Cervical Cancer Screening New Guidelines and Management

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Agenda
1. List indications for cervical cancer screening in 2013
2. Understand the use of new HPV testing in cervical cancer screening.
3. Discuss current guidelines for abnormal cytology

Cervical cancer Screening

- Recognition of the possible harms from over screening and over treatment
  - Recognition of natural history of CIN
  - Recognition of new screening tools

Recommendations

- March 2012
- Evidence based consensus conference
- ACS, ASCCP, and ASCP
  - American Cancer Society
  - American Society for Colposcopy and Cervical Pathology
  - American Society for Clinical Pathology
  - Plus 25 other organizations.
  - Supported by ACOG, SGO

Methods

- Benefit Outcomes
- Harm Outcomes
- Risk Based Strategies
  - Preventing all cervical cancer is unrealistic.
  - Reasonable risk is determined by the strategy of cytology alone as a benchmark.
  - Women at similar cancer risk should be managed alike.

Our Task - CMS

2004
- Medicare
- Medicaid
  - Medicare 42 million people
  - Medicaid 52 million people
  - *Note: About 7 million individuals are “dual eligibles,”
  - Total of 87 million people covered by Medicaid and/or Medicare.
- Screening
  - 35% Will show up for screening ~ 30.4 million
  - Cost of screening/followup/procedures ~ $362/person
  - Total Cost ~ $11 Billion
  - AVAILABLE: ~ $ 8.5 Billion
  - Need to Cut ~ 23% of paps
Cervical Cancer Screening

2013

- Design optimal screening for the US population
- Start Screening at age 21
  - Screen with HPV DNA Testing q 3 years (until 30 then q5)
- If < 30 yo Cytology alone
  - Negative – repeat testing in 1 year
  - Positive – colposcopy
- If 30 – 65 yo – Cytology alone
  - Negative – repeat testing in 3 years
  - Positive – colposcopy
  - May increase to 5 years if add HPV 16/18 and both Negative

Age of 1st Screening

Recommendations
- Cervical cancer screening should begin at age 21 years.
- Women under the age of 21 should not be screened
  - Regardless of the
    - Age of sexual initiation
    - Pregnancy
    - Abnormal Bleeding

Cervical cancer incidence and mortality by age in the US

SEER 1975 - 2009

Why 21 Years Old

- Age to begin screening
- Rationale and Evidence.
  - Cervical cancer rare in adolescents and young women
  - May not be prevented by cytology screening
  - The incidence of cervical cancer in this age group has not changed with increased screening
  - Leads to unnecessary evaluation and treatment of lesions with high probability of regressing spontaneously
    - Overtreatment
    - Subsequent increased risk of reproductive problems
    - Represents a net harm

Cervical Cancer Screening

- > 65 yo – No Screening IF:
  - Evidence of adequate negative prior screening
  - No history of CIN2+ within the last 20 years
  - Screening should not be resumed for any reason, even if a woman reports having a new sexual partner.
  - Prior Hysterectomy – Any Age: No Screening IF:
    - No history of CIN2 +
    - Evidence of adequate negative prior screening is not required
    - Screening should not be resumed for any reason, including if a woman reports having a new sexual partner.
  - Screening if HPV vaccinated
    - No Changes to recommendations

21 – 29 years Old

Recommendations
- Cytology alone every 3 years
  - There is insufficient evidence to support a longer screening interval (i.e., >3 years).
  - HPV testing should not be used to screen women in this age group
    - either as a stand-alone test or as a cotest with cytology.
21 – 29 yo

- **Rationale and Evidence**
- **Studies**
  - No significant difference in cancer reduction between a 2- and 3-year screening interval
  - Screening q 3 years - best balance of benefits and harms
  - High prevalence of HPV in women under the age of 30
  - HPV testing should not be used to screen women in this age group due to the potential harms

**Rationale and Evidence**

**Studies**

No significant difference in cancer reduction between a 2- and 3-year screening interval

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High prevalence of HPV in women under the age of 30

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**Recommendations – Screening Periodicity women age 21–29**

**Rationale and Evidence.**

- Modeling studies
  - No screening life time risk - 32 cancers per 1000 Interventions
  - Every 3 yr – 5-8/1000
  - 1080/1000
  - Every 1 yr – 3/1000

