Cervical Cancer Screening in Developing Countries

Sue J. Lee, M.D.
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Outline

• Epidemiology
• Screening- Cytology, VIA, HPV Test
• Modes of Treatment
• HPV vaccine
• Barriers with Implementation
• Conclusions
Epidemiology- US

- Ranks 14\textsuperscript{th} in female cancer
- 2003 cervical cancer incidence: 8.1 per 100,000
- Incidence ↓ 75\%, and mortality ↓ 70\% since 1950s

Epidemiology- US

Cervical cancer (invasive) SEER incidence* and death rates, by race and year – United States, 1975-2003


*Per 100,000 persons and age –adjusted to the 2000 U.S. standard population.
How do we achieve this success in developing countries?
Epidemiology- Global

• 2\textsuperscript{nd} most common cancer in women worldwide

• Most common cancer among women in developing countries

• 85\% of all new cases and deaths occur in developing countries
Globally: Wide Disparities

Global Picture of Cervical Ca

Global Picture of HIV

WHO/UNAIDS, 2008
Cervical Cancer = Years of Life Lost

- Aim: Compare YLL to AIDS, TB, maternal conditions, and cancers
- Outcome:
  - Responsible for > 150,000 deaths and 2.3 million YLL worldwide
  - Largest cause of YLL from cancer in developing world
  - Latin America, Caribbean, Eastern Europe: cervical cancer contributes more to years of lost life than TB, maternal conditions, or AIDS.

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Criteria for Good Screening Test

- High Sensitivity & Specificity
- High Positive Predictive Value
- Simplicity & Low Cost
- Acceptable to Patients & Clinicians
Effect of Screening with Cytology

Screening in Low-Resource Areas

• Screening, dx, tx all on-site
• Low-cost, low-technology screening test
• Wide coverage, accessible to women
• Educational Programs
• Evaluation of Screening Program

Cytology: Globally Feasible??
Not All Cytology is Equal

• Conventional vs. Liquid Based Cytology
  – Conventional: more common in developing areas, less expensive
  – LBC: used in developed world

• Difference in Sensitivity & Specificity
  – Sensitivity consistently lower in developing countries

*Cronje HS. Int J Gynaecol Obstet 2004;84:101-8*
Screening- Cytology

- Advantages
  - “Standard of care”
  - Validated & accepted
  - Infrastructure may already be in place
  - Untrained HCW able to perform
  - Common language for referral
  - High specificity

- Disadvantages
  - Infrastructure required
  - High-quality cytology labs & cytopathologists
  - Transport specimen
  - Communication of results
  - Follow-up, colposcopy
  - Low sensitivity
  - ? Cost-effective
Visual Inspection with Acetic Acid (VIA)

“The detection of intraepithelial or preclinical invasive cervical neoplasias should not depend on the possession of a colposcope.”

Manual for Visual Inspection
Screening- VIA/VILI

- Visual Inspection with acetic acid (VIA): can be done with naked eye or low magnification
  - Speculum exam
  - Application of dilute 3-5% acetic acid to the cervix
  - Abnormal tissue appears white

- Visual Inspection with Lugol’s Iodine (VILI)
  - Uses Lugol’s Iodine instead of acetic acid
  - Abnormal tissue appears unstained
## VIA Reporting

<table>
<thead>
<tr>
<th>VIA Result</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>No AWE, polyp, cervicitis, inflammation, Nabothian cysts; metaplasia</td>
</tr>
<tr>
<td>Positive</td>
<td>Sharp, well-defined AWE usually touching SCJ, leukoplakia, warts</td>
</tr>
<tr>
<td>Suspicious for cancer</td>
<td>Visible ulcerative, warty growth, bleeding to touch</td>
</tr>
</tbody>
</table>
VIA/VILI negative
VIA/VILI positive
VIA Suspicious for Cancer
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Number of cases</th>
<th>Detection of ESS and Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>Denny et al.</td>
<td>Italy</td>
<td>2000</td>
<td>84</td>
</tr>
<tr>
<td>Tian et al.</td>
<td>China</td>
<td>1323</td>
<td>80</td>
</tr>
<tr>
<td>Li et al.</td>
<td>China</td>
<td>1083</td>
<td>80</td>
</tr>
<tr>
<td>Lin et al.</td>
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<td>80</td>
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<tr>
<td>Zhang et al.</td>
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<tr>
<td>Deng et al.</td>
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<td>1083</td>
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</tr>
<tr>
<td>Bao et al.</td>
<td>China</td>
<td>1083</td>
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<tr>
<td>Denny et al.</td>
<td>South Africa</td>
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<td>South Africa</td>
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<td>80</td>
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</tbody>
</table>

