Cervical Cancer Screening Update and Implications for Annual Exams

George F. Sawaya, MD
Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
Department of Epidemiology and Biostatistics
University of California, San Francisco
Director, Cervical Dysplasia Clinic, San Francisco General Hospital

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

- To understand the latest cervical cancer screening guidelines (updated in 2012)
- To understand areas of existing controversy
- To understand the current role of the bimanual pelvic examination in the context of less-than-annual screening

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
- High hysterectomy rates in the US account for much protection
- Most effective approach: screen unscreened and poorly-screened women
From virus to cancer

Cytology Primer

- ASC-US: atypical squamous cells of undetermined significance
- LSIL: low-grade squamous intraepithelial lesion
- HSIL: high-grade squamous intraepithelial lesion
- ASC-H: ASC, cannot rule out HSIL
- AGC: atypical glandular cells
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: proximal cancer precursor

Whom would you screen?

• 18-year-old, sexually active for 1 month, no prior Pap tests
• 35-year-old, normal Pap test 1 year ago
• 55-year-old, prior removal of uterus and ovaries (no cervical abnormalities)
• 70-year-old, screened regularly over lifetime with no prior abnormalities
• All of the above
• None of the above
United States recommendations: the big 3

- American College of Obstetricians and Gynecologists (ACOG) 2012: Screening for Cervical Cancer. Number 131, November 2012

Guidelines do not apply to immunocompromised women (HIV+), those with in utero DES exposure and those with prior CIN 2 or 3.

Sawaya et al Ann Int Med 2015

Evidence Review

Evidence Synthesis

Number 86

Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Garfield Road
Rockville, MD 20850
wwwahrq.gov

Contract No. HHS-290-2007-10057-I, Task Order No. 3

Prepared by:
Oregon Evidence-based Practice Center
Portland, Oregon

Evidence Based Practice Center: Evidence Report, May 2011

- Liquid-based and conventional cytology do not differ
- HPV testing finds more precancerous lesions but has unclear effects on cancer and on harms (e.g., additional colposcopies)
- HPV positivity incurs short-term adverse psychological effects
- Women with negative HPV tests and normal cytology may be at particularly low risk


Age to Begin Screening

- ACS/ASCCP/ASCP (2012): begin at age 21
- ACOG (2012): same
- USPSTF (2012): same

All agree: *do not screen before age 21 years*
USPSTF: “D” recommendation
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, cone biopsy) on pregnancy

Potential adverse effects of LEEP

- Preterm delivery: 70% increase
- Low birth weight: 82% increase
- Preterm premature ROM: 169% increase

*Lancet* 2006 367:489-98

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

- Perinatal mortality: 187% increase
- Severe preterm delivery: 178% increase
- Extreme low birthweight: 186% increase

*BMJ* 2008 Sep 18;337

No randomized trials; evidence inconsistent.
**Screening frequency: ages 21-29**

- **ACS/ASCCP/ASCP (2012):** cytology every 3 years
- **ACOG (2012):** same
- **USPSTF (2012):** same

All agree: *no annual screening*
ACS/ASCCP/ASCP: “Women of any age should not be screened annually by any screening method.”
ACOG: Choosing Wisely campaign: no annual Pap tests

All agree: *no HPV testing for primary screening*
USPSTF: “D” recommendation women under 30

---

**FAQ #1: Should I screen a 21-year-old virgin?**

Not the intention of the USPSTF when they stated “regardless of sexual history”.

ACOG: “Speculum examinations for cervical cancer screening should begin at age 21 years, irrespective of sexual activity of the patient.”

Prevalence of HPV among virgins: 1.7%, 0.3% for HPV-16

Screening frequency: ages 30-65

- ACS/ASCCP/ASCP (2012): screen every 3 years with cytology alone or every 5 years with cytology plus hrHPV testing (‘preferred’ strategy, but a ‘weak’ recommendation)

- ACOG (2012): same as ACS/ASCCP/ASCP

- USPSTF (2012): screen every 3 years with cytology alone or every 5 years with cytology plus hrHPV testing (but only for ‘women who want to lengthen the screening interval’)

No clinical role for testing for low-risk HPV types.

FAQ #2: Should I screen a 51-year-old virgin?

No official guidance.