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30 – 65 Years Old

- **Screening Periodicity women age 30-65**
- **Recommendations**
  - Preferred: Cytology and HPV testing (“cotesting”) every 5 years
  - Acceptable: Cytology alone every 3 years
- **Insufficient evidence to change screening intervals in this age group following a history of negative screens.**

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30 – 65 yo

- **Rationale and Evidence.**
- **The addition of HPV testing to cytology**
  - Increased detection of prevalent CIN3
  - Concomitant decrease in CIN3+ or cancer detected in subsequent rounds of screening
  - Diagnostic lead-time
  - Lower risk permitting a longer interval
  - Incident cancer rates similar to or lower
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Management

- HPV Positive, Cytology Negative Cotests
- Recommendations
- Repeat both tests in 12 months
- Colposcopy if either positive
- Routine screening if both negative

Note:
- Subsequent year:
- Use genotyping HPV 16 alone or combination HPV16/18

Rationale and Evidence

HPV Positive, Cytology Negative Cotests
- Consistent observational studies of risk lower than
  - HPV + with
    - ASCUS
    - LGSIL
- Therefore, colposcopy not recommended
- HPV 16 highest risk and HPV 18 next leading
- Recommendation for colposcopy if genotyping used.

HPV 16 / 18 Genotyping

- HPV Positive, Cytology Negative Cotests
- Aside from management of HPV-positive, cytology negative women

No other clinical indications have sufficient evidence to recommend HPV genotype-specific testing for HPV16 or HPV16/18.

ASCUS and HPV Negative

Recommendations

Continue with routine screening as per age specific guidelines.

ASCUS and HPV Negative

Recommendations

Rationale and Evidence.
- Risk of precancerous lesions is very low
- Not qualitatively different from a negative cotest.
- In the largest study, the risk of CIN3 at enrollment with HPV-negative ASC-US
  - 0.28%
  - At 5 years 0.54%

Journal of Lower Genital Tract Disease, 16:3, 2012
HPV Testing Alone

**Recommendations**
- In most clinical settings, women ages 30-65 years should NOT be screened with HPV testing alone as an alternative to co-testing at 5-year intervals or cytology alone at 3-year intervals.

**Rationale and Evidence.**
- HPV testing alone for primary screening studies, HPV testing more sensitive than cytology alone and is almost as sensitive as co-testing.
- 2-5% additional CIN3+ are detected among women with HPV-negative, cytology positive.
- Negative HPV test provided greater reassurance against CIN3+ in the subsequent 5-7 years than cytology alone and is nearly as reassuring as a negative cotest.
- Therefore an acceptable screening interval for use of HPV testing alone should be comparable to that of co-testing.

**New Rationale and Evidence.**
- HPV testing alone for primary screening women > 30 years coupled with cytology testing (for follow-up) of HPV positive results.
- May reduce the increase in false positives (and their related harms) that would result from HPV testing alone.

> 65 Years Old

**Recommendations**
- Adequate negative prior screening and no history of CIN2+ within the last 20 years.
- Should NOT be screened for cervical cancer with any modality.
- Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner.
- Nothing wrong with speculum exam alone.

> 65 Years Old

**Recommendations**
- Women Older Than Age 65 With a History of CIN2, CIN3, or Adenocarcinoma in Situ.
- Following spontaneous regression or appropriate management of CIN2, CIN3, or AIS, routine screening should continue for at least 20 years.
- Even if this extends screening past age 65.
Prior Hysterectomy

Rationale and Evidence

- Vaginal cancer is an uncommon gynecologic malignancy
- Its age-specific incidence is similar to or less than that of other cancers for which screening is not performed, such as breast cancer in men
- Abnormal vaginal cytology is rarely of clinical importance.

Prior HPV Vaccination

Recommendations

- Screening After Vaccination
- Screening practices should not change on the basis of HPV vaccination status.

Vaccination Program

Future

- Identifying strategies to increase screening coverage in unscreened or under-screened women, in whom a significant proportion of invasive cancers occur.
- Self collection HPV
- How best to manage women with HPV-positive, cytology-negative cotesting results or more generally, HPV-positive results
  - Reflex genotyping, new biomarkers
  - Journal of Lower Genital Tract Disease, 16:3, 2012
Future

- Future research might support HPV testing alone for screening
- Prospective studies among older women are needed to establish the optimal age to cease screening among known HPV-negative women.
- HPV vaccination decreases the efficiency of current methods of cervical cancer screening, but conference participants judged that it is premature to modify screening in the U.S. based on vaccination history.
- There is a continuing need to validate HPV tests.

