How HPV drives new cervical cancer screening guidelines

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Disclosure

• I do not have financial relationships with pharmaceutical or device manufacturers
• This talk does not discuss unapproved uses of tests
• I have received honoraria and expense reimbursement from ASCCP for guidelines development.
Learning objectives

• Participants should be able to screen women for cervical cancer, applying the epidemiology and natural history
  – of human papillomavirus infections
  – and of consequent preinvasive/invasive cervical lesions

that underlie new guidelines
What is the objective of screening?

• To reduce morbidity/mortality from cervical cancer
  – Not to find abnormal Paps or CIN
  – Not to find HPV infection
Why isn’t finding lesions the objective of screening?

- CIN/SIL/HPV are surrogate markers, not inevitable cancer precursors
  - Only 30-50% of CIN3 progress to cancer
- Finding CIN/SIL/HPV not destined to cause morbidity/mortality
  - Increases anxiety/stigma/treatment pain & complications/cost
  - Without benefit to patients
Then why do we look for lesions?

• We can’t tell which lesions will progress.
• But we want to target only:
  – Persistent HPV infections
  – CIN 3 (no margin for obs before cancer)
  – CIN2 in older women (no risk to pregnancies)
  – Persistent CIN2 and CIN2,3 in younger women
Selecting optimal screening test

- Minimizing cancer morbidity/mortality
  AND
- Minimizing harms from overdiagnosis

Requires balancing sensitivity/specificity

⇒ Use a sensitive screen at long intervals to allow regression of self-limited lesions
Reducing cervical cancer risk to zero is not feasible

• Some cancers are not preventable:
  – Even if LEEP for HPV+, hyst at 30, which would carry unacceptable morbidity:
    • Rapid onset cancers in women 20-30yo
    • Adenocarcinomas missed by cytology
    • Tight gap junction neoplasms that don’t exfoliate

• Consensus focuses on level of risk that is acceptable given potential harms of screening
## What were the old standards?

<table>
<thead>
<tr>
<th></th>
<th>1987</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start?</strong></td>
<td>18yo or at sexual debut</td>
<td>21yo or 3y after sexual debut</td>
</tr>
<tr>
<td><strong>How often?</strong></td>
<td>Annually</td>
<td>Annually till 30 (Q2y if LBP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3y after 3neg unless DES/HIV+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3y if Pap/HPV test</td>
</tr>
<tr>
<td><strong>When to stop?</strong></td>
<td>Death?</td>
<td>Age 70 if 3 prior consecutive/sat/documentated neg Paps within 10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After hyst for benign disease</td>
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</table>

American Cancer Society, 1987, 2002
The old standards worked

Impact of Cervical Cytology in U.S.

Incidence of invasive cervical cancer
U.S. - from SEER
## Annual cancer risk, US women


<table>
<thead>
<tr>
<th>Tissue</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>232,340</td>
<td>39,620</td>
</tr>
<tr>
<td>Lung</td>
<td>110,110</td>
<td>72,220</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>773,680</td>
<td>24,530</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>49,560</td>
<td>8,190</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,240</td>
<td>14,030</td>
</tr>
<tr>
<td>Cervix</td>
<td>12,340</td>
<td>4,030</td>
</tr>
<tr>
<td>Vulva/vagina/other gyn</td>
<td>7,590</td>
<td>1,830</td>
</tr>
</tbody>
</table>
Current cervical cancer risk is low

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CaCx rate/100,000 U.S. women</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19yo</td>
<td>0.2</td>
</tr>
<tr>
<td>20-24yo</td>
<td>2.6</td>
</tr>
<tr>
<td>25-30yo</td>
<td>7.8</td>
</tr>
<tr>
<td>30-34yo</td>
<td>11.4</td>
</tr>
<tr>
<td>35-39yo</td>
<td>14.4</td>
</tr>
</tbody>
</table>

SEER 1992-96, all races: Risk in Africa is >30
Age-standardized cancer incidence and mortality are low in regions with screening.

Ca Cancer J Clin 2011;61:69-90
Residual risk of cervical cancer

- >40 million Paps annually in US
- >2 million abnormal Paps annually (5%)
- >200,000 CIN2,3 annually (0.5% of all screens)

→ Many are cancers that screening/Rx will prevent
→ Cancer risk in unscreened women remains high
More on residual risk

• >50% of cervical cancers occur in un- or underscreened women
• About 1 in 8 cancers follow mismanaged abnormal screening tests

→ Only ~30% of cancers are screen failures
→ More frequent screening won’t prevent cancer in unscreened women.

Why change?

