Alternatives to Cytology: New Perspectives for Screening of Cervical Cancer

Saloney NAZEER
Objective of the Project

• To evaluate the feasibility, applicability and cost-effectiveness of different approaches to screening of cervical cancer in different resource settings
## Annual Estimates of New Cases Globally

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>795 000</td>
<td>313 000</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>450 000</td>
<td>300 000</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>165 000</td>
<td>101 000</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>142 000</td>
<td>42 000</td>
</tr>
</tbody>
</table>

WHO/IARC, 1999
Incidence of Cervix uteri cancer ASR (World) All ages

The map illustrates the incidence of cervical cancer across different regions of the world. The color coding represents various incidence rates, with regions shaded from green (rates < 9.7) to red (rates < 91.5). The data is based on IARC 1998.
## Available Control Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cases (%)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Diet</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Infections</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Screening</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cervix</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Breast</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Treatment</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>
## Time to show Important Impact of Different Measures

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Time (in yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>30</td>
</tr>
<tr>
<td>Diet</td>
<td>10-50</td>
</tr>
<tr>
<td>Infections</td>
<td>40</td>
</tr>
<tr>
<td>Screening</td>
<td>5-10</td>
</tr>
<tr>
<td>Treatment</td>
<td>5</td>
</tr>
</tbody>
</table>
Prerequisites of a successful screening programme

A CANCER is suitable for screening if:

• a cancer is a major health problem justifying screening
• natural history of disease - long enough detectable pre clinical phase
• significant proportion of preclinical lesions progress to clinical disease
• available acceptable treatment
Screening Test

- is valid for identifying preclinical lesions
- acceptable (to patient & physician)
- screening interval
- affordable
Characteristics of an Organized Screening Program

- Identification of target Population
- Measures for high coverage and attendance
- Clear screening protocol: health objectives
- Adequate field facilities
- Adequate facilities for diagnosis, Rx and FU
- Information system (cancer registry)
- Evaluation and monitoring (Process and Outcome quality indicators)
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
Alternatives to Cytology

- Visual Inspection of the cervix
  * Simple - Clinical Downstaging
  * Acetic Acid Aided - VIA
- Gynoscopy
- Cervicography
- Speculoscopy
- Fournier transformed Infrared Spectroscopy
- Laser induced Fluorescence
- HPV Detection / vaccines
WHO International Study Group

INTERNATIONAL NETWORK ON CONTROL OF GYNAECOLOGICAL CANCERS (INCGC)
INCGC
The Philosophy/Aims&Objectives

• To establish collaboration amongst International Players
• To standardise research methodology
• To translate research findings into interventions

“Model Protocol for RCT / Demonstration Project”
Pilot Demonstration Project for cervical cancer Screening & Management in a Selected Region in Pakistan (Lahore District)

In collaboration with WHO & MOH Pakistan
## Estimated Cases of Cx Ca in Regions and Selected Countries

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>New Cases/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>15 700</td>
</tr>
<tr>
<td>Latin America</td>
<td>44 000</td>
</tr>
<tr>
<td>Europe</td>
<td>47 200</td>
</tr>
<tr>
<td>USSR</td>
<td>31 300</td>
</tr>
<tr>
<td>Africa</td>
<td>36 900</td>
</tr>
<tr>
<td>China</td>
<td>131 500</td>
</tr>
<tr>
<td>India</td>
<td>120 000</td>
</tr>
<tr>
<td>Japan</td>
<td>9 700</td>
</tr>
<tr>
<td>Other Asian</td>
<td>70 300</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>1 200</td>
</tr>
</tbody>
</table>

Source: WHO, 1999
Cervical Cancer in Pakistan: Epidemiology

- Total population - 130 million
- Rural population - 70%
- Male/Female ratio - 45:55
- Community - Muslims (90%); Christians; Zoroastrians
- Literacy rate - 30%
Cervical Cancer in Pakistan: Epidemiology

Hospital based data:

- 3rd common cancer in women (following Breast & Oral CA)
- 60% of all genital tract CA
- 70-80% stage III / IV
- 89% in the age group 30-55 yrs
- Majority in low socio-economic class
Objectives of the Project

- evaluate effect of health education
- evaluate VIA as a screening test
- evaluate performance of cytology
- evaluate feasibility, acceptability & cost-benefit of different screening methods
AIM of the Project

• To devise a national screening programme in Pakistan for Cervical Cancer
Materials & Methods

Project Areas:

- Lahore District - population of 700 000
- Three rural and periurban areas - CHUNG, RAIWIND and BURKI
- Comparable socio-economic & demographic backgrounds
- Similar health care facilities
- Equal access to the district's teaching hospitals, namely Sir Ganga Ram Hospital and Mayo Hospital
Project Phases:

