Disclosures

• I have no relevant disclosures to make.
Objectives of Screening

- Prevent morbidity and mortality from cervical cancer
- Prevent overzealous management of precursor lesions that most likely will regress or disappear and for which the risks of management outweigh the benefits
Natural History of Cervical Cancer

HPV infection

CIN 1

Avg. 6-24 mo

CIN 2,3

Avg. 10-13 yrs

Invasive CA

HPV disappearance

Avg. 6-12 mo.
The strengths and limitations of cervical cancer screening
Cervical Cancer Prevention

Widespread introduction of the Pap begins

Conventional Pap smear

1949

2000’s
Cervical Cancer Incidence (SEER) and U.S. Death Rates,* 1975-2005

Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
*Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
Being rarely or never screened is the major contributing factor to most cervical cancer deaths today.
Who are the Rarely and Never Screened?

**Descriptions**
- Minorities
- Low SES*
- Foreign born
  - Living in the US < 10 years
- No usual source of health care

**Where are the data?**
- US Census
- NCHS Cervical cancer mortality
- BRFSS\(\mu\)
- NHIS**

* Socio-economic status
  National Center for Health Statistics, CDC
\(\mu\) Behavioral Risk Factor Surveillance System, CDC
** National Health Interview Survey, CDC
System Failures Leading to Cervical Cancer Diagnosis

- Women do not come in for screening
- Health care providers do not screen women at visits
- Colposcopy for abnormal screen not done
- Patient gets cervical cancer
- Patient does not get appropriate therapy

Courtesy of Connie Trimble, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Retrospective Study of Cervical Cancers Diagnosed at Kaiser Northern California

Pap results 3-36 months prior to diagnosis

N=833

Failure to screen
No Pap 464 (56%)

Failure in detection
1st Pap WNL 263 (32%)

Failure to follow-up
1st Pap abnormal 106 (13%)

No visit 19%
1-2 visits 18%
>3 visits 63%

Proportion of Women Receiving Cervical Cancer Screening, NHIS*, United States, 2000

<table>
<thead>
<tr>
<th>Group</th>
<th>% Pap test past 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>82%</td>
</tr>
<tr>
<td>Insured</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85%</td>
</tr>
<tr>
<td>No</td>
<td>62%</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
</tr>
<tr>
<td>US born</td>
<td>83%</td>
</tr>
<tr>
<td>Foreign born in U.S. &lt;10 yrs</td>
<td>61%</td>
</tr>
</tbody>
</table>

*National Health Interview Survey
Prevalence of Pap Tests during last 3 years, by education level, U.S.

https://www.cdc.gov/nchs/data/hus/hus07.pdf

Cervical cancer prevention: Where have we been and where are we going?

Widespread introduction of the Pap begins

<table>
<thead>
<tr>
<th>Conventional Pap smear</th>
<th>LBC</th>
<th>HPV testing</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949</td>
<td>1996</td>
<td>2000’s</td>
<td></td>
</tr>
</tbody>
</table>
Why isn’t “finding lesions” the objective of screening?

- Don’t know which lesions will progress.
- Need to place emphasis on:
  - **Persistent** HPV infections
  - *CIN 3* (no margin for error)
  - *CIN 2* in older women
  - Persistent CIN 2 and CIN 2/3 in non-adolescent women
Consensus Conference
Sponsored by

- American Society of Colposcopy and Cervical Pathology (ASCCP)
- American Cancer Society (ACS)
- American Society of Clinical Pathology (ASCP)
ACS/ASCCP/ASCP Guidelines Development Process

2009-2011 – A steering committee from the 3 organizations created 6 working groups and a data group to direct the evidence evaluation

Participating organizations:
AHRQ, AAFP, ABOG, ACHA, ACOG, ASHA, ASC, ASCT, CAP, CDC, CMS, FDA, NCI, NCCN, NPWH, PPFA, SCC, SGO, SGOC, AHRQ/USPSTF, VHA
Guidelines Development Evidence Review

- Used “Grading Recommendations Assessment, Development, and Evaluation” system (GRADE)
- Articles retrieved 1995 to mid-2011
- WGs reviewed and graded evidence “critical, important, nice to know”
- WGs developed recommendations -- “strong” or “weak” depending on the quality of the evidence
6 topic areas identified:

- Optimal screening intervals
- Screening women 30+
- Managing discordant cytology/HPV results
- Exiting women from screening
- Impact of HPV vaccination on screening
- Potential for primary HPV testing (no Pap)
Guidelines Development Process Assumptions

• Preventing all cervical cancer is unrealistic
  – No screening test has 100% sensitivity
• Reasonable risk is determined by a strategy of performing cytology alone at 2-3y intervals
  – Screening strategies with similar outcomes are acceptable
• Women at similar risk for cancer should be managed the same
Guidelines Development
Process Assumptions

• Conventional and liquid-based cytology perform similarly
• HPV tests should have ≥90% sensitivity for CIN2+ and CIN3+
  ▪ Comparability of all FDA-approved HPV tests cannot be assumed
  ▪ Utility of unapproved/laboratory developed tests is unknown, and tests should not be used in screening
Benefits of screening

