An Update on Cervical Cancer Screening Recommendations and on the DOH BCC Program

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NM Nurse Practitioner Council
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I have no commercial relationships related to this talk.
Updated Objectives

• Summarize cancer screening and diagnostic services provided to NM women over the past 20 years through the DOH NM Breast & Cervical Cancer Early Detection (BCC) Program and partners like you

• Cite the most current cervical cancer screening recommendations published in March 2012 by:
  – US Preventive Services Task Force (USPSTF)

• Recognize that development of these recommendations involved a systematic review of the scientific literature to assess the relative risks/benefits of screening
What is cancer screening?

• My working definition:
  – A means of detecting early signs of cancer or pre-cancer in appropriate populations of asymptomatic people in order to decrease cancer deaths through subsequent diagnosis and treatment.
• Please see summary fact sheet provided
Screening for Cervical Cancer
Cause of Cervical Cancer

Human Papillomavirus (HPV)

- Double stranded DNA virus
- Virus integrates into host cell genome
Human Papillomavirus (HPV)

<table>
<thead>
<tr>
<th>High-risk types (oncogenic or cancer-associated)</th>
<th>Low-risk types (non-oncogenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82</td>
<td>6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81</td>
</tr>
</tbody>
</table>

- HPV types 16 and 18 cause 70% of cervical cancers and 50% of high grade cervical precancer (CIN3).
Infection with HPV

Persistent infection over 2-5 yrs progresses to precancer

Precancer progresses to invasive cancer
Composite data summary on CIN regression, persistence and progression

<table>
<thead>
<tr>
<th></th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>56%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Oster AG Int J Gynecol Pathol. 1993*
Risk factors for persistent HPV infections

• Duration
  – 66% of infections persistent for 18 months still present at 24 months

• Age
  – 50+ age group 47% more likely to have persistent infection than ≤ 20 age group

• HPV type
  – 16 and 18 confer highest risk for persistence AND progression to high-grade lesions

• Immunocompromise (e.g., HIV, transplant Rx)
Comparison of cytologic (Pap) and histologic (colposcopic biopsy) results
How effective is cytology-based screening for cervical cancer?

• When introduced to screening naïve populations:
  – 60-90% ↓ in cervical cancer rates within 3 yrs
  – ↓ in morbidity and mortality is consistent and equally dramatic across populations

• Most cases of cervical cancer in U.S. occur in women rarely or never screened
BCC Program Clinical Guidelines

• Screening average-risk women:
  – United States Preventive Services Task Force (USPSTF) recommendations
    • Our main focus today

• Screening higher-risk women; diagnostic follow-up
  – American Congress of OB/GYN (ACOG)
  – American Society for Colposcopy & Cervical Pathology (ASCCP)
  – National Comprehensive Cancer Network (NCCN)
  – BCC Program Medical Advisory Board
    • Beyond the scope of this presentation
U.S. Preventive Services Task Force (USPSTF)

• Mandated by congress

• Convened by the U.S. Public Health Service 1984

• Since 1988 under the Agency for Health Research and Quality (AHRQ) U.S. DHHS

• Independent panel of private-sector experts in prevention and primary care

Courtesy of Alan Waxman, MD, MPH
USPSTF Membership

• 16 public health professionals, mostly academics
  • Epidemiologists
  • Senior faculty in primary care specialties
    – Family medicine
    – Internal Medicine
    – Pediatrics
    – Obstetrics and gynecology
• Chief medical officer of state health department
• Medical director of large health organization
• Dean of school of public health

Courtesy of Alan Waxman, MD, MPH
Steps the USPSTF Takes to Solicit Public Input and Make a Recommendation

Develop Research Plan
Task Force members work with researchers from an Evidence-based Practice Center (EPC) to create a draft Research Plan that guides the recommendation process.

Public Comment Opportunity
The draft Research Plan is posted on the USPSTF Web site for public comment.

Devolve Evidence Report
Using the final Research Plan, the research team at the EPC independently gathers and reviews the available published evidence and creates a draft Evidence Report.

Public Comment Opportunity
The draft Evidence Report is critiqued by external national subject matter experts.

Public Comment Opportunity
The draft Evidence Report is posted on the USPSTF Web site for public comment. (Future Step in 2013)

The EPC reviews all comments, addresses them as appropriate, and creates a final Evidence Report.

Develop Recommendation
Task Force members discuss the Evidence Report and deliberate on the effectiveness of the service.

