CERVICAL CANCER SCREENING SCENARIOS for pan-Canadian Cervical Screening Initiative

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Acknowledgements

• Anthony Miller
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Objectives

• Target setting: incidence rate
  • What will the incidence rate be in the future if we continue with the status quo?
  • What would the incidence rate be if we increased screening participation to 80%? Altered our screening programs? Introduced primary HPV DNA testing?

• If we switch to primary HPV DNA testing:
  • What are the health outcomes?
  • How much will it cost?
  • Is it cost-effective in Canada compared to cytology?
## Assumptions

<table>
<thead>
<tr>
<th>Screening Inputs</th>
<th>Baseline assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment period</td>
<td>2015 onward</td>
</tr>
<tr>
<td>Recruitment age for PAP screening</td>
<td>21-69 years old (25, 30-69)</td>
</tr>
<tr>
<td>Interval years between initial rescreen</td>
<td>3 (5, 10)</td>
</tr>
<tr>
<td>Screening participation</td>
<td>70%</td>
</tr>
<tr>
<td>Screening modalities</td>
<td>Pap or HPV DNA test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccination Inputs</th>
<th>Baseline assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Vaccine deployment year</td>
<td>2007</td>
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<tr>
<td>Vaccine type</td>
<td>Quadrivalent</td>
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<tr>
<td>Vaccination coverage</td>
<td>70% (50%, 90%)</td>
</tr>
<tr>
<td>Proportion protected</td>
<td>100%</td>
</tr>
<tr>
<td>Degree of protection</td>
<td>100%</td>
</tr>
</tbody>
</table>
Incidence per 100,000

Triennial PAP 21-69: 70% ppt: No vacc

*non-age-standardized
Incidence per 100,000

 STATUS QUO + vaccination

*non-age-standardized
Incidence of cervical cancer in 2037

If unspecified, age = 21-69
and interval = x 3 years

*non-age-standardized
Mortality per 100,000

Triennial PAP 21-69: 70% ppt: No vacc

*non-age-standardized
Mortality per 100,000

- **Triennial PAP 21-69: 70% ppt: No vacc**
- **Triennial PAP 21-69: 70% ppt: (70%V)**

*non-age-standardized*
Mortality per 100,000

- Triennial PAP 21-69: 70% ppt: No vacc
- Triennial PAP 21-69: 70% ppt: (70%V)
- Triennial PAP 21-69: 70% ppt (90% V)

*non-age-standardized

Herd immunity
Mortality per 100,000 in 2037

If unspecified, age = 21-69 and interval = x 3 years

- Triennial PAP 21-69: 70% ppt (70%V)
- Triennial PAP 25-69: 70% ppt (70%V)
- Triennial PAP 30-69: 70% ppt (70%V)
- Triennial PAP 21-69: 80% ppt: No vacc
- PAP 21-69 every 5 yrs: 70% ppt (70%V)
- Triennial PAP 21-69: 70% ppt: No vacc
- No vaccination or screening

Mortality (per 100,000)
Incremental Cost-Effectiveness Ratios (ICERs)

- **Reject** (dominated)
- **Consider** (more expensive but saves more lives)
- **Consider** (less expensive but saves fewer lives)
- **Accept** (dominant)
No vaccine, no screening

Vaccine, screen x 3, 21-69

Vaccine, screen x 5 years

Vaccine, screen x 10

Vaccine, screen 30-69

Vaccine, screen 25-69

*3% discount rate
## Cost-effectiveness ratios*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Total Cost (in '000,000's)</th>
<th>Total QALYs (in '000's)</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccine, no screening</td>
<td>$12,016</td>
<td>998,016</td>
<td>-</td>
</tr>
<tr>
<td>Vaccine, no screening</td>
<td>$11,840</td>
<td>998,253</td>
<td>DOMINANT</td>
</tr>
<tr>
<td>Vaccine, cytology 21-69 x 10 years</td>
<td>$19,811</td>
<td>998,390</td>
<td>$21,000</td>
</tr>
<tr>
<td>Vaccine, cytology 21-69 x 5 years</td>
<td>$25,421</td>
<td>998,448</td>
<td>$31,000</td>
</tr>
<tr>
<td>Vaccine, cytology 30-69 x 3 years</td>
<td>$29,867</td>
<td>998,482</td>
<td>$38,000</td>
</tr>
<tr>
<td>Vaccine, cytology 25-69 x 3 years</td>
<td>$31,438</td>
<td>998,488</td>
<td>$41,000</td>
</tr>
<tr>
<td>Vaccine, cytology 21-69 x 3 years</td>
<td>$33,027</td>
<td>998,491</td>
<td>$44,000</td>
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<tr>
<td>No vaccine, cytology 21-69 x 3 years</td>
<td>$35,572</td>
<td>998,383</td>
<td>$64,000</td>
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</tbody>
</table>