* Excess cases without protocol in overweight and may not reflect adjustment for covariates bias.
VIA vs. Cytology

- Cross-sectional study, Zimbabwe
  - n=10,934 screened with both cytology & VIA
  - Screening done by 6 trained nurse-midwives
  - 15 primary care clinics.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIA (n=2130)</td>
<td>76.7 (70.3-82.3)</td>
<td>64.1 (61.9-66.2)</td>
</tr>
<tr>
<td>Pap (n=2092)</td>
<td>44.3 (37.3-51.4)</td>
<td>90.6 (89.2-91.9)</td>
</tr>
</tbody>
</table>

VIA Advantages

- Simple, easy to learn
- Different healthcare workers can be trained
- Minimal lab infrastructure needed
- Inexpensive, low costs to start-up & sustain
- Requires 1 visit, immediate result
- Screen & Treat
- Integrate into primary health care services
VIA Disadvantages

- Moderate specificity, unnecessary tx in single visit approach
- Health, cost implications of over-treatment
- Need for training & quality control
- Evaluator dependent
- Less accurate in post-menopausal women
- Not uniformly accepted
VIA appears to be a more appropriate screening modality for resource-poor areas, but is it cost-effective?
What is Most Cost-Effective?

- Computer-based model applied to 5 countries: India, Kenya, Peru, S. Africa, Thailand
  - Screening methods: cytology, VIA, HPV Test
  - Number of visits: 3 vs. 2 vs. 1- visit strategies
  - Outcomes: lifetime risk of cancer, years of life saved, lifetime costs, and cost-effectiveness ratios (cost per year of life saved).

VIA is Cost Effective

• VIA or HPV test in 1 or 2 visits are cost-effective alternatives to 3-visit cytology-based screening.
  – Screened women once @ age 35 yr
  – Decrease cervical cancer risk by 25-36%
  – Cost < $500 per year of life saved

Can VIA Prevent Invasive Cancer?

- Cluster randomized trial in India
  - 49,311 intervention grp (VIA); 30,958 control grp
  - Intervention grp: VIA, Colpo/Bx, Immediate Cryo
  - Control grp: education on screening & cervical ca
  - Intention to treat analysis
  - **Primary outcome**: VIA affects cervix cancer incidence and mortality

VIA Decreases CIN 2+

VIA Decreases Cervical Cancer

VIA Decreases Mortality

VIA does seem to have a promising role in decreasing disease burden, but what other methods can be used?
Screening- HPV Test

• HPV Test: Hybrid Capture 2 (HC2)
  – High-risk HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
  – Sensitivity/Specificity depends on the use of the test

• Uses of HPV Test
  – Triage for ASCUS
  – Follow-up treatment for CIN
  – Primary screening
HPV Test Sensitivity/Specificity

- Primary Screening: 25 cross-sectional studies (US, Europe, India, Peru, Brazil, Zimbabwe, S. Africa)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>89.7%</td>
<td>88.2%</td>
</tr>
<tr>
<td>N.Amer/Europe</td>
<td>98.1%</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

HPV is more sensitive than Pap

Screening Algorithm - HPV Test

WOMEN AGED 30 - 64 YEARS
FAST HPV DNA TEST

Negative

5 - 10 YEAR RECALL

Positive

VISUAL INSPECTION WITH ACETIC ACID

Normal

HPV & VISUAL INSPECTION WITH ACETIC ACID AT 12 - 24 MONTHS

Abnormal

IMMEDIATE TREATMENT

Screening- HPV Test

• Advantages
  – High sensitivity
  – Automated, objective test
  – Local labs
  – Screen & Treat
  – Self sampling

• Disadvantages
  – Lower specificity
  – Geographic heterogeneity of results
  – Quality control, test parameters
  – Expensive cost $
VIA vs. HPV Test

- RCT for non-cytology based screen & treat to determine safety & efficacy of VIA, HPV testing
  - South Africa: 6,555 women; 35-65 years
  - All had both HPV test & VIA then randomized
    - Cryo if HPV⊕ OR Cryo if VIA⊕ OR delayed eval
  - Outcome measured CIN2+ @ 6, 12 mo

