Cost-Effectiveness of Cervical Cancer Screening Strategies: Examples from Different World Regions

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Sue J. Goldie, M.D., M.P.H.

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Cervical Cancer Control

- **Public health success** in countries with cytology (Pap smear) screening programs where mortality has been reduced by 75%
- **Public health failure** in developing countries where ~90% of all cervical cancer deaths occur
  - Infrastructure and technological expertise for cytology programs not available
  - Three visits for screening, diagnosis, and treatment not feasible
Overview of Decision-Analytic Methods

- Develop mathematical model of the natural history of disease.
- Synthesize clinical and economic data from multiple sources (clinical trials, cohort studies, national surveys, databases).
- **Calibrate** model to achieve the best fit to epidemiological data; **validate** model by predicting outcomes consistent with observations from independent data.
- “Simulate” different interventions to estimate consequences (e.g., life-expectancy, quality of life, costs).
Objectives

• To develop and validate models of the natural history of cervical cancer in developed and developing country populations.

• To conduct formal cost-effectiveness analysis of alternative cervical cancer screening strategies.
Cost-Effectiveness of Management Strategies for Atypical Squamous Cells of Undetermined Significance in the United States*

Jane J. Kim, PhD; Thomas C. Wright, MD; Sue J. Goldie, MD, MPH

* JAMA (2002)
Introduction

- Cervical cancer control has been largely successful in the U.S., where annual screening is recommended.
- More than 2 million U.S. women are diagnosed with an equivocal result referred to as “atypical squamous cells of undetermined significance” (ASCUS).
- The clinical response to an ASCUS result varies widely and has been the subject of heated debate.
Cervical Cancer Model

Healthy → HPV ⇔ Low-grade lesion → High-grade lesion → Local Cancer
Regional Cancer → Distant Cancer
Cervical Cancer Model

Healthy

HPV

Low-grade lesion

High-grade lesion

Local Cancer

Regional Cancer

Distant Cancer
Cervical Cancer Model

Healthy → HPV → Low-grade lesion → High-grade lesion → Local Cancer

HPV → Healthy

Low-grade lesion → High-grade lesion

High-grade lesion → Regional Cancer

Regional Cancer → Distant Cancer
Cervical Cancer Model

Healthy HPV Low-grade lesion High-grade lesion Local Cancer Regional Cancer Distant Cancer
Cervical Cancer Model

Healthy → HPV → Low-grade lesion → High-grade lesion → Local Cancer

Healthy ← HPV ← Low-grade lesion ← High-grade lesion ← Regional Cancer

Healthy ← HPV ← Low-grade lesion ← High-grade lesion ← Distant Cancer
Cervical Cancer Model

Healthy → HPV → Low-grade lesion → High-grade lesion → Local Cancer

HPV → Low-grade lesion

Low-grade lesion → High-grade lesion

High-grade lesion → Regional Cancer

Regional Cancer → Distant Cancer
Cervical Cancer Model

Healthy → HPV → Low-grade lesion → High-grade lesion → Local Cancer

- Low-Risk
- High-Risk

Regional Cancer

Distant Cancer
Predictive Validity (1)

Age (year)

Prevalence of HPV

15-19
20-24
25-29
29-33
34-39
40-49

Model
Published Data
Predictive Validity (2)

Prevalence of Low-Grade Lesions

Age (year)

Model
Data
Strategies

1. Ignore ASCUS result (least aggressive)
2. Immediate colposcopy (most aggressive)
3. Repeat Pap smear at 6-month intervals (most common)
4. Human Papillomavirus (HPV) DNA testing (new)
## Routine Pap Smear Screening

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity (CIN 1)</th>
<th>Sensitivity (CIN 2,3)</th>
<th>Specificity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid-based</td>
<td>70% (55-90)</td>
<td>80% (60-95)</td>
<td>95% (92-98)</td>
<td>$30 (17-45)</td>
</tr>
<tr>
<td>Conventional</td>
<td>56% (50-70)</td>
<td>64% (55-75)</td>
<td>95% (92-98)</td>
<td>$17 (13-30)</td>
</tr>
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</table>
Incremental Cost-Effectiveness Ratio

Net increase in health care cost

Net gain in health effect

- measure of “value” for resources
- data for comparative analysis
## Cost-Effectiveness Results
(2-year Liquid-Based Pap)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs (US $)</th>
<th>LE (years)</th>
<th>C/E ($/YLS)</th>
<th>C/E ($/QALY)</th>
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<tbody>
<tr>
<td>No Screen</td>
<td>210</td>
<td>28.6987</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>Ignore ASCUS</td>
<td>1,420</td>
<td>28.7874</td>
<td>13,700</td>
<td>12,300</td>
</tr>
<tr>
<td>HPV Test</td>
<td>1,710</td>
<td>28.7939</td>
<td>44,400</td>
<td>36,100</td>
</tr>
<tr>
<td>Repeat Paps</td>
<td>1,820</td>
<td>28.7937</td>
<td>dominated</td>
<td>dominated</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>1,870</td>
<td>28.7941</td>
<td>905,300</td>
<td>667,300</td>
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Interpreting Cost-Effectiveness Results

The Commission on Macroeconomics and Health recently defined interventions that have a cost-effectiveness ratio less than the GDP per capita as very cost-effective.
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Conclusions

• A strategy of repeat Pap (the most common strategy) is more costly and less effective than HPV testing.

