Trends in Cervical Cancer Screening: Is There More than 1 Best Option?

Using the risk paradigm to develop future guidelines

Mark Schiffman
Nicolas Wentzensen
## Current options for cervical cancer screening

<table>
<thead>
<tr>
<th></th>
<th>Cytology</th>
<th>HPV</th>
<th>Cotesting (Cytology and HPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity for precancer</strong></td>
<td>Lowest</td>
<td>Higher</td>
<td>Highest</td>
</tr>
<tr>
<td></td>
<td>Shortest (lowest NPV)</td>
<td>Longer (greater NPV)</td>
<td>Longest (greatest NPV)</td>
</tr>
<tr>
<td><strong>Repeat interval for negative screen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triage test required</strong></td>
<td>For equivocal cytology results</td>
<td>For all positive results</td>
<td>For HPV-positive, cytology-negative results</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td>Colposcopic biopsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPV=negative predictive value
Screening assays and diagnostic tests only imperfectly capture the underlying true state.

**True state**
- Normal cervix
- Infection (→) Clearance (←)
- HPV infection
- Progression (→) Regression (←)
- Precancer
- Invasion (→)
- Cancer

**Management**
- Routine screening
- Repeat testing
- Outpatient treatment
- Inpatient treatment

**CIN histology**
- Normal
- CIN1
- CIN2
- CIN3
- Cancer

**LAST histology**
- Normal
- LSIL
- HSIL
- Cancer

**Cytology**
- NILM
- ASC-US
- LSIL
- HSIL
- Cancer

**HPV test**
- Negative
- Positive
There are only few different management options across the whole range of risk.
Development of new risk-based guidelines

• Guidelines set risk levels, not algorithms for specific assays/combinations

• Agree on management options and associated risk levels
  – (Exit)
  – Regular screening interval
  – Accelerated return
  – Colposcopy
  – Treatment
Current recommendation for HPV-based screening

- HPV Test
  - Negative: Routine Screening
  - 12 other hrHPV +: Follow up in 12 months
  - Type 16/18 Positive: Colposcopy
Future options

- **HPV Test and cytology**
  - **Negative**: 51, 39, 68, 35, 59, 56, 66
    - Cytology
      - Follow up in 12 months
    - Routine Screening
  - **Type 16 Positive**: 18, 31, 33, 45, 52, 58
    - HPV Test and p16/Ki-67
      - HSIL+
        - Colposcopy
        - Follow up in 12 months
      - Follow up in 12 months
    - Cytology
    - ASCUS+
    - Colposcopy

- **Routine Screening**

- **HPV Test and p16/Ki-67**
  - 51, 39, 68, 35, 59, 56, 66
  - Cytology
  - Follow up in 12 months

- **Type 16 Positive**
  - 18, 31, 33, 45, 52, 58
  - HPV Test and p16/Ki-67
    - HSIL+
      - Colposcopy
      - Follow up in 12 months
    - Cytology
    - ASCUS+
    - Colposcopy
Cutting out the complexity

Screening test(s)

- Routine Screening
- Follow up in 12 months
- Colposcopy
Advantages

• Separate guidelines discussion from assay evaluation

• Many new assays are being evaluated, would need to update new guidelines repeatedly (especially for triage options)

• Instead, assays with comparable risk levels can be integrated in existing algorithms

• International studies can provide risk estimates for individual strategies, even if thresholds are different
Challenges

• Absolute risk at which time point?
  – Consider 1-year risk for immediate colpo, 3-year risk for regular screening interval etc.

• Portability of absolute risk?
  – Assay comparisons in one population with reference tests
  – HPV/cytology needed as benchmark?

• Acceptance by regulatory agencies, companies?
Questions for the community:

• How challenging is the complexity of current screening and management options?

• Is a “black box” approach (with optional display of the underlying risk-based algorithm) helpful?

• How can it be integrated?
  – App
  – Electronic medical records
  – Lab report