Prevention of Cervical Cancer: What is new in cytology?

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France
Prevention of Cervical Cancer: What is new in cytology?

- Lesion and Biomarkers
- Key points in organisation
- Vaccination
493,243 new cases of cervical cancer worldwide
Incidence of Cervical Cancer in Europe

60,000 NEW CASES PER YEAR

Age-adjusted incidence rates per 100,000 women per year

Globocan 2002: ASR (World)
Incidence and Mortality from Cervical Cancer
27 Member States of the European Union, estimates 2004

Arbyn et al., Ann Oncol. 2007b
HR-HPV and cervical cancer

Hepatitis B and liver cancer
Hepatitis C and liver cancer
Tobacco and lung cancer

no effect
HPV types and cervical cancer

Muñoz N., Bosch F.X., et al, IJC 2004
### Prevalence HPV and cytology/histology

<table>
<thead>
<tr>
<th>DIAGNOSTIC</th>
<th>HPV-ADN +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cytology</td>
<td>9-10 % (HPV 16/18: 2-3%)</td>
</tr>
<tr>
<td>Precancerous lesions</td>
<td>80-90 % (HPV 16/18: 50% )</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>95-100 % (HPV 16/18: 70%)</td>
</tr>
</tbody>
</table>

*De Sanjose et al 2006; Clifford et al 2003; Muñoz et al 2003*
HPV prevalence in the general population

- **NORth** (Canada): 13%
- **NORth** (USA): 22%
- **CENTRAL** (Mexico, Costa Rica): 15%
- **South** (Colombia, Argentina): 15 - 17%
Risk factors for cervical cancer incidence

- HPV in women + 35 ys ≥ 10%
- Multiple sexual Partners
- Early sexual Initiation
- Prostitution
- CO, Tobacco, HIV ...
- High parity
- No screening
- No education for screening
- Men Sexual behavior

HPV in women + 35 ys ≥ 10%
≥ 10%
Screening: secondary prevention

- **Initial Infection with Papilloma virus**
- **Persistent infection**
  - Productive infection CIN1/LSIL
- **Transforming infection**
  - Precancerous lesions CIN2/3
- **Clearance of infection**

Local infection:
- First year
- 5 years
- 10 years and more

Intraepithelial lesions:
- Cancer

Cervical cancer
1. Viral Pénétration

2. Rare Event: Transforming Infection

3. Frequent Event: Replication of viral DNA

4. Frequent Event: Productive Infection

Assemblage of virions: L1, L2

Expression of E6 and E7 genes

E1, E2, E4

Inactivation of pRb by the protein E7 inducing an over-expression of p16\textsuperscript{INK4a}
HR HPV copies by ISH in intermediate and superficial cells
p16 immuno-positivity in CIN 1
p16 immuno-positive in HGCIN

CIN 2

CIN 3
p16 positive abnormal basal cells
CINtec Cytology: First Generation Single Staining

- Applying morphological interpretation criteria to p16 positive cells only

Locator Function

Interpretation Function
The Sensitivity and Specificity of $p16^{\text{INK4a}}$ Cytology vs HPV Testing for Detecting High-Grade Cervical Disease in the Triage of ASC-US and LSIL Pap Cytology Results

Karin J. Denton, MD,¹* Christine Bergeron, MD, PhD,²* Petra Klement,³ Marcus J. Trunk, MD,³† Thomas Keller, PhD,⁴ and Ruediger Ridder, PhD,³ for the European CINtec Cytology Study Group‡

Key Words: Cervical intraepithelial neoplasia; Cervical cytology; Atypical squamous cells of undetermined significance; ASC-US; Low-grade squamous intraepithelial lesion; LSIL; Triage; $p16^{\text{INK4a}}$; Immunocytochemistry; Human papillomavirus; HPV

DOI: 10.1309/AJCP3CD9YKYFJDQL
CIINtec® PLUS: p16/Ki-67
p16 PLUS Ki-67: An Advanced Biomarker Combination

