IS THE PAP TEST OBSOLETE?

Prof Greta Dreyer
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South Africa
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CONTENT

• DIFFERENT EPIDEMIOLOGY IN (SOUTH) AFRICA
• LIMITATIONS OF CYTOLOGY
• ALTERNATIVES TO THE PAP TEST = HPV BASED TECHNOLOGIES
  • VACCINES
  • SCREENING TESTS
• FUTURE ROLE OF CYTOLOGY
• CONCLUSION
# History of cervical cancer screening

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1928</td>
<td>Papanicolaou developed Papanicolaou technique</td>
</tr>
<tr>
<td>1941</td>
<td>Papanicolaou &amp; Trout: Pap smear screening</td>
</tr>
<tr>
<td>1949</td>
<td>Mass Pap smear screening</td>
</tr>
<tr>
<td>1949</td>
<td>HPV seen on electron microscope</td>
</tr>
<tr>
<td>1963</td>
<td>HPV DNA identified</td>
</tr>
<tr>
<td>1976</td>
<td>Zur Hausen &amp; Gisam found HPV DNA in warts</td>
</tr>
<tr>
<td>1983</td>
<td>Possible cancer link between HPV and cancers</td>
</tr>
<tr>
<td>1984</td>
<td>Zur Hausen identifies HPV 16 in cervical cancer</td>
</tr>
<tr>
<td>2006</td>
<td>Bethesda System for reporting Pap results</td>
</tr>
<tr>
<td>2007</td>
<td>Vaccines against cervical cancer</td>
</tr>
<tr>
<td>2020</td>
<td><strong>NO PAPANICOLAOU ANY MORE??</strong></td>
</tr>
</tbody>
</table>
WHY THE QUESTION?
OBSOLETE IF:

• Not really effective
• Replaced by better

• No role in:
  • Future prevention programmes
  • Future diagnostic programme
SOUTH AFRICA

Cervical cancer data

• High prevalence
• Younger ages
• Late presentation
• Poor survival rates
• Impact of high HIV prevalence

Cervical cancer screening

• Limited resources
• Cytology-based
• Increased screening intervals
• Opportunistic & variably implemented
DID THE PAP FAIL IN AFRICA and SOUTH AFRICA?

i.e. Pap not really effective?

NO…but...

CYTOLOGY-BASED SCREENING did Coverage, response, re-call

And HIV...
Organised screening with short screen interval has greatly reduced the incidence of cervical cancer.

Age-standardized incidence of invasive cervical cancer and coverage of screening; England, 1971–1995

Invasive cervical cancer

National call-recall introduced

Coverage

HPV associated cancers

- Cervical cancers - 99.9%
- Anal cancers - 85%
- Vaginal cancers - 70%
- Vulvar cancers - 40%
- Penile cancers - 40%
- Mouth cancers - 25%
- Throat cancers - 35%

http://www.cdc.gov/cancer/hpv/statistics/
PREVALENCE OF CERVICAL ABNORMALITY

Snyman LC 2013
Cytological abnormality by age category

Prevalence (%) vs. Age groups (years):

- SqCa
- HSIL
- LSIL
- ASCUS

Age groups:
- <25
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- ≥55
Cytology vs HPV results - HPV 16 / 18

Age-specific hrHPV and cytological abnormalities

Prevalence (%)

Age groups (years)

ASCUS  LSIL  HSIL  SqCa  HPV 16/HPV18
Paradigm shift needed for cervical cancer: HPV infection is the real epidemic
Prevalence of HPV infection & cervical lesions in the developed world and South African population

# Prevalence of screen results: Cytology results, single round

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>SA - PTA 2010+</th>
</tr>
</thead>
<tbody>
<tr>
<td>NILM</td>
<td>96</td>
<td>82</td>
</tr>
<tr>
<td>ASCUS</td>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>LSIL</td>
<td>1.2</td>
<td>3</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.21</td>
<td>9</td>
</tr>
<tr>
<td>Ca</td>
<td>0.005</td>
<td>0.5</td>
</tr>
</tbody>
</table>
**Prevalence of screen results:**