Public Comment Opportunity
The draft Recommendation is posted on the USPSTF Web site for public comment.

Finalize Recommendation
The Task Force reviews all comments, addresses them as appropriate, and creates a final Recommendation.

The Evidence Report is finalized and published.

The Task Force votes to ratify the final Recommendation.

Publish & Disseminate Final Recommendation
The final Recommendation and supporting Evidence Report are posted on the Task Force Web site.

Final Recommendations also are made available through electronic tools, peer-reviewed journals, and consumer guides.
Grading of Evidence and Strength of Recommendations

• Recommendations graded based on
  – Quality of evidence
    • Randomized controlled trials (RCTs) highest quality
  – Strength of recommendations
    • For or against intervention
    • Based on level of confidence of *relative balance of strengths and harms*

Courtesy of Alan Waxman, MD, MPH
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.</td>
</tr>
<tr>
<td>C</td>
<td>Note: <em>The following statement is undergoing revision.</em> Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
</tr>
<tr>
<td>I Statement</td>
<td>The USPSTF concludes that current evidence is insufficient to assess the balance of benefits &amp; harms of the service.</td>
</tr>
</tbody>
</table>
This recommendation statement applies to women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).
### How have USPSTF 2012 recommendations changed since 2003?

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age to start screening</td>
<td>3 yrs p sexual debut or age 21 (whichever 1\textsuperscript{st})</td>
<td>Age 21; do NOT screen before age 21</td>
</tr>
<tr>
<td>Using liquid based Pap</td>
<td>Insufficient evidence</td>
<td>No clinically significant difference vs conventional</td>
</tr>
<tr>
<td>How often to Pap screen</td>
<td>“At least every 3 years”</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Using HPV test for primary screening</td>
<td>Insufficient evidence</td>
<td>Option to co-test with Pap every 5 yrs in women 30+; do NOT use before age 30</td>
</tr>
</tbody>
</table>
What evidence and methods support the changes in the 2012 USPSTF cervical cancer screening recommendations?
5 Key Questions (KQ):

KQ1: When should cervical cancer screening begin?

KQ2: How does liquid-based cytology compare to conventional cytology?

KQ3: What are the benefits of using HPV testing as a screening test?

KQ4: What are the harms of liquid-based cytology?

KQ5: What are the harms of using HPV testing as a screening test?
Focus on relative balance

BENEFITS

RISKS???
Methods

• Oregon EPC reviewed 4,262 abstracts & 641 full articles
• Focused on studies conducted in countries with well-developed cervical CA screening
• Included 66 articles reporting on 35 studies
• At least 2 investigators critically appraised each study
• Poor quality studies excluded
• Summarized using qualitative synthesis
KQ1: When should cervical cancer screening begin?
High risk HPV infection is very common in adolescents and young women
Invasive Cervical Cancer is Exceedingly Rare in Adolescents

http://seer.cancer.gov/faststats

Courtesy of Alan Waxman, MD, MPH
Rate of Progression, CIN 3 to Cancer


• Increases with age
  – Age 80: 10% per year
  – Age 20-24: 0.5% per year
  – Adolescents: negligible

Courtesy of Alan Waxman, MD, MPH
Pap Less Protective at Younger Ages

• Large British study looked at odds of developing cancer based on whether or not women had Pap in prior 3 yr interval
  – “Cervical screening in women ages 22-24 had little or no impact on the rates of invasive cervical cancer up to age 30”
  • Sasieni P et.al BMJ 2009:339

Courtesy of Alan Waxman, MD, MPH
Potential Harms of Screening and Diagnosis

• Anxiety related to (+) screening results

• False (+) screening tests leading to colposcopies and biopsies
  – Pain, bleeding, discharge

• Colposcopy is also an imperfect test
  – Reproducibility of CIN diagnoses?
  – NTCC trial: 2 blinded pathologists from pool of 9 agreed on CIN2 diagnosis less than 50% of the time
Potential Harms of Treatment

- Excisional treatments (LEEP, conization)
  - Pain, bleeding, discharge
  - Future adverse pregnancy outcomes
    - Preterm delivery, low birthweight, perinatal mortality
Overdiagnosis and Overtreatment

• Many precancerous cervical lesions regress spontaneously, and others grow so slowly that they will not become clinically meaningful during a woman's lifetime.