- Simultaneous expression of anti-proliferative p16 protein and proliferation marker Ki-67 should exclude each other in cells under normal physiological conditions

- Co-detection of p16 PLUS Ki-67 in the same cell
  - Serves as an indicator of cell cycle de-regulation
  - Correlates with the presence of HR-HPV induced oncogenic transformation
  - Provides an objective criterion to identify those women who are likely to harbor high-grade disease
Screening systems in Europe

- **Organised screening:**
  - More effective & cost-effective
  - Finland, UK, Ireland, Denmark, Sweden, The Netherlands, Italy, Norway, Slovenia

- **Opportunistic screening:**
  - Overscreening of screened & underscreening
  - Heterogenous quality
  - In most other countries: France, Germany, part of Italy, Spain, Greece, Portugal.....
EUROPEAN GUIDELINES FOR QUALITY ASSURANCE IN CERVICAL CANCER SCREENING

Editors

Marc Arbyn (Belgium), Ahti Anttila (Finland), Joe Jordan (UK), Guglielmo Ronco (Italy), Ulrich Schenck (Germany), Nereo Segnan (Italy), Helene Wiener (Austria), Lawrence von Karsa (France), John Daniel (France)
EU guidelines

- Cytology continues to be the standard screening method
- Conventional & LBC are accepted
- First of all: screening should be well organised
  - Reach the target population
  - Monitor quality
  - Register screening/follow-up, link it the cancer registry
Age standardised incidence of invasive cervical cancer and coverage of screening (England, 1971–95)

## Reduction of Invasive Ca and screening interval

<table>
<thead>
<tr>
<th>Screening frequency</th>
<th>% reduction in the cumulative rate</th>
<th>Number of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>93.5</td>
<td>31-44</td>
</tr>
<tr>
<td>3 years</td>
<td>90.8</td>
<td>12-15</td>
</tr>
<tr>
<td>5 years</td>
<td>83.6</td>
<td>7-8</td>
</tr>
<tr>
<td>10 years</td>
<td>64.1</td>
<td>4</td>
</tr>
</tbody>
</table>

IARC 1986
## Audit of Invasive Ca in France and London

<table>
<thead>
<tr>
<th>Category</th>
<th>(n=550)</th>
<th>(n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never screened</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>underscreened (&gt; 5 years)</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Normal pap smears ≤ 3 years</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>No follow up after abnormal results</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Cancer after conservative treatment</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

*SFPCPCV Boulanger et al, Guy and St Thomas Herbert et al 2006*
Profile of interval cancers

- Interval cancers significantly more likely to be seen in screen-detected cancers (SD), especially 1A
- Similar association between interval cancers and younger age groups
- Same associations in London and Southampton

Herbert et al BJOG 2009
Sensitivity and PPV of LBC (n= 22708) compared with conventional cytology (n=22 466) for CIN

<table>
<thead>
<tr>
<th></th>
<th>CIN 1</th>
<th>CIN 2 +</th>
<th>CIN 3 +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive if ASC-US+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Conventional cytology</td>
<td>0.82 (184)</td>
<td>0.37 (84)</td>
<td>0.24 (53)</td>
</tr>
<tr>
<td>- LBC cytology</td>
<td>1.38 (313)</td>
<td>0.44 (99)</td>
<td>0.20 (45)</td>
</tr>
<tr>
<td><strong>Relative sensitivity (95% CI)</strong></td>
<td>1.68 (1.40 to 2.02)</td>
<td>1.17 (0.87 to 1.56)</td>
<td>0.84 (0.56 to 1.25)</td>
</tr>
<tr>
<td>- PPV Conventional cytology</td>
<td>27.84</td>
<td>12.7</td>
<td>8.02</td>
</tr>
<tr>
<td>- PPV LBC cytology</td>
<td>23.41</td>
<td>7.4</td>
<td>3.37</td>
</tr>
<tr>
<td><strong>Relative PPV (95% CI)</strong></td>
<td>0.84 (0.72 to 0.98)</td>
<td>0.58 (0.44 to 0.77)</td>
<td>0.42 (0.29 to 0.62)</td>
</tr>
</tbody>
</table>

