A Brave New World? The Rationale for, and Barriers to, Adopting Molecular Testing for Cervical Cancer Prevention

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American Society for Clinical Pathology (ASCP)
November, 2011

Disclaimers, Disclosures, & Conflict of Interest

• I have work with a number of companies (e.g., Qiagen, Roche, GenProbe, and Norchip/Biomerieux) and groups (e.g., PATH) on the research, development, and the validation of new assays. Under a fair broker policy, I work collaboratively with them and serve as a unpaid technical advisor. I have Non-Disclosure Agreement with Roche to help them analyze data from the ATHENA trial. I do not receive any personal compensation from these diagnostic companies.

• I serve on a Merck Data and Safety Monitoring Board (Compensated)

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Abstract

Objectives: To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Results

Our search strategy did not find any randomised controlled trials of the parachute.
Always Beware of Observational Data!

proof of global warming


Courtesy of Dr. Walter Kinney

Today's Talk

• Natural History of HPV: Rational Basis for Cervical Cancer Prevention
• Evidence for HPV Testing
• Management of HPV Positives
• Screening Intervals/Risk-Based Approach
• Barriers to Adoption
• Appeal: Screening in the Developing World

Etiologic Contribution of HPV Genotypes

Fraction of Cancers

HPV Genotype

16 18 45 31 X 33 52 58 35 59 56
### Regional Variation of HPV Genotypes in CxCa

![Graph showing regional variation of HPV genotypes in CxCa](image)

<table>
<thead>
<tr>
<th>Region</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>(2058)</td>
</tr>
<tr>
<td>North America</td>
<td>(160)</td>
</tr>
<tr>
<td>Latin America</td>
<td>(3404)</td>
</tr>
<tr>
<td>Africa</td>
<td>(544)</td>
</tr>
<tr>
<td>Asia</td>
<td>(2641)</td>
</tr>
<tr>
<td>Oceania</td>
<td>(170)</td>
</tr>
</tbody>
</table>

de Sanjose et al., Lancet Oncol, 2010

### New Model of Cervical Carcinogenesis

![Diagram showing the new model of cervical carcinogenesis](image)

- **Transient infection**
- **Persistent HPV**

![Stages of cervical cancer progression](image)

- Normal cervix → Infection → Transient infection → Persistent HPV → Precancer → Cancer

### Natural History Profile of Prevalent HPV

![Graph showing natural history profile of prevalent HPV](image)

- Clearance (100%-%Persistence)

Schiffman et al., Lancet, 2007
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**Sensitivity: CIN2+**

- Cuzick et al., IJC, 2006
- Mayrand et al., NEJM, 2007
- Castle et al., LO, 2011

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**% Cytology and HPV Positive: No CIN**

- Cytology Positivity
- HPV Positivity

---
Lead Time Detection = ∆ Cancer Incidence

Hazard ratios (HR) of cervical cancer deaths rates

<table>
<thead>
<tr>
<th>Study group</th>
<th>Rate/100,000</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25.8</td>
<td>1.00</td>
</tr>
<tr>
<td>HPV</td>
<td>12.7</td>
<td>0.52 (0.33-0.83)</td>
</tr>
<tr>
<td>Cytology</td>
<td>21.5</td>
<td>0.89 (0.62-1.27)</td>
</tr>
<tr>
<td>VIA</td>
<td>20.9</td>
<td>0.86 (0.60-1.25)</td>
</tr>
</tbody>
</table>

CI: Confidence interval

Comparative efficacy of visual inspection with acetic acid, HPV testing and conventional cytology in cervical cancer screening: a randomized intervention trial in Osmanabad District, Maharashtra State, India

Sankaranarayanan et al., NEJM, 2009

CIN3+ Risk Following a Negative Screening Test

Dillner et al., BMJ, 2008

Page # 6
Cervical cancer incidence rates among screen negative women by study group (2000-2007)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cancer cases</th>
<th>Number of women</th>
<th>Age Standardized Incidence rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>8</td>
<td>24,380</td>
<td>3.7</td>
</tr>
<tr>
<td>Cytology</td>
<td>22</td>
<td>23,762</td>
<td>15.5</td>
</tr>
<tr>
<td>VIA</td>
<td>25</td>
<td>23,032</td>
<td>16.0</td>
</tr>
</tbody>
</table>

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Selected Real World Performance

Cumulative Incidence of CIN3+

Years Since Enrollment

Katki et al., Lancet Oncol, 2011

HPV Predicts CIN3+ Over 18 Years

Castle et al., submitted
Cytology Misses Glandular Disease

Bray et al., CEBP, 2005
set.aspx?id=10717420248

HPV Testing Does Not

Katki et al., Lancet Oncol, 2011

Different Algorithms: Tradeoffs in Se and Sp

<table>
<thead>
<tr>
<th>HPV/Pap (est. prevalence)</th>
<th>Pap</th>
<th>Pap w/ HPV Triage</th>
<th>HPV and Pap Cotesting</th>
<th>HPV Primary Screening w/ Cytology Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV+/HSIL (0.45%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/HSIL (0.05%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>E.S</td>
</tr>
<tr>
<td>HPV+/ASC-H (0.05%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/ASC-H (0.15%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>E.S</td>
</tr>
<tr>
<td>HPV+/ASC-H (0.18%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/ASC-H (0.02%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>E.S</td>
</tr>
<tr>
<td>HPV+/LSIL (1.6%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/ASC-US (0.05%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/ASC-US (2.5%)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>HPV+/NILM (4%)</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>HPV+/NILM (8%)</td>
<td>S</td>
<td>S</td>
<td>E.S</td>
<td>E.S</td>
</tr>
</tbody>
</table>
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HPV16 and HPV18 Genotyping