• Immediate colposcopy (considered the most effective strategy) is more costly but provides only hours of life-expectancy benefit compared with HPV testing.

• Cost-effectiveness ratios associated with HPV testing for ASCUS in the context of every two- or three-year screening is attractive compared with other well-accepted public health interventions.
Example 2

Cost-Effectiveness of HPV DNA Testing in the UK, the Netherlands, France, and Italy*

Jane J. Kim, PhD; Thomas C. Wright, MD; Sue J. Goldie, MD, MPH

# Country-Specific Policies

<table>
<thead>
<tr>
<th>Screening Interval</th>
<th>UK</th>
<th>Netherlands</th>
<th>France</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>20-65</td>
<td>30-60</td>
<td>25-65</td>
<td>25-65</td>
</tr>
<tr>
<td>Coverage</td>
<td>84%</td>
<td>80%</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>Equivocal result</td>
<td>Repeat Pap</td>
<td>Repeat Pap</td>
<td>None</td>
<td>Colposcopy</td>
</tr>
</tbody>
</table>

- 3, 5 years
- 5 years
- 3 years
- 3 years
Strategies

1. Pap smear throughout lifetime
   HPV test *to triage women with equivocal results*

2. Pap smear until age 30
   HPV test *instead of Pap smear* after 30

3. Pap smear until age 30
   HPV test *in combination with Pap smear* after 30
# Country-Specific Data

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost*</th>
</tr>
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<tbody>
<tr>
<td>Pap</td>
<td>58 - 80%</td>
<td>93 - 98%</td>
<td>$36 - 94</td>
</tr>
<tr>
<td>HPV Test</td>
<td>88 - 90%</td>
<td>91 - 95%</td>
<td>$47 - 121</td>
</tr>
<tr>
<td>Pap + HPV Test</td>
<td>94 - 96%</td>
<td>88 - 93%</td>
<td>$70 - 146</td>
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* All costs expressed in 2001 international dollars; includes lab, office visit, patient time, and transportation.
## Cost-Effectiveness Ratios*

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<tr>
<td>HPV Test as Triage</td>
<td>6,300</td>
<td>3,400</td>
<td>8,100</td>
<td>10,100</td>
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<tr>
<td>HPV Test Alone (&gt;30)</td>
<td>19,800</td>
<td>21,800</td>
<td>24,200</td>
<td>38,100</td>
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<tr>
<td>HPV Test + Pap (&gt;30)</td>
<td>49,300</td>
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* CE-ratios expressed in I$ per QALY-gained.
** All strategies assume same frequency as status quo policy.
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<tr>
<td>GDP per capita</td>
<td>30,200</td>
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<td>29,100</td>
<td>25,600</td>
</tr>
</tbody>
</table>
Conclusions

• Policies incorporating HPV testing (either for triage of equivocal results or for primary screening in women >30) will provide greater benefit than the status quo.

• At current screening frequencies of every 3 to 5 years, the use of HPV testing as a primary screening test (alone or combined with a Pap smear) has an attractive cost-effectiveness ratio.
Example 3

Cost-Effectiveness of Cervical Cancer Screening in Kenya, India, Peru, South Africa, Thailand*

S. Goldie, L. Gaffikin, J. Goldhaber-Fiebert, A. Gordilla, C. Levin, C. Mahe, T. Wright

Engender Health, International Agency for Research on Cancer, JHPIEGO Corporation, Pan American Health Organization, Program for Appropriate Technology in Health

Sponsored by the Bill & Melinda Gates Foundation

* NEJM (2005)
Proposed Alternatives

- **Simplify Pap Strategy**
  - eliminate diagnostic confirmation step (2\textsuperscript{nd} visit)

- **Visual Inspection Methods (VIA)**
  - acetic acid applied to cervix, inspected by naked eye
  - no lab services required, provides immediate result

- **HPV DNA testing**
  - test for high-risk HPV types in cervical smear
  - minimal training and quality control constraints, self-collected specimens are possible
Strategies

- **Screening test:** Pap, VIA, or HPV
- **Number of clinical contacts:** 1-visit, 2-visit, 3-visit
- **Frequency:** 1x, 2x, 3x, 5-year
- **Optimal target age:** 20 – 50 (5 year intervals)
# Screening Test Performance