• Identifying these lesions may result in unnecessary surveillance, diagnostic tests, and treatments with the associated harms.
Which is greater when deciding whether to screen adolescents for cervical cancer?
Risks Outweigh Benefits
Conclusions for KQ1:
When should screening begin?

• Screening women younger than 21 does not appear to offer substantial benefit.
  – High prevalence of HPV
  – Transient nature of cytologic abnormalities
  – Rare occurrence of cervical cancer
  – Adverse future reproductive outcomes and other harms
What do adolescents need?

Per ACOG 2009:

• Critical that sexually active adolescents be counseled and tested for STDs and counseled regarding sex and contraception.
  – “…may be carried out without cervical cytology screening and, in the asymptomatic patient, without the use of a speculum.”
KQ2: How does liquid-based cytology (LBC) compare to conventional cytology (CC)?

KQ4: What are the harms of LBC?
## Performance of LBC vs CC

<table>
<thead>
<tr>
<th>Cytology Cutoff</th>
<th>Sensitivity/Relative Detection Ratio (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
<th>False Positive Rate (95% CI)*</th>
<th>Unsatisfactory Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LBC</td>
<td>CC</td>
<td>LBC</td>
<td>CC</td>
<td>LBC</td>
</tr>
<tr>
<td>Detection of CIN3+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NETHCON</td>
<td>ASC-US+</td>
<td>1.05 (0.86–1.29) (adjusted)</td>
<td>NA</td>
<td>1.17 (0.99–1.39)</td>
<td>0.89 (0.82–0.98)</td>
</tr>
<tr>
<td></td>
<td>LSIL+</td>
<td>NR</td>
<td>NA</td>
<td>1.17 (1.01–1.36)</td>
<td>NR</td>
</tr>
<tr>
<td>NTCC</td>
<td>ASC-US+</td>
<td>0.84 (0.56–1.25)</td>
<td>NA</td>
<td>0.42 (0.29–0.62)</td>
<td>1.93 (1.72–2.21)</td>
</tr>
<tr>
<td></td>
<td>LSIL+</td>
<td>0.72 (0.46–1.13)</td>
<td>NA</td>
<td>0.40 (0.26–0.62)</td>
<td>1.72 (1.42–2.07)</td>
</tr>
<tr>
<td>Taylor 2006</td>
<td>ASC-US+</td>
<td>75.8 (57.7–88.9)</td>
<td>87.9 (71.8–96.6)</td>
<td>84.2 (82.9–85.5)</td>
<td>84.5 (83.0–86.0)</td>
</tr>
<tr>
<td></td>
<td>LSIL+</td>
<td>66.7 (48.2–82.0)</td>
<td>72.7 (54.5–86.7)</td>
<td>93.6 (92.6–94.4)</td>
<td>93.9 (92.9–94.9)</td>
</tr>
<tr>
<td></td>
<td>HSIL+</td>
<td>54.5 (36.4–71.9)</td>
<td>63.6 (45.1–79.6)</td>
<td>97.8 (97.2–98.3)</td>
<td>97.1 (96.4–97.8)</td>
</tr>
</tbody>
</table>
Which test is better?
Even balance based on test performance
Conclusions for KQ2 & 4: LBC vs CC?

- LBC did not differ from CC in:
  - Absolute test performance
    - Sensitivity, specificity
  - Detection of CIN
- LBC may yield fewer unsatisfactory slides
- Cost, feasibility and local factors may also need to be considered
KQ3: What are the benefits of using HPV testing as a screening test?

KQ5: What are the harms of using HPV testing as a screening test?
Studies reviewed several strategies for screening with HPV testing*

- Primary screening with HPV test alone
- Reflex cytology with (+) HPV
- Co-testing: combination HPV and cytology
- Reflex HPV testing with ASCUS or LSIL cytology

*Best studied is Hybrid Capture 2 test (HC2)
USPSTF initially posted an “I” recommendation for screening with HPV

- “Incomplete reporting of results for all screening rounds… limits our ability to determine the net benefit of HPV-enhanced testing strategies.”

- “More complete evidence is needed before HPV-enhanced primary screening is widely adopted for women aged 30 years or older.”
European RCTs: cytology vs co-testing
How to identify the better test

• The better screening test should identify more CIN 3+ and cancer in the first round of screening and less in the second.
  – Higher sensitivity
  – Suggests better prevention due to treatment of pre-cancer between rounds one and two.

