CERVICAL CANCER SCREENING: WHAT'S CURRENT, WHAT'S CHANGING & WHY WE CAN'T KEEP UP

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OBJECTIVES

• Review current cervical cancer screening guidelines and the supporting evidence
• Review the new alternatives presented in 2015 and the supporting evidence
• Review data regarding physician adherence to current guidelines and discuss barriers to adherence

CURRENT SCREENING GUIDELINE REVIEW

• Updated March 2012
• No screening prior to age 21 unless immune compromised or hx of cervical cancer
• Age 21-29: cytology alone at 3 year intervals if normal results
• Age 30-64: co-testing (cytology & HPV) at 5 year intervals if normal results
• Age >65: discontinue from screening if no CIN 2+ in last 20 years & adequate screening
• These are SCREENING recommendations, once there is an abnormal result the patient enters into SURVEILLANCE which carries different recommendations

DISCLOSURES

• I do not engage in any lucrative deals that require disclosure.

REVIEW OF CURRENT GUIDELINES

• Carcinogenic HPV prevalence is high (almost 20%) in teens/early 20s
• Often these infections will resolve without treatment and by not testing an anxiety provoking situation can be avoided
• Co-testing women >30 years old with cytology and HPV testing at 5 year intervals increases detection of CIN 3+ (AIS), risk same as cytology alone at 1-3 year intervals
• Number of colposcopies is minimized and therefore harm is minimized

WHY THE CHANGES IN 2012?

• Carcinogenic HPV prevalence is high (almost 20%) in teens/early 20s
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Changes from 2006 Guidelines

- More clear pathway for long-term follow-up of CIN 2+ (treated/untreated) using co-testing
- Co-testing reduces follow-up visits for those >30
- Current screening algorithm reduces visits even for some <30
- Women 21-24 are managed more conservatively due to their low risk of progression of precursor lesions and low risk of developing cervical cancer

Rationale for Longer Screening Intervals

- Sensitivity of single pap test?
- Cancer risk 18 months after 3 negative paps: 1.5/100,000
- Cancer risk 36 months after 3 negative paps: 4.7/100,000
- >99,997 women screened unnecessarily to help 3
- Risk of high grade lesion at 3 years after normal pap similar to that at 1 year
- What are the harms of screening more frequently?
FDA APPROVED HPV TESTS

- Digene Hybrid Capture 2 High-Risk HPV DNA Test: Approved 2003
- Cervista™ HPV HR and Genfind™ DNA Extraction Kit: Approved 2009
- Cervista™ HPV 16/18: Approved 2009
- Cobas HPV Test: Approved 2011 for cotesting and in August 2014 was approved for primary HPV testing (detects 12 HPV types & specifically identifies 16/18).
- APTIMA® HPV Assay: Approved 2011

- Of note, many locally developed and validated tests are currently being used to save $$ in larger hospital systems

CURRENT USPSTF RECOMMENDATION

When to use HPV testing
- All women over age 30 in conjunction with cytology
- As REFLEX for those age 21-29
- Grade A

When not to use HPV testing
- Women age 21-29
- Alone
- Grade D

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- Women age 21-29
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In the NEWS quite a bit in 2015: NYT, NPR, HEALTH Magazine, FDA Panel Recommendation, ASCCP/SGO joint recommendation

Cobas HPV test only one with FDA indication for now

Internationally there were 4 randomized trials (POBASCAM, Swedescreen, ARTISTIC, NYCC): 176,464 women 20-64 yrs old, randomized to HPV or cytology alone or co-testing in Sweden, Netherlands, England, Italy and followed a median of 6.5 years

60-70% greater protection with HPV against invasive cancer compared to pap test. Largest gain in protection against adenoCA in women ages 30-35

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PRIMARY HPV SCREENING

- Over 47,000 women, 21 and older screened with pap and HPV test
- Colposcopy for any abnormal pap or positive HPV x 3 years
- HPV more sensitive, less specific
- Co-test only increases sensitivity <5% compared to HPV only with 1/3 more positives
- "Triage using HPV 16/18 is better than cytology to detect CIN 2+

QUESTIONS SO FAR?

PRIMARLY HPV SCREENING

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ATHENA TRIAL

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INTERIM PRIMARY HPV GUIDELINES

- ASCCP and SGO
- Primary HPV screening with Cobas HPV Test
- Begin at age 25
- For now initiate cytology alone between ages 21-24
- Screen every 3 years

- Women age 25-29
  - 21% had a positive HPV test
  - Only 7% abnormal with cytology alone

WHICH TYPES OF HPV DO WE CARE ABOUT?

- 16, 18
- 31, 33, 35, 45, 52, 58, 59
- Those high-lighted in red are contained in the new Gardasil 9 vaccine (plus types 6, 11)

PERFORMANCE OF SCREENING STRATEGIES IN WOMEN AGE ≥ 25 YEARS

<table>
<thead>
<tr>
<th>No. of CIN 3+ detected</th>
<th>Total at Baseline</th>
<th>Year 1-3</th>
<th>Total Missed CIN3+</th>
<th>No. of Screening Tests</th>
<th>No. of Colposcopies</th>
<th>Colpos per CIN3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>179</td>
<td>163</td>
<td>168</td>
<td>25,152</td>
<td>2026</td>
<td>10.8</td>
</tr>
<tr>
<td>Cotesting</td>
<td>240</td>
<td>143</td>
<td>97</td>
<td>107</td>
<td>82,989</td>
<td>12.9</td>
</tr>
<tr>
<td>Primary HPV</td>
<td>294</td>
<td>197</td>
<td>97</td>
<td>53</td>
<td>52,651</td>
<td>10.9</td>
</tr>
</tbody>
</table>

* Total Number CIN 3+ Cases 347

MOST RECENT PRIMARY HPV STUDY

- Tertiary care hospital
- 1000 women aged 25-65
- Samples tested by all three methods: cytology alone, cytology/HPV cotest and HPV primary
- HPV testing noted to have greater sensitivity compared to cytology for detecting cervical precancerous lesions but lower specificity (detected some early infections that hadn’t shown cytologic changes yet)
- Comparable results to co-testing for detection of CIN2+ or CIN 3+ irrespective of patient age
- Could replace co-testing in some clinical situations

IS IT TIME TO START HPV PRIMARY SCREENING?

