Primary HPV Testing in a Canadian Organized Cervical Cancer Screening Program

A Randomized Controlled Trial
(funded by the Canadian Institutes of Health Research)
ISRCTN79347302

HPV FOCAL Study
Pap Smear Screening: The BC Experience

- Pap smear testing commenced in British Columbia (BC) in 1949
- Single Computer Database for all Pap Smears since 1983 – linked to Cancer Registry
- Single Cytology Laboratory for all BC (1.52 million women aged 20-69)
- Interprets ~550,000 smears annually.

Age-standardized rate per 100,000

Year of death

Analysis of Cervical Cancer Cases (failures) for BC in 2002

Invasive Cervical Cancer 165 (100%)

- Under Age 30: 9
  - Never screened: 23
  - Diagnosed at first screen: 20
  - Not screened in 7 years prior to diagnosis: 40
  - HSIL identified within 7 years of diagnosis: 10

- Over Age 30: 156 (95%)
  - Screened: 133 (81%)
  - No cancer detected at first screen: 113 (68%)
  - Screened in 7 years prior to diagnosis: 73 (44%)
  - Screened and no HSIL diagnosed: 63 (38%)
FOCAL Trial Objectives

To establish the efficacy of HPV DNA testing as a stand-alone screening test, followed by cytology triage (LBC) for HPV positive women:

- Appropriate screening interval for HPV negative women
- Cost-effectiveness of HPV testing for primary screening within the context of an organized Canadian cervical cancer screening program
**Trial Arms**

**Control Arm** – Initial LBC sample: Cytology testing. Negatives screened again in 2 years (cytology testing) and 4 years (HPV and Cytology testing).

**Intervention Arm** – Initial LBC sample: HPV DNA Testing (cytology triage of HPV positives). HPV negative women screened again in 4 years (HPV and cytology testing, to compare to Control arm at 4 years).

**Safety-Check Arm** – Initial LBC sample: HPV DNA testing (cytology triage of HPV positives). HPV negative women screened again in 2 years (with cytology, to compare to Control arm at 2 years).
Methods

Initially blinded, randomized controlled, three arm trial

• Sample size: 11,000 per arm - 33,000 total

• Population: women aged 25 to 65 years of age. Two centres: Vancouver & Victoria

• Initial screen followed by second or third screening round (depending on arm) (2-4 yr participation)
Trial Organisation

• Study Centre in BC Cancer Agency which manages the Cytology Laboratory, Cervical Cancer Screening Program (CCSP) and Provincial Cancer Registry.
• Family Physicians (FP) participating in trial were recruited through the CCSP.
• Patients are individually consented by FP’s supported by study centre.
Important Trial Design Elements

- LBC collection utilized for cytology and HPV assessment
- All testing based on a single specimen (no patient recall)
- For subjects randomized to initial HPV with a positive result subsequent cytology interpretation is performed with knowledge of HPV status.
- Standardized colposcopy performed at 2 centres
- Blinded pathology interpretation
- Inclusion of a two year Safety-Check arm
Study Population
- Age Distribution

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>% of Cohort</th>
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<tbody>
<tr>
<td>25-29</td>
<td>7.63%</td>
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<tr>
<td>30-34</td>
<td>9.06%</td>
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<tr>
<td>35-39</td>
<td>13.89%</td>
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<tr>
<td>40-44</td>
<td>15.97%</td>
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<tr>
<td>45-49</td>
<td>17.35%</td>
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<tr>
<td>50-54</td>
<td>14.94%</td>
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<tr>
<td>55-59</td>
<td>12.47%</td>
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<tr>
<td>60+</td>
<td>8.69%</td>
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Epidemiological Info (6305 FOCAL Participants)

- Mean age of study participant (in all arms): 46

Top 3 Reported
- (ethnicity): British 55%; Western European 16.3%; Other 14.7%
- : Married 65.4%; Single 14.2%; Divorced 9.8%
- : University Grad 47%; Trade certificate/College 30%; High school complete 14.3%
Other variables:

- Employment: 78.4% currently working
- Smoking History: Ever smoked 39.5%; Mean age started smoking: 16.5 yrs  
  Still smoking: 18.7%
- Sexual History: Mean age of sexual debut 18.8 yrs  
  Lifetime no. of male sexual partners: 2-5 (34.7%); 6-10 (23.1%); 1 (21.3%)
Initial Round – Screening Results

As of 7th March 2010, screen available for 11,838 subjects

Control Arm:

- 3769/3938 (95.7%) cytology negative, 52 (1.3%) ASCUS with 39 HPV-
- Referred for colposcopy – 130 (3.3%)

Combined Intervention and Safety Check Arms:

- 7290/7893 (92.4%) HPV DNA Neg, 365 (4.6%) with Negative Cytology
- Referred for colposcopy – 238 (3.0%)
Control Arm
- Screen Positivity Rates by Age

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<td>30-34</td>
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<td>35-39</td>
<td>2.6%</td>
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<td>2.5%</td>
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<td>1.1%</td>
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<tr>
<td>60+</td>
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Combined Intervention/Safety Arms
- Screen Positivity Rates by Age

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Initial Round – Pathology Results

Control Arm:
• Results available on 112 subjects
• PPV’s Cin3+: 12% (13), Cin2+: 32% (36)
• Estimated Cin3+ rate per subject: 3.8/1,000
• Estimated Cin2+ rate per subject: 10.6/1,000

Combined Intervention and Safety Check Arms:
• Results available on 213 subjects
• PPV’s Cin3+: 18% (38), Cin2: 38% (81)
• Estimated Cin3+ rate per subject: 5.4/1,000
• Estimated Cin2+ rate per subject: 11.5/1,000
Current Trial Status

- Full recruitment expected by December 2011
- Final analysis anticipated 2016
FOCAL Trial Investigators and Collaborators

Vancouver
Dr. Kathy Ceballos
Dr. Andrew Coldman
Darrel Cook
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Dr. Mel Krajden
Dr. Ruth Martin
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Laurie Smith
Dr. Gavin Stuart
Dr. Dirk van Niekerk

Montreal
Dr. Eduardo Franco

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority
HPV Testing

HPV positive

HPV negative

Cytology Testing

HPV positive and ≥ASC-US

HPV positive and cytology negative

Colposcopy

Treatment based on colpo results

6 month repeat protocol

48 month screen with cytology and HPV testing

4-Year Intervention Arm