Cervical Cancer Screening Update and Implications for Annual Exams

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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
• ~80 million women at risk in the US
• Most effective approach: screen unscreened and poorly-screened women


<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Female Rate</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>

Effect of hysterectomy

- Absolute rates and age-specific patterns of cervical cancer incidence vary by race.
- White women: peak incidence at 65 to 69 years of age (corrected rate 83% greater than uncorrected)
- Black women: hysterectomy corrected incidence increased steadily with age up to age 65 to 69 years (corrected rate 126% greater than uncorrected)

Rostitch, Cancer, 2014

From virus to cancer

Schiffman and Wright NEJM 2003;348(6):489-490

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: proximal cancer precursor

United States recommendations: the big 3

• American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society of Clinical Pathologists (ACS/ASCCP/ASCP) 2012 C4 Cancer J Clin 2012
• American College of Obstetricians and Gynecologists (ACOG) 2012. Screening for Cervical Cancer. Number 131, November 2012
• US Preventive Services Task Force (USPSTF) 2012
Cervical cancer screening. At http://
www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm
Guidelines do not apply to immunocompromised women (HIV+), those with in utero DES exposure and those with prior CIN 2 or 3.

Evidence Review

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
1400 Independence Avenue
Washington, DC 20201
www.ahrq.gov
Contract No. HHS 290-2007-10085-I, Task Order No. 9

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 (“no screening” under age 21)
- ACOG (2012): same
- USPSTF (2012): begin at age 21 “regardless of sexual history”, “D” recommendation (don’t screen under age 21)

All agree: do not screen before age 21 years

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

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

No randomized trials; evidence inconsistent.

Screening frequency: ages 21-29

- ACS/ASCCP/ASCP (2012): cytology every 3 years
- ACOG (2012): cytology every 3 years
- USPSTF (2012): cytology every 3 years (“A”)

All agree: no annual screening
ACS/ASCCP/ASCP: “Women of any age should not be screened annually by any screening method.”

All agree: no HPV testing for primary screening
USPSTF: “D” recommendation women under 30
So, should we screen virgins at age 21?

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.”

ACOG Committee Opinion No. 534 August 2012

Screening frequency: ages 30-65

- ACS/ASCCP/ASCP (2012): screen every 3 years with cytology alone or every 5 years with cytology plus HPV 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 HPV testing (but only for “women who want to lengthen the screening interval”)

Do you perform co-testing (HPV plus cytology) for screening women aged 30-65?

1. Yes, every year
2. Yes, every 3 years
3. Yes, every 5 years
4. No

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.”

**Current controversy**

Should co-testing (HPV plus cytology) be *preferred* over cytology alone?

**Commonly used HR HPV DNA tests**

- **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**: tests for one or more of 14 oncogenic HPV types; type-specific testing available (16, 18)

**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.”
**USPSTF: Co-testing caveat**

- “Women choosing co-testing … should be aware that positive screening results are more likely with HPV-based strategies… and that some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results.”

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

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

**Option 1:**
- Repeat HPV testing and cytology at 12 months.
- If still HPV+ or LSIL+, perform colposcopy.
- If both are normal (or ASC-US/HPV-), repeat co-testing in 5 years.

**Option 2:**
- Perform HPV 16/18 testing.
  - If positive, perform colposcopy.
  - If negative, repeat HPV testing and cytology at 12 months. If HPV-, cyto normal or ASC-US, repeat co-testing in 5 years; if HPV+ and/or LSIL+, perform colposcopy.

**Age to End Screening**

- **ACS/ASCCP/ASCP (2012):** end at age 65 in those with adequate negative prior screening (see next slide)
  - Once ended, do not resume screening in women who have new partners.

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

- **USPSTF (2012):** end at age 65 in those with adequate negative prior screening

**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
**Ending screening: regardless of age**

- 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

![Cobas HPV test flowchart](https://usdiagnostics.roche.com/en/hpv_ctng.html)

**What about the bimanual exam?**
ACOG: bimanual pelvic examinations

- “No evidence supports the routine internal examination of the healthy, asymptomatic patient before age 21 years…” but
- “Annual pelvic examination of patients 21 years of age or older is recommended by the College.”
- Recommendation based on expert opinion
- “No evidence supports or refutes the annual pelvic examination or speculum and bimanual examination for the asymptomatic, low-risk patient.”

ACOG Committee Opinion No. 534 August 2012

Routine exams

“...The decision to perform an internal pelvic examination, breast examination, or both should be made by the physician and the patient after shared communication and decision making.”

“Concerns, such as individual risk factors, patient expectations, or medical–legal concerns may influence the decision to perform an internal pelvic examination or clinical breast examination.”

ACOG Committee Opinion No. 534 August 2012

After removal of the uterus and ovaries in asymptomatic, low-risk* women

“The decision to receive an internal examination can be left to the patient…”

“Annual examination of the external genitalia should continue.”

*no history of vulvar intraepithelial neoplasia, cervical intraepithelial neoplasia grade 2+, immunocompromise and in utero DES exposure

ACOG Committee Opinion No. 534 August 2012

Screening Pelvic Examination in Adult Women: A Clinical Practice Guideline From the American College of Physicians

- Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the utility of screening pelvic examinations for the detection of pathology in asymptomatic, nonpregnant, adult women.
- Methods: This guideline is based on a systematic review of the published literature in the English language from 1966 through January 2016 and considered various sources including clinical practice guidelines, clinical practice recommendations, and emerging clinical practice recommendations. The guideline reflects the current and recommendations using the evidence available.

ACF recommends against performing screening pelvic exams in asymptomatic, nonpregnant adult women
ACOG Response

- “the College 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.
- Pelvic examinations also 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.


Do you perform bimanual pelvic exams in asymptomatic women?

1. Yes
2. No

Survey: Bimanual Exams

- 521 US OB/GYNs
- Nearly all perform bimanual pelvic examinations in asymptomatic women across the lifespan
- 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.

Henderson et al AJOG 2012

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
**Summary**

- No cytology screening prior to age 21
- Annual cytology not recommended for most women
- Annual screening is recommended for high-risk women: e.g., immunocompromised (HIV+)
- Co-testing (HPV 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 are poor candidates for co-testing (HPV 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)
- Be aware of limited data on benefits and harms of bimanual exams in asymptomatic women

**Questions**