- Cancer is the ideal endpoint but unrealistic
- CIN3 is a reliable surrogate marker for sensitivity
- CIN2 is equivocal (a combination of CIN1 and CIN3)
  - hard to diagnose—poor inter-rater reliability
  - often regresses
  - a threshold for treatment
Guidelines Development Process Assumptions

- Screening interval
  - Risk of developing invasive cancer before next screen should be unlikely
  - Earlier detection of CIN3+ is a benefit
- Even studies with less sensitive tests show similar CIN3 detection--no increased cancer risk during later screening rounds
Guidelines Development Process Assumptions

- Possible harms of screening
  - Anxiety over a positive test
  - Stigma of an STI
  - Pain/bleeding from procedures
  - Treatment-related pregnancy complications
- Number of colposcopies is a marker for harms
Treatment saves lives, but at what cost?

- Women with LEEP more likely to have
  - Preterm birth (O.R. 1.7)
  - LBW (O.R. 1.8)
  - PPROM (O.R. 2.7)
- Single studies show association with perinatal death, incompetent cervix
- Risk rises with depth and number of LEEP s
- Similar findings after conization or laser treatment
- Absolute risk increase is small

Bruinsma et al BJOG 2007;114:70-80
Guidelines Development Evidence Review Process

- Recommendations posted to ASCCP website for public comment 10/19-11/9/11
  - Revisions made based on comments as needed
- Consensus conference held 11/17-18/2012
- Discussion of draft recommendations by attendees
- Recommendations approved by at least a 2/3 majority of delegates
2012 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines

Saslow, Solomon, Lawson, et al. JLGTD, March 14, 2012 (online)
New ACS/ASCCP/ASCP Guidelines

When to begin screening

Cervical cancer screening should begin at age 21.

Women < 21 should not be screened regardless of age of sexual onset

Guidelines do not apply to special populations – hx of cervical cancer, DES exposure, & immune-compromise

Saslow, Solomon, Lawson, et al. JLGTD, March 14, 2012 (online)
# Cervical Cancer Incidence by Age Group, USCS*, 1998-2002

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>0.1</td>
</tr>
<tr>
<td>20-29</td>
<td>4.5</td>
</tr>
<tr>
<td>30-39</td>
<td>13.9</td>
</tr>
<tr>
<td>40-49</td>
<td>16.5</td>
</tr>
<tr>
<td>50-64</td>
<td>15.4</td>
</tr>
<tr>
<td>65+</td>
<td>14.6</td>
</tr>
<tr>
<td>All ages</td>
<td>9.4</td>
</tr>
</tbody>
</table>

*United States Cancer Statistics includes data from CDC’s National Program of Cancer Registries and NCI’s Surveillance, Epidemiology and End Results Program.

Adolescent Needs

- Care for contraception and STI screening/treatment.
- No Pap test
- No speculum exam for asymptomatic women
- STI testing can be done using urine
Screening for ages 21-29

- Cytology alone every 3 years
- HPV testing “should not be used to screen”
  - Not as a component of cotesting
  - Not as a primary stand-alone screen
Rationale for Longer Pap Screening Intervals

- Sensitivity of single Pap test 50-70%
  - Cancer risk 18mo after 3 neg Paps = 1.5/100,000
  - Cancer risk 36mo after 3 neg Paps = 4.7/100,000
  → 99,997 women screened unnecessarily to help 3
- Risk of HSIL/cancer <3 years after negative Pap not significantly higher than risk after 1 year
- Longer Pap screening intervals (e.g., 5y) inappropriate for mobile US population

Rationale for Longer Pap Screening Intervals-2

• Screening harms: lifetime risk of colposcopy
  – Screening q3y: 760 colpos/1000 women
  – Screening q2y: 1080 colpos/1000 women
  – Screening annually: 2000 colpos/1000 women

Prevalence of HPV by Age, Manchester, U.K.

Rationale for Avoiding HPV Tests Among Women Ages 21-29

- Prevalence of carcinogenic HPV approaches 20% in teens and early 20s
- Most carcinogenic HPV infections resolve without intervention
- Identifying carcinogenic HPV that will resolve leads to repeated call-back, anxiety, and interventions without benefit
Screening For Women Ages 30-64

- Cytology + HPV testing (Cotesting) every 5 years is preferred

- Cytology alone every 3 years is acceptable
Rationale for Cotesting, Ages 30-64

• Increased detection of prevalent CIN3
• Decreased CIN3 in subsequent screening rounds
• Achieves risk of CIN3 equal to cytology alone @ 1-3year intervals
• Enhances detection of adenocarcinoma/AIS
• Minimizes the increased number of colposcopies, thus it reduces harms.
Why Not Cotesting for All Women 30-64?

- Some sites may lack access to HPV testing
  - Financial
  - Logistical
- Cytology remains effective
  - Requires more frequent visits
  - Requires more colposcopy for equivocal results
Why Not Annual Cotesting?

• High NPV of one cotest means most abnormal screens at 1-3y intervals are transient HPV infection, not precancer
• Potential harms are amplified without benefit
Rapid clearance of HPV in Women ≥30


* Histological progression
Managing ASC-US/HPV negative tests

• “Women with ASC-US cytology and negative HPV test results should continue screening per age-specific guidelines.”