|                |                  |                  |                  |
| **Positive if LSIL+** |                 |                  |                  |
| - Conventional cytology | 0.55 (123)      | 0.31 (70)        | 0.20 (44)        |
| - LBC cytology     | 0.95 (211)      | 0.32 (73)        | 0.14 (32)        |
| **Relative sensitivity (95% CI)** | 1.70 (1.36 to 2.12) | 1.03 (0.74 to 1.43) | 0.72 (0.46 to 1.13) |
| - PPV Conventional cytology | 38.80          | 22.08            | 13.88            |
| - PPV LBC cytology  | 36.76           | 12.72            | 5.57             |
| **Relative PPV (95% CI)** | 0.95 (0.80 to 1.13) | 0.58 (0.43 to 0.78) | 0.40 (0.26 to 0.62) |

Comparison of liquid based cytology with conventional cytology for detection of cervical cancer precursors: a randomised controlled trial

89,784 women (aged 30-60 yrs), national cervical screening programme
49,222 assigned to the ThinPrep arm and 40,562 to the conventional arm

- CIN 1 1.01 (0.85 to 1.19)
- CIN 2 1.00 (0.84 to 1.20)
- CIN 3 0.97 (0.86 to 1.29)

Less unsatisfactory smears 0.30 (0.23 to 0.38)

Siebers AG, Klinkhamer, PJ, Grefte PM et al JAMA 2009, 302, 1809-10
### NTCC study – review of LBC by external experts—Percent cross-sectional

**Sensitivity**

Cytology positive if **ASCUS+**

<table>
<thead>
<tr>
<th>Endpoint <strong>CIN2+ histology</strong></th>
<th>Pooled</th>
<th>Expert 1</th>
<th>Expert 2</th>
<th>Expert 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External Experts</strong></td>
<td>70.9 (63.1 to 78.7)</td>
<td>74.6 (61.6 to 87.5)</td>
<td>68.2 (54.1 to 83.3)</td>
<td>69.9 (56.5 to 83.4)</td>
</tr>
<tr>
<td><strong>Original</strong></td>
<td>76.2 (68.8 to 83.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Difference †</strong></td>
<td>-5.3 (-16.0 to +5.4)</td>
<td>-2.5 (-20.5 to +15.5)</td>
<td>-8.3 (-27.3 to +10.7)</td>
<td>-5.1 (-23.6 to +13.4)</td>
</tr>
</tbody>
</table>

*Confortini et al Cancer Cyto 2010*

*Figures in brackets 95% confidence intervals   † external minus original*
**NTCC study – review of LBC by external experts—Percent cross-sectional Specificity**

*Cytology positive if ASCUS+*

<table>
<thead>
<tr>
<th>Endpoint CIN2+ histology</th>
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<tr>
<td></td>
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<td><strong>Pooled</strong></td>
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<tr>
<td><strong>Expert 1</strong></td>
</tr>
<tr>
<td><strong>Expert 2</strong></td>
</tr>
<tr>
<td><strong>Expert 3</strong></td>
</tr>
<tr>
<td><strong>External Experts</strong></td>
</tr>
<tr>
<td>90.7  (90.3 to 91.0)</td>
</tr>
<tr>
<td>87.6  (86.9 to 88.4)</td>
</tr>
<tr>
<td>87.0  (86.1 to 87.8)</td>
</tr>
<tr>
<td>97.1  (96.7 to 97.5)</td>
</tr>
<tr>
<td><strong>Original</strong></td>
</tr>
<tr>
<td>94.1  (93.8 to 94.4)</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
</tr>
<tr>
<td>-3.4  (-3.9 to -2.9)</td>
</tr>
<tr>
<td>-6.3  (-7.2 to -5.4)</td>
</tr>
<tr>
<td>-7.3  (-8.2 to -6.4)</td>
</tr>
<tr>
<td>+3.1  (+2.5 to +3.7)</td>
</tr>
</tbody>
</table>

*Confortini et al accepted for Cancer Cyto*
LBC vs Conventional
Pro or Contra: is it the question?

