Cervical Cancer Prevention Update: 2010 and Beyond

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I have no financial interests in any product I will discuss today.

Main Questions Addressed

• At which age should screening begin and end?
• How often should women be screened?
• What techniques should be used?
• What are current recommendations for HPV vaccination?
• Focus on guidelines, rationale and evidence
Case

A 19-year-old woman has been sexually active for the last 2 years. She presents for her first prescription for oral contraception. A Pap smear is performed and is interpreted as atypical squamous cells of undetermined significance (ASC-US); a reflexive test for human papillomavirus is positive. Next steps?

Focus

United States prevention guidelines
• American Cancer Society (ACS) 2002.
• American College of Obstetricians and Gynecologists (ACOG) 2009
• US Preventive Services Task Force (USPSTF) 2002
• ASCCP Guidelines 2007 (selected) http://www.asccp.org
• ACIP (CDC) Guidelines for HPV Vaccination (May 2010)

Cytology Primer

• ASC-US: atypical squamous cells of undetermined significance
• LSIL: low-grade squamous intraepithelial lesion
• HSIL: high-grade squamous intraepithelial lesion
• AGC: atypical glandular cells of undetermined significance (AGUS)
Histology Primer

Cervical intraepithelial neoplasia (CIN)
Graded based on proportion of epithelium involved
• CIN 1: indicates active HPV infection; treatment
discouraged since spontaneous resolution is high
• CIN 2: most are treated, but about 40% resolve
over 6 month period; treatment may be deferred in
young women
• CIN 3: the most proximal cancer precursor, also
known as carcinoma in situ
Adenocarcinoma in situ: widely considered a cancer
precursor

SEER Cervical Cancer Rates:
2003-2007

Incidence Rates by Race

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>8.1 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>7.9 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>10.1 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>7.5 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>7.7 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.0 per 100,000 women</td>
</tr>
</tbody>
</table>


Age to Begin Screening:
US Guidelines

❖ American Cancer Society (2002): Begin
approximately 3 years after the onset of vaginal
intercourse and no later than age 21

❖ American College of Obstetricians and
Gynecologists (2009): begin at age 21; “screening before
age 21 should be avoided”

screening within 3 years of onset of sexual activity or age
21 (whichever comes first)
Age to Begin Screening: Rationale

- Most dysplastic lesions low-grade and transient
- Long progression time of preinvasive lesions to invasive cancer
- Potential adverse effects of treatment (e.g., LEEP) on pregnancy

Potential adverse effects of LEEP

<table>
<thead>
<tr>
<th>Effect</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>70%</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>82%</td>
</tr>
<tr>
<td>Preterm premature ROM</td>
<td>169%</td>
</tr>
</tbody>
</table>

Lancet 2006 367:489-98

Potential severe adverse effects of cone biopsy (not LEEP or cryotherapy)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>187%</td>
</tr>
<tr>
<td>Severe preterm delivery</td>
<td>178%</td>
</tr>
<tr>
<td>Extreme low birthweight</td>
<td>186%</td>
</tr>
</tbody>
</table>

No randomized trials. BMJ 2008 Sep 18;337

Age to End Screening: US Guidelines

- **ACS (2002):** Women who are age 70 and older who have had 3 or more documented, consecutive, normal tests, with no abnormal tests within the 10 years prior may elect to cease screening
- **ACOG (2009):** same as the ACS and USPSTF “between the ages of 65 and 70” but not among women with multiple partners
- **USPSTF (2003):** Women who are age 65 and older who have had 3 or more documented, consecutive, normal tests, may cease screening

ACOG, ACS and USPSTF: screening following total hysterectomy with removal of the cervix for benign disease is not indicated.

*ACOG (2003):* If hysterectomy for CIN 2 or 3, may stop screening after 3 normal tests. ACOG (2009): Continued routine screening recommended.
Age to End Screening: Rationale

- Small benefits in well-screened women

- Risks incurred due to false-positive testing

Choice of cytology screening method, liquid-based cytology versus conventional cytology: US Guidelines

- **ACS (2002):** Screening should be performed annually with conventional cervical cytology smears OR every 2 years using liquid-based cytology

- **ACOG (2009):** does not distinguish between LBC and conventional cytology. Both deemed ‘acceptable’.

- **USPSTF (2003):** “Overall, the quality of this literature is poor for the purposes of making decisions about choice of screening systems in US populations.”

ARS: Among those who use liquid-based cytology, what was the *main* reason for conversion from conventional cytology?

1. Liquid-based cytology is more sensitive (finds more disease)

2. Patient demand

3. Liquid-based cytology allows for easier use of HPV testing

4. My lab stopped reading conventional cytology
Choice of cytology screening method, liquid-based cytology versus conventional cytology:
Rationale and Evidence

Liquid Compared With Conventional Cervical Cytology
A Systematic Review and Meta-analysis
Marc Arbyn, MD, Christine Beyer, MD, Paul El lahmer, MD,
Pierre Martin-Belah, MD, Albert G. Siden, MD, and John Sloton, MD

“LBC is neither more sensitive nor more specific in the detection of high-grade dysplasia than conventional cytology.”