*3% discount rate applied*
Average annual cost (2015-2025)

- **No vaccination or screening**
- **No screening: 70%V**
- **PAP 21-69 every 10 years: 70% ppt (70%V)**
- **PAP 21-69 every 5 yrs: 70% ppt: (70%V)**
- **Triennial PAP 30-69: 70% ppt (70% V)**
- **Triennial PAP 25-69: 70%ppt (70% V)**
- **Triennial PAP 21-69: 70% ppt (70%V)**
- **Triennial PAP 21-69: 70% ppt (50%V)**
- **Triennial PAP 21-69: 70% ppt (90% V)**
- **Triennial PAP 21-69: 70% ppt: No vacc**

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- Cost of HPV vaccination
- Screening cost
- Cost non-cancer treatment (excluding warts)
- Cost of treating warts
- Cost of cancer treatment
Average annual screening cytology count (2015-2025)

- PAP 21-69 every 10 years: 70% ppt (70%V)
- PAP 21-69 every 5 yrs: 70% ppt: (70%V)
- Triennial PAP 30-69: 70% ppt (70% V)
- Triennial PAP 25-69: 70%ppt (70% V)
- Triennial PAP 21-69: 70% ppt: (50%V)
- Triennial PAP 21-69: 70% ppt (70%V)
- Triennial PAP 21-69: 70% ppt (90% V)
Average annual colposcopy count (2015-2025)

- No vaccination or screening
- No screening: 70%V
- PAP 21-69 every 10 years: 70% ppt (70%V)
- PAP 21-69 every 5 yrs: 70% ppt: (70%V)
- Triennial PAP 30-69: 70% ppt (70% V)
- Triennial PAP 25-69: 70%ppt (70% V)
- Triennial PAP 21-69: 70% ppt (90% V)
- Triennial PAP 21-69: 70% ppt (70%V)
- Triennial PAP 21-69: 70% ppt (50%V)
- Triennial PAP 21-69: 70% ppt: No vacc
Mortality per 100,000

*Not comparable to cytology results, but comparable to each other

No difference in mortality

- HPV DNA 30-69 every 5 years (70%V)
- HPV DNA 25-69 every 5 years (70%V)

*non-age-standardized
Considerations

• Due to little empirical data on sexual behaviour, long-term data on vaccine efficacy, and existing questions around the development and progression of lesions and HPV-related cancers, higher degree of parameter uncertainty

• Uncertainty around future performance of cytology due to reduced prevalence

• Due to very low prevalence of cervical cancer, estimates are subject to higher degree of Monte Carlo uncertainty
Conclusions

• By 2037, an incidence of 6 per 100,000 is projected, assuming that screening programs remains unchanged (70% cytology x 3 years in 21-69).
• Increasing the start age of screening to 25 or 30 has little impact on cervical cancer incidence or mortality and generates cost-savings.
• Increasing the screening interval to every 5 or 10 years is more cost-effective, however is associated with increased mortality.
Next Steps

• Primary HPV DNA testing
  • 21-29 : cytology, 30-69 HPV
  • 21-34: cytology, 35-69 HPV
  • HPV only with cytology triage

• Different screening strategies in vaccinated vs unvaccinated cohorts

• Vaccinating boys

• Oropharyngeal, vulvar, vaginal and anal cancers

• Vaccine effectiveness or longevity
Knowledge fuels enhanced decision-making

For health or policy leaders, decision-makers, or researchers, knowledge is power — it fuels important functions such as decision-making, planning, and budgeting. When faced with the challenge of how to invest scarce health-care dollars, sound knowledge is critical.

The Cancer Risk Management Model is a web-based, dynamic micro-simulation tool that helps guide cancer control decision-making

Whether you are involved in screening, diagnosis, treatment, palliative or end-of-life care, now you can strengthen your decision-making efforts with customized cancer control projections. This population-based model helps you assess the cost/benefit of various cancer control strategies by projecting their impact on Canada’s population health and economics — at any point in time, and for all provinces and territories — via a web-based platform.