Better understanding of HPV natural history

All cervical cancer is due to HPV infection but few HPV infections lead to cervical cancer

- >60% of women contract HPV within 2y of first sex
  - Most contract carcinogenic types, esp. HPV 16
- 90% of women clear HPV within 2y
- Only persistent high risk infections cause cancer
  - HPV- women are at low risk, even if previously infected.
Why change?

→ Low risk of CIN3+ after most abnormal Paps

• Traditionally, Paps prompted evaluation only when high grade (Pap grade III-V)
  – Lesser abnormalities were followed
• That changed in 1988
  – Bethesda system added ASC/LSIL categories
• Most Pap tests now are ASC/LSIL (5-7%)
  – HSIL only reported in 0.5% of Paps
If annual Pap testing works, why change?

- Low risk of CIN3+ after most abnormal Paps
  - CIN2+ is found in <30% of women with HPV+ ASC-US and LSIL
  - This is true despite HPV being found in 100% of HPV+ ASC-US, 85% of LSIL

- Most abnormal Paps reflect self-limited HPV infections, not precancer
Development of HPV DNA Positivity

60% of the college students had been HPV DNA positive by 2 years of follow-up and 80% became positive with increased follow-up.
HPV cumulative incidence among women sexually active but HPV- at enrollment

Weighted prevalence of low-risk and high-risk HPV among US women 14–59yo, CDC
30-month rates of clearance/persistence/progression of oncogenic HPV among women <30yo, US NCI, Guanacaste
Rodriguez AC et al. JNCI 2008;100:513-7
Rapid clearance of HPV in Women ≥30

* Histological progression

Projected Prevalence of HPV and CIN by Age

What is the natural history of LSIL/CIN1 in adolescents?

Moscicki AB et al. Lancet 2004;364:1678-83
Similar high likelihood of clearance of newly acquired HPV in young women

Why isn’t more just better?
Harms from overscreening

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

5y CIN3+ risk after neg cotest similar to 1y risk after neg Pap: Extend intervals
More harms to screening

- 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, # LEEPs
- Similar findings after CKC or laser cone
- Absolute risk increase is small

## What are the 2011 standards?

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<td>Q3y Paps</td>
<td>Q3y Paps ages 21-29</td>
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<tr>
<td></td>
<td>Q5y cotests</td>
<td>Q5y cotest ages 30-64 preferred</td>
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<tr>
<td></td>
<td>No preference</td>
<td>Q3y Paps remain an option</td>
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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: 3 organizations created 6 working groups as well as a data group to aid in evidence evaluation

- Participating organizations:
  AHRQ, AAFP, ABOG, ACHA, ACOG, ASHA, AmSoc Cytopath, AmSoc Cytotech, CDC, Ctrs for Medicare/Medicaid, CAP, FDA, NCI, NCCN, NPWH, PPFA, SCC, SGO, SGOC, USPSTF, Veterans Health Admin
Assumptions

- Benefits of screening
  - Cancer is the ideal endpoint but unrealistic
  - CIN3 is a reliable surrogate marker for sensitivity
  - CIN2 is hard to diagnose, often regresses: not a target for screening, though still a target for treatment
Assumptions

• Harms of screening
  – Anxiety over a positive test
  – Stigmatization
  – Pain/bleeding from procedures
  – Treatment-related pregnancy loss
  – Number of colposcopies is a marker for these
Assumptions

• Preventing all cervical cancer is unrealistic
  – No test has 100% sensitivity

• Reasonable risk is determined by the strategy of cytology alone at 2-3y intervals
  – Screening strategies with similar results acceptable

• Women at similar risk for cancer should be managed alike
Assumptions

- Conventional and liquid-based cytology perform similarly in preventing cancer.
- HPV tests should have $\geq 90\%$ sensitivity for CIN3+ and CIN2+.
  - Comparability of FDA-approved HPV tests can’t be assumed.
  - Utility of unapproved/exempt tests is unknown, so these should not be used in screening.
Evidence review

- Recommendations posted to ASCCP website for public comment 10/19-11/9/11
  - Revisions made based on comments as needed
- Consensus conference 11/17-18/11
- After discussion, recommendations approved by at least 2/3 majority
Changes from 2002 guidelines

• Retains 21yo start to screening
  – No longer 3y after sex or 21yo, as before 2002
• Longer Pap screening intervals
  – Screen q3y ages 21-29—was annually
  – Screen q3y 30-65
• New technology allows long interval:
  – Cotesting preferred q5y over Paps
• Stop at age 65, not 70
  – Retains guideline to stop after hyst for benign disease
When to start screening

• "Begin at age 21 years"
• Younger women “should not be screened regardless of the age of sexual initiation or other risk factors.”
Rationale for later screening start