- Quality of the sample is improved significantly
- Advantage to perform ancillary HPV testing or molecular markers
- Shorter reading time
- Most Cytologists prefer LBC

CP and LBC are both recommended in EU guidelines for CC screening. The choice results from a cost-effect evaluation.
Thinprep Imager: accuracy of reading LBC vs CP

• LBC using the ThinPrep Imager detected 1.3 more cases of CIN 2+ per 1000 women screened than CP with a LSIL as the threshold for referral for colposcopy

• 3.1 more biopsies per 1000 women screened were required to detect these cases

Davey E. et al., Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study, BMJ Jul 2007;335:31
Primary screening by HPV testing

- HPV testing is significantly more sensitive and less specific than cytology.
- The combination of HPV testing and cytology marginally improves the sensitivity of HPV testing alone.
- HPV testing specificity can be improved:
  - after 35 years
  - with a higher threshold of virological detection
  - by a new HPV testing at one year after a positive result
  - by a triage of positive cases by cytology, p16, genotyping, RNA.
Age-Specific Evaluation of Primary Human Papillomavirus Screening vs Conventional Cytology in a Randomized Setting

Maarit Leinonen, Pekka Nieminen, Laura Kotaniemi-Talonen, Nea Malila, Jussi Tarkkanen, Pekka Laurila, Ahti Anttila

Background

Human papillomavirus (HPV) DNA testing has shown higher sensitivity than cytology for detecting cervical lesions, but it is uncertain whether the higher sensitivity is dependent on the age of the woman being screened. We compared the age-specific performance of primary HPV DNA screening with that of conventional cytology screening in the setting of an organized population-based cervical cancer screening program in Finland.

Methods

From January 1, 2003, to December 31, 2005, randomized invitations were sent to women aged 25–65 years for routine cervical cancer screening by primary high-risk HPV DNA testing (n = 54,207) with a Hybrid Capture 2 assay followed by cytology triage for women who were HPV DNA positive or by conventional cytology screening (n = 54,218). In both screening arms, cytology results of low-grade squamous intraepithelial lesion or worse triggered a referral for colposcopy. Relative rates (RRs) of detection to assess test sensitivity, specificity, and positive predictive values (PPVs) with 95% confidence intervals (CIs) were calculated for the histological endpoints of cervical intraepithelial neoplasia (CIN) grade 1 or higher (CIN 1+), CIN grade 2 or higher (CIN 2+), and CIN grade 3 or higher (CIN 3+). All statistical tests were two-sided.

Results

The overall frequency of colposcopy referrals was 1.2% in both screening arms. Women younger than 35 years were referred more often in the HPV DNA screening vs the conventional screening arm (RR = 1.27, 95% CI = 1.01 to 1.60). The prevalence of histologically confirmed CIN or cancer was 0.59% in the HPV DNA screening arm vs 0.43% in the conventional screening arm. The relative rates of detection for CIN 1, CIN 2, and CIN 3+ for HPV DNA screening with cytology triage vs conventional screening were 1.44 (95% CI = 0.99 to 2.10), 1.39 (95% CI = 1.03 to 1.92), and 1.22 (95% CI = 0.78 to 1.92), respectively. The specificity of the HPV DNA test with cytology triage was equal to that of conventional screening for all age groups (99.2% vs 99.1% for CIN 2+, P = .13). Among women aged 35 years or older, the HPV DNA test with cytology triage tended to have higher specificity than conventional screening. The PPVs for HPV DNA screening with cytology triage were consistently higher than those for conventional screening. In both screening arms, the test specificities increased with increasing age of the women being screening, whereas the highest PPVs were observed among the youngest women being screened. Overall, 7.2% of women in the HPV DNA screening arm vs 6.6% of women in the conventional screening arm were recommended for intensified follow-up, and the percentages were highest among 25- to 29-year-olds (21.9% vs 10.0%, respectively).

