What’s the Latest? HPV and Cervical Cytology Update

Kevin A. Ault, MD
Tuesday, July 26, 2016
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<tr>
<th>Commercial Interest</th>
<th>Role</th>
<th>Status</th>
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<td>No Relevant Disclosures</td>
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Objectives

• Identify ways to screen women for cervical dysplasia according to the recent national guidelines
• Recommend counseling for women concerning HPV vaccination
• Discuss decreasing barriers to HPV vaccination in their clinical settings and communities
Why an update?

- Updated cervical cancer screening recommendations in 2012 and 2016 (now include “primary screening”)
- A “second generation” polyvalent HPV became available for use in 2015
- HPV vaccine uptake remains low
- More available data on increasing vaccine uptake
Cervical Cancer Rates 2004-2008 USA, by Race/ethnicity

Source: CDC 2012
Natural History of HPV Infection and Potential Progression to Cervical Cancer

- **Initial HPV Infection**
- **Continuing Infection**
- **CIN 1**
- **CIN 2/3**
- **Invasive Cervical Cancer**

Pinto and Crum 2000
Burden of Disease – HPV and the Cervix

- In developed world, most costs associated with detection and treatment of pre-malignant disease
- Long duration between initial exposure and development of cervical dysplasia or cancer
- Cost in USA - $ 6.6 Billion
- Cervical cancer in USA in poorly screened populations ie health disparity

Chesson et al 2012
The Pap smear in the 21st Century

- Sensitivity of pap smear is problematic
- HPV testing is extremely sensitive
  - All cervical cancers are due to HPV
  - But most HPV resolves without clinical disease
- Combinations of tests may emphasize strengths and decrease weaknesses (ie “co-testing”)
**Table 1. Screening Methods for Cervical Cancer for the General Population: Joint Recommendations of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology**

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<tr>
<th>Population</th>
<th>Recommended Screening Method</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Women younger than 21 years</td>
<td>No screening</td>
<td></td>
</tr>
<tr>
<td>Women aged 21–29 years</td>
<td>Cytology alone every 3 years</td>
<td></td>
</tr>
<tr>
<td>Women aged 30–65 years</td>
<td>Human papillomavirus and cytology cotesting (preferred) every 5 years</td>
<td>Screening by HPV testing alone is not recommended*</td>
</tr>
<tr>
<td></td>
<td>Cytology alone (acceptable) every 3 years</td>
<td></td>
</tr>
<tr>
<td>Women older than 65 years</td>
<td>No screening is necessary after adequate negative prior screening results</td>
<td>Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue routine age-based screening for a total of 20 years after sequential regression or appropriate management of CIN 2, CIN 3, or adenocarcinoma in situ</td>
</tr>
<tr>
<td>Women who underwent total hysterectomy</td>
<td>No screening is necessary</td>
<td>Applies to women without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years</td>
</tr>
<tr>
<td>Women vaccinated against HPV</td>
<td>Follow age-specific recommendations (same as unvaccinated women)</td>
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from the American College of Obstetricians and Gynecologists, 2016
Primary HPV Screening in the USA

• Approved by FDA in 2014 based on > 40,000 subject trial aka “ATHENA”
• Similar sensitivity to current “co-testing” strategy (both cytology and HPV)
• Since positive predictive value will be low, will need secondary triage

See Castle et al 2011
Triage of Primary HPV Results

See Huh et al 2015
Pros & cons of Primary Screening

• Complex algorithm
• Age dependent rate of HPV + will lead to excess colposcopies in ages 25-29
• Interval between tests unknown i.e. no definition of “routine screening”
• Approximately 6 % of HSIL pap smears at HPV negative with 22 % CIN3 +

See Huh et al 2015 and Chelmow 2015
External Genital Warts - Diagnosis by Age Australia

Summary of current ACIP recommendations – 2015

• routine vaccination of adolescent females and males aged 11–12 years with 3 doses of HPV vaccine. The vaccination series can be started as young as age 9 years.

• “Catch up” to age 26

• Three versions of the HPV vaccine currently available, “second generation” is 9 valent

See [http://www.cdc.gov/vaccines/pubs/ACIP-list.htm#hpv](http://www.cdc.gov/vaccines/pubs/ACIP-list.htm#hpv) or MMWR
HPV Types that Cause Cervical Cancer - Global Survey

Percent of cervical cancers worldwide caused by HPV type

HPV 16
+ HPV 18
+ HPV 45
+ HPV 31
+ HPV 33
+ HPV 52
+ HPV 58

Top cancer-causing types of HPV
- HPV 16
- HPV 18
- HPV 45
- HPV 31
- HPV 33
- HPV 52
- HPV 58

De San Jose et al 2010
Potential Impact of HPV9 Vaccine – USA 2015 by cancer site

Saraiya et al 2015
Estimated HPV Vaccination Coverage among Adolescents Aged 13-17 Years in United States, 2006-2014

Data from CDC – slide courtesy of Dr. Melinda Wharton
Figure 3
HPV Vaccination Rates of Adolescent Girls ages 13-17, by State

Completion of 3 dose HPV vaccine series among females ages 13-17, 2014

Estimated vaccine coverage for females ages 13-17
- <30% (7 states)
- 30 – 39.7% (14 states)
- 39.8 – 44.9% (19 states)
- ≥45% (10 states + DC)

2014 U.S. average = 39.7%

NOTES: Share of females ages 13-17 who have received all 3 doses of the HPV vaccine series. *Statistically significant (p<.05) percentage point change from 2013.
Top 5 Reasons Not to Vaccinate

• Not needed, unnecessary
• Not sexually active
• Safety Concerns
• Lack of disease specific knowledge
• No provider recommendation

Source: CDC/ACIP Meeting June 2013
Missed Opportunities – HPV Vaccination

• 84 % of unvaccinated adolescent girls had a visit where another vaccine was given
• “Best practice” – electronic prompts, centralized databases, scheduled follow up, catch up in young adults
• If 80 % of current adolescents were vaccinated then 53,000 cases of cervical cancer would be prevented

MMWR July 2013
Major Weaknesses of Provider Recommendations

• “Risk based” strategies
• Lack of urgency (delayed to future visit)
• Weaker recommendation for males
• Correlation of high quality recommendation – a) child is due for adolescent vaccines b) strong recommendation c) prevents multiple cancers and d) elicit questions

Gilkey et al 2015
Conclusions

- Refined cervical cancer screening guidelines recommend “co-testing” in age range at highest risk
- Newest version of the HPV vaccine could prevent 90% of cervical cancers
- Provider recommendation best predictor of HPV vaccine uptake
“Thank you ever so much”

Any questions?

Kevin A. Ault, MD
Department of Obstetrics and Gynecology
3901 Rainbow Blvd
University of Kansas Medical Center
Kansas City KS USA 66160
kault2@kumc.edu or Twitter @kevinault