Making sense of the new Pap smear screening guidelines.

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Case

- 17 year old G1P0010 with first sexual encounter at age 15. Lifetime 2 partners. Smokes ½ pack per day. She never received the HPV vaccine and has never had a Pap smear. She has no gynecologic or other health complaints and her medical history is unremarkable. After a recent miscarriage, she presents with her mother who would like her to have a Pap smear and discuss contraception options.
Introduction

• Pap smear screening guidelines and management of abnormalities have been revised several times over the past decade to incorporate new evidence and technologies.

• ASCCP (American Society for Colposcopy and Cervical Pathology) 2012 Updated consensus guidelines
  • www.asccp.org
  • App available

• ACOG Practice Bulletin number 140 December, 2013
ASCCP App

Key Patient Information

- **Age:** 21 to 24
- **HPV Status:** Unknown
- **Pregnant:** No

Initial Testing Information

- **Cytology Results:** Normal

Recommendation

Colposcopy

Guideline Algorithm

Management of Women Ages 21-24 yr with Atypical Squamous Cells Cannot Rule Out High-Grade St. (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Next Steps

Add Colposcopy Followup Result
Add Initial Colposcopy Followup

NO CIN
CIN 1
CIN 2
CIN 3
AIS

Observation with Colposcopy & Cytology @ 6 Month Intervals

Guideline Algorithm

Next Steps
Add 6 Month Colposcopy and Cytology Results
Participating Organizations contributing to ASCCP consensus guidelines

AHRQ, AAFP, ABOG, ACHA, ACOG, ASHA, ASC, ASCT, CAP, CDC, CMS, FDA, NCI, NCCN, NPWH, PPFA, SCC, SGO, SGOC, AHRQ/USPSTF, VHA

Reviewed world literature and from analyses of a large 7 year clinical database involving 1.4 million women.
Again!!!!!!???'????????!!!!!!!

- Frequent changes in established guidelines frustrating.
- Do they really need to change and become more complex?
- What about them is really new?

- The task is to balance the risk of overtreatment with the risk of missing disease that progresses to cancer.
- The current guidelines are based on the best available data.
- Expert consensus guidelines provide a framework for care that is optimal for most patients.
- We should always respect our clinical judgment and the patients informed wishes.
Most important changes

• Defining acceptable risk and when to return to routine screening after treatment or resolution of abnormalities given the longer screening intervals.

• Improving incorporation of HPV testing

• Applying age stratified guidelines previously developed for adolescents, to individuals 21-24 years.

• Integrating new data on risk of high-grade precursor lesions and cancer
Goal of Pap Guidelines

• 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 treatment outweigh the benefits
• Screening guidelines apply to women with no symptoms.
Possible harms of screening

- Anxiety over a positive test
- Stigma of an STI
- Pain and bleeding from procedures
- Time and expense
- Treatment-related pregnancy complications
  - Women with LEEP more likely to have
    - Preterm birth (O.R. 1.7)
    - LBW (O.R. 2.7)
    - PPROM (O.R. 2.7)
  - Risk of incompetent cervix and above complications rises with depth and number of LEEP procedures (similar with laser or cone)
- Overall absolute risk increase is small
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).
Cervical Cancer

- Of the ~3,700 deaths, the number one risk factor was being rarely or never screened.
- Characteristics of those not screened
  - Minorities
  - Low socio-economic status
  - Foreign born living in US for < 10 years
  - No usual source of ambulatory health care
- System failures
  - Women do not come in for screening
  - Health care providers do not screen at the visit
  - Colposcopy for abnormal screen not done
  - Patient does not follow through with treatment after colposcopy
# Cervical Cancer Incidence

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate per 100,000</th>
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<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>
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<tr>
<td>40-49</td>
<td>16.5</td>
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<tr>
<td>50-64</td>
<td>15.4</td>
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<tr>
<td>65+</td>
<td>14.6</td>
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</tbody>
</table>

Saraiya M et al. Obstet Gynecol 2007; 109:360-70
Natural History of Cervical Cancer

- ~1 Year: Transient Infection
- HPV Infection
- 2–5 Years: Persistent Infection
- Over 2 Years
- 4–5 Years: Low-Grade Dysplasia CIN 1
- 4–5 Years: High-Grade Dysplasia CIN 2/3
- 8–15 Years
- Invasive Cancer
HPV (Human Papilloma Virus)

- Cause of nearly all cervical cancer
- 60% caused by HPV 16
- 15% caused by HPV 18
- The remainder caused by 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- Most venereal warts caused by Type 6 and 11
- Most infections are transient with little risk of progression and are gone by 1 year.
- Persistent infection at 1 and 2 years strongly predicts subsequent risk of progression to CIN 2-3 which are true cancer precursors.
- Lifetime cumulative risk of HPV infection is 80%
Rapid clearance of HPV (>30y/o)

* Histological progression

CIN (cervical intraepithelial neoplasia) Post-colposcopy terminology

- **CIN 1** has high rate of regression and can be managed expectantly
- **CIN 2** usually a mixed lesion with low and high grade features
- **CIN 3** and adenocarcinoma are clear cancer precursors