Recommend discussing recommendation, benefits and harms of screening and making a plan based on patient preferences and values.
**USPSTF Conclusion: Co-testing**

“Although there is evidence of harms of strategies that incorporate HPV testing in women age 30 to 65 years, the USPSTF concludes that there is *adequate* evidence that the longer screening interval for HPV testing with cytology reduces the magnitude of these harms by decreasing the opportunity for false-positive test results.”

---

### Modeling

<table>
<thead>
<tr>
<th></th>
<th>False positives</th>
<th>Colposcopies</th>
<th>CIN 2-3</th>
<th>Cancers</th>
<th>Cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology q3 years, ages 21-65</td>
<td>350</td>
<td>758</td>
<td>80</td>
<td>8.5</td>
<td>1.55</td>
</tr>
<tr>
<td>Cytology q3 years until age 30 then co-testing q5 years</td>
<td>281</td>
<td>625</td>
<td>85</td>
<td>7.1</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Per 1000 women screened over a lifetime.

NB: Women with normal cytology and persistent HPV+ were returned to routine screening if colposcopy was normal.

“Modeling studies support similar benefits of co-testing every 5 years and cytology every 3 years, demonstrating small differences in expected cancer cases and cancer deaths.”
USPSTF: Co-testing caveat

• “The percentage of U.S. women undergoing co-testing who will have a normal cytology test result and a positive HPV test result (and who will therefore require additional testing) ranges from 11% among women age 30 to 34 years to 2.6% among women age 60 to 65 years.”

What to do with women who are hrHPV positive but have normal cytology?

Recommendations by ACS/ASCCP/ASCP and ACOG (2012)

Option 1:
- Repeat hrHPV testing and cytology at 12 months.
- If still hrHPV+ or cytology+, perform colposcopy.
- If both are normal, repeat co-testing in 3 years.

Option 2:
- Perform HPV 16/18 testing.
- If positive, perform colposcopy.
- If negative, repeat HPV testing and cytology at 12 months. If HPV-, cytology normal, repeat co-testing in 3 years; if hrHPV+ and/or cytology+, perform colposcopy.

App available from ASCCP.
Age to End Screening

- ACS/ASCCP/ASCP (2012): end at age 65 in those with adequate negative prior screening

- ACOG (2012): same

- USPSTF (2012): same

FAQ 3: What is “adequate negative prior screening”?

3 consecutive negative cytology results  
or  
2 consecutive negative co-tests

within the 10 years before ceasing screening,  
with the most recent test occurring within the  
past 5 years
FAQ 4: Should I re-start screening in women over age 65 who acquire new partners?

No

as per ACS/ASCCP/ASCP

Ending screening after hysterectomy

- ACOG, ACS and USPSTF: all agree that screening following total hysterectomy with removal of the cervix for benign disease is not indicated. USPSTF: “D” recommendation

- ACOG (2003): If hysterectomy for CIN 2 or 3, may stop screening after 3 normal tests.
- ACOG (2012): Continued routine screening (cytology ever 3 years) recommended for 20 years.
USPSTF: Co-testing caveat

• “Because HPV test results may be positive among women who would otherwise be advised to end screening at age 65 years on the basis of previously normal cytology results alone, the likelihood of continued testing may increase with HPV testing.”

On the horizon

Cobas HPV test (14 HR types): FDA approved as a primary screening test beginning at age 25 years

So, when do we do hrHPV testing?

• **Management of ASC-US**
  - if hrHPV positive, colposcopy
  - if hrHPV negative, co-testing in 3 years
  Can also just repeat cytology in 1 year

• **Management of women after colposcopy**
  hrHPV plus cytology in one year: no other strategies recommended (by ACOG/ASCCP)

FAQ #5: How should I screen women who only have (or ever had) sex with women?

No differently
FAQ #6: If I am not doing annual cytology, do I still need to perform an annual pelvic exam (external, speculum, bimanual)?

In which asymptomatic woman would you recommend/perform a routine bimanual examination?

- 18-year-old, sexually active for one month
- 35-year-old, no new partners for 5 years
- 55-year-old, prior removal of the entire uterus and ovaries
- 70-year-old, not sexually active for 10 years
- All of the above
- None of the above
ACOG: bimanual pelvic examinations

- “No evidence supports or refutes the annual pelvic examination or speculum and bimanual examination for the asymptomatic, low-risk patient.”
- The exam “seems logical”.
- “Annual pelvic examination of patients 21 years of age or older is recommended by the College.”
- Recommendation based on expert opinion

ACOG Committee Opinion No. 534 August 2012

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Randomized Controlled Trial

- Randomized trial of 78,216 women aged 55-74
- Annual screening with CA-125 for 6 years and transvaginal U/S for 4 years (n=39,105) versus usual care (n=39,111)
- 10 US screening centers
- Followed a median of 12 years
- Bimanual examination originally part of the screening procedures but was discontinued

JAMA. 2011;305(22):2295-2303
The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial

Figure 2. Ovarian Cancer Cumulative Cases and Deaths

More cancers found but no effect on mortality.

