The implications of HPV screening for colposcopy

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Wolfsburg
Germany
Genesis of cervical cancer

**Normal cervix**

- Age, STD
- Immunodeficiency
- HPV-Type
- Parity
- Smoking

**HPV-Infection**

- CIN 1/2

**Persisting HPV-Infection**

- 10-40%

**CIN III**

- 10-25%

- Integration of HPV-DNA
- Genetical Factors?

**CANCER**

- > 7 years

- For full cycle

Deutsches Ärzteblatt (2006) 103:2946

Petry, Wolfsburg

Transformationzone and HPV
Primary HPV testing is superior to cytology in structured / organized screening programmes

- Primary HPV screening but not cytology reduced cervical cancer mortality.  
  *NEJM 2009, 360:1385*

- HPV based screening is significantly more effective than cytology in preventing invasive cervical cancer  
  *Lancet Oncology 2010*

- A negative HPV test excludes CIN3+ for >6yrs with better sensitivity than a negative Pap smear for 3 years  
  *BMJ 2008, 337:1754*

Randomized controlled studies on primary HPV screening

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>18.403</td>
</tr>
<tr>
<td>Sweden</td>
<td>12.527</td>
</tr>
<tr>
<td>Finland</td>
<td>108.425</td>
</tr>
<tr>
<td>Italy</td>
<td>94.370</td>
</tr>
<tr>
<td>England</td>
<td>24.510</td>
</tr>
<tr>
<td>Canada</td>
<td>10.154</td>
</tr>
</tbody>
</table>
Baseline results: relative sensi for CIN2+

Cytology best → HPV best

<table>
<thead>
<tr>
<th>Country Type</th>
<th>Study Year</th>
<th>Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Developing countries</td>
<td>Sankar, 2005</td>
<td>0.88 (0.76, 1.03)</td>
</tr>
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<td>Industrialised countries, CP</td>
<td>Ronco, 2006*</td>
<td>1.43 (1.00, 2.04)</td>
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<td>Bulkmans, 2007</td>
<td>1.64 (1.17, 2.31)</td>
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<tr>
<td></td>
<td>Mayrand, 2007</td>
<td>1.69 (0.83, 3.45)</td>
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<tr>
<td></td>
<td>Naucler, 2007</td>
<td>2.42 (1.06, 5.91)</td>
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<td>Ronco, 2008*</td>
<td>1.92 (1.28, 3.30)</td>
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<tr>
<td></td>
<td>Leinonen, 2009</td>
<td>1.45 (1.13, 1.86)</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.847)</td>
<td></td>
<td>1.53 (1.33, 1.75)</td>
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<tr>
<td>Industrialised countries, LBC</td>
<td>Kitchener, 2009</td>
<td>1.06 (0.87, 1.31)</td>
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<tr>
<td>Overall (I² = 76.9%, p = 0.000)</td>
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Detection rate ratio

-- HPV- vs cytology based screening

CIN3+ in 2nd round among in women with negative screen test at baseline

Cytology best → HPV best

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<tr>
<td>Ronco, 2010* (Phase 1 &amp; 2)</td>
<td>0.48 (0.21, 1.11)</td>
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<td>Kitchener, 2009</td>
<td>0.52 (0.28, 0.97)</td>
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<tr>
<td>Overall (I² =0.0%, p=0.93)</td>
<td>0.47 (0.35, 0.63)</td>
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Detection rate ratio

*Age >=35 years
“HPV testing is at least as good”

• The World Health Organisation (WHO) via the International Agency for Research on Cancer (IARC) has stated:

"There is sufficient evidence, based on surrogate markers, that the efficacy of HPV testing, using a validated system, as the primary screening modality can be expected to be at least as good as that of conventional cytology".

Need for pilot projects

• Is HPV screening accepted by the public and health professionals
• Will it lead to a drop or increase of participation in screening program
• Is it cost efficient
• Can benefits seen in trials be confirmed in daily life projects
• How should women with abnormal screening results be managed?
What is the role of colposcopy?

A screening test to identify cervical precursors?

Sensitivity of screening colposcopy for CIN2/3: 13.3%
A Schneider et al; 2000:89:529

What is the role of colposcopy?

