HPV-based screening for prevention of cervical cancer

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What we know about HPV based screening

- More sensitive than cytology for HGCIN.
- Detects earlier persistent HGCIN that cytology would have detected later.
- Prevents more cancers than cytology-based screening (cancer risk reduced by 60-70%).
- Longer screening intervals safe.
- Some triage of HPV+ women needed. Cytological triage with HPV repeat validated.
Invasive cancers: Pooled analysis of EU RCTs

- Individual data of all 4 RCTs in industrialised countries that had published results over two screening rounds pooled.
- 176,464 women enrolled
- Median follow-up 6.5 years
- 1,214,415 person-years of observation
- 107 invasive carcinomas identified

- One study (NTCC) referred all HPV+ women for colposcopy. The others triaged by cytology and repeat HPV testing
Pooled analysis of the Swedescreen, POBASCAM, NTCC and ARTISTIC

Cumulative incidence of ICC by arm. All recruited women

Solid lines: HPV group.
Dotted lines: cytology group

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>≤2.5 yrs from enrolment</th>
<th>&gt;2.5 yrs from enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled RR</td>
<td>0.60</td>
<td>0.79</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>(0.40-0.89)</td>
<td>(0.46-1.36)</td>
<td>(0.25-0.81)</td>
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</tbody>
</table>

Management of HPV+ women

• With direct referral to colposcopy (NTCC study) biopsy rate double in HPV than in cytology arm

• With cytological triage (all other studies) biopsy rate similar in both arms
### Proportion of women who had biopsy by arm and study and HPV/cytology ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Cytology arm</th>
<th>HPV arm</th>
<th>ratio* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTCC</td>
<td>1127 (2.4)</td>
<td>2538 (5.4)</td>
<td>2.24 (2.09-2.39)</td>
</tr>
<tr>
<td>POBASCAM</td>
<td>1533 (7.0)</td>
<td>1535 (7.0)</td>
<td>1.01 (0.94-1.08)</td>
</tr>
<tr>
<td>Swedescreen</td>
<td>701 (11.2)</td>
<td>675 (10.8)</td>
<td>0.97 (0.87-1.07)</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>528 (8.6)</td>
<td>1716 (9.3)</td>
<td>1.08 (0.97-1.19)</td>
</tr>
<tr>
<td><strong>Pooled RR</strong></td>
<td></td>
<td></td>
<td>1.35 (1.30-1.40)</td>
</tr>
<tr>
<td>(Fixed effects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I² (p heterogeneity between studies)</strong></td>
<td></td>
<td></td>
<td>99.1% (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Pooled RR</strong></td>
<td></td>
<td></td>
<td>1.02 (0.97-1.07)</td>
</tr>
<tr>
<td>(Fixed effects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTCC excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I² (p heterogeneity between studies)</strong></td>
<td></td>
<td></td>
<td>30.7% (p=0.236)</td>
</tr>
</tbody>
</table>

Screening interval

• Risk of cancer 3.5 years after normal cytology 15.4 per $10^5$.
• Risk of cancer 5.5 years after negative HPV 8.7 per $10^5$
Risk of invasive carcinoma after a negative entry test (HPV- in HPV arm and cytology- in cytology arm)

Solid lines: HPV group.
Dotted lines: cytology group

Pooled RR
0.30 (0.15-0.60)

<table>
<thead>
<tr>
<th></th>
<th>3.5 years</th>
<th>5.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>cytology</td>
<td>15.4 (CI 7.9-27.0)</td>
<td>36.0 (23.2-53.5)</td>
</tr>
<tr>
<td>HPV</td>
<td>4.6 (1.1-12.1)</td>
<td>8.7 (3.3-18.6)</td>
</tr>
</tbody>
</table>

observations censored 2.5 yrs after CIN2 or CIN3 detection, if any

Triage

• Clear that needed but not which is the best way.

• Many biomarkers studied, plausibly will increase (need for systematic review)
  – genotyping
  – P16/Ki67 - RNA E6/E7 - Onco E6
  – methylation human genes - methylation viral genes

• Focus on properties of overall triage strategy (including interval to repeat, test at repeat etc.) not just of triage test

• Study triage strategies for women previously screened by HPV.
  – Currently, studies virtually only in women at 1st HPV.
Reflex triage test(s)
- cytology
- cytology + HPV16/18

Probability that CIN2+ present sufficiently high

Sensitivity of reflex test and interval 1

Risk of ICC in interval sufficiently low

Reflex triage test(s) - HPV - cytology

New test - HPV - cytology

Interval 1

New screening round

Interval 2

% positives to reflex test with HPV interval 1

Positive

Colposcopy

Negative

Positive

Colposcopy

Negative

Sensitivity of reflex and repeat tests and interval 2
Conclusions for High Income Countries

• Use HPV as primary test

• Intervals of at least 5 years

• Triage HPV positive women

• Organise