Physician survey: bimanual exams, 2012

Reasons cited as “very important” included adherence to standard medical practices (45%), patient reassurance (49%), detection of ovarian cancer (47%), and identification of benign uterine (59%) and ovarian (54%) conditions.
Risk of unnecessary surgery: ~1-1.5% (limited evidence)
ACOG Response

- “continues to firmly believe in the clinical value of pelvic examinations, through which gynecologists can recognize issues such as incontinence and sexual dysfunction.”
- While not evidence-based, the use of pelvic exams is supported by the clinical experiences of gynecologists treating their patients.
- allow gynecologists to explain a patient’s anatomy, reassure her of normalcy, and answer her specific questions, thus establishing open communication between patient and physician.


ACOG: focus on other important issues in women’s health

immunizations, smoking cessation, breast disease (CBE), depression screening, violence screening, STI screening, family planning, wellness

Chelmow et al Obstet Gynecol 2012;119:695-9

ACOG: Well-woman Task Force Report
October 2015
Summary

- No cytology screening prior to age 21
- Annual cytology not recommended for most women
- Annual screening is recommended for high-risk women: immunocompromised (HIV+), prior CIN2+, in utero DES exposure
- Co-testing (hrHPV plus cytology) every 5 years may be equivalent to cytology every 3 years for women aged 30-65 years

Summary

- Women aged 30-65 who are resistant to screening every 5 years poor candidates for co-testing (hrHPV plus cytology)
- Screen HPV vaccinated women same as others
- Screening with (conventional) cytology alone (without HPV testing) every 3 years is still a great option (and perhaps the least complicated)
- What we do at SFGH/UCSF in your syllabus.
- Be aware of limited data on benefits and harms of bimanual exams in asymptomatic women
Questions
**Table 1: Cervical cancer screening**

<table>
<thead>
<tr>
<th>Age to begin</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method and intervals, by age</td>
<td>Ages 21-65: cytology every 3 years or Ages 21-29: cytology every 3 years, then Ages 30-65: cytology plus hrHPV testing every 5 years (co-testing)</td>
</tr>
<tr>
<td>Co-testing is reserved for women ages 30-65 wanting to lengthen their screening interval to every 5 years.</td>
<td></td>
</tr>
<tr>
<td>Age to end</td>
<td>65†</td>
</tr>
</tbody>
</table>

These are 2012 recommendations by the USPSTF, ACOG and ACS. hrHPV indicates high-risk human papillomavirus.

*Recommendations apply to women with no prior diagnosis of cervical intraepithelial neoplasia grade 2 or a more severe lesion or cervical cancer, women who are not immunocompromised (e.g., HIV infected) and women with no in utero exposure to diethylstilbestrol.

†only among women with 3 consecutive negative cytology results or 2 consecutive negative cytology plus hrHPV tests within 10 years before cessation of screening, with the most recent test performed within the last 5 years. Screening should not resume after cessation even if a woman acquires new sexual partners. Routine screening should continue for at least 20 years after treatment of CIN2 or CIN3, even if this extends screening past age 65.

---

**Special populations**

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Screen as above</th>
</tr>
</thead>
<tbody>
<tr>
<td>After total hysterectomy</td>
<td></td>
</tr>
<tr>
<td>If no prior CIN2, 2/3 or 3</td>
<td>Screening should not be performed.</td>
</tr>
<tr>
<td>If prior CIN2, 2/3 or 3</td>
<td>End screening after 3 normal annual vaginal cytology tests (2003 ACOG recommendation)*</td>
</tr>
<tr>
<td>Women with HIV infection or immunocompromise</td>
<td>Annual screening after 2 normal cytology tests 6 months apart in the year following initial HIV diagnosis or immunocompromised state</td>
</tr>
<tr>
<td>After diagnosis and treatment of cervical cancer</td>
<td>Surveillance as per gynecologic oncology protocols</td>
</tr>
</tbody>
</table>

CIN indicates cervical intraepithelial neoplasia.