Conclusions

Primary HPV DNA screening with cytology triage is more sensitive than conventional screening. Among women aged 35 years or older, primary HPV DNA screening with cytology triage is also more specific than conventional screening and decreases colposcopy referrals and follow-up tests.

Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial


Summary
Background Human papillomavirus (HPV) testing is known to be more sensitive, but less specific than cytology for detecting cervical intraepithelial neoplasia (CIN). We assessed the efficacy of cervical-cancer screening policies that are based on HPV testing.

Methods Between March, 2004, and December, 2004, in two separate recruitment phases, women aged 25–60 years were randomly assigned to conventional cytology or to HPV testing in combination with liquid-based cytology (first phase) or alone (second phase). Randomisation was done by computer in two screening centres and by sequential opening of numbered sealed envelopes in the remaining seven centres. During phase one, women who were HPV-positive and aged 35–60 years were referred to colposcopy, whereas women aged 25–34 years were referred to colposcopy only if cytology was also abnormal or HPV testing was persistently positive. During phase two, women in the HPV group were referred for colposcopy if the HPV test was positive. Two rounds of screening occurred in each phase, and all women had cytology testing only at the second round. The primary endpoint was the detection of grade 2 and 3 CIN, and of invasive cervical cancers during the first and second screening rounds. Analysis was done by intention to screen. This trial is registered, number ISRCTN81678807.

Findings In total for both phases, 47,001 women were randomly assigned to the cytology group and 47,369 to HPV testing. 33,851 women from the cytology group and 32,998 from the HPV-testing group had a second round of screening. We also retrieved the histological diagnoses from screening done elsewhere. The detection of invasive cervical cancers was similar for the two groups in the first phase (nine in the HPV group vs seven in the HPV group, p=0.62); no cases were detected in the HPV group during round two, compared with nine in the cytology group (p=0.004). Overall, in the two rounds of screening, 18 invasive cancers were detected in the cytology group versus seven in the HPV group (p=0.028). Among women aged 35–60 years, at round one the relative detection (HPV vs cytology) was 2.00 (95% CI 1.44–2.77) for CIN2, 2.08 (1.47–2.95) for CIN3, and 2.03 (1.60–2.57) for CIN2 and 3 together. At round two the relative detection was 0.54 (0.23–1.28) for CIN2, 0.48 (0.21–1.11) for CIN3, and 0.51 (0.28–0.93) for CIN2 and 3 together. Among women aged 25–34 years, there was significant heterogeneity between phases in the relative detection of CIN3. At round one the relative detection was 0.93 (0.52–1.64) in phase one and 3.91 (2.02–7.57) in phase two. At round two the relative detection was 1.34 (0.46–3.84) in phase one and 0.20 (0.04–0.93) in phase two. Pooling both phases, the detection ratio of CIN2 for women aged 25–34 years was 4.09 (2.24–7.48) at round one and 0.64 (0.23–1.27) at round two.

Interpretation HPV-based screening is more effective than cytology in preventing invasive cervical cancer, by detecting persistent high-grade lesions earlier and providing a longer low-risk period. However, in younger women, HPV screening leads to over-diagnosis of regressive CIN2.
## INVASIVE CERVICAL CANCER BY SCREENING GROUP, AGE AND SCREENING ROUND

<table>
<thead>
<tr>
<th></th>
<th>HPV group</th>
<th>Cytology group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages pooled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round one</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Screening round two</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total over first two rounds</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Women age 35-60 years at recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round one</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Screening round two</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total over first two rounds</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Women age 25-34 years at recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round one</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Screening round two</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total over first two rounds</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Ronco et al. Lancet Oncol 2010
### Relative cross-sectional sensitivity and relative referral rate of HPV testing with p16-INK4A triage vs. conventional cytology

