Optimizing the clinical value of HPV test

10th Asia-pacific Congress of Medical Virology
15-18 Oct 2015
Taipei

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Estimated contribution of HPV

Cervical cancer: ~ 100%
Anal cancer: ~ 90%
Vagina, vulva, penile cancers: ~ 40%
Oropharyngeal cancer: 15-75%
HPV & cervical cancer
Cervical Cytology Screening

Georgios N. Papanikolaou

- Sensitivity ~50%
- Require regular repeat screening
- ~3-5% of low-grade, self-limiting abnormalities
Alternatives / adjuncts to cytology screening

- HPV infection
- p16\(^{\text{INK4a}}\)
- Ki-67
- Topoisomerase IIA
- Minichromosome Maintenance 2
- Etc........
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>No. of patients with POSITIVE result</td>
<td>___________________________ %</td>
<td>No. of patients with NEGATIVE result</td>
</tr>
<tr>
<td>Total no. of patients with disease</td>
<td></td>
<td>Total no. of patients without disease</td>
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**Performance of HPV test**
Natural History of High-Risk HPV Infection

- **~1 Year**
  - Transient Infection
  - Normal cervix

- **2–5 Years**
  - Persistent Infection

- **4–5 Years**
  - Low-Grade Dysplasia (CIN 1)

- **9–15 Years**
  - High-Grade Dysplasia (CIN 2/3)
  - Invasive Cancer

- **Over 2 Years**
  - Normal cervix

HPV Infection
Approaches to improve the clinical performance of HPV tests

1. Transient vs. oncogenic HPV infection
1. Detect oncogenic phenotype of HPV

- HPV E6/E7 mRNA: +
- HPV E6/E7 protein: +/−
- E2 disruption/integration: ?
- Methylation: ?
Arbyn et al.
Int J Cancer 2013;132:101
Meta-analysis
Triage for ASCUS

APTIMA
14 Hr HPV E6/7 mRNA

Hybrid Capture 2
13 Hr HPV DNA
Comparing HPV DNA vs mRNA tests in women with abnormal cytology

Meta-analysis
12 publications
CIN2+ as outcome
Burger et al. Gynecology Oncology 2011; 120:430.
Approaches to improve the clinical performance of HPV tests

2. High-risk vs. super high-risk HPV infection
2. Detect “super” high-risk HPV types
3,607 cervical cancer cases, 25 countries, 75% tested by GP5+ / 6+

Sub-Saharan Africa

North Africa

Central America

Europe / North America

South Asia

Hong Kong

17% Squamous cell CA
6% Adenocarcinoma
Meta-analysis on attribution of HPV58 in cervical cancers (worldwide)

HPV58 in HPV-positive cervical cancers
4.9 (4.5-5.3)% in Asia
Significantly higher than Americas, Europe and Africa, $P < 0.001$

Meta-analysis on attribution of HPV58 in cervical cancer (Asia)

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of studies</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Western</td>
<td>2</td>
<td>371</td>
</tr>
<tr>
<td>South-east</td>
<td>5</td>
<td>895</td>
</tr>
<tr>
<td>Southern</td>
<td>8</td>
<td>1622</td>
</tr>
<tr>
<td>Eastern</td>
<td>29</td>
<td>6957</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44</strong></td>
<td><strong>9845</strong></td>
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HPV58 in HPV-positive cervical cancers
6.4 (5.9-7.0)% in Eastern Asia
Significantly higher than others, P < 0.001

Prevalence of HPV58 in cervical cancer (SCC) in East Asia

Shanghai: 26%
Korea: 16%
Hong Kong: 10%
Taiwan: 10%
Japan: 8%
2. Detect “super” high-risk HPV types

Choose “supra” high-risk types

based on

contextual-specific epidemiological data
Approaches to improve the clinical performance of HPV tests

3. Infection vs. disease prevalence of target population
**Sensitivity**

- No. of patients with POSITIVE result
  ___________________________ %
- Total no. of patients with disease

**Specificity**

- No. of patients with NEGATIVE result
  ___________________________ %
- Total no. of patients without disease

**Positive & Negative Predictive Value**

Probability of a test result correctly indicates the presence / absence of disease
Performance of HPV test

- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
2080 women enrolled for cervical screening

Average for 21-45 yr : 10.8%  ~ 1 / 10

3. Select target population

**HPV infection**

**Cancer**

Age group (yrs)

Percentage

No. of cases
Approaches to improve the clinical performance of HPV tests

4. Positive vs. negative predictive value
Performance of HPV test

- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
4. Make use of “long-lasting” negative-predictive value

Single HPV DNA test

- HPV16 +
- HPV18 +
- HPV31 +
- Other Hr HPV +
- Hr HPV -

20,000 women
Khan et al. JNCI 2005; 97: 1072
Schiffman et al. JNCI 2011; 103: 368.
Considerations for applying HPV test

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<tr>
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<th>Specificity</th>
<th>Savings</th>
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Thank you