**CIN2+ cases /100 screened (5-10yr)**

<table>
<thead>
<tr>
<th>HPV result</th>
<th>Pap result</th>
<th>US prevalence</th>
<th>CIN 2+ cases USA (1.5)</th>
<th>SA prevalence</th>
<th>CIN 2+ cases SA (12-16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV -</td>
<td>Cytol -</td>
<td>92</td>
<td>0.28</td>
<td>44</td>
<td>0.13</td>
</tr>
<tr>
<td>HPV -</td>
<td>Cytol +</td>
<td>2.2</td>
<td>0.04</td>
<td>1.2</td>
<td>0.02</td>
</tr>
<tr>
<td>HPV +</td>
<td>Cytol -</td>
<td>4</td>
<td>0.40</td>
<td>38</td>
<td>4 - 8</td>
</tr>
<tr>
<td>HPV +</td>
<td>Cytol +</td>
<td>2.2</td>
<td>1.10</td>
<td>16</td>
<td>8</td>
</tr>
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</table>
Paradigm shift needed for cervical cancer:
HPV infection is the real epidemic

Correct response to epidemic?
Try harder with cytology?
LIMITATIONS OF CYTOLOGY

• SENSITIVITY ISSUES
  – Misses CIN2+
  – Fails to predict CIN2+
  – Fails to predict cancer
  – Fails to prevent cancer

• SHORT SCREEN INTERVAL
  – Current SA 10 year interval
  – Dependant on high coverage
HISTOLOGY TYPES
CERVICAL CANCERS 2011 (n=270)
LIMITATIONS OF CYTOLOGY

• **INTIMATE EXAMINATION**
  – Non-response to call
  – (also positive)

• **HEALTH CARE WORKER**
  – Expensive and scarce
  – Quality of sample

• **HEALTH CARE INFRASTRUCTURE**
  – Expensive and rare
  – (also positive)
ALTERTNATIVES TO CYTOLOGY

- VACCINES ONLY
  - Ethics...

- VISUAL INSPECTION TECHNIQUES
  - VIA, VILI
  - No predictive effect

- MOLECULAR TESTS
  - HPV tests
  - Cell dependant and non-cell dependant, to be developed
Papillomavirus – phylogenetics

Figure adapted from de Villiers EM, et al. Virology 2004; 324:17–27.
VACCINES WILL SOLVE THE PROBLEM...

Vaccine and non-vaccine HPV types in cervical cancer

- HPV 16: 52%
- HPV 18: 17%
- HPV 16 & 18: 2%
- HPV 31: 3%
- HPV 45: 3%
- HPV 52: 3%
- HPV 58: 3%
- Other types: 15%
The most common HPV types according to grade of cervical lesion

- **LSIL/CIN1**
  - HPV 16: 62%
  - HPV 18: 12%
  - HPV 45/31: 6%
  - Other: 20%

- **HSIL/CIN2/3**
  - HPV 16: 37%
  - HPV 18: 11%
  - HPV 45/31: 7%
  - Other: 45%

- **Invasive cervical cancer**
  - HPV 16: 9%
  - HPV 18: 10%
  - HPV 45/31: 20%
  - Other: 61%

<table>
<thead>
<tr>
<th>Resource</th>
<th>Option</th>
<th>Description</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>A</td>
<td>Established cytology based screening</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Current screening by co-testing</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Proposed screening in vaccinated cohorts</td>
<td>V</td>
</tr>
<tr>
<td>Medium</td>
<td>D</td>
<td>SA: Current cytology based screening</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>E</td>
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<td>V</td>
</tr>
<tr>
<td>Low</td>
<td>F</td>
<td>Minimum screening</td>
<td>±V</td>
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SA = South Africa, V = HPV vaccination, C = cytology based screening, H= hrHPV based screening, VI = visual inspection based screening

## Prevention strategies in different resourced settings

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<th>50</th>
<th>60</th>
<th>70</th>
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SA = South Africa, V = HPV vaccination, C = cytology based screening, H= hrHPV based screening, VI = visual inspection based screening

Future of cervical cancer prevention in South Africa

• Vaccination!