- From persistent infection to invasive cancer is slow (8-12 years)
- Threshold for treatment is CIN 2 or greater
  - Especially in young and pregnant women
Pap smear

- The cornerstone of the most successful screening program in the history of medicine.
- ASCUS
- ASC-H
- AGUS – The “G” stands for send to the Gynecologist
- LSIL – usually associated with a transient HPV infection
  - 28% have CIN 1 or CIN 2
- HSIL – usually associated with persistent HPV infection
- 2/3 of all CIN presents with ASCUS and LSIL
- Unsatisfactory
New Guidelines - Adolescents

• Begin screening at age 21 regardless of sexual onset

• 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

• New guidelines do not apply to patients with history of cervical cancer, DES exposure, or immune-compromised patients.
New Guidelines – 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
  • May be used as a reflex to stratify ASCUS
Why extend the screening interval?

- Sensitivity for a single Pap 50-70%
  - much higher for high grade lesions

- Risk of HSIL / cancer <3 years after negative Pap not significantly higher than risk after 1 year
Why not screen with HPV test?

• Prevalence of HR HPV approaches 20% in teens to early 20s
• Most HR HPV infections resolve without intervention
• Identifying HR HPV that will resolve still leads to call-backs, anxiety, interventions without benefit, and wasted healthcare resources.
Screening for Women ages 30-64

• Cytology + HPV testing (Cotesting) every 5 years is preferred
• Cytology alone every 3 years is acceptable

• Rationale for 5 year cotesting in this group
  • Increased detection of prevalent CIN 3
  • Achieves risk of CIN 3 equal to cytology alone at 1-3 year intervals
  • Enhances detection of adenocarcinoma
  • Reduces number of colposcopies
Why not use HPV test alone

• Not enough evidence to support this

• No US prospective trials to date

• Harms undefined

• April 25th, 2014. FDA Approved an HPV test to be used alone for screening in 25 and up population.
When to stop screening

• Stop at age 65 if:
  • 3 consecutive negative Paps within 10 years of stopping
  • 2 consecutive negative HPV tests within 10 years of stopping
  • No CIN 2 or higher within the last 20 years
• Per ASCCP “Screening should not resume for any reason, even if a woman reports having a new sexual partner.”
• Stop after hysterectomy with removal of cervix and no history of CIN 2+ (bullets above do are not required in this group)
Rationale for stopping

• CIN 2+ is rare after 65
• Most abnormal screens even HPV+, are false positives and do not reflect precancer
• *** Benefit harm ratio for colposcopy / biopsy / treatment changes → Harms are magnified
• Incident HPV infections at this point are unlikely to lead to cancer within remaining lifetime.
• Vaginal cancer after removal of cervix 7/million
• 663 vag cuff Paps needed to find one VAIN
• 2,066 women followed after hyst for 89 months → 3% had VAIN, 0 had cancer
• Comparable to risks of breast cancer in a man → no screening recommended

When NOT to stop at 65

- If history of CIN 2, CIN 3, or AIS
  - Continue routine screening for at least 20 years after disease even if past age 65

- Guidelines are guidelines. They are not law, and they may or may not help you in a case of failure to diagnose cancer.
Unsatisfactory Pap

• If no co-test, repeat 2-4 months
• If HPV + \(\rightarrow\) colposcopy
• If 2 unsatisfactory Paps in a row \(\rightarrow\) colposcopy
Satisfactory but no endocervical cells

- 21-29 years $\rightarrow$ Routine screening in 3 years with cytology

- 30 years and older $\rightarrow$ HPV result will guide management
  - HPV negative – routine screening with cotesting in 3-5 years
  - HPV positive
    - either repeat in one year with cotesting OR
    - Immediate genotyping for 16-18 types 😞

- If HPV testing not done, then HPV testing is the next step.
What about generation Gardasil?

- Per ASCCP, “Recommended screening practices should not change on the basis of HPV vaccination.”
- Vaccination against HPV 16 and 18
  - Reduces CIN 3+ by 17-33%
  - Reduces colposcopy by 10%
  - Reduces treatment by 25%
- Rationale for not changing based on patient recall, number of patients who didn’t complete series, HPV naivety
## 2012 Standards

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<th>USPSTF</th>
<th>ACS/ASCCP/ASCP</th>
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<tbody>
<tr>
<td><strong>When to start?</strong></td>
<td>21yo</td>
<td>21yo</td>
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<tr>
<td><strong>How often?</strong></td>
<td>Q3y Paps&lt;br&gt;Cotesting $\geq$ 30 years&lt;br&gt;q 5 yrs to lengthen the screening interval</td>
<td>Q3y Paps ages 21-29&lt;br&gt;Q5y cotesting ages 30-65&lt;br&gt;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&lt;br&gt;After hysterectomy for benign disease</td>
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</tbody>
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Important take home message

• The biggest gain in reducing the incidence and mortality would be achieved by increasing primary screening among women rarely or never screened.