MULTICENTRIC STUDY OF CERVICAL CANCER SCREENING AND TRIAGE WITH HUMAN PAPILLOMAVIRUS TESTING

THE ESTAMPA STUDY

Maribel Almonte
International Agency for Research on Cancer
Lyon, France
**THE ESTAMPA STUDY**

Multicentric study of cervical cancer screening with HPV testing and assessment of triage methods in Latin America

**AIMS:**

To investigate the performance of emerging cervical cancer screening and triage techniques among women 30 years and older

To evaluate the feasibility of different approaches for implementation of organised HPV-based screening programmes
The ESTAMPA Study

- ~50,000 women aged 30-64 years screened with HPV testing (and Pap)
- HPV positives referred to colposcopy
  - 2-3 biopsies of observed lesions
- HPV positives with <CIN2 recall at 18m
  - HPV test, no other test
  - HPV positives referred to colposcopy
- CIN2+ treated with LLETZ

Study Outcomes

✓ CIN3+ detected at entry
**The ESTAMPA Study**

- **Triage tests:** Pap, LBC, p16/ki67 dual-stained cytology, VIA, HPV genotyping, methylation, and triage strategies (e.g., short-term repeat HPV test)

- Specimens collected at initial screening used for triage evaluation simulating reflex-testing whenever possible

- Triage tests except Pap not used for clinical management

- Testing done locally, in regional hubs or in expert centres outside the region

- Not all tests/strategies evaluated in all centres (e.g., VIA: Bolivia, Colombia, Honduras, Paraguay, Peru; HPV 16/18 genotyping: centres that used COBAS)
ESTAMPA STUDY POPULATION AS OF APRIL 2020

- 39,829 women with HPV results
  - HPV positive: n=5,605 (14%)
    - Colposcopy: n=5,105 (91%)
      - With Pap results: n=4,661
        - With 2nd HPV results: n=4,026
        - With HPV VIA results: n=1,994
        - With HPV16/18 results: n=1,605

11 study centres
5 study centres
12 study centres
5 study centres
**Pap as Triage of HPV Positives**

- Pap was done at all study centres
  - HPV testing not yet included in national cervical screening guidelines or not yet implemented
  - HPV status was unknown when smears arrived at laboratories

- Laboratories were classified by:
  - Type of organization: public or private
  - Pap interpretation protocol: cytotechnician interpreting all followed by pathologist confirming abnormal Paps or pathologists interpreting all preparations

- In one centre, only Paps from HPV positives were prepared and interpreted
  - But as a public health laboratory, ESTAMPA smears were prepared and interpreter within a larger number of smears provided by many health clinics
VALIDATION OF THE 8-HPV TYPE ONCOE6/E7 CERVICAL TEST

HYPOTHESIS

Adding detection of other high-risk HPV types oncoproteins might increase the sensitivity of the 16/18 oncoprotein test (OncoE6, Arbor Vita) without losing much specificity

➢ Under an NCI Affordable Cancer Technologies Award we teamed-up with Arbor Vita to develop/validate a new oncoprotein test

OBJECTIVE

➢ Develop and validate the 8-HPV Type OncoE6/E7 for CIN3+ and cancer detection within the ESTAMPA study (convenient sub-sample)
VALIDATION OF THE 8-HPV TYPE ONCOE6/E7 CERVICAL TEST

Convenient sample of 872 women

<table>
<thead>
<tr>
<th>STATUS AT INITIAL SCREENING</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>HPV Negative</td>
<td>123</td>
</tr>
<tr>
<td>Colposcopy Negative</td>
<td>124</td>
</tr>
<tr>
<td>Biopsy Negative</td>
<td>125</td>
</tr>
<tr>
<td>CIN1</td>
<td>129</td>
</tr>
<tr>
<td>CIN2</td>
<td>120</td>
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<tr>
<td>CIN3</td>
<td>153</td>
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<tr>
<td>Cancer</td>
<td>98</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>872</strong></td>
</tr>
</tbody>
</table>

