Epidemiology of HPV and Cervical Cancer

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Brdo, Slovenia
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International Agency for Research on Cancer
Lyon, France

Educational day of national cervical cancer screening programme ZORA
The epidemiology of HPV and cervical cancer

1. Natural history
   Brief historical perspective, causality assessment

2. The IARC HPV Prevalence Surveys
   HPV prevalence in the general population
   HPV distribution in cancer and precursor lesions

3. Burden of HPV and cervical cancer
   Population attributable fraction, current incidence rates

4. Time trends and impact of screening
   Separating the effects of screening versus underlying risk factors
   Quantifying the impact of screening in the Nordic countries

International Agency for Research on Cancer
World Health Organization
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Human papillomavirus: a key discovery to improve the prevention of cervical cancer (vaccine + HPV test-based screening)

- Sexually transmitted
- Non enveloped dsDNA virus, simple capsid of 2 proteins L1 and L2
- Common virus with >100 types identified
- Infects cutaneous and mucosal epithelia of women and men
  - 13 high risk types causing cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
  - HPV 16,18 – most important

Current VLP-based vaccines have nearly >90% efficacy in preventing HPV16/18-related cervical infection and severe dysplasia in women who have not be previously infected.
HPV and cervical cancer, historical perspective

• One of the most important scientific discoveries of the past 30 years, comparable from the public health perspective to the discovery of the association between smoking and lung cancer

• Seminal work from Harald zur Hausen group, discovering that HPV16 can be detected in cervical cancer tissue

• Zur Hausen was awarded the Nobel Prize in Physiology or Medicine in 2008

• Enormous involvement of epidemiologists, molecular biologists, vaccinologists, and clinicians ended up with the development of prophylactic vaccine (could prevent about 70-80% of cervical cancer cases)
Causality criteria for the HPV and CC model

- **Strength of the association**: one of the strongest associations ever observed in epidemiology (ORs ≈ 50-100);
- **Consistency**: in several studies across different countries and populations;
- **Specificity**: some degree of specificity for HPV types;
- **Temporality**: established by several studies, follow-up etc. HPV precede cervical precursor lesions by a number of years;
- **Biological gradient**: viral load is linked to higher risk of progression;
- **Biological plausibility**: observations in humans, in vitro and animal experiment. Several studies on biological mechanisms of immunity, cellular growth, DNA repair, etc;
- **Analogy**: analogous to other examples of animal PV and carcinomas.

**HPV, the first ever identified “necessary cause” of human cancer**
Natural History

Pre-cancerous lesions

- CIN1
- CIN2
- CIN3

The Nobel Committee for Physiology or Medicine 2008
Illustration: Annika Röhl

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Natural History

Hormonal factors
- Long-term OC use
- High parity
- Early age at FTP
- Tobacco smoking

HPV types and variants
- Pre-cancerous lesions
  - CIN1
  - CIN2
  - CIN3

Host factors
- Genetic susceptibility
- Immunological factors

Genetic susceptibility

Immunological factors
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IARC Multi-centre HPV Prevalence Surveys

- The establishment of the viral aetiology of cervical cancer has raised the hopes for primary and secondary prevention through HPV vaccination and HPV DNA test-based screening, respectively.

- The planning of such interventions requires population-based epidemiological data on age and type-specific HPV prevalence in women with and without cancer.

- To this end, the International Agency for Research on Cancer (IARC) has carried out surveys in representative samples of women worldwide.¹

- Priority has been given to countries where there is lack of previous HPV studies and even data on cervical cancer.

¹ supported by Bill and Melinda Gates Foundation
IARC Multi-centric HPV Prevalence Survey

- Population-based samples of approx. 1000 women
- 100 women per 5-year age group (15-19 to 65+)
- Standard HPV testing by GP5+/6+ PCR for 36 types
- Standard questionnaire on several characteristics
IARC HPV Surveys, sexually active women, 15-59 yrs (1995-2013)