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear</td>
<td>63% (33-90)</td>
<td>94% (75-98)</td>
</tr>
<tr>
<td>Visual inspection (VIA)</td>
<td>76% (56-90)</td>
<td>84% (64-98)</td>
</tr>
<tr>
<td>HPV DNA test</td>
<td>88% (58-95)</td>
<td>93% (77-97)</td>
</tr>
</tbody>
</table>
Screening Cost Components

Component Cost (I$ 2000)

Screen Type/Country

- India
- Thailand
- Peru
- Kenya
- S Africa

Staff
Disposable Supplies
Equipment and Lab
Woman (Time)
Woman (Transport)
Results: Thailand

No Screening
Results: Thailand

- 1 Visit HPV, 1X: $170/YLS
- 1 Visit VIA, 1X: $109/YLS
- No Screening
Results: Thailand

- No Screening
- 1 Visit VIA, 1X: $109/YLS
- 1 Visit HPV, 1X: $170/YLS

29 - 33% cancer reduction
Results: Thailand

No Screening

45-49% cancer reduction

1 Visit VIA, 1X
$109/YLS

1 Visit VIA, 2X
$277/YLS

1 Visit HPV, 1X
$170/YLS

1 Visit HPV, 2X
$310/YLS
Results: Thailand

- No Screening: $109/YLS
- 1 Visit VIA, 1X: $277/YLS
- 1 Visit HPV, 1X: $170/YLS
- 1 Visit VIA, 2X: $277/YLS
- 1 Visit HPV, 2X: $310/YLS
- 1 Visit HPV, 3X: $658/YLS

60% cancer reduction
Results: Thailand

- **1 Visit VIA, 1X**: $109/YLS
- **1 Visit HPV, 1X**: $170/YLS
- **1 Visit VIA, 2X**: $277/YLS
- **1 Visit HPV, 2X**: $310/YLS
- **1 Visit HPV, 3X**: $658/YLS
- **2x per lifetime**
- **3x per lifetime**

Discounted Total Lifetime Cost (I$ 2000)
### CE Ratios* for Strategies on Efficient Frontier

Screening and treatment in a single visit

<table>
<thead>
<tr>
<th>Strategy</th>
<th>India</th>
<th>Kenya</th>
<th>Peru</th>
<th>S.Africa</th>
<th>Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIA, 1x lifetime</td>
<td>10</td>
<td>134</td>
<td>124</td>
<td>-</td>
<td>109</td>
</tr>
<tr>
<td>HPV, 1x lifetime</td>
<td>-</td>
<td>-</td>
<td>152</td>
<td>467</td>
<td>170</td>
</tr>
<tr>
<td>VIA, 2x lifetime</td>
<td>91</td>
<td>319</td>
<td>-</td>
<td>-</td>
<td>277</td>
</tr>
<tr>
<td>HPV, 2x lifetime</td>
<td>-</td>
<td>705</td>
<td>453</td>
<td>1,093</td>
<td>310</td>
</tr>
<tr>
<td>VIA, 3x lifetime</td>
<td>268</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV, 3x lifetime</td>
<td>591</td>
<td>1,119</td>
<td>1,145</td>
<td>2,458</td>
<td>658</td>
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CE Ratios* for Strategies on Efficient Frontier Screening and treatment in a single visit

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<tr>
<td>GDP per capita</td>
<td>462</td>
<td>371</td>
<td>2,051</td>
<td>2,620</td>
<td>1,874</td>
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Summary of Results

• Previous recommendations: Pap smear 3x per lifetime at ten year intervals (e.g., age 20, 30, 40)

• Pap smears are consistently both less effective and less cost-effective than VIA and HPV testing.

• Optimal age to screen is between 35-45 years of age; optimal interval is every 5 years, not every 10 years.

• Cervical cancer incidence could decrease up to ~30-50% with 1 or 2 screenings.
Reduction in Lifetime Risk of Cancer

Total Lifetime Costs Per Woman ($)

- **1x Lifetime VIA**
  - $110-$130 per YLS
  - (India, Kenya, Peru, Thailand)

- **3x Lifetime HPV**
  - $590-$2,500 per YLS
  - (India, Kenya, Peru, South Africa, Thailand)

- **2-year Cytology**
  - $34,500-$56,400 per YLS
  - (US)

- **2-year Cytology (Liquid)**
  - $174,200-$452,600 per YLS
  - (US)

- **3- and 5-year Cytology**
  - $6,800-$25,600 per YLS
  - (UK, Netherlands, France, Italy)

- **2-year Cytology (Liquid)**
  - $174,200-$452,600 per YLS
  - (US)

- **1-year Cytology (Liquid)**
  - >$1 million per YLS
  - (US)
For countries with existing screening programs, substitution of annual Pap smears with more sensitive tests (i.e., HPV test or liquid-based Pap) without modification of the screening interval will not be cost-effective;

These options in the context of every 2-3 year screening, would provide comparable or better cancer protection than the status quo and would be reasonably cost-effective.

For countries with limited resources, screening efforts should target women age 35 or older, and efforts should focus on attaining high coverage of single lifetime screening before increasing the frequency of screening.