Table 3. Pathological Diagnoses of Cervical Intraepithelial Neoplasia

## Screening Summary

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>44-78%</td>
<td>91-96%</td>
</tr>
<tr>
<td>VIA</td>
<td>67-79%</td>
<td>49-86%</td>
</tr>
<tr>
<td>HPV DNA</td>
<td>66-100%</td>
<td>61-96%</td>
</tr>
<tr>
<td>VIAM</td>
<td>62-73%</td>
<td>86-87%</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>44-77%</td>
<td>85-90%</td>
</tr>
</tbody>
</table>

Rapid HPV Test

• Batch Test: careHPV
  – HPV DNA
  – Vaginal/cervical specimen
  – <2.5 hours

• Strip test
  – E6 protein biomarker
  – Cervical specimen
  – 15 min
Rapid HPV Test in Rural China

• Cross-sectional Study
  – n=2530 women, 30-54 years
  – All women examined with
    ▪ careHPV vaginal, cervical swabs,
    ▪ LBC
    ▪ HC2
    ▪ VIA
    ▪ Colpo
  – Outcome: clinical accuracy of careHPV as rapid screening test?

## Rapid HPV Test: a Promising Screening Test

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<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>careHPV cervical</td>
<td>90.0 (83-97)</td>
<td>84.2 (82.7-85.7)</td>
</tr>
<tr>
<td>careHPV vaginal</td>
<td>81.4 (72.3-90.5)</td>
<td>82.4 (80.8-83.9)</td>
</tr>
<tr>
<td>HC2</td>
<td>97.1 (93.2-100)</td>
<td>85.6 (84.2-87.1)</td>
</tr>
<tr>
<td>LBC</td>
<td>85.3 (76.9-93.7)</td>
<td>97.0 (96.3-97.7)</td>
</tr>
<tr>
<td>VIA</td>
<td>41.4 (29.9-53.0)</td>
<td>94.5 (93.6-95.4)</td>
</tr>
</tbody>
</table>

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• **Modes of Treatment**
• HPV vaccine
• Barriers with Implementation
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Modes of Treatment

• Cryotherapy
• LEEP
• Cervical conization
• Hysterectomy
• Chemoradiation
1st Symposium on Prevention of Cervical Cancer, Nicaragua
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HPV Vaccine

• Quadravalent vaccine HPV 6,11,16,18
  – FDA approved June 2006, ages 9-26 yr
  – 3 IM injections 0, 2, 6 months
  – $360 for 3 injections
  – Cross protection against other HPV types (45,31)

• Bivalent Vaccine HPV 16, 18
  – 3 IM injections 0, 1, 6 months

• Primary prevention: for prophylaxis not therapeutic

• Both vaccines > 90% efficacious against ≥ CIN 2
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Barriers
Barriers to HPV Vaccine

- Target: prior to onset of sexual activity (9-13 yr)
  - Vaccinating adolescents for a STI
- Vaccinating school-age children and adolescents
- Duration of vaccine
- Cancer vaccine, prophylactic vaccine for a cancer not likely to develop for decades
  - Full effect of vaccination will take 30-40 yrs
- Competing with other new vaccines
Barriers to HPV Vaccine

- Gender-specific immunization
- Costs: 2.2 billion people live in countries which have GNI < $825 per capita

World Bank 2006
Solutions?

• Bridge pediatric immunization, sexual & reproductive health, cancer communities
  – May serve as a future model for HIV vaccine
• Manufacture vaccine locally to reduce costs
• More outreach, mobile vaccination programs
So what is the answer for developing countries?
Conclusions

• Country-specific solutions need to be found, while being aware of criteria that enabled successful screening programs.
• VIA or HPV test in 1 or 2 visits are cost-effective alternatives to 3 visit pap based screening.
• Aim to screen women once in their lifetime, 30-40 years old
Conclusions

• Additional work is needed to develop rapid, user-friendly, low-cost HPV tests.

• Increase distribution of HPV vaccine.

• Increase accessibility of services and quality care
Sources


Ottaviano M, La Torre P. Examination of the cervix with the naked eye using acetic acid test. Am J Obstet Gynecol 1982;143:139-42.

More Sources


More Sources


Online resources:
http://www.path.org/cervical-cancer.php
http://www.iarc.fr/
Thank you!

- Dr. Jennifer Unger
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- Dr. Megan Huchko
- Dr. Chiang & Dr. Eschenbach
- Daniele Moreni