- Great question! We don’t follow the current screening guidelines as it is
- Need cobas test
- If you want to do this, you need to get the test from Dynacare lab (only commercial lab that carries in MKE), if your lab does not carry that specific brand. I can’t speak to insurance coverage for payment yet
- Reduces number of tests overall, simpler algorithm but still needs some work.
- Increases colpos numbers especially in younger women age 25-29, but detects more CIN3+ with same absolute ratio (12:1)
- Major guidance bodies in the US (USPSTF, ACOG) are currently reviewing this new information to update their recommendations.
2 Key Clinical Questions

- What is the effectiveness of human papillomavirus (HPV) testing, with or without cytology, as a primary screening strategy for reducing cervical cancer mortality and incidence compared with currently recommended screening strategies for women in the United States?
- Does the effectiveness of HPV testing to reduce cervical cancer outcomes vary by subpopulation (e.g., age, race/ethnicity, screening history, HPV immunization status, and socioeconomic status)?
- For each primary screening strategy, how does the rescreening interval relate to future cancer incidence or progression?
- Does the appropriate rescreening interval for each primary screening strategy vary by subpopulation (e.g., age, race/ethnicity, screening history, HPV immunization status, and socioeconomic status)?
- What are the potential adverse effects of HPV testing, with or without cytology, as a primary screening strategy compared with currently recommended screening strategies for women in the United States?
- Do the adverse effects vary by subpopulation (e.g., age, race/ethnicity, and HPV immunization status)?
- Do the adverse effects vary by screening strategy, including by rescreening interval?

Questions?

- Let's keep rolling
- More than 2/3 through!

Provider Adherence

Personal Vignette

- My first position out of residency (2012) was at a large FQHC in another state
- Providers in my system were still performing yearly cytology on all patients >21
- It took 2 years of hard work to get them to adopt the updated 2012 guidelines

Annals Article from October 2015

- Cost-effective analysis of cervical cancer screening practices in New Mexico (only state-wide registry in the US)
- 3-4 years of data

<table>
<thead>
<tr>
<th>Proportion of Women Screening at Different Frequencies</th>
<th>Base-Case Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>3.3</td>
</tr>
<tr>
<td>2 years</td>
<td>6.3</td>
</tr>
<tr>
<td>3 years</td>
<td>10.5</td>
</tr>
<tr>
<td>4 years</td>
<td>15.2</td>
</tr>
<tr>
<td>5 years</td>
<td>14.4</td>
</tr>
<tr>
<td>None</td>
<td>14.4</td>
</tr>
</tbody>
</table>
Analysis of co-testing is limited because use was so infrequent (<20% in women aged 30-65 years)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cancer Incidence Reduction</th>
<th>Cancer Mortality Reduction</th>
<th>Lifetime Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>22%</td>
<td>19%</td>
<td>221</td>
</tr>
<tr>
<td>Current Practice</td>
<td>46.6%</td>
<td>36.4%</td>
<td>1017</td>
</tr>
<tr>
<td>Cytology q 3 yrs</td>
<td>80.9%</td>
<td>66.7%</td>
<td>1152</td>
</tr>
<tr>
<td>Cytology q 5 yrs</td>
<td>93.1%</td>
<td>93.0%</td>
<td>1496</td>
</tr>
<tr>
<td>Annual Cytology</td>
<td>91.4%</td>
<td>90.3%</td>
<td>2860</td>
</tr>
</tbody>
</table>

Current cervical cancer screening practice in the US is inefficient in all simulations due to variable screening frequency, inappropriate HPV triage testing, poor adherence to diagnostic and treatment referrals

Limitations: is the screening practice in New Mexico generalizable to the entire United States?

Burden of cervical cancer incidence and mortality in New Mexico largely mimics that of the general population so the answer to the above question is yes, probably.

Pilot study from 2009-2010 of 82 providers at 6 FQHCs (serving low-income, uninsured women) that examined beliefs about guideline-consistent screening interval recommendations

Providers who recommended a 3-year interval (that was the guideline at that time) after a normal co-test were more likely to report that extending routine screening to 3 years would be good, easy and beneficial compared to those who still recommended annual screening after a negative co-test

Providers who recommended the extended interval were significantly more likely to perceive support for that practice from specialty organizations and journals and national health organizations.

Found that provider recommendations were not dictated by provider demographics, but by positive beliefs

Current guidelines recommend cytology alone every 3 years in women age 21-29 and co-testing with cytology and HPV every 5 years in women age 30-65

Primary HPV testing every 5 years starting at age 25 is an approved alternative with the cobas test. It will take several more years for this to become more mainstream.

Clinicians are terrible at following recommended cervical cancer screening guidelines and finding ways to both educate patients and physicians will improve adherence will improve the system as a whole