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>833</td>
</tr>
<tr>
<td>Mongolia</td>
<td>969</td>
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<tr>
<td>Vanuatu</td>
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<td>Nigeria</td>
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<tr>
<td>Bhutan</td>
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<td>Poland</td>
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<tr>
<td>China, Shenzhen</td>
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<tr>
<td>Argentina</td>
<td>978</td>
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<tr>
<td>India</td>
<td>1891</td>
</tr>
<tr>
<td>China, Shenyang</td>
<td>685</td>
</tr>
<tr>
<td>China, Shanxi</td>
<td>662</td>
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<tr>
<td>Chile</td>
<td>955</td>
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<tr>
<td>Colombia</td>
<td>1834</td>
</tr>
<tr>
<td>Georgia</td>
<td>1309</td>
</tr>
<tr>
<td>Korea</td>
<td>863</td>
</tr>
<tr>
<td>Mexico</td>
<td>1340</td>
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<tr>
<td>Vietnam, Ho Chi Minh</td>
<td>922</td>
</tr>
<tr>
<td>Italy, Turin</td>
<td>1013</td>
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<tr>
<td>Thailand, Lampang</td>
<td>1035</td>
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<tr>
<td>Nepal</td>
<td>932</td>
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<tr>
<td>Iran</td>
<td>825</td>
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<td>Netherlands</td>
<td>3304</td>
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<td>Algeria</td>
<td>759</td>
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<tr>
<td>Thailand, Songkla</td>
<td>706</td>
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<tr>
<td>Spain</td>
<td>911</td>
</tr>
<tr>
<td>Pakistan</td>
<td>899</td>
</tr>
<tr>
<td>Vietnam, Hanoi</td>
<td>994</td>
</tr>
</tbody>
</table>

Legend:
- Red: HPV 16 or 18
- Orange: Other high-risk type
- Yellow: Low-risk type only
Age-specific high-risk HPV prevalence in 9 European Union countries and Switzerland (mainly HC2 and GP5+/GP6+)
Age-specific prevalence of high-risk HPV types in selected areas. IARC HPV prevalence Surveys (GP5+/GP6+)
Summary findings of the IARC HPV prevalence Surveys

- The very heavy burden of HPV infection in certain areas, i.e., Guinea, Nigeria, Mongolia, and Pacific Islands, calls for urgent effective interventions.

- “Western” age-specific curve of HPV prevalence should not be taken as the “natural history of HPV infection”.

- Vaccination and screening are priorities in countries where HPV is very common, even if no good cervical cancer data exist.
8 most common HPV types in 30,743 cases of invasive cervical cancer by region

- **Africa** (n=2,011)  
  - HPV type distribution: 16% 18% 45% 33% 35% 52% 51% 52%
  - Most common type: 16% (71%)

- **Eastern Asia** (n=11,651)  
  - HPV type distribution: 16% 18% 58% 52% 33% 31% 45% 59%
  - Most common type: 16% (68%)

- **Europe** (n=9,015)  
  - HPV type distribution: 16% 18% 31% 33% 45% 35% 58% 52%
  - Most common type: 16% (76%)

- **North America** (n=2,485)  
  - HPV type distribution: 16% 18% 45% 31% 33% 52% 35% 58%
  - Most common type: 16% (73%)

- **South/Central America** (n=3,010)  
  - HPV type distribution: 16% 18% 31% 33% 45% 35% 58% 52%
  - Most common type: 16% (71%)

- **West/Central Asia** (n=2,051)  
  - HPV type distribution: 16% 18% 45% 33% 31% 35% 58% 52%
  - Most common type: 16% (82%)

International Agency for Research on Cancer

World Health Organization
IARC meta-analyses of HPV-type distribution: among HPV-positive samples of increasing severity

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>HPV 16</th>
<th>HPV 18</th>
<th>HPV 31</th>
<th>HPV 33</th>
<th>HPV 45</th>
<th>HPV 52</th>
<th>HPV 58</th>
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<tbody>
<tr>
<td>Normal</td>
<td>278633</td>
<td></td>
<td></td>
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<tr>
<td>ASCUS</td>
<td>4639</td>
<td>58.1%</td>
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<tr>
<td>LSIL</td>
<td>9952</td>
<td>76.0%</td>
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<td></td>
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<td>HSIL</td>
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<tr>
<td>SCC</td>
<td>23351</td>
<td>90.2%</td>
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</tr>
</tbody>
</table>