A method to take guided punch biopsies?

Sensitivity of colposcopy:
The sensitivity for CIN 2+ of an online colpophotographic assessment of high-grade disease was 39%
What is the role of colposcopy?

1. A method to identify the type and abnormalities of the transformation zone
2. A management concept for women at increased risk for cervical cancer. This includes a deep knowledge about the limitations of cytology, histology, HPV-testing and the method colposcopy itself.

HPV-testing for risk stratification in women aged 30+ years
**Wolfsburg Cervical Cancer Prevention Project**

*Women > 29 years*

**HPV-Test**

**Pap smear**

- **HPV-HR neg**
  - **Pap neg**
  - **ASCUS/LSIL**
    - Observation
    - HSIL
    - Colposcopy
  - Repeat HPV+Pap after 5 years
  - Routine exam annually

- **HPV-HR pos**
  - **Pap pos**
  - Repeat Pap 6mon
  - Repeat HPV Pap / HPV-HR pos
  - Colposcopy (immediate)

- **HPV-HR pos**
  - **Pap neg**
  - Colposcopy

**93.07%**

**N= 19,472** (Dec 2010)

**Assumed failure rates 2006 – 2011**

*(assumption before start of the project)*

<table>
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<tr>
<th>Method</th>
<th>False negative cancers</th>
<th>False negative CIN3+</th>
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<tr>
<td>Cytology</td>
<td>3-4</td>
<td>40-60</td>
</tr>
<tr>
<td>HPV testing</td>
<td>0-1</td>
<td>2-5</td>
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<td>0-1</td>
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Based on (sometimes misread) German data we expected
7 to 12 invasive cervical cancer cases
80-120 CIN3 cases (20,000 participants mean observation 3.5 yrs)
Assumed screening sensitivity HPV 98% / Pap 50%
Assumed colpo sensitivity for detection of CIN3 / cancer in HPV+ or Pap + 97%
Colposcopy protocol

• Type I and type II transformation zones with visible SCJ underwent punch biopsies of all visible lesions
• Type III TZ underwent endocervical curettage and in case of visible lesions punch biopsies
• Alle CIN3+ lesions and most CIN2 underwent invasive treatment
• All ≤CIN1 lesions were followed with annual HPV testing and in case of persistence with colposcopy

Core results after 5 years

• Participation > 90% of the target population
• Acceptance excellent (<1% wanted to stay with the annual Pap smear screening)
• Good adherence with patient pathways (79% for HPV+/Pap- and 91% for HPV+/Pap+)
• Very low rate of false negative HPV and colpo results
Improved detection of CIN3/Ca

N=158, 157 HC2+
Pap I oder Pap II

Pap IV oder V

Pap IIw Pap III Pap IId

HPV screening will reduce cervical cancer incidence in Wolfsburg

HPV screening will reduce cervical cancer incidence in Wolfsburg

Time interval
Since last normal Pap smear

N=19
590 Participants were transferred to colposcopy within 51 months (=3.11%)

Total screening population: 18,952

Risk of CIN3 / Cancer
Triage of Pap neg, HPV pos cases by Dual Stain for p16/Ki-67

Pap neg, HPV pos
n=427

DS pos
n=109
- No HGCIN
  n=75
  68.8%
- CIN2+
  n=34
  31.2%

DS neg
n=318
- No HGCIN
  n=315
  99.1%
- CIN2+
  n=3
  0.9%

25.5% 74.5%

Risk for CIN3 / cervical cancer
HPV positive / Pap negative 5%

- DS p16 / Ki67
  - positive
    - 1.25%
    - HPV + Ztto -
      - pos / pos
    - negative
      - 3.75%
      - HPV + HPV after 12 Mon
        - neg / neg
          - 2.00%
          - Pap + HPV in 5 yrs

Performance of colposcopy

- N= 158 CIN3+ within 5 years
Observed failure rates 2006 – 2011
(compared with predicted rates January 2006)

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The implications of HPV screening for colposcopy

• Compared with conventional Pap smear screening, the management of HPV screening requires even more expertise.

• A maximum harvest of the potential benefits of HPV screening will rely on a good control of patient pathways and a high quality colposcopy management.