*Journal of Lower Genital Tract Disease, 16:3, 2012*

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HPV Testing

- The hallmarks of HPV testing
  - Greater sensitivity but lower specificity for CIN3+ and CIN2+
  - Better reproducibility than cytology
- Several U.S. Food and Drug Administration (FDA)-approved HPV tests are commercially available,
- None yet approved for primary, stand-alone screening

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Studies

**ATHENA study**

- 40,901 women
  - 10% tested Cobas HPV positive
    - Specifically identifies types HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels.
  - 6% had abnormal cytology
  - 431 women were diagnosed with CIN2 or worse
  - 274 with CIN3 or worse

$Lancet$ Oncol 2011; 12: 880–90

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Co-testing

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Kaiser Study 2003

- N = 35,715
- Co-tests (HPV DNA + PAP)
  - 93.4% HPV Neg
  - 4.3% Pap negative/HPV positive
  - Risk of CIN2, CIN3 < 2-7%, all detected by repeat testing

HPV 16/18 Test

- The FDA-approved indications for the HPV 16/18 test are:
  - Women 30 years and older used adjunctively in combination with cervical cytology to assess the presence or absence of specific high-risk HPV types.
  - Used adjunctively in patients with ASC-US cervical cytology results, to assess the presence or absence of specific high-risk HPV types.
  - The results of this test are not intended to prevent women from proceeding to colposcopy.

HPV 16/18 Genotyping

Concerns over genotyping

- Use in cytologically positive women
- Under diagnosis if 16/18 negative
- Over treatment if 16/18 positive without diagnosis
- Use in under 30 population
- Now able to determine persistent positive 16 or 18
- Clinical data?

HPV DNA Testing for Screening

Current status of science - 2009

- Large number of cross-sectional studies demonstrating superiority of HPV DNA testing compared to cytology
- More sensitive and less variability than Pap
- Randomized screening trials are now being completed
- Data appears to be simply overwhelming

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RCTs of HPV Testing in Screening

- HART trial: UK (Cuzick et al., Lancet, 2003)
- POHASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004)
- Indian Trial (Osunabod) (Sankaranarayanan et al.)
- ARTISTIC trial: UK (Kitchener et al.)
- NTCC Indian Study (Ronce et al., Lancet Oncol, 2006)
- SWEDESCAN: Swedish trial (Naudier et al., NEJM 2007)
- CCCaNT study: Canada (Mayrand et al., JNCI 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Coldman et al.)
**HPV DNA Testing for Screening**

**Current status of science - 2012**

- **Italian Study**
  - 33,000 women
  - 50% increased detection with HPV testing

- **Swiss Study**
  - 13,000 women
  - 34% increase in detection

- **Canadian**
  - >10,000 women
  - 97 v 55% sensitivity

Ronco et al. (2005) JNCI

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**HPV Screening**

- A negative HPV test was significantly more protective than normal cytology over three rounds
- Screening interval could be extended to 6 years if HPV testing replaced cytology as the primary screening test
- HPV genotype – vaccination considerably reduce high grade cytology
- Implications for primary screening,
  - Could maintain current levels of HPV with greatly reduced rates of high grade cytology
  - Very small cumulative risk of CIN2+ (0.08%) and CIN3+ (0.05%)

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**HPV Screening Trial**

- **India Trial**
  - 131,746 healthy women ages of 30 - 59 years
  - HPV alone, cytologic testing, VIA (Visual Inspection after Acetic Acid) or standard care
  - HPV vs Control
    - Hazard Ratio - 0.47 - for advanced cancer
    - Hazard Ratio HPV testing - 0.52 - for death
  - No significant reductions were observed in cytologic-testing group or VIA group

Sankaranarayanan NEJM 2009

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**Future New Screening**

- 2013 Design optimal screening for the US population
- Start Screening at age 21
  - Screen with HPV DNA Testing q 3 years until 30 yo
  - If + HPV reflex with Cytology
    - After 30 yo, HPV q 5 years
      - If + HPV reflex to Genotype for 16/18
      - If + HPV 16/18 do Colposcopy
      - If – HPV 16/18 reflex to cytology
      - If + Cytology, then Colposcopy
Cervical Cancer Screening

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