• **PHASE I**  PREPARATORY  
  June 1996 - September 1996

• **PHASE II**  INTERVENTION  
  January 1997 - June 1997
  - Knowledge Attitude and Practice (KAP) Survey  
  - Health Education  
  - Training

• **PHASE III**  - Data Collection  
  July 1997 - December 1998
Target Population

- Total female Population: ± 50 000
- Target Population (*WHO criteria*)
- Sexually active women aged 30-60 years: ± 15 000
- Population census data
Data Collection

• **KAP Survey**
  Preprepared questionnaire by lady health workers

• **Screening & Management**
  All women aged 30-60 yrs, who presented at the hospital gynae.out-patient clinics
  (June 1997 - Dec. 1998)
Methodology

1080 women - aged 30-60 yrs
M/H - Gynae examination

VIA - 3% A.A.

Acetowhite lesion

Papsmear conventional

Colposcopy - SGRH

Punch Bx/histology

No Acetowhite lesion

Recall 3 yrs

CIN I: Rx infec. Rpt 12 wks
CIN II: Cryo or elec. Coag
CIN III: Cold knife cone
RESULTS

KAP Survey

- No. of women (30-60 yrs): 15,000
- Education: 85% uneducated / 15% primary school
- Mean age at marriage: 20.6 yrs
- Parity: 0-15 ( >25% had >5 children)
- Low socio-economic status
- Knowledge about general health: poor
- Knowledge about cervical cancer: 0%
- Reluctance to visit a clinic if not ill: 100%
RESULTS

Screening & Management

• No. of women: 1080
• Age: 30-60 yrs (median 40.2)
• All were married with median parity of 7.5
Results of VIA and Pap-smears compared with Histologic diagnosis

<table>
<thead>
<tr>
<th>VIA</th>
<th>PAP</th>
<th>No.</th>
<th>Lost</th>
<th>Colposcopy</th>
<th>Biopsy</th>
<th>Mild Disp.</th>
<th>Mod. Disp.</th>
<th>Severe Disp</th>
<th>CIS</th>
<th>Inv. Ca</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>100</td>
<td>10</td>
<td>90</td>
<td>66</td>
<td>4</td>
<td>6</td>
<td>24</td>
<td>16</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>212</td>
<td>32</td>
<td>180</td>
<td>90</td>
<td>6</td>
<td>56</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>56</td>
<td>16</td>
<td>40</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>712</td>
<td>20</td>
<td>204</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1080</td>
<td>78</td>
<td>514</td>
<td>178</td>
<td>20</td>
<td>68</td>
<td>34</td>
<td>18</td>
<td>12</td>
<td>26</td>
</tr>
</tbody>
</table>
Results (contd.)

• Histology was the reference point

• Dysplasia all grades: 14 %
  LSIL - 2%
  HSIL - 12%

• Invasive cancer: 1.2%
Comparison of VIA and Histology

<table>
<thead>
<tr>
<th>VIA</th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>134</td>
<td>22</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>26</td>
<td>178</td>
</tr>
</tbody>
</table>
Comparison of Pap-smear and Histology

<table>
<thead>
<tr>
<th>Pap Smear</th>
<th>Histology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>80</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>26</td>
</tr>
</tbody>
</table>
## RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap-smear</td>
<td>47.4%</td>
<td>84.6%</td>
<td>53.6%</td>
</tr>
<tr>
<td>VIA</td>
<td>88.1%</td>
<td>15.4%</td>
<td></td>
</tr>
</tbody>
</table>
Consensus Conference, Tunis 1999

