Human Papilloma Virus (HPV) Screening

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State-of-the-Art in Cervical Cancer Screening  (*Int J Can; 2000*)

- IEC + Organized screening programmes
- Pap-smear: the proven method
- Screen every woman at age 45
- When resources permit screen 10yrly at age 35, 45, 55
- If resources available, screen 5yrly age 35-59
- Once coverage achieved (80%)- expand to age 25 (if resources available)
Reduction in cumulative incidence of invasive cervical cancer over the age range 35-64 yrs, with different frequencies of screening (WHO, 1992)

<table>
<thead>
<tr>
<th>Frequency of screening</th>
<th>Percentage reduction in cumulative incidence</th>
<th>No. of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>2 years</td>
<td>93</td>
<td>15</td>
</tr>
<tr>
<td>3 years</td>
<td>91</td>
<td>10</td>
</tr>
<tr>
<td>5 years</td>
<td>84</td>
<td>6</td>
</tr>
<tr>
<td>10 years</td>
<td>64</td>
<td>3</td>
</tr>
</tbody>
</table>
Pap Smears

- Sensitivity: 11 to 99%
- Specificity: 14 to 97%
- False negative: 5 to 55%
  - Errors of Commission: laboratory errors-1/3
  - Errors of Omission: sampling errors-2/3
- Costs

*Fahey et al: 1995*
Potential Role of HPV in Screening

• Primary screening

• Triage of ASCUS / LSIL: improve management

• Post Treatment Surveillance (CIN / Insitu): to monitor complete excision
Limitations on Epidemiology data

- Logistic difficulties / Ethical issues
- Variable end points (cytology vs histology)
- Possible effect of biopsies on the future course of a cervical lesion
- Different definition & Dx of precancerous lesions
- Variety of populations studied: (age, disease state, concommitent STDs)
- Variety of HPV assays used
- Variable research methodologies
Detectable preclinical phase (DPCP)

Birth | Onset sexual activity | Dysplasia | Carcinoma *in situ* | Invasive Cancer | Death

Average age:

- 13  18  35  50  55 years

Examinations here unlikely to find cancers

- 8% of cancers

Examinations here are cost-effective

- 92% of cancers
Natural History of HPV

- Largely sexually transmitted
- Risk factors: No. of sexual partners in the last few years; age at first intercourse
- Peak incidence: 20-24 yrs
- Incidence gradually declines up to 40-45 yrs
- May begin to increase slowly thereafter

(ref: Schifman et al 1993; Bosch et al, 1995; Burk et al, 1996; Dillner et al, 1996; Meijir et al, 1999)
Natural History of HPV

- 80% infections transient: median range 12 mnths-no risk of CIN
- 10-20% infections persistent: high risk of CIN - only 30% of these progress if untreated
- Minor Cyto abnormality with HPV-: low risk of progression within 3-4 years
- RR of progression 40-180
- Persistence is the important factor for disease progression

Factors influencing persistence

- Age: > 30-35 yrs
- ? Viral load: high
- ? Viral type: 16
- ? Viral integration
- ? Viral RNA transcripts
Prevalence

In general population

• Prevalence: 4-44% (Data not comparable)
  age 20-30 yrs - 10-30%
  age> 30 yrs - 3-10%
Prevalence

In cervical lesions

- Squamous carcinoma: 95% association
- HSIL/CIN II, III: 75 -95%
- LSIL/CINI: 60%
- ASCUS: 30%
- Adenocarcinoma: 60% association

### Recherche de HPV haute risque par HC II, Genève -‘99-00

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Manque</th>
<th>Pas Faits</th>
<th>Art. Insuffisant</th>
<th>HPV Négatif</th>
<th>HPV Positif</th>
<th>Total</th>
<th>% HPV Négatif</th>
<th>% HPV Positif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negatif</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>36</td>
<td>5</td>
<td>42</td>
<td>88%</td>
<td>12%</td>
</tr>
<tr>
<td>AGUS</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>45</td>
<td>9</td>
<td>61</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>ASCUS</td>
<td>7</td>
<td>71</td>
<td>58</td>
<td>710</td>
<td>217</td>
<td>1063</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>Lésion Bas Grade</td>
<td>3</td>
<td>51</td>
<td>20</td>
<td>160</td>
<td>338</td>
<td>572</td>
<td>32%</td>
<td>68%</td>
</tr>
<tr>
<td>Total des cas</td>
<td>10</td>
<td>127</td>
<td>81</td>
<td>951</td>
<td>569</td>
<td>1738</td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>