International Agency for Research on Cancer

World Health Organization
HPV types 16, 18, 45 and 58: by region

**HPV16**

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal</th>
<th>Low-grade</th>
<th>High-grade</th>
<th>ICC</th>
<th>ICC: Normal ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>13.1 ± 3.3</td>
<td>16.8 ± 5.5</td>
<td>30.3 ± 5.2</td>
<td>53.1 ± 4.4</td>
<td>4.07</td>
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<tr>
<td>Eastern Asia</td>
<td>17.0 ± 10.9</td>
<td>21.1 ± 5.7</td>
<td>37.9 ± 7.1</td>
<td>61.7 ± 5.9</td>
<td>3.64</td>
</tr>
<tr>
<td>W/C Asia</td>
<td>29.5 ± 14.7</td>
<td>30.8 ± 14.4</td>
<td>68.4 ± 16.4</td>
<td>73.0 ± 4.6</td>
<td>2.48</td>
</tr>
<tr>
<td>Europe</td>
<td>22.8 ± 3.4</td>
<td>25.9 ± 3.1</td>
<td>54.4 ± 5.6</td>
<td>66.7 ± 2.0</td>
<td>2.92</td>
</tr>
<tr>
<td>North America</td>
<td>26.3 ± 16.2</td>
<td>24.7 ± 4.3</td>
<td>56.8 ± 3.1</td>
<td>61.2 ± 3.2</td>
<td>2.33</td>
</tr>
<tr>
<td>S/C America</td>
<td>16.1 ± 7.8</td>
<td>25.1 ± 9.1</td>
<td>52.6 ± 8.1</td>
<td>59.5 ± 2.8</td>
<td>3.69</td>
</tr>
<tr>
<td>Oceania</td>
<td>17.6 ± 2.7</td>
<td>24.7 ± 9.2</td>
<td>53.9 ± 3.5</td>
<td>62.6 ± 5.4</td>
<td>3.55</td>
</tr>
</tbody>
</table>

**HPV18**

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal</th>
<th>Low-grade</th>
<th>High-grade</th>
<th>ICC</th>
<th>ICC: Normal ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>8.3 ± 1.9</td>
<td>8.3 ± 1.7</td>
<td>9.2 ± 2.8</td>
<td>19.8 ± 4.1</td>
<td>2.39</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>9.1 ± 1.3</td>
<td>8.3 ± 1.9</td>
<td>7.4 ± 1.9</td>
<td>15.8 ± 2.6</td>
<td>1.73</td>
</tr>
<tr>
<td>W/C Asia</td>
<td>6.3 ± 2.3</td>
<td>6.8 ± 2.7</td>
<td>6.3 ± 5.0</td>
<td>15.1 ± 3.7</td>
<td>2.39</td>
</tr>
<tr>
<td>Europe</td>
<td>8.8 ± 1.2</td>
<td>9.1 ± 1.5</td>
<td>7.7 ± 1.1</td>
<td>16.4 ± 4.6</td>
<td>1.87</td>
</tr>
<tr>
<td>North America</td>
<td>9.5 ± 6.6</td>
<td>9.5 ± 1.4</td>
<td>9.6 ± 2.7</td>
<td>19.6 ± 4.3</td>
<td>2.06</td>
</tr>
<tr>
<td>S/C America</td>
<td>6.2 ± 3.4</td>
<td>6.8 ± 4.4</td>
<td>9.4 ± 3.5</td>
<td>12.7 ± 4.5</td>
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<tr>
<td>Oceania</td>
<td>8.3 ± 2.0</td>
<td>8.6 ± 5.1</td>
<td>9.6 ± 1.7</td>
<td>21.2 ± 4.2</td>
<td>2.56</td>
</tr>
</tbody>
</table>