• CIN3 risk of ASC-US/HPV neg <2%, below threshold for colposcopy.
“Women cotesting HPV positive and cytology negative should be followed with either (1) repeat cotesting in 12 months, or (2) immediate HPV genotype-specific testing for HPV16 alone or HPV 16/18. Direct referral to colposcopy is not indicated”
(1) Repeat cotest in 12 months

- If either repeat test is positive, refer to colposcopy
- If both tests are negative, return to routine screening.
(2) Immediate HPV genotyping

- If HPV 16 or HPV16/18 positive, refer directly to colposcopy.
- If HPV 16 or HPV 16/18 negative, repeat cotest in 12 months and then...
  - If either repeat test is positive, refer to colposcopy
  - If both tests are negative, return to routine screening.
Managing HPV+/Cytology- Cotests

Rationale

- Consistent observational data indicate short term risk of CIN3 far below risk threshold of HPV+/ASC-US and LSIL used for colposcopy referral
- Evidence from cohort studies shows majority of transient infections clear by 12 months allowing most to return to routine screening without excessive risk.
Predicted Impact of Pap Screening on Cancer Incidence

Myers E 2006 ASCCP Biennial Meeting Las Vegas, NV
When to Stop Screening

- Stop at age 65 for women with adequate negative prior screening, no CIN2+ within the last 20y.

**Definition of adequate negative screening:**

- 3 consecutive negative Paps or
- 2 consecutive negative HPV tests

  (Tests within 10 years of stopping; most recent within 5 years.)
Stop screening at age 65

• Screening “should not resume for any reason, even if a woman reports having a new sexual partner.”
Rationale for stopping at 65 years

- **CIN2+ is rare after age 65**
  - Most abnormal screens, even HPV+, are false + and do not reflect precancer
- HPV risk remains 5-10%
- Colposcopy/biopsy/treatment more difficult
  - Harms are magnified
- **Incident HPV infection unlikely to lead to cancer within remaining lifetime**

Chen HC et al. JNCI 2011;103:1387-96;
Rodrigues AC et al. JNCI 2009;101:721-8
When to stop screening - 2

• Stop after hysterectomy with removal of cervix and no history of CIN2+

• “Evidence of adequate negative prior screening is not required”
Rationale for stopping after Hysterectomy

- Vag cancer rate is 7/million/year
- 663 vag cuff Paps needed to find one VAIN
- 2,066 women followed after hyst. for average 89 months
  - 3% had VAIN, 0 had cancer
- Risk of Pap abnormality after hyst = 1%.
- Compare risk of breast cancer in men for which screening is not recommended.

Pearce KF et al. NEJM 1996;335:1559-62;
Piscitelli JT et al. AJOG 1995;173:424-30
When **NOT** to stop at age 65 years

If history of CIN2, CIN3, or AIS
- Continue “routine screening” for at least 20 years, “even if this extends screening past age 65.”
Screening a Vaccinated Cohort

“Recommended screening practices should not change on the basis of HPV vaccination.”

- Vaccination against HPV 16/18
  - Reduces CIN3+ by 17-33%
  - Reduces colposcopy by 10%
  - Reduces treatment by 25%

- But who is vaccinated?
  - Recall? Completed series? HPV naïve?

HPV as a Primary Screening Test

• Strong NPV of HPV test suggests it might replace cotesting, but test specificity lacking
  – Follow-up to HPV+ test remains unclear
    • Pap? Repeat HPV in 1y? Genotyping? Colpo?
  – Knowing HPV status biases cytology reports to abnormal
  – Harms undefined
  – No US prospective trials

• “In most clinical settings, women ages 30-65 should not be screened with HPV testing alone.”
### 2012 Standards

<table>
<thead>
<tr>
<th></th>
<th>USPSTF</th>
<th>ACS/ASCCP/ASCP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start?</strong></td>
<td>21yo</td>
<td>21yo</td>
</tr>
<tr>
<td><strong>How often?</strong></td>
<td>Q3y Paps Cotesting ≥ 30 years q 5 yrs to lengthen the screening interval</td>
<td>Q3y Paps ages 21-29 Q5y cotesting ages 30-65 Q3y Paps remain an option</td>
</tr>
<tr>
<td><strong>When to stop?</strong></td>
<td>65 if adequate prior screens</td>
<td>Age 65 if 3 neg Paps or neg HPV After hysterectomy for benign disease</td>
</tr>
</tbody>
</table>
• “The biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among women rarely or never screened. . .

• Clinicians, hospitals, health plans, and public health officials should seek to identify and screen these women.”

ACS, 20002
Caveats

- Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view recommendations as dictates. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients.

- Users of guidelines may reasonably conclude that following some strong recommendations based on high quality evidence will be a mistake for some patients. No clinical practice guideline or recommendation can take into account all of the often compelling unique features of individual patients and clinical circumstances. Thus, nobody charged with evaluating clinician’s actions, should attempt to apply recommendations in rote or blanket fashion.