Effectiveness of a two-stage strategy with HPV testing followed by VIA for cervical cancer screening in a low income setting

Joel FOKOM DOMGUE, MD, MPH
Cameroon

Abstract code: 18094

Disclosure of Interest: None Declared
Background 1

Cervical cancer: commonest and most deadly cancer in women in limited resource settings (LRS)

Worldwide incidence of cervical cancer by 100,000 women (WHO, 2012)
Background 2

- Cervical cytology: effective in rich countries, but financial and technical limitations in LRS
- HPV testing: viable alternative to cytology for cervical cancer screening: more reliable, more sensitive but less specific → overtreatment
- Need for triage HPV-positive women before treatment
- Visual inspection with acetic acid (VIA): simple, affordable test, higher specificity than HPV testing

Joel FOKOM DOMGUE

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World Health Organization (WHO, 2013) advocated a sequential testing (HPV test followed by VIA) for cervical cancer screening. Accuracy of this strategy for primary screening is not known. 

The aim of this study: to assess the effectiveness of this two-stage screening strategy.
Methods 1

- Study population
  - Women aged 30 – 65 years old (y.o.) in Cameroon
  - Non pregnant, with a cervix, willing to participate

- Screening procedure
  - Education about cervical cancer and how to perform self-sampling for HPV testing
  - Samples analysed using the PCR system of the Abbott RealTime High Risk HPV assay
  - VIA followed by four-quadrant biopsies and ECC in all HPV-positives and a random sample of HPV-negatives (no colposcopy)
Methods 2

- Screening procedure (cont’d)
  • Women with CIN grade 2 or worse treated (cryotherapy, conisation or hysterectomy as indicated)
  • Those with <CIN2 counselled and advised to repeat the HPV testing after 24 months

- Definition of disease and positive tests
  • Disease threshold: CIN grade 2 or worse (CIN2+)
  • HPV positivity: presence of at least one high-risk HPV type in the specimen (as specified by the manufacturer)
  • VIA positivity: according to IARC guidelines
Results 1

- Patients characteristics
  • Total number of women: 540
  • Low socio-economic and educational level +++
  • Median age: 41 y.o.
  • Age at first sexual intercourse: 17 y.o.

- HPV prevalence
  • Invalid HPV tests: 11 (excluded from the analyses)
  • HPV negative results: 383 women
  • HPV prevalence: 27.0%
### Distribution of biopsy results according to the HPV and VIA status of women

<table>
<thead>
<tr>
<th>Biopsy results*</th>
<th>HPV+ N=106 (50.3%)</th>
<th>HPV- N=102 (49.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIA+ n=16 (7.7%)</td>
<td>VIA- n=90 (43.3%)</td>
</tr>
<tr>
<td></td>
<td>VIA+ n=7 (3.4%)</td>
<td>VIA- n=95 (45.7%)</td>
</tr>
<tr>
<td>Negative (n=188)</td>
<td>9 (4.8)</td>
<td>79 (42.0)</td>
</tr>
<tr>
<td>CIN 1 (n=9)</td>
<td>3 (33.3)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>CIN 2 (n=5)</td>
<td>3 (60.0)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>CIN 3 (n=4)</td>
<td>1 (25.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Cancers (n=2)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>CIN2+ (n=11)</td>
<td>4 (36.4)</td>
<td>7 (63.6)</td>
</tr>
</tbody>
</table>

*: A total of 208 women with valid VIA and biopsy results among those who were recalled for further assessment.
### Results 3

**VIA performance for CIN2+ detection with respect to the HPV status of women**

<table>
<thead>
<tr>
<th>HPV status</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>36.4 (15.2-64.2)</td>
<td>87.4 (79.2-92.6)</td>
<td>25.0 (10.2-49.5)</td>
<td>92.2 (84.8-96.2)</td>
</tr>
<tr>
<td>(N=106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-</td>
<td>not calculable*</td>
<td>93.1 (86.5-96.6)</td>
<td>00.0 (00.0-35.4)</td>
<td>100.0 (96.1-100.0)</td>
</tr>
<tr>
<td>(N=102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total **</td>
<td>36.4 (15.2-64.6)</td>
<td>90.4 (85.4-93.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>(N=208)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: All CIN2+ were HPV positive. **: all women with interpretable biopsy and VIA results
NA: not applicable
## Results 4

Estimated performance for CIN2+ detection of HPV testing alone and sequential testing (HPV testing followed by VIA)*

<table>
<thead>
<tr>
<th></th>
<th>HPV testing alone</th>
<th>HPV testing followed by VIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity % (95% CI)</strong></td>
<td>100.0 (79.6-100.0)</td>
<td>33.3 (15.2-58.3)</td>
</tr>
<tr>
<td><strong>Specificity % (95% CI)</strong></td>
<td>74.5 (70.6-78.1)</td>
<td>96.7 (94.8-97.9)</td>
</tr>
<tr>
<td><strong>PPV % (95% CI)</strong></td>
<td>10.3 (6.3-16.3)</td>
<td>22.7 (10.1-43.4)</td>
</tr>
<tr>
<td><strong>NPV % (95% CI)</strong></td>
<td>100.0 (99.0-100.0)</td>
<td>98.0 (96.4-99.9)</td>
</tr>
</tbody>
</table>

*: after adjustment for verification bias

- 66%

+22%
Conclusion

- A two-stage screening strategy with HPV testing followed by VIA, improves the specificity of cervical cancer screening, but at the cost of an important loss of sensitivity

- Ways to improve VIA (magnification?, positivity criteria?) or other triage tests (VILI?, E6/E7 detection?) are warranted to increase the positive predictive value of an HPV-based screening strategy without markedly impairing its sensitivity
Acknowledgements

- The National Cancer Control Committee, Cameroon
- The Department of Obstetrics and Gynecology, Geneva University Hospitals, Switzerland
- The Faculty of Medicine and Biomedical Sciences, Cameroon

Thank you for your attention
Why a so low VIA sensitivity?

• In accordance with some studies:
  • Labani et al., 2014 (4.656 women, screening by nurses, India) Se: 21.9%
  • Gravitt et al., 2010 (population-based study, JHPIEGO, India) Se: 26.3%
  • Slawson el al., 1992 (USA) Se: 29%

• Strengths of our study: bias minimised
  • Use of histology alone as gold standard (unlike most studies)
  • 4-quadrant Biopsies and ECC taken in women irrespective of VIA results and without colposcopy (imperfect gold standard)
Why a so low VIA sensitivity?

• Strength of our study: bias minimised (cont’d)
  • Biopsies interpreted by two experienced pathologists blinded to both HPV and VIA results (few misclassification errors)
  • VIA performed by two well-trained and experienced gynecologists
  • Study performed under field conditions (unlike most studies performed as part of demonstration projects)

→ accuracy measures obtained here are definitely more accurate
Why were both cancers VIA negative?

Possible explanations:

• Inability of screeners to properly identify the SCJ in some women, and to inadvertently classify as negative, VIA that should have been considered inconclusive

• Endocervical localization of the cancer cases (adenocarcinomas)

→ importance of performing ECC in all women in studies on VIA accuracy, no matter the VIA results