<table>
<thead>
<tr>
<th>Age 35-60</th>
<th>Relative sensitivity for CIN2+</th>
<th>Relative sensitivity for CIN3+</th>
<th>Relative Referral Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV testing ≥ 1pg/ml with no triage</td>
<td>1.63 (1.25-2.12)</td>
<td>1.52 (1.06-2.19)</td>
<td>2.38 (2.21-2.57)</td>
</tr>
<tr>
<td>HPV testing ≥ 1pg/ml and p16 (1+ cells staining)</td>
<td>1.53 (1.15-2.02)</td>
<td>1.32 (0.88-1.95)</td>
<td>1.08 (0.96-1.21)</td>
</tr>
</tbody>
</table>

Carozzi et al. Lancet Oncol 2008
Relative cross-sectional sensitivity and relative referral rate of HPV testing with p16-INK4A triage vs. conventional cytology

<table>
<thead>
<tr>
<th>Age 25-34</th>
<th>Relative sensitivity for CIN2+</th>
<th>Relative sensitivity for CIN3+</th>
<th>Relative Referral Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV testing ≥ 1 pg/ml with no triage</td>
<td>3.50 (3.11-5.82)</td>
<td>2.61 (1.21-5.61)</td>
<td>3.64 (3.17-4.19)</td>
</tr>
<tr>
<td>HPV testing ≥ 1 pg/ml and p16 1+ cells staining</td>
<td>3.01 (1.82-5.17)</td>
<td>2.52 (1.18-5.78)</td>
<td>1.15 (0.96-1.37)</td>
</tr>
</tbody>
</table>

Carozzi et al. Lancet Oncol 2008
Primary HPV screening for cervical cancer in Europe

Prerequisites:

- Screening population: after 35ys?
- Follow up of HPV (+) cyto (-) patients
- Test DNA, RNA, genotyping, p16?

Risks:

Overdiagnosis and overtreatment of regressive lesions
Anxiety of HPV + patients
Overcosts in non organized screening systems
Vaccination: Primary Prevention

- Initial Infection with Papilloma virus
- Persistent infection
- Precancerous lesions CIN2/3
- Cancer
- Clearing of infection

First year: local infection
5 years: Intraepithelial lesions
10 years and more: Cancer
Vaccination should precede the infection.
Timeline for Impact of Prophylactic HPV Vaccine

Target vaccination age

20 yrs initial impact
30 yrs - full impact

Incidence
Mortality

Age

Incidence
Mortality
Theoretical impact of a vaccine including HPV 16/18:
Potential reduction on abnormal Pap smears

- HSIL: 30-50%
- LSIL: 10-20%
- ASC-US: 10-20%
Theoretical impact of a vaccine including HPV 16/18: Small reduction on abnormal Pap smears

<table>
<thead>
<tr>
<th>Abnormal smears</th>
<th>Before vaccination</th>
<th>After vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>France*</td>
<td>USA**</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.26</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>LSIL</td>
<td>1.15</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>ASC-US</td>
<td>1.42</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.83</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20%</td>
</tr>
</tbody>
</table>

Risk Stratification HPV Screening cyto neg Women 30+
Lower PPV of HPV testing in vaccinated women

Follow-Up Time (months)

Cumulative Incidence Rate of ≥CIN3

- HPV16+
- HPV18+
- HPV+
- HPV+/-HPV16-/18-
- HPV-

Khan et al. JNCI 2005 vol 97
Prevention of Cervical Carcinoma in Europe

• Should be organized: for vaccinated and non vaccinated women
• HPV primary screening considered in organized systems only:
  ➔ Control: age, screening interval and follow up of abnormal results
  ➔ Cytology will be used for the triage
• Screening for vaccinated women: begin later and do less often
• Self sampling for non participating women
Extending access to cervical screening

- Drivers of screening success
  - Coverage
  - Quality
  - Follow-up of positive cases
There is still some place for the cytology

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