Solid Input = Solid output = Sound decision-making, planning, and budgeting

The Canadian Partnership Against Cancer developed the model to support the Canadian cancer control strategy and the model is available for policy-makers, researchers, and planners in government ministries and public sector organizations. Drawing on a solid
Appendix
Prevalence of HPV 16/18

Number of infected females

- **No vaccination**
- **70% vaccinated**

POP (lifetime)
Prevalence of HPV 16/18

Number of infected females

POP (lifetime)
Incidence of cervical cancer in 2037 with varying vaccination rates

<table>
<thead>
<tr>
<th>Vaccination Rate</th>
<th>Incidence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine, Pap 21-69, 50% ppt</td>
<td>6.3</td>
</tr>
<tr>
<td>Vaccine, Pap 21-69, 70% ppt</td>
<td>5.8</td>
</tr>
<tr>
<td>Vaccine, Pap 21-69, 90% ppt</td>
<td>5.5</td>
</tr>
</tbody>
</table>
Mortality (per 100,000)

Triennial PAP 21-69: 70% ppt (90% V)
Triennial PAP 21-69: 70% ppt (70%V)
Triennial PAP 25-69: 70% ppt (70% V)
Triennial PAP 21-69: 70% ppt (50%V)
Triennial PAP 30-69: 70% ppt (70% V)
Triennial PAP 21-69: 80% ppt: No vacc
PAP 21-69 every 5 yrs: 70% ppt: (70%V)
Triennial PAP 21-69: 70% ppt: No vacc

*non-age-standardized
Mortality per 100,000 in 2037

- Vaccine, Pap x 10 years: 3.1
- Vaccine, Pap x 5 years: 3.0
- No vaccine, Pap 21-69: 2.8
- Vaccine, Pap 21-69, 70% ppt: 2.6
- Vaccine, Pap 25-69: 2.6
- Vaccine, Pap 21-69, 90% ppt: 2.6
- No-vaccine, Pap 30-69: 2.5
- No-vaccine, Pap 21-69: 2.4

*non-age-standardized
Lifetime cost and QALY

* 3% discount
Figure 1: Primary cervical screening with HPV testing (women 30-65)\(^2\) (adapted from Cuzick et al. 2008 (13)).

HPV DNA testing in women 30-65 years of age

- **Negative**
  - Repeat HPV DNA testing at 5 year intervals until age 65

- **Positive**
  - Cytology test
    - **Negative**
    - Repeat HPV testing at 12 months
      - **Negative**
      - **Positive**
  - **Positive (≥ASCUS)**
    - Colposcopy
      - **Positive**

## Cost of screening test

<table>
<thead>
<tr>
<th></th>
<th>Cytology</th>
<th>HPV DNA test</th>
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</thead>
<tbody>
<tr>
<td>Family physician visit</td>
<td>$67.82</td>
<td>$67.82</td>
</tr>
<tr>
<td>Tray fee</td>
<td>$10.99</td>
<td>$10.99</td>
</tr>
<tr>
<td>Lab cost - tech</td>
<td>$3.12</td>
<td>$3.12</td>
</tr>
<tr>
<td>Lab cost - pathologist</td>
<td>$93.24</td>
<td>$93.24</td>
</tr>
<tr>
<td>Test</td>
<td>n/a</td>
<td>$85.67</td>
</tr>
<tr>
<td>Total</td>
<td>$175.17</td>
<td>$260.85</td>
</tr>
<tr>
<td>Parameter: Cervical cancer screening and pre-cancer treatment costs</td>
<td>Cytology (PAP) screen</td>
<td>Cytology (PAP) reassessment</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Base case scenario (default)</td>
<td>175.17</td>
<td>141.05</td>
</tr>
<tr>
<td>Vaccine types</td>
<td>Quadrivalent vaccination</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>Scenario</td>
<td>Base case scenario (default)</td>
<td>500</td>
</tr>
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</table>
Parameter: Sensitivity and specificity of cytology

<table>
<thead>
<tr>
<th>Cytology type - Conventional cytology</th>
<th>Scenario - Base case scenario (default)</th>
<th>Cytology result</th>
<th>Progression status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All cells normal</td>
</tr>
<tr>
<td>Conventional cytology</td>
<td>Base case scenario (default)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical squamous cells of undetermined significance (ASC-US)</td>
<td>97</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Atypical squamous cells, maybe high grade lesion (ASC-H)</td>
<td>97</td>
<td>1.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Low grade squamous intraepithelial lesion (CIN1)</td>
<td>41</td>
<td>12</td>
<td>2.83</td>
</tr>
<tr>
<td>High grade squamous intraepithelial lesion (CIN2 or CIN3)</td>
<td>20</td>
<td>5</td>
<td>4.14</td>
</tr>
<tr>
<td>Atypical glandular cells (AGC)</td>
<td>20</td>
<td>5</td>
<td>2.65</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (AIS)</td>
<td>131.86</td>
<td>9.74</td>
<td>2.26</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>0</td>
<td>6</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Parameter: Sensitivity and specificity of colposcopy