*2012 ACOG recommends cytology every 3 years for 20 years after the initial CIN2+ treatment and post-treatment surveillance
**Table 2. Management of initial screening test results**

<table>
<thead>
<tr>
<th>Management of Initial Screening Test Results</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory cytology</td>
<td>Repeat cytology in 2-4 months</td>
</tr>
<tr>
<td>Satisfactory cytology, but no endocervical cells</td>
<td>Repeat cytology in 3 years*</td>
</tr>
<tr>
<td>Atypical squamous cells, undetermined significance (ASC-US), hrHPV negative</td>
<td>Routine screening in 3 years</td>
</tr>
<tr>
<td>ASC-US, hrHPV unknown</td>
<td>Cytology in 12 months. Colposcopy for any abnormality. If normal, resume routine screening.</td>
</tr>
<tr>
<td>Normal cytology, hrHPV positive, HPV 16/18 negative Low-grade squamous intraepithelial lesion (LSIL), hrHPV negative</td>
<td>Cytology plus HPV testing in 12 months. Colposcopy for any abnormality. If both normal, repeat cytology plus HPV testing in 3 years.</td>
</tr>
<tr>
<td>ASC-US, hrHPV positive</td>
<td>Ages 21-24: Cytology in 12 months (colposcopy for ASC-H or HSIL+) and at 24 months (colposcopy for any abnormality). If all normal, routine screening.</td>
</tr>
<tr>
<td>Normal cytology, hrHPV positive on 2 consecutive tests Normal cytology, hrHPV positive, HPV 16/18 positive LSIL, hrHPV positive or unknown</td>
<td>Age 25+: Colposcopy†</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL) Atypical squamous cells, cannot exclude HSIL (ASC-H)</td>
<td>Colposcopy†</td>
</tr>
<tr>
<td>Atypical glandular cells (AGC)§ Adenocarcinoma in situ</td>
<td>Colposcopy with endocervical curettage; endometrial biopsy if abnormal bleeding, chronic anovulation or age 35+</td>
</tr>
</tbody>
</table>

hrHPV indicates high-risk human papillomavirus. HSIL+ indicates HSIL, AGC, AIS or cancer.
*2012 ACOG/ASCCP: cytology plus hrHPV testing preferred over repeat cytology alone
†Colposcopy should be performed even if hrHPV is negative. Endocervical curettage should not be performed in pregnancy.
§If atypical glandular cells are specified as endometrial, endometrial biopsy is indicated.

**Pregnant women**

| ASC-US | Age 21-24, manage as per non-pregnant women. Age 25+, if colposcopy indicated, may defer to 6 weeks post-partum. |
| LSIL  | Age 21-24, manage as per non-pregnant women. Age 25+, colposcopy is recommended but may be deferred to 6 weeks post-partum. |

**Women with HIV infection:** manage as per average-risk women (as per ASCCP 2012)

*All patients should be advised about smoking cessation and HIV testing should be offered.*
### Table 3. Management after initial colposcopy

<table>
<thead>
<tr>
<th>Indication for initial colposcopy</th>
<th>Findings at colposcopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication for initial colposcopy</strong></td>
<td><strong>Findings at colposcopy</strong></td>
</tr>
</tbody>
</table>
| Normal cytology, hrHPV positive on 2 consecutive tests | Age 25+: Cytology plus hrHPV testing in 12 months; colposcopy for any abnormality. If both normal, routine screening. Ages 21-24: Cytology alone in 12 months (colposcopy for ASC-H or HSIL+) and at 24 months (colposcopy for any abnormality). If all normal, routine screening.  
**CIN** indicates cervical intraepithelial neoplasia. hrHPV indicates high-risk human papillomavirus testing. SIL indicates squamous intraepithelial lesion. HSIL+ indicates HSIL, AGC, AIS or cancer.  
*2012 ACOG/ASCCP: for women aged 25+, cytology plus hrHPV testing in 12 and 24 months; colposcopy for any abnormality. If all normal, repeat cytology plus hrHPV testing in 3 years. If cytology and HPV testing at 3 years normal, routine screening.  
†Review of prior cytology, histology and colposcopic findings may be warranted, especially when potential risks of excision may exceed benefit.  
§Excisional procedures are deferred in pregnant women to the postpartum period unless cancer is suspected.  
^2012 ACOG/ASCCP: If all normal, cytology alone (women under 30) or cytology plus hrHPV testing (women 30+) in 3 years. If testing at 3 years normal, resume routine screening. |
| Normal cytology, hrHPV positive, HPV 16/18 positive |  
| Atypical squamous cells of undetermined significance (ASC-US) on 2 consecutive tests |  
| ASC-US, hrHPV positive |  
| Low-grade SIL (LSIL) |  
| Atypical glandular cells (AGC), not otherwise specified | Cytology plus hrHPV testing in 12 and 24 months; colposcopy for any abnormality. If all normal, routine screening.  
^See Table 4 |
| High-grade SIL (HSIL) |  
| Atypical squamous cells, cannot exclude HSIL (ASC-H) | Colposcopy and cytology at 6 and 12 months, if colposcopy adequate and endocervical curettage negative.  
^ If all normal, routine screening.  
| Diagnostic excisional procedure, if colposcopy inadequate †§ |
| Atypical glandular cell, favor neoplasia Adenocarcinoma in situ | Diagnostic excisional procedure § |