• Total CIN 3+ should be lower in those who test negative in the first round.
  – Better negative predictive value

Courtesy of Alan Waxman, MD, MPH
European Researchers Protest

• Letter to Editor 11/11 *Annals of IM*
  – “all RCTs conducted in industrialized countries have shown a similar reduction in CIN3+ after HPV testing”

• USPSTF responds 2/12
  – “Since the publication of our report, complete second-round results from another trial (POBASCAM) suggest a similar pattern of reduced cancer incidence”
## Results

<table>
<thead>
<tr>
<th>Baseline screen</th>
<th>Co-testing</th>
<th>Cytology</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>12 (0.06%)</td>
<td>6 (0.03%)</td>
<td>0.166</td>
</tr>
<tr>
<td>CIN 3+</td>
<td>171 (0.86%)</td>
<td>150 (0.75%)</td>
<td>0.239</td>
</tr>
<tr>
<td>CIN 3</td>
<td>159 (0.80%)</td>
<td>144 (0.72%)</td>
<td>0.387</td>
</tr>
<tr>
<td>CIN 2+</td>
<td>267 (1.34%)</td>
<td>215 (1.07%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second round</th>
<th>Co-testing</th>
<th>Cytology</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>4 (0.02%)</td>
<td>14 (0.07%)</td>
<td>0.031</td>
</tr>
<tr>
<td>CIN 3+</td>
<td>88 (0.45%)</td>
<td>122 (0.62%)</td>
<td>0.023</td>
</tr>
<tr>
<td>CIN 3</td>
<td>84 (0.43%)</td>
<td>108 (0.55%)</td>
<td>0.096</td>
</tr>
<tr>
<td>CIN 2+</td>
<td>160 (0.82%)</td>
<td>184 (0.93%)</td>
<td>0.234</td>
</tr>
</tbody>
</table>
5 yr cumulative risk of CIN 3+ in >300,000 women screened with Pap plus HPV cotesting.
Harms of screening with HPV test

- Short term anxiety/distress with (+) test

- More sensitive but less specific than cytology alone
  - More false (+)
  - More cumulative colposcopies?
  - ARTISTIC study: repeat co-testing
    - Cumulative colposcopy referrals for women < 35 (17.1%) vs women 35-60 (6.0%)

- Potential for overdiagnosis and overtreatment
Women ≥ 30: Co-testing vs Pap alone

BENEFITS

RISKS
Women < 30: HPV screening (with or without Pap) vs Pap alone
American Cancer Society 2012 Guidelines

- ACS/ASCCP/ASCP Consensus Conference on the Role of Molecular Testing
  - Nov. 18-20, 2011 Bethesda, MD
- 25 participating professional organizations
- 40 content experts from various disciplines divided into 6 workgroups with clearly defined questions.

Courtesy of Alan Waxman, MD, MPH
ACS 2012 Guidelines (cont)

- **Systematic Review:** 2,000 abstracts reviewed
  - 600 publications considered, sorted and sent to workgroups for further Inclusion/Exclusion review
  - Workgroups addressed questions using GRADE system of evaluation of evidence

- **Consistent with USPSTF recommendations**
  - Except specify that co-testing every 5 yrs is the preferred screening alternative for women 30-65 although cytology alone every 3 yrs is acceptable
The “annual” Pap test is dead!

A PAP TEST FOREVER FOR WOMAN EVERY YEAR!

-American Cancer Society 1957

Courtesy of Alan Waxman, MD, MPH
Screening women ages 21-65 as proposed
Discussion?
While Key Questions 1-5 have been addressed, there still may be one lingering question......
Shouldn’t women get a Pap test every year???

A PAP TEST FOR EVERY WOMAN EVERY YEAR!

-American Cancer Society 1957

Courtesy of Alan Waxman, MD, MPH
How much protection do we lose by not doing Pap tests every year?

- Percentage reduction in rate of invasive cervical cancer in cohort of women aged 35 - 64 with different frequencies of screening
  - Assumes at least negative Pap prior to age 35
  - Next Pap 1 yr: 93.5%
    - 30 Paps required over 30 years
  - Next Pap 2 yrs: 92.5%
    - 15 Paps required over 30 years
  - Next Pap 3 yrs: 90.8%
    - 10 Paps required over 30 years
  - Next Pap 5 yrs: 83.6%
    - 8 Paps required over 30 years

Courtesy of Alan Waxman, MD, MPH

IARC Br. Med Jl. 293:1986
Newfoundland Labrador
Welcome to the Big Land