M. Tötsch, DPC - Geneva
Testing Methodologies

• Southern blotting
• Dot blot
• Filter in situ hybridisation (FISH)
• In situ hybridisation
• Hybrid capture HCI / HC II
• Polymerase chain reaction (PCR)
• Others: LCR, NASBA, in situ PCR
Prerequisites

SCREENING TEST:

• is valid for identifying pre-clinical lesions
• acceptable (easy to apply, no pain, no side-effects)
• screening interval
• affordable
## Comparisons of HPV with Cytology

<table>
<thead>
<tr>
<th>Author</th>
<th>HPV Test</th>
<th>Sensitivity for HSIL</th>
<th>Specificity for HSIL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Cytology</td>
<td>HPV</td>
</tr>
<tr>
<td>Reid 1991</td>
<td>SB</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Schneider 1996</td>
<td>HC</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Ratnam 1999</td>
<td>HC</td>
<td>37.9</td>
<td>86.2</td>
</tr>
<tr>
<td>Cuzick 1999</td>
<td>HC II</td>
<td>79</td>
<td>95.2</td>
</tr>
<tr>
<td>Schiffman 1999</td>
<td>HC II</td>
<td>75.2</td>
<td>89.6</td>
</tr>
</tbody>
</table>
Issues to be resolved

• Age - appropriate for testing
• Testing methodology / Test interpretation
• Viral persistence - surrogate markers for
• Test sensitivity & specificity
• Acceptability - psychological impact
• Quality control measures
• Health economics - costs for high volume application
# Ongoing & Planned Studies of HPV Testing

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Location</th>
<th>Population</th>
<th>Size</th>
<th>Investigations</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nazeer</td>
<td>Suisse</td>
<td>Screening</td>
<td>2000</td>
<td>HPV HC II, Colpo, Liq Base cyt</td>
<td>Ongoing</td>
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<tr>
<td>Schiffman</td>
<td>USA</td>
<td>Ascus/LSIL smears</td>
<td>1500</td>
<td>HPV HCII Cervicogy, Liq base cyt</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Cuzick</td>
<td>UK</td>
<td>Screening Age 30-60</td>
<td>12 000</td>
<td>HPV HC II</td>
<td>Ongoing</td>
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<tr>
<td>Dillner</td>
<td>Sweden</td>
<td>Screening Age 32-68</td>
<td>10 000</td>
<td>HPV HC II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Meijers/Walboomers</td>
<td>Netherlands</td>
<td>Screening</td>
<td>44 000</td>
<td>HPV HCII</td>
<td>Pilot</td>
</tr>
<tr>
<td>Hakama</td>
<td>Finland</td>
<td></td>
<td>100 000</td>
<td>HPV New Techs</td>
<td>Planning</td>
</tr>
</tbody>
</table>
Conclusions

• HPV is **more sensitive** than cytology for high grade CIN - but has **low specificity** than cytology esp. in young women

• HPV testing cannot currently be recommended for widespread implementation
Conclusions

• May be appropriate in certain limited situations - management of borderline smears esp in women >30 yrs

• May be used to disinvest in screening programmes - reduce No. of smears/ colposcopy / increased screening intervals
Conclusions

• Negative predictive value is uncertain - safety associated with reduced surveillance of HPV -ve women

• Lack of evidence regarding independence of the two tests
Conclusions

• Longitudinal studies with an appropriate follow-up (6 yrs) are required to:

- determine appropriate screening intervals
- examine cumulative incidence of Cx Ca 1,3,5,10,15 yrs after various screening histories
Depistage du cancer du col

- **Normal**
  - 36 mois si 3 x 12 mois normal
  - Cytologie (-) + HPV (-)
  - 3 frottis normaux sur 2 ans avant de revenir au frottis triennal après traitement des dysplasies

- **ASCUS**
  - Detection HPV
  - HPV (-) 6 mois
  - Cytologie (+)

- **AGUS/LSIL**
  - Detection HPV
  - HPV (+) Colpo
  - 12 mois Colpo/Biopsie/Chir.

- **HSIL**
  - Colposcopie/Biopsie/Chirurgie
  - Frottis + HPV après chi 6-12-24 mois
  - 3 normaux 1 Pathologique
  - 3 frottis normaux sur 2 ans avant de revenir au frottis triennal après traitement des dysplasies

- **Hôpitaux Universitaires de Genève**