Obstet Gynecol Jan 2008

Randomized Trial: Netherlands

Comparison of Liquid-Based Cytology With Conventional Cytology for Detection of Cervical Cancer Precursors
A Randomized Controlled Trial

JAMA, 2009; 302(16):1757-1764

Randomized Trial: Netherlands

- Siebers et al, N=89,784
- Cluster randomized trial (327 practices): liquid-based cytology versus conventional cytology
- No difference in positivity rate or CIN found
- Fewer unsatisfactory tests with LBC (NNT=126)
- Conclusion: no difference

JAMA, 2009; 302(16):1757-1764
Screening Frequency: US Guidelines

- **ACS (2002):** At or after age 30, women who have had 3 consecutive, technically satisfactory normal results may be screened every 2 to 3 years†
- **ACOG (2009):** Age 21-29, *every 2 years*, then *every 3 years* for women aged 30+ who have had 3 consecutive, technically satisfactory normal results
- **USPSTF (2003):** “every 1 to 3 years”

†Exceptions: women who are immunocompromised, HIV infected, have a history of *in utero* diethylstilbestrol exposure and/or have a history of CIN 2 or 3

*Exceptions: women who are immunocompromised (due to organ transplantation, chemotherapy, chronic corticosteroid treatment), HIV infected and/or have a history of *in utero* diethylstilbestrol exposure

Screening Frequency: Rationale

- After several normal tests, small likelihood of missed disease
- New preinvasive lesions have a long time to invasion
- Screening for uncommon diseases is associated with many false-positive tests if tests used are not very specific

Areas of Uncertainty

- Physicians should inform women that an annual gynecologic exam ‘may still be appropriate’ (as per ACOG, 2009) but unclear what this means
- Continued screening of women over age 65 or 70 with multiple partners (new exposures?) may be warranted

Editorial: Sawaya *NEJM* December 2009
HPV DNA testing with cytology as a primary screen
(age 30 and over): US Guidelines

❖ ACS (2002): For women aged 30 and over, as an alternative
to cervical cytology testing alone, screening may be performed
every 3 years using conventional or liquid-based cytology
combined with a test for DNA from high-risk HPV types.
Frequency of testing should not be more often than every 3
years.

❖ ACOG (2009): same as above, “an appropriate screening
strategy”

❖ USPSTF (2003): “insufficient to recommend for or against…
“…poor evidence to determine the benefits and potential
harms of HPV screening as an adjunct or alternative to regular
Pap smear screening. Trials are underway…”

HR HPV DNA testing

• Hybrid Capture 2®: tests for one or more of 13 high-risk
(oncogenic) HPV types; the low-risk probe has no clinical
utility
• Cervista: tests for one or more of 14 high-risk (oncogenic)
HPV types; type-specific testing available (16, 18)

Adding HR HPV DNA (HC2) testing
to cytology: what to do with HPV
positive/Pap normal women?

Recommendation: Repeat HPV DNA testing and cervical
cytology at 12 months.
If still HPV+, do colposcopy; if ASC-US+, manage per ASCCP
If both are normal, routine screening AT 3 YEARS

Wright et al AJOG 2007 October
www.asccp.org
Adding HR HPV DNA (HC2) testing to cytology: what to do with HPV positive/Pap normal women?

About 8-11% of women ages 30-55 in the US will have a positive HPV test (HC2) and a normal Pap test (Ann Int Med April, 2008)

At Kaiser NC, about 3-7% of women ages 30-55 will have a positive HPV test (HC2) and a normal Pap test (Obstet Gynecol March 2009)

Recent Randomized Trials of HPV testing using HC2: passive response

<table>
<thead>
<tr>
<th>Site</th>
<th>N (year)</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Italy</td>
<td>11,810 (2010)</td>
<td>CC vs LBC+HPV (passive response to HPV+)</td>
<td>LBC+HPV: more positive tests (17 vs 4%), more CIN 1, 2, but not CIN 3+</td>
</tr>
<tr>
<td>UK</td>
<td>24,510 (2009)</td>
<td>LBC vs LBC+HPV (passive response to HPV+)</td>
<td>Adding HPV: more positive tests (22 vs 13%), more CIN 2, but not more CIN 3+</td>
</tr>
</tbody>
</table>

CC=conventional cytology; LBC=liquid-based cytology; HC2=Hybrid Capture 2

Recent Randomized Trials of HPV testing using HC2: active response to HPV

<table>
<thead>
<tr>
<th>Site</th>
<th>N (year)</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>12,662 (2010)</td>
<td>CC vs HPV</td>
<td>HPV: more positive tests (13 vs 4%), more CIN 1, 2 and 3+ (15 more cases)</td>
</tr>
<tr>
<td>Italy</td>
<td>33,364 (2010)</td>
<td>CC vs LBC+HPV, CC vs HPV</td>
<td>LBC+HPV: more positive tests (13 vs 3.6%), more CIN 1, 2, but not CIN 3+; HPV: more positive tests (13 vs 3.1%), more CIN 1, 2 and 3+ (18 more cases)</td>
</tr>
<tr>
<td>Finland</td>
<td>108,425 (2009)</td>
<td>CC vs HPV with CC triage</td>
<td>No difference in positivity rates or CIN 3+ found.</td>
</tr>
<tr>
<td>India</td>
<td>131,746 (2009)</td>
<td>CC vs HPV vs control (active response/immediate tx)</td>
<td>HPV: more positive tests than cytology (10 vs 7%), decreased mortality vs ctrl</td>
</tr>
</tbody>
</table>