- Cervical cancer rare in teens (<1:1,000,000)
- Early onset CaCx may not be preventable
- HPV—including HRHPV—occurs in over 80% of sexually active adolescents
- HPV infections usually transient
Others start screening later

• Europeans begin screening at 25-30 years of age
  – Screen only every 3-5 years
  – But they have central screening systems with organized recall
When to start screening

• Sexually active adolescents need care for contraception and STD screening/treatment
  – These don’t require Pap testing
  – No speculum needed for asymptomatic women
  – STD testing can be done using urine
Screening intervals

- Ages 21-29
  - Cytology alone q3y
  - HPV testing “should not be used to screen”
    - Not as a component of cotesting
    - Not as a primary stand-alone screen
Rationale for longer intervals

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

Rationale for avoiding HPV tests

- Prevalence of HRHPV approaches 20% in teens-early 20s
- Most carcinogenic HPV infections resolve without intervention
- Identifying HRHPV that will resolve leads to repeated call-back, anxiety, interventions without benefit
Screening intervals

• Ages 30-65
  – Cotesting (cytology + HPV test) q5y (preferred)
  – Cytology alone q3y (acceptable)
Why prefer cotesting?

- Adding HPV tests to cytology
  - Increases detection of prevalent CIN3
  - Decreases CIN3 in subsequent screening rounds
  - Therefore lower risk after neg screen
  - So a 5y interval between screens achieves risk of CIN3 equal to that after cytology alone done at 1-3y intervals
Why prefer cotesting?

- Adding HPV tests to cytology
  - Enhances detection of adenocarcinoma/AIS
  - Q3y vs q5y cotests: 10y cancer risk for 40yo woman was about 0.6%
  - Extending screening to q5y minimizes the increased number of colposcopies, so reduces harms of a more sensitive test.
Why not cotesting?

• Some sites may lack access to HPV testing
  • Financial, logistical
• Cytology remains effective
  – It just requires more frequent visits, more colposcopy for equivocal results
Why not annual cotesting?

• High NPV of one cotest means most abnormal screens at 1-3y intervals represent transient HPV infection, not precancer
• Harms are amplified without benefit
When to stop screening

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

• Screening “should not resume for any reason, even if a woman reports having a new sexual partner.”
When to stop screening

• Adequate negative prior screening is defined as
  – 3 consecutive negative cytology results or
  – 2 consecutive negative cotests
  – within the 10 years before ceasing screening
  – with the most recent test within 5 years.
Rationale for stopping at 65yo

- CIN2+ is rare after age 65
  - Most abnormal screens, even HPV+, are false positive, i.e., don’t reflect precancer
- HPV risk remains 5-10%
- Colpo/biopsy/treatment more difficult
  - Harms are magnified
- Incident HPV infection unlikely to lead to cancer within remaining lifetime

Rationale for stopping after hyst

• Vag cancer rate is 7/million/yr
• 663 vag cuff Paps needed to find one VAIN
• 2066 women followed after hyst for avg 89mo
  – 3% had VAIN, 0 had cancer
• Risk of Pap abnormality after hyst = 1%
  – Most abnormal screens, even HPV+, are false positive, i.e., don’t reflect precancer
  – Equal risk of breast cancer in men--mammography?

When to stop screening

• Stop at hysterectomy with removal of cervix and no history of CIN2+
• “Evidence of adequate negative prior screening is not required”
When NOT to stop at 65yo

- History of
  - Prior Cervical or endometrial cancer
  - In utero DES exposure
  - HIV infection or other immunocompromise

- If Hx CIN2, CIN3, or AIS
  - Continue “routine screening” for at least 20 years, “even if this extends screening past age 65.”
Impact of vaccination

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

• Vaccination is against HPV 16/18
  – Reduces CIN3+ by 17-33%
  – Reduces colposcopy by 10%
  – Reduces therapy by 25%

• But who is vaccinated?
  – Recall? Completed series? HPV naïve?

HPV as a primary screen

• Strong NPV of HPV test suggests this might replace cotesting
  – Follow-up to +HPV test remains unclear
    • Pap? Repeat HPV in 1y? Genotyping? Colpo?
  – Knowing HPV status skews cytology reads to abnl
  – Harms are undefined
  – No U.S. prospective trials

• “In most clinical settings, women ages 30-65 should not be screened with HPV testing alone.”
Summary: the 2011 standards

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Conclusion

• “Perhaps the largest immediate gain in reducing burden of cervical cancer incidence and mortality could be attained by increasing access to screening (regardless of the test used) among women who are currently unscreened or screened infrequently.”

ACS, 20012