• Improved screening tests

• Increased screening coverage

• Treatment of those who need it
HPV testing as primary SCREENING?
Comparison of cervical cancer screening assays

- HPV positive normal cells destined to stay normal
- HPV positive normal cells destined to be abnormal
- HPV positive abnormal cells
- HPV positive cancer cells

- Detected by HPV DNA testing
- Detected by HPV E6/E7 mRNA testing

(sometimes) detected by cytology
HPV tests

- HPV DNA genotyping

- High risk HPV DNA (hrHPV DNA) (pos vs neg)

- HrHPV DNA plus partial genotyping (types 16 & 18)

- High risk HPV E6/E7 mRNA

- Partial ‘genotyping’ HPV mRNA
VALUE ADDED BY HPV TEST:

• Improved accuracy of
  – Diagnosis
  – Prognosis

• Very high sensitivity and NPV

• Self-collection

• Screen interval

• Primary screening tool
### Abnormal HPV, PAP NEG and risk to have histology CIN 2+

<table>
<thead>
<tr>
<th>HPV result POS</th>
<th>CIN 2+ risk 5-10 years</th>
<th>USA prevalence 4%</th>
<th>CIN 2+ CASES/100 USA</th>
<th>SA prevalence 37%</th>
<th>CIN 2+ CASES/100 SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+/18</td>
<td>17%</td>
<td>1.3</td>
<td>0.22</td>
<td>13</td>
<td>2.2</td>
</tr>
<tr>
<td>Rest of top 4</td>
<td>13%</td>
<td>0.7</td>
<td>0.1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Rest of top 8</td>
<td>&lt;1</td>
<td>0.05</td>
<td>8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Rest of hrHPV</td>
<td>3%</td>
<td>&gt;1</td>
<td>&lt;0.05</td>
<td>8</td>
<td>?</td>
</tr>
<tr>
<td>TOTAL</td>
<td>10%</td>
<td>4</td>
<td>1.7</td>
<td>37</td>
<td>3.7</td>
</tr>
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</table>
Cervical cancer screening using HPV tests:
High negative predictive value (NPV)

- A negative HPV test provides long-term risk stratification: 5-10 years of reassurance of not developing CIN3 and even stronger reassurance of not developing invasive cancer among HPV negative women → Permits safe and cost-effective lengthening of the cervical screening interval.

J Natl Cancer Inst 2011;103:368-83
FLOW DIAGRAM A

hrHPV Test Screen

- **Negative**
  - Repeat HPV Test 10 yearly

- **Other high-risk HPV POS**
  - **Negative**
  - Follow Up in 2-5 years
  - **Any POS**
  - Treat
  - Follow Up in 2-5 years

- **Highest Risk HPV POS**
  - **Triage: Cytology**
  - **Negative**
  - Follow Up in 2-5 years
  - **Any POS**
  - Treat
  - Follow Up in 2-5 years

*Highest risk HPV Pos*
- Top 6 high risk HPV DNA Pos, or
- High risk HPV RNA Pos or
- Cytology proliferation marker Pos
Cytology as triage?
# Prevalence of screen results: Double testing

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<td>Cytol +</td>
<td>2.2</td>
<td>1.2</td>
</tr>
<tr>
<td>HPV +</td>
<td>Cytol -</td>
<td>4</td>
<td><strong>38 Persistent high risk</strong></td>
</tr>
<tr>
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<td>Cytol +</td>
<td>2.2</td>
<td>16</td>
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HPV and cytology as dual test?
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<td>4</td>
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</tr>
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<td>2.2</td>
<td>16</td>
</tr>
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</table>
IMMUNO-CYTO-TESTS

• Find abnormal cells between rubbish
• Differentiate almost normal from really normal cells
• Removes human factor
• Salvages sampling error
• Improves sensitivity
• Reduces ‘grey’ results
Proposed cervical cancer prevention model for South Africa?

- **Vaccine dose**
- HPV screening in HIV negative ♀ & ♀ with unknown status
- HPV screening in HIV positive ♀
Screening test with HPV has higher sensitivity

Cytology possibly as triage test for risk

Diagnostic rather than screening test

Use with molecular markers to identify transformed cells
FUTURE ROLE OF CYTOLOGY IN SCREENING AND TREATMENT

Not to be phased out before alternatives are phased in!!

Dual test will not add much value compared to HPV primary

Add cytology only if HPV positive