Screening Visit

- 50,000 Women 30-64
- HPV Negative
  - Exit Routine Recall
- HPV Positive, Pap Abnormal
  - VIA
  - COLPOSCOPY VISIT
  - DRY SWAB
  - HPV
  - PC
  - HPV POSITIVE, Pap ABNORMAL
  - Blood
  - CIN3+

International Agency for Research on Cancer

World Health Organization
CONCLUSIONS AND NEXT STEPS

• Results from evaluations of Pap, VIA, Repeat HPV test and HPV16/18 as triage for HPV positives for CIN3+ detection:
  ➢ Pap and HPV16/18 having limited sensitivity ≤ 60%, while the repeat HPV testing strategy and VIA show moderate sensitivity (~86%)
    ▪ Pap sensitivity was significantly higher in the laboratory with smears only from HPV positives
    ▪ Adding Pap ASCUS+ to triage by HPV non-16/18 positives increased the sensitivity by ~10-15%
    ▪ VIA high sensitivity possibly due to examiners with large expertise
  ➢ Pap had the highest specificity (~85%) followed by HPV16/18 (~77%), while the other two had limited specificity of ≤50%

• The new 8-HPV Type OncoE6/E7 Test preliminary validation showed limited sensitivity but high specificity for individual oncoprotein HPV types
  – Six HPV oncoproteins (16, 18, 31, 33, 45, 52) contributed to reach overall test sensitivity for CIN3+ and cancer threshold; HPV oncoproteins 35 and 58 not relevant in this population
CONCLUSIONS AND NEXT STEPS

➢ No single triage test/strategy offers a final answer yet, but further evaluation is ongoing/planning:
  ▪ Pap when HPV status is known
  ▪ VIA at screening clinic and at colposcopy to account for potential correlation between VIA and colposcopy results
  ▪ Dual-stained cytology (p16/ki67), HPV full genotyping & methylation
  ▪ Colposcopy as triage of HPV positives, using 18m visit to confirm disease

➢ Using a convenient sample, the first results of the new 8-HPV Type OncoE6/E7 showed limited sensitivity (60%) but high single oncoprotein specificity (>95%) to detect CIN3+
  ▪ 93% negative in HPV negatives (no colposcopy), 79% in negative colposcopy (no biopsy), 76% in histology<CIN2
  ▪ A further refined version of the test will be evaluated in the ESTAMPA screening population: stand alone and triage

• All screening techniques/strategies will be evaluated alone/combination using HSIL (main study outcome under LAST), including cases detected at initial and 18m screening visits
ESTAMPA INVESTIGATORS

- IARC: M Almonte (PI), A Baena, ML Rol, T Ramirez
- Argentina: MA Picconi, M Rodriguez De la Pena, J Mural, A Moreno, S Tatti, L Fleider
- Bolivia: C Teran, B Flores, O Lora, J Penaranda
- Colombia: C Wiesner, R Murillo, GI Sanchez, M Celis, Y Salgado, S Martinez
- Costa Rica: A Calderon, E Gonzalez, D Guillen, R Herrero (PI), C Sosa
- Honduras: A Ferrera, J Figueroa, Y Cabrera, B Salgado
- Mexico: A Cruz, P Hernandez
- Uruguay: G Rodriguez, A Beracochea, N Perez, B Caserta, L Garcia
- Paraguay: L Mendoza, E Kasamatsu, M Ortega, MI Rodriguez, V Villagra
- Peru: G Venegas, Y Bellido, J Arias-Stella, F Doimi
- Other: P Adsul (UNM, USA), S Arrossi (ICS, Argentina), T Darragh (UCSF, USA), S Luciani (PAHO), N Broutet (HRP/WHO), R Murillo (U Javeriana, Colombia), AP Ortiz & M Soto (Puerto Rico)