CC=conventional cytology; LBC=liquid-based cytology; HC2=Hybrid Capture 2
HPV DNA testing as a triage test for ASCUS cytology

ASCCP (2007): colposcopy, repeat cytology or HPV testing are all acceptable, but prefer HPV triage if LBC used or with co-collection; do not perform HPV testing in women under age 21.

ASCCP Guidelines Highlights (2007)

- ASC-H: colposcopy for all women
- LSIL: colposcopy for all women (except pregnant women, adolescents and post-menopausal women as below)
- AGC (atypical glandular cells): colposcopy (new uses of HPV testing here)

ASCCP Guidelines Highlights (2007)

- Adolescents with ASC-US or LSIL (age 20 and younger): repeat cytology at 12 and 24 months. If ASC-US/LSIL at 12 months, repeat cytology again 12 months later; if ASC-US+, colposcopy. Colposcopy at any time for HSIL+.
- Pregnant women with ASC-US or LSIL: acceptable to defer colposcopy to 6 weeks post-partum
- Post-menopausal women with LSIL: colposcopy, repeat cytology or HPV testing are all acceptable
HPV Vaccination

- Gardasil -- HPV 16/18/6/11 ("HPV4")
- Cervarix -- HPV 16/18 ("HPV2")

CDC- Advisory Committee on Immunization Practices (ACIP) Recommendations (May 2010):

Females

- routine vaccination of females aged 11 or 12 with 3 doses of either HPV2 (Cervarix) or HPV4 (Gardasil)
- second dose administered 1 to 2 months after the first dose; third dose administered 6 months after the first dose
- vaccination recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series; vaccination can start at age 9 years
- ideally, vaccine should be administered before potential exposure to HPV through sexual contact

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?_a=Fmm5920a4_e

HPV4 (Gardasil) phase 3 trial outcomes: CIN3+ among women negative to 14 HPV types

Munoz et al JNCI 2010
HPV4 (Gardasil) phase 3 trial outcomes: CIN3+ among all women enrolled

Munoz et al
JNCI 2010

CDC- Advisory Committee on Immunization Practices (ACIP) Recommendations (May 2010):
Females

- Recommends vaccination with HPV2 (Cervarix) or HPV4 (Gardasil) for prevention of cervical cancers and precancers
- Both might “protect against other HPV-related cancers”
- HPV4 (Gardasil) recommended also for prevention of genital warts

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?s_cid=mm5920a4_e

CDC- Advisory Committee on Immunization Practices (ACIP) Recommendations (May 2010):
Females

Special circumstances:
- can be given to women with equivocal or abnormal Pap tests
- can be given to lactating women
- can be given to immunocompromised women although response to vaccine and vaccine effectiveness may be less than in immunocompetent women
- not recommended for use in pregnancy
CDC- Advisory Committee on Immunization Practices (ACIP) Recommendations (May 2010):

Males

3-dose series of HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts.

HPV4 would be most effective when given before exposure to HPV through sexual contact.

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a5.htm?s_cid=mm5920a5_e

American Cancer Society

Similar recommendations as ACIP except:

In women ages 18-26, decision to vaccinate should be based on a discussion about sexual history due to:

- Limited effect of vaccination on overall incidence of CIN 2/3 in women with 2-4 lifetime partners
- No data about efficacy in women with >4 lifetime partners
- No cost-effectiveness data in 19-26 year old

http://caonline.amcancersoc.org/cgi/content/full/57/1/7

Case

A 19-year-old woman has been sexually active for the last 2 years. She presents for her first prescription for oral contraception. A Pap smear is performed and is interpreted as atypical squamous cells of undetermined significance (ASC-US); a reflexive test for human papillomavirus is positive.

Next steps?

First: she should not have been screened for cervical cancer.
Second: HPV testing should not have been performed; ACTION: ignore the HPV test and repeat the Pap in one year; if ASC-US/LSIL, repeat in one year. Colposcopy if HSIL.
Third: don’t let anything stand in her way of good contraception
Fourth: prudence of vaccination is unclear
What we do at
San Francisco General Hospital

- Encourage delayed screening initiation (not sooner than 21)
- Encourage lengthening of screening intervals to 2-3 years in women over age 30 with 3+ normal Pap tests
- Encourage screening discontinuation of low-risk women (over age 65 with h/o normal tests, those without a cervix)
- We do not do HPV testing
- We do not hold birth control hostage for want of a Pap test.