**HPV45**

<table>
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<tr>
<th>Region</th>
<th>Normal</th>
<th>Low-grade</th>
<th>High-grade</th>
<th>ICC</th>
<th>ICC: Normal ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>5.9 ± 2.0</td>
<td>4.4 ± 3.8</td>
<td>4.1 ± 3.1</td>
<td>11.0 ± 2.2</td>
<td>1.85</td>
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<tr>
<td>Eastern Asia</td>
<td>2.7 ± 0.8</td>
<td>1.2 ± 0.5</td>
<td>2.0 ± 1.0</td>
<td>3.0 ± 1.3</td>
<td>1.12</td>
</tr>
<tr>
<td>W/C Asia</td>
<td>6.3 ± 6.9</td>
<td>2.1 ± 3.0</td>
<td>7.1 ± 4.2</td>
<td>5.7 ± 2.7</td>
<td>0.90</td>
</tr>
<tr>
<td>Europe</td>
<td>6.0 ± 1.3</td>
<td>4.6 ± 1.2</td>
<td>3.7 ± 1.0</td>
<td>4.7 ± 0.7</td>
<td>0.78</td>
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<tr>
<td>North America</td>
<td>5.2 ± 0.8</td>
<td>5.6 ± 1.2</td>
<td>4.8 ± 1.7</td>
<td>5.5 ± 1.9</td>
<td>1.05</td>
</tr>
<tr>
<td>S/C America</td>
<td>3.4 ± 1.6</td>
<td>4.5 ± 1.7</td>
<td>4.8 ± 3.0</td>
<td>6.1 ± 0.9</td>
<td>1.79</td>
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<tr>
<td>Oceania</td>
<td>3.7 ± 1.4</td>
<td>6.5 ± 1.7</td>
<td>4.2 ± 1.5</td>
<td>5.3 ± 2.1</td>
<td>1.41</td>
</tr>
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</table>

**HPV58**

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal</th>
<th>Low-grade</th>
<th>High-grade</th>
<th>ICC</th>
<th>ICC: Normal ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>10.7 ± 5.1</td>
<td>10.8 ± 5.6</td>
<td>11.2 ± 4.4</td>
<td>1.3 ± 0.6</td>
<td>0.12</td>
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<tr>
<td>Eastern Asia</td>
<td>7.5 ± 2.2</td>
<td>13.5 ± 3.6</td>
<td>19.6 ± 1.8</td>
<td>10.2 ± 3.9</td>
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<td>W/C Asia</td>
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<td>10.7 ± 9.9</td>
<td>2.8 ± 1.9</td>
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<tr>
<td>Europe</td>
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<td>5.8 ± 0.9</td>
<td>1.4 ± 0.3</td>
<td>0.26</td>
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<tr>
<td>North America</td>
<td>5.9 ± 1.1</td>
<td>7.6 ± 1.5</td>
<td>6.8 ± 1.5</td>
<td>1.4 ± 1.1</td>
<td>0.24</td>
</tr>
<tr>
<td>S/C America</td>
<td>5.9 ± 1.8</td>
<td>6.8 ± 3.9</td>
<td>9.5 ± 2.4</td>
<td>2.8 ± 1.0</td>
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<tr>
<td>Oceania</td>
<td>5.6 ± 1.6</td>
<td>9.1 ± 4.7</td>
<td>5.8 ± 2.3</td>
<td>0.8 ± 0.7</td>
<td>0.15</td>
</tr>
</tbody>
</table>
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Cancer incidence 2008 attributable to infection and HPV-associated in both sexes (de Martel et al, Lancet Oncol 2012)

- More developed regions:
  - 5.6 million new cancer cases
  - 2.1% attributable to HPV (i.e. 120,000 cancer cases)
  - 5.3% attributable to other infections

- Less developed regions:
  - 7.1 million new cancer cases
  - 6.9% attributable to HPV (i.e. 490,000 cancer cases)
  - 16% attributable to other infections
HPV-associated cancer burden 2012

Overall 4.4 %

International Agency for Research on Cancer

Work in progress: preliminary estimates (personal correspondence, M Plummer)
HPV-associated cancer burden 2012

Number of cases (thousands) % attributable to HPV

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
<th>% Attributable to HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix uteri</td>
<td>530,000</td>
<td>100%</td>
</tr>
<tr>
<td>Oropharynx, tonsils and base of tongue</td>
<td>25,500</td>
<td>25.6%</td>
</tr>
<tr>
<td>Vulva</td>
<td>15,000</td>
<td>43%</td>
</tr>
<tr>
<td>Anus</td>
<td>28,000</td>
<td>88%</td>
</tr>
<tr>
<td>Penis</td>
<td>12,500</td>
<td>50%</td>
</tr>
<tr>
<td>Vagina</td>
<td>11,000</td>
<td>70%</td>
</tr>
</tbody>
</table>