Khan et al., JNCI, 2005

Short-Term HPV Persistence

Kjaer et al., JNCI, 2011
Triage of HPV+ Women: Data from ATHENA

Castle et al., Lancet Oncol, 2011

HSIL ≥ LSIL ≥ ASC-US

HPV16/18+ or HSIL
HPV16/18+ or ≥ LSIL
HPV16/18+ or ≥ ASC-US
HPV16/18+ or ≥ ASC-US
HPV16/18+ or ≥ ASC-US

HSIL

Biomarkers/Test
- HPV E6/E7 mRNA/protein
- HPV integration
- 3p, 5p gain TERC
- mcm2/Top2a
- P16 (w/ or w/o Ki-67)
- Pap Test
- HPV Genotyping

Normal

HPV-infected

Progression (e.g., CIN)

Cytological abnormalities

HPV DNA

Proliferation & Replication

Chromosomal Abnormalities

HPV oncogene expression

HPV particle production

HPV Integration

Courtesy of Dr. Nicolas Wentzensen, NCI

HPV+ w/o or w/ p16INK4a Triage (vs. Cytology)

<table>
<thead>
<tr>
<th>Age 35-60</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>1.52 (1.06-2.19)</td>
<td>2.38 (2.21-2.57)</td>
</tr>
<tr>
<td>HPV testing ≥ 1pg/ml and p16+ cells staining</td>
<td>1.32 (0.88-1.95)</td>
<td>1.08 (0.96-1.21)</td>
</tr>
</tbody>
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Carozzi et al., Lancet Oncol, 2008
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CIN3+ Risk Following a Negative Test

Dillner et al., BMJ, 2008
Screening Intervals: Impact on Screening Tests

Katki et al., Lancet Oncol, 2011

Screening Intervals: Impact on Diagnostic Yields

Katki et al., Lancet Oncol, 2011

Harmonizing Management According To Risk

Castle et al., JLGTD, 2008
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Barriers to Adoption: Medical Community

| • Cytology is the standard of care and has been successful in reducing the burden of cervical cancer. |
| • Management of HPV-positive women is not optimized. |
| An HPV-based screening program shifts Pap testing from the entire population to those who have the necessary cause of cervical cancer. |
| • Lengthening screening intervals may impact compliance. |
| Probably less of an issue for countries other than in the US. Any woman who wouldn’t appreciate fewer pelvics? |
| • Cost effective? |
| Programmatically, does the extension of the screening interval compensate for the costs of first screening with HPV? |
| Our Pap testing performs better than what has been reported. |
| What is your evidence? To truly assess performance, one must assess the disease in the Pap negatives. |

Barriers to Adoption: Patient

• HPV as a STI
• We need to educate patients about HPV’s relationship with abnormal Pap. Testing HPV+ does not necessarily mean that you got HPV from your immediate partner.

• “Although the psychosocial effect was initially worse for women allocated to HPV triage, over the full year of follow-up this intervention was better for women’s psychosocial health than repeat smear testing.” McCaffery et al., BMJ, 2010
• “No significant adverse psychosocial effects were detected.” Kitchener et al., Health Technol Assess, 2009
• “The findings suggest that testing positive for HPV may have an adverse psychosocial impact, with increased anxiety, distress and concern about sexual relationships.” McCaffery et al., BJOG, 2004
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Estimated Age-Standardized CxCa Incidence Rate Per 100,000

- GLOBOCAN 2008 (IARC)
- Schiffman & Castle, NEJM, 2005

The Promise of Cervical Cancer Prevention

- Schiffman & Castle, NEJM, 2005
The Forecast Calls For Pain

The Menu of Options

Screen and Treat in South Africa
**Final Talking Points**

1. **Developed world: Make it smarter.**
   The optimal balance between benefit and harm is achieved by screening at the least frequent ‘safe’ (acceptable risk) interval in the general population. Using HPV to first screen the population and then conduct Pap or Pap augmented with biomarkers among those who are HPV positive (have the causal factor) permits good sensitivity and extension of intervals among the HPV-negative women. Fewer clinic visits, pelvic exams, and screens translates into better programmatic specificity and potential cost savings. Use risk to decide who gets what when.

2. **Developing World/Underserved: Make it available.**
   Cervical cancer screening programs can provide immediate benefit to women and be used as a catalyst to improve healthcare delivery by increasing capacity for laboratory and pathology services in low- and middle-income countries.