Cervical Cancer Prevention Update

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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?
• Focus on recommendations, rationale and evidence
Case
A 20-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?

United States prevention recommendations
- ASCCP Guidelines 2007 (selected) http://www.asccp.org
- Draft recommendations by ACS/ASCCP/ASCP and USPSTF (released October 18, 2011)

Background
- ~12,000 cervical cancer cases and 4,200 deaths per year in the US (ACS, 2010)
- ~50-60% of cases occur in never- and poorly-screened women
- ~80 million women at risk in the US
- Most effective approach: screen unscreened and poorly-screened women
- Cervical cancers HPV-related: Nobel Prize 2008
- HPV infection common (70%+ lifetime risk), cervical cancer uncommon (~3% lifetime risk if no screening)

*Obstet Gynecol 94:307-10
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 a 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


<table>
<thead>
<tr>
<th>Incidence Rates by Race</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<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”

❖ US Preventive Services Task Force (2003): begin 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 pre-invasive lesions to invasive cancer
• Potential adverse effects of treatment (e.g., LEEP, cone biopsy) on pregnancy

Potential adverse effects of LEEP

<table>
<thead>
<tr>
<th>Condition</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>Condition</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>

*Bmj 2008 Sep 18,337*

No randomized trials.
**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

- **USPSTF (2003):** Women who are *age 65 and older* who have had 3 or more documented, consecutive, normal tests, may cease screening

- **ACOG (2009):** same as the ACS and USPSTF "between the ages of 65 and 70" but not among women with multiple partners

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

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**Age to End Screening: Rationale**

- Small benefits in well-screened women
- Risks incurred due to false-positive testing

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**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."
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 J. Ashyr, MD, MSc, Christine Bergstrom, MD, MSc, Paul Radek, MD, MSc, Perre Martijn-Metra, MD, MSc, Albert E. Sisti, MD, and John Buttin, MD, MSc

"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, thereafter may screen every 3 years for women who have had 3 consecutive, technically satisfactory normal results†
- USPSTF (2003): Age 21-65, every 1 to 3 years

†Exceptions: women who are immunocompromised, HIV infected, have a history of in utero DES 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 DES 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

The changes: cervical cancer

In November 2009, the American College of Obstetricians and Gynecologists (ACOG, Practice Bulletin 109) made the following changes:

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation for Cytologic Screening</th>
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<tbody>
<tr>
<td>Under 21 yr</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>21 to 29 yr</td>
<td>Screen every 2 yr</td>
</tr>
<tr>
<td>30 to 65 or 70 yr</td>
<td>May screen every 3 yr*</td>
</tr>
<tr>
<td>Between 65 and 70 yr</td>
<td>May discontinue screening</td>
</tr>
</tbody>
</table>

* This recommendation applies only to women with three consecutive negative cytologic tests; exceptions include women with human immunodeficiency virus infection, compromised immunity, a history of cervical intraepithelial neoplasia grade 2 or 3, or exposure to diethylstilbestrol in utero.

† This recommendation applies only to women with three or more consecutive negative cytologic tests and no abnormal tests in the preceding 10 years; exceptions include women with multiple sexual partners.

Sawaya GF N Engl J Med 2009 361;26 2503-2505

Patient Preferences: What do women want?

- 63% want annual Pap tests
- 12% would have Pap tests every 6 months or more often if cost not an issue
- 65% feel they would never stop having Pap tests
- 69% would try to get Paps “as often as I do now” if MDs recommended testing “less often”
- 50% think that suggestions for less-than-annual tests are based on saving money

Sirovich et al. Am J Med 2005 Feb;118(2)
HR HPV DNA testing

- **Hybrid Capture 2**: tests for one or more of 13 oncogenic HPV types; the low-risk probe has no clinical utility
- **Cervista**: tests for one or more of 14 oncogenic HPV types; type-specific testing available (16, 18)
- **Cobas HPV test (approved 4/11)**: tests for one or more of 14 oncogenic HPV types; type-specific testing available (16, 18)

Do you use HPV testing with cytology as a primary screening test in women aged 30 (not for ASC-US triage)?

1. Yes
2. No

Among those using HPV testing with cytology as a primary screening test in women aged 30 (not for ASC-US triage), what is the main reason?

1. As part of a routine check for sexually transmitted diseases
2. To identify low-risk women for screening every 3 years
3. To identify high-risk women for more vigilant surveillance
### 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…”

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

Recommendations by ASCCP and ACOG:
- Repeat HPV DNA testing and cervical cytology at 12 months.
- If still HPV+, perform colposcopy; if ASC-US+, manage per ASCCP guidelines
- If both are normal, routine screening AT 3 YEARS
  
  Wright et al. *AJOG*

Alternate recommendation by ASCCP:
- Perform HPV 16/18 testing, and if positive, perform colposcopy.
- If negative, repeat both at 12 months.

### 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)
Strategies for Using HPV Testing and Cytology in Primary Screening: Randomized trials

<table>
<thead>
<tr>
<th>HPV testing added to cytology:</th>
<th>UK, Italy</th>
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<tbody>
<tr>
<td>- passive response to HPV+ (e.g., US guidelines)</td>
<td>Italy</td>
</tr>
<tr>
<td>- active response to HPV+ (colposcopy)</td>
<td>Italy, India</td>
</tr>
<tr>
<td>HPV alone: active response to HPV+ (colposcopy) plus immediate treatment</td>
<td>Finland</td>
</tr>
<tr>
<td>HPV alone: active response to HPV+ is cytology (colposcopy if cytology is positive)</td>
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HPV testing versus cytology

- HPV testing generally more sensitive (finds more CIN 3) and less specific (more false-positive tests; more CIN 1 and 2)
  - In women 25-60, HPV testing positivity 7.9% versus 2.8% and identified 1 additional case of CIN3 per 1000 women screened
- A promising strategy: HPV testing first followed by cytology of HPV+ (not an FDA-approved use); trial results anticipated soon.
- Central question: are any new strategies better than cytology alone?

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 liquid-based cytology 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

Evidence Based Practice Center: Evidence Report, May 2011

- Liquid-based and conventional cytology do not differ

- Unclear effect of HPV testing for primary screening on cancer and on harms (e.g., additional colposcopies)

- For ASC-US triage, HPV testing has slightly higher sensitivity and similar specificity for CIN2+, but no data on CIN3+

- HPV positivity incurs short-term adverse psychological effects

- Women with negative HPV tests and normal cytology may be at particularly low risk, but unclear how this compares to women with 3+ normal cytology tests

Draft Recommendations: USPSTF (10/18/11)

• Under age 21: no screening (“D”)
• Ages 21-65: cytology every 3 years (“A”)
• Aged 65+ years in adequately screened women (3 consecutive negative cytology results within the prior 10 years): no screening (“D”)
• After hysterectomy for benign reasons: no screening (“D”)
• Liquid-based and conventional cytology: “no clinically important differences”

Draft Recommendations: ACS/ASCCP/ACSP (10/18/11)

• Ages 21-65: cytology every 3 years
• Ages 30+: HPV testing plus cytology preferable to cytology (or HPV) alone, every 3-5 years
• Aged 65+ years: screening may end if adequate prior screening “3 consecutive negative cytology results or 2 negative HPV tests (3 years apart) within the last 10 years”
• No difference in intervals based on cytology method

Case

A 20-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