AIMS & OBJECTIVES

• Review & assess completed & ongoing research studies on Cx Ca /HPV/STD and their relevance to screening for Cx Ca
• Review & revise, current WHO Guidelines
• Revise strategies to successfully carry out these recommendations esp. in DCs
<table>
<thead>
<tr>
<th>STUDY</th>
<th>TYPE of STUDY</th>
<th>SCREENING TESTS</th>
<th>PATIENT POPULATION</th>
<th>RESULTS</th>
</tr>
</thead>
</table>
| University of Zimbabwe and JHPIEGO Zimbabwe 1999 | Cross-sectional | • VIA  
• Pap  
• Colposcopy/Biopsy | Age 25-55 yrs attending PHC clinics.                                                | Sensitivity: 76.7%  
Specificity: 64.1%  
44.3%  
90.6% |
| T.Wright et al               | Cross-sectional | Pap  
VIA  
HPV  
Cerviography | 35-60 yrs Peri-urban community unscreened                                           | 78/95%  
67/84%  
58/92%  
73/86% |
| Singh et al Delhi            | ???           | VIA  
Gyno  
Cyto  
(colpo/histo) | 3000 women                                                                            | HSIL                           |
| Croije et al Bloemfontein    | ???           | Cyto  
Cervico  
VIA  
Cyto  
Cervico  
VIA  
Speculo | 3000 women  
1000 women                                                                | 37.8%/99  
50.3% /77%  
51.2%/ 49%  
60/96%  
48.9/86.8%  
80/46.3%  
82/ 39.5% |
<table>
<thead>
<tr>
<th>STUDY</th>
<th>TYPE of STUDY</th>
<th>SCREENING TEST</th>
<th>PATIENT POPULATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorincz et al</strong> New York 1998</td>
<td>Cohort Study</td>
<td>Hybrid Capture</td>
<td>265 women with ASCUS and LSIL by Colposcopy (mean age 27 yrs)</td>
<td>Sensitivity: LSIL 86% HSIL 93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liquid Based Cytology Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kinney et al</strong> USA 1999</td>
<td>Cohort Study</td>
<td>Liquid based cytology Hybrid Capture</td>
<td>995 women with ASCUS from Gynae Clinics</td>
<td>Sensitivity HPV – 89.2% Repeat Pap 76.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cuzick et al</strong> UK 1999</td>
<td>Cross -sectional</td>
<td>Conventional Pap PCR /SHARP Hybrid Capture</td>
<td>3103 women, &gt; 35 yrs Routine GP Clinics</td>
<td>PCR= 87.3% HPV Hybrid Capture =88.9% Pap –79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T. Wright et al</strong> Cape Town</td>
<td>Cross -sectional</td>
<td>Cytology VIA Hybrid Capture Cervicography</td>
<td>1415 women 36-60 yrs</td>
<td>67.9% sensitivity of both HPV Hybrid Capture (self collected) and Pap</td>
</tr>
</tbody>
</table>
## Different Screening Methods Compared to PapSmear

<table>
<thead>
<tr>
<th>TEST</th>
<th>LINKS</th>
<th>SCIENTIFIC</th>
<th>T</th>
<th>SE/SP</th>
<th>C</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap</td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Polar Probe</td>
<td>+</td>
<td>?</td>
<td>??</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>VIA</td>
<td>+</td>
<td>+</td>
<td>+-</td>
<td>?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Automation</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Speculoscopy</td>
<td>+</td>
<td>+</td>
<td>??</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tumor Marker</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>??</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cervicography</td>
<td>-</td>
<td>+</td>
<td>+-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thin Prep</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HPV Test</td>
<td>-</td>
<td>+</td>
<td>--</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HPV Vaccine</td>
<td>+ +</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down Staging</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T = Training  - SE = Sensitivity  - C = Cost  - TE = Technology
Links = Means referrals when compared to Pap test
Conclusion / Discussion
Conclusion / Discussion

• Screening for cervical cancer reduces incidence of & mortality from invasive disease (upto 90%)

• Is applicable as a public health policy

• However, a single format cannot be applicable for all countries / regions
Conclusion / Discussion

• Limitations of cytology based screening programmes (*esp in DCs*):
  - cost for population based application
  - lack of quality assurance - suboptimal
  - logistical issues

• Low compliance / High drop out rate
Conclusion / Discussion

*New alternative techniques - holding promise*

- **VIA** sensitivity comparable (70%)
  specificity low (14-30%)

? PPV & NPV
? Efficacy & QC
? Cost ( overtreatment)
Conclusion / Discussion

- **HPV** sensitivity comparable (80-90%)
  specificity lower (high false + < 30 yrs)

  - PPV & NPV (risk of reduced surveillance)
  - Efficacy & QC
  - Cost (pop. based screening)
  - Benefit independent of cytology
Conclusion / Discussion

• Sequential screening with a low cost, simple test e.g. Visual Inspection with Acetic Acid (VIA)

• Followed by a more objective test e.g. Pap smear or HPV detection on selected sub-group

• Disinvest in screening programme (screen 10 yrly)
Conclusion / Discussion

• All new techniques need to be evaluated in RCTs for specificity; quality control; cost-effectiveness; efficacy

• HPV vaccines: 30 years to evaluate; logistics not defined
Conclusion / Discussion

Pap smear the only proven method

**Step-up approach**

- Screen every woman at age 45
- When resources permit screen 10 yrly at age 35, 45, 55
- If resources available, screen 5 yrly age 35-59
- Once coverage achieved (80%)- expand to age 25 (if resources available)
Cervical Cancer Control

- Mortality in developing countries: 27 deaths per 100,000
- Mortality in developed countries: 6 deaths per 100,000

Effect of screening:

- Effect of health education
- Visual inspection
- Standard therapy

Screening introduced in developed countries

Time
Parting Comment

The decision to establish and continue screening programmes depends on:

• the factual evidence

• a compromise between different elements of programmes, individualised to the needs of different populations