*All patients should be advised about smoking cessation and HIV testing should be offered.*
Table 4. Choosing treatments for CIN2*, CIN2/3* and CIN3

<table>
<thead>
<tr>
<th>Ablation</th>
<th>Use if the following criteria met:</th>
</tr>
</thead>
</table>
| **Cryotherapy** | • adequate colposcopy  
|              | • lesion(s) completely visible, not covering more than 75% of the ectocervix and can be covered entirely with the cryoprobe  
|              | • under age 40†                                                                                   |
| **Laser**    | Use as for cryotherapy and for large (≥2 cm) and/or multifocal lesions, with or without vaginal involvement. |

<table>
<thead>
<tr>
<th>Excision</th>
<th>Use if criteria for ablation not met.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop excision</strong></td>
<td>Use if criteria for ablation not met.</td>
</tr>
<tr>
<td><strong>Cone biopsy</strong></td>
<td>Use if criteria for ablation not met and instead of loop excision if: suspicion for malignancy or cervical architecture distorted (e.g., prior cervical treatments, severely atrophic cervix).</td>
</tr>
</tbody>
</table>

*In women of childbearing potential with CIN2 and CIN2/3 (but not CIN3), colposcopy and cytology every 6 months for up to 24 months is acceptable if colposcopy is adequate. Routine screening may resume after 2 normal cytology tests and colposcopies and a normal cytology plus hrHPV test a year later. We recommend ablation in women under age 40 when criteria are met.

†Cryotherapy failure rates increase with age and exceed 30% over a 6-year period in women aged 40+ treated for CIN3.

Table 5. Follow-up after treatment of CIN2, CIN2/3 and CIN3

<table>
<thead>
<tr>
<th>Hysterectomy</th>
<th>Screening may end after 3 normal annual vaginal cytology tests (2003 ACOG recommendation)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy or laser ablation; loop excision or cone biopsy with negative margins</td>
<td>Cytology with or without colposcopy at 6 months, followed by cytology at 12 months and then annual cytology for at least 20 years†</td>
</tr>
<tr>
<td>Loop excision or cone biopsy with positive margins</td>
<td>Cytology and endocervical curettage (non-pregnant women) with or without colposcopy at 6 months, followed by cytology at 12 months and then annual cytology for at least 20 years†</td>
</tr>
</tbody>
</table>

*2012 ACOG/ASCCP recommendation: cytology alone every 3 years for 20 years after the initial CIN treatment and post-treatment surveillance
†2012 ACOG/ASCCP recommendation: cytology plus hrHPV testing in 12 and 24 months; colposcopy for any abnormality. If all normal, cytology plus hrHPV testing in 3 years. If cytology and HPV testing at 3 years normal, routine screening.

Table 6. Follow-up after treatment of adenocarcinoma in situ

<table>
<thead>
<tr>
<th>Hysterectomy</th>
<th>Annual cytology. After 3 consecutive, normal tests, cytology may be performed every 3 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone biopsy</td>
<td>Colposcopy with cytology, HPV testing and ECC in 6 months, then cytology and ECC 12 and 18 months later followed by cytology and ECC every year until hysterectomy. Colposcopy for ASC+.</td>
</tr>
</tbody>
</table>

All patients should be advised about smoking cessation and HIV testing should be offered.