<table>
<thead>
<tr>
<th>Progression status</th>
<th>Less than LSIL</th>
<th>LSIL</th>
<th>CIN2 or CIN3: lesion satisfactory and visible</th>
<th>CIN2 or CIN3: lesion not satisfactory</th>
<th>AIS</th>
<th>Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection and no lesion</td>
<td>88</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infected but no lesion</td>
<td>88</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Warts</td>
<td>88</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CIN1</td>
<td>22</td>
<td>62</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CIN2</td>
<td>8</td>
<td>10</td>
<td>47</td>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CIN3</td>
<td>8</td>
<td>10</td>
<td>18</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (AIS)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Parameter: Sensitivity and specificity of HPV DNA test

<table>
<thead>
<tr>
<th>HPV_INFECTION</th>
<th>No infection and no lesion</th>
<th>Infected but no lesion</th>
<th>Warts</th>
<th>CIN1</th>
<th>CIN2</th>
<th>CIN3</th>
<th>Adenocarcinoma in situ (AIS)</th>
<th>Cervical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not infected with HPV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infected with HPV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
TREATMENT PATHWAYS
Stage 1B1

Fertility is an issue

Age: <40 40% 40+ 0%

Specialist Diagnostic Workup

Parameter for Fertility:
For women < age: 40

Cure rate 85%

Surgery

0%
Cones and nodes
0%
Laparoscopic
0%
Laparotomy

100%
Radical trachelectomy & nodes
30%
Laparoscopy
10%
Laparotomy

Surveillance

5%
No recurrence
Cured

5%
Local recurrence
Go to LR1

85%
No radiation
Surveillance

100%

85%
No recurrence
Go to LR2

10%
Local Recurrence
Go to DR

15%
Distant Recurrence
Go to DR

Higher Risk Factors (cure rate 70%)

Radical hysterectomy and nodes (sentinel nodes)
20%
Laparoscopy
80%
Laparotomy

5%
Radical hysterectomy and nodes (sentinel nodes)

100%
Hysterectomy and nodes (sentinel nodes)
5%

80%
Laparoscopy
20%
Laparotomy

Hysterectomy and nodes (sentinel nodes)

Stage 2

Specialist Diagnostic Workup

100%

Radiation +/- chemo

85%
Chemoradiation

10%
Ext + Int Radiation

5%
Ext + Int Radiation with Extended field +/- chemo

30%
Distant Recurrence

55%
No recurrence

15%
Local Recurrence

100%
Surveillance

100%
Cured

Go to LR5

Go to DR
Stage 3 (A+B)

Surgery
- Ureteric or colonic obstruction
- Ureteric obstruction
- Colonic obstruction/fistula (colostomy)

Radiation + chemo
- Chemoradiation
- Ext + Int Radiation
- Ext + Int Radiation with Extended field + chemo

Events handled by survivors
- No recurrence
- Local Recurrence
- Distant Recurrence

Supportive Care (see Stage 4b)

Surveillance

Cured

Go to LR6

Go to DR
**Stage 4A**

- **Surgery**
  - Lymphatic or colonic obstruction
  - Genitourinary obstruction

- **Radiation + Chemotherapy**
  - Chemoradiation
  - Bladder + Int Radiation
  - Bladder + Int Radiation with extended field + chemo

- **Events handled by survival curves**
  - No recurrence
  - Local Recurrence: Go to LRT
  - Distant Recurrence: Go to DR

**Note:**
- For those with ureteric obstruction, 20% are assumed to receive stents and 80% are assumed to receive nephrostomy; we may further simplify this to assume 100% nephrostomy as the cost information was only provided for it, not stents.

**Note for the arrow coming directly from Local Recurrence box:**
- There is no Surveillance box from Local recurrence to Supportive Care (direct line) because follow-up is managed through supportive care and end of life care.
- There will not be Specialist Diagnostic Workup indicated in DR sheet (i.e., a Local Recurrence event leads directly to the treatment) since there is no Distant Recurrence event arising from local recurrence for this path.
Stage 4B

*Note:
- Percents in the Palliative care box may not add to 100% as some patients may get more than one of these treatments (for simplicity, these % are used to obtain a cost for the palliative care box, they are not used in the flow of patients in the overall treatment diagram)
Distant recurrence

Specialist Diagnostic Workup

50% Palliative Care
- 50% Palliative radiotherapy
- 83% Chemotherapy

40% Supportive care only

100% End of life care

Death

*Note:
- Percents in the Palliative care box may not add to 100% as some patients may get both treatments (for simplicity, these % are used to obtain a cost for the palliative care box, they are not used in the flow of patients in the overall treatment diagram)