FDA
- 2010, Merck quadrivalent approved for boys
- 2012 ACIP recommends quadrivalent formulation for boys 11 to 21
HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis

- L1 gene of HPV DNA
- Inside HPV
- L1 gene inserted into a plasmid
- Eukaryotic Cell
- Transcription
- mRNA
- Translation
- Capsid proteins

Empty viral capsid (VLP)

Elicits immune response in host

HPV
Quadrivalent Phase III Trials: Future I Per Protocol Population

- Per-protocol population
- “Naive” to vaccine HPV types at enrollment
- Did not become infected during first 6 mos
- Received all three doses of vaccine
- Demonstrates vaccine effectiveness in uninfected women

Prophylactic Efficacy Against HPV 6/11/16/18–Related CIN or AIS, VIN/VaIN/Genital Warts in Per-Protocol Population

Subjects were free of HPV 6, 11, 16, 18 infection through 1 month Postdose 3.

- CIN or AIS: 100% efficacy, n=2,258
- VIN/VaIN/Genital Warts: 100% efficacy, n=2,279

95% confidence interval: 94%–100%.

Quadrivalent Phase III Trials: Future I Intention-to-Treat Population

Intention-to-treat population
• Includes all women studied
• Demonstrates vaccine effectiveness in general population

Prophylactic Efficacy for HPV 6/11/16/18–Related CIN/AIS, VIN/VaIN/Genital Warts Intent to Treat Population

## Bivalent Vaccine Phase III Trial: Impact on CIN2+

<table>
<thead>
<tr>
<th>Type of HPV</th>
<th>Number of Cases</th>
<th>Placebo</th>
<th>6 mo efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 31</td>
<td>2</td>
<td>25</td>
<td>92%</td>
</tr>
<tr>
<td>HPV 33</td>
<td>12</td>
<td>25</td>
<td>51.9%</td>
</tr>
<tr>
<td>HPV 45</td>
<td>0</td>
<td>4</td>
<td>75.7%</td>
</tr>
<tr>
<td>HPV 52</td>
<td>12</td>
<td>14</td>
<td>ns</td>
</tr>
<tr>
<td>HPV 58</td>
<td>6</td>
<td>17</td>
<td>64.5%</td>
</tr>
</tbody>
</table>

Quadrivalent Vaccine Efficacy Among 24 to 45 yo Women

• 3,819 women
• Multi-center, international, randomized, placebo controlled trial.
• Stratification to 24-34 or 35-45 yrs
• Cervicovaginal sampling performed q ~6 months x 48 mo, with Colpo for ≥ASC-US
• Endpoints: Combined incidence persistent infection, CIN, or EGLs caused by HPV 6, 11, 16, or 18
• 1/3 HPV infection by serology and/or PCR
Quadrivalent Vaccine efficacy against HPV6/11/16/18 persistent infection, CIN and EGL, **24 to 45 yo**

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>Vaccine (N=1,910)</th>
<th>Placebo (N=1,907)</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Cases</td>
<td>n</td>
<td>Cases</td>
</tr>
<tr>
<td>Persistent HPV, CIN or EGL</td>
<td>1,601</td>
<td>10</td>
<td>1,599</td>
<td>86</td>
</tr>
<tr>
<td>Persistent infection</td>
<td>1,581</td>
<td>9</td>
<td>1,586</td>
<td>85</td>
</tr>
<tr>
<td>CIN</td>
<td>1,581</td>
<td>1</td>
<td>1,584</td>
<td>17</td>
</tr>
<tr>
<td>-CIN 2/3+</td>
<td>1,581</td>
<td>1</td>
<td>1,584</td>
<td>6</td>
</tr>
<tr>
<td>Ext Genital Lesion</td>
<td>1,600</td>
<td>0</td>
<td>1,599</td>
<td>7</td>
</tr>
<tr>
<td>-Condyloma</td>
<td>1,600</td>
<td>0</td>
<td>1,599</td>
<td>7</td>
</tr>
<tr>
<td>-VIN &amp;/or VAIN 2/3</td>
<td>1,600</td>
<td>0</td>
<td>1,599</td>
<td>0</td>
</tr>
</tbody>
</table>
Quadrivalent vaccine efficacy against HPV6/11/16/18 persistent infection, CIN and EGL, **24 to 45 yo**

<table>
<thead>
<tr>
<th>Intent to Treat</th>
<th>Vaccine (N=1,910)</th>
<th>Placebo (N=1,907)</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent HPV infxn, CIN or EGL</td>
<td>1,886 116</td>
<td>1,883 214</td>
<td><strong>47</strong></td>
<td><strong>34.58</strong></td>
</tr>
<tr>
<td>Persistent infection</td>
<td>1,856 110</td>
<td>1,857 221</td>
<td><strong>49</strong></td>
<td><strong>36.60</strong></td>
</tr>
<tr>
<td>CIN</td>
<td>1,862 29</td>
<td>1,861 55</td>
<td><strong>48</strong></td>
<td><strong>16.68</strong></td>
</tr>
<tr>
<td>- CIN 2/3+</td>
<td>1,862 21</td>
<td>1,861 27</td>
<td>22</td>
<td>&lt;0.58</td>
</tr>
<tr>
<td>Ext Genital Lesion</td>
<td>1,884 11</td>
<td>1,882 12</td>
<td>9</td>
<td>&lt;0.63</td>
</tr>
<tr>
<td>- Condyloma</td>
<td>1,884 0</td>
<td>1,882 0</td>
<td>n/a</td>
<td>&lt;0.81</td>
</tr>
<tr>
<td>- VIN &amp;/or VAIN 2/3</td>
<td>1,884 2</td>
<td>1,882 0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
CRVT: Bivalent Vaccine Efficacy in Women

<table>
<thead>
<tr>
<th>Site</th>
<th>Study Arm</th>
<th>n</th>
<th>Persistent HPV 16/18</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anus</td>
<td>HPV2</td>
<td>1003</td>
<td>8</td>
<td>84% (67-93)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>986</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>HPV2</td>
<td>1003</td>
<td>10</td>
<td>88% (77-94)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>986</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer, Lancet Onc 2011
## CRVT: Per Dose Bi-Vaccine Efficacy

<table>
<thead>
<tr>
<th>Total Doses</th>
<th>Study Arm</th>
<th>n</th>
<th>Persistent HPV 16/18</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>HPV2</td>
<td>2957</td>
<td>25</td>
<td>81% (71-88)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3010</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HPV2</td>
<td>422</td>
<td>3</td>
<td>84% (50-96)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>380</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>HPV2</td>
<td>196</td>
<td>0</td>
<td>100% (67-100)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>188</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer JNCI 2011
Efficacy vs. Public Health Benefit

100 vs. 0
Efficacy = 100%

10 vs. 0
Efficacy = 100%

1 vs. 0
Efficacy = 100%

Population A
Population B
Population C

Events

Courtesy of P. Castle
ACS Recommendations for HPV Vaccine
Use to Prevent Cervical Cancer

- **Routine HPV vaccination for females age 11-12**
  - Can begin as young as 9 years
  - Catch up for females 13 to 18

- **Insufficient data to recommend for or against universal vaccination of 19-26 yo women.** (decision should be based on informed discussion btwn woman and provider)
• HPV vaccination is safe and effective
• For purpose of cervical cancer prevention, quadrivalent/bivalent formulations equivalent
• Prevents persistent HPV infection in the cervix and lower genital tract among immune competent unexposed individuals
• Some cross reactivity with related HPV types occurs, clinical implications of cross protection is uncertain
How are we doing?
HPV Vaccine Coverage: Adolescents

• National Immunization Survey-Teen collects a national estimate of coverage for 13 to 17yo
• Random-digit--dialed sample of households
• Surveys mailed to vaccination providers
• Response rate 58.7%
• 17,835 adolescents with provider-verified vaccination records
<table>
<thead>
<tr>
<th>Dose</th>
<th>2007 n=2947</th>
<th>2008 n=17,835</th>
<th>2009 n=20,066</th>
<th>2010 n=19,257</th>
<th>2011 n=23,564</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>25%</td>
<td>37%</td>
<td>44%</td>
<td>49%</td>
<td>53%</td>
</tr>
<tr>
<td>≥3</td>
<td>--</td>
<td>18%</td>
<td>26%</td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td>Series comp</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>70%</td>
<td>71%</td>
</tr>
</tbody>
</table>

## Female Adolescent HPV Vaccine Coverage by Race/Ethnicity & FPL-2011

<table>
<thead>
<tr>
<th>HPV Vaccine Dose(s)</th>
<th>Race/Ethnicity</th>
<th>Federal Poverty Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>n=15970</td>
<td>n=2408</td>
<td>n=3234</td>
</tr>
<tr>
<td>≥1</td>
<td>48%</td>
<td>56%</td>
</tr>
<tr>
<td>≥3</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Series Comp</td>
<td>75%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Dorrel MMWR 2012
Relative Role of Host and Contextual Factors in Cervical Cancer Disparities

**Contextual Factors**
- Availability of services
- Immigration status
- Systemic obstacles
- Cultural/linguistic
- Insurance status
- Educational
- Geographic

**HPV Persistence Type**

**Vulnerable Population**

**Resilient Population**
Conclusion

• Cervical cancer prevention efforts must balance safety and potential benefit
• New practice guidelines based on improved understanding of the disease process and limitations of screening and vaccine
• Policy decisions should be made from a societal perspective, while personal choices must reflect individual preferences and perception of risk
• *Primum non nocere*
fcisco@u.arizona.edu

520 626 8539

www.womenshealth.arizona.edu
## HPV Testing Approaches

### DNA

**Hybrid Capture 2** – pooled 13 hrHPV

**Cervista** – Target amp
14 hrHPV and 16/18.

**Cobas HPV Test** – RT-PCR based (L1 gene)
reps12 pooled hrHPV
types & 16/18

### RNA

**Aptima HPV test** –
detects E6/E7 mRNA 14 hrHPV
Several molecular laboratories develop their own HPV assays. Usually PCR-based.

- Internal/laboratory validation but not clinically validated
- Unclear what a "positive" or "negative" result means