All cancer sites World

- 95.6%
- 620,000 new cases in 2012 attributable to HPV

Work in progress: preliminary estimates (personal correspondence, M Plummer)
ASRs of cervical cancer in Europe, 2012

58,000 new cases
24,000 deaths
Trends in cervical cancer incidence in selected countries

Age-standardised (world) incidence rates, age 30-74 years
Age-standardised incidence rates of cervical cancer

Northern Europe

ASR per 100000 (world)

- Denmark
- Finland
- Norway
- Sweden
- UK, England
- The Netherlands

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Age-standardised incidence rates of cervical cancer

Western and Southern Europe

ASR per 100000 (world)

Austria
France (regional)
Italy (regional)
Spain (regional)

International Agency for Research on Cancer
World Health Organization
Age-standardised incidence rates of cervical cancer in Central and Eastern Europe.
Age-standardised incidence rates of cervical cancer

Central and Eastern Europe

ASR per 100000 (world)

- Estonia
- Lithuania
- Bulgaria
- Russia
- Latvia
- Croatia
- Slovenia

International Agency for Research on Cancer
World Health Organization
• Cervical cancer trends, worldwide

Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors

Salvatore Vaccarella *, Joannie Lortet-Tieulent, Martyn Plummer, Silvia Franceschi, Freddie Bray
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Screening *versus* underlying risk factors

- **Screening** should deflect trends downward across *targeted age groups*, and should become apparent as **Period effect**, in populations where it has been introduced;

- **Changing exposure to etiologic factors** in successive generations of women (i.e., modifications in the population prevalence of persistent infection with oncogenic HPV) should be visible as **Cohort effect**.

*Can we distinguish these effects?*
Age-period-cohort (APC) models

- Utilise a log-linear model to describe incidence rates $\lambda(a,p)$ with the effects for \textit{age}, \textit{period} and \textit{cohort}:

  $$\log[\lambda(a,p)] = A + P + C$$

  with $A$, $P$, and $C$ referring to the effects of age, period and cohort

- However....
Knowledge of two of age, period and cohort leads to knowledge of the third and non-identifiability.

The model is not-identifiable.
Age-period-cohort (APC) models

Identifiability problem

Possible solution

to use external information to add a constraint to one of the 3 variables, in order to extract identifiable answers for each of the parameters

(Vaccarella et al, 2014, BJC)
(Vaccarella et al, 2013, EJC)
(Bray et al, 2005, CEBP)
Relationship between age and incidence of CC

Constraint: same risk at ages 45-49 and 65-69 years

(Plummer et al, 2011, IJC)
Age-period-cohort analysis

Results
Denmark

rate-scale for age-effects
relative risk scale for period and cohort effects
Denmark

**Rate-scale** for age-effects and ASR
**Relative risk scale** for period and cohort effects
Denmark

**Rate Ratio**

**Rates per 100000**

**Age**

**Birth Cohort**

**Period**

1967, Organized screening programme
Russian Federation

ASR

rate-scale for age-effects and ASR
relative risk scale for period and cohort effects
Quantify the cervical cancer epidemic that has been prevented by screening

- In 4 Nordic countries
- With over 50 years of cancer incidence data
- Counterfactual scenario

50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence
Projections of ASRs in a no-screening scenario

Assumption: declines in period effects are due to screening
Cervical cancer cases prevented by screening in Denmark, 1956-2010:
Cervical cancer cases prevented by screening in Denmark, 1956-2010:

1967, Screening programme
Cervical cancer cases prevented by screening in Denmark, 1956-2010:

Rates would have been higher than in sub-Saharan Africa

1967,
Screening programme
Cervical cancer cases prevented by screening in Denmark, 1956-2010:

Incident cases (1961-2010):
- Expected: 53,210
- Actual: 25,704 (48.3%)
- Prevented: 27,506 (51.7%)

International Agency for Research on Cancer
World Health Organization
Nearly 50% of cervical cancer cases might have been prevented by screening in the Nordic Countries, 1956-2010
(no screening $\rightarrow$ increase due to changes in sexual habits)

According to a counterfactual scenario based on ad hoc refined age-period-cohort model (Vaccarella et al)
### Five decades of cervical cancer screening: Observed and projected number of incident cases and ASRs, age 30-74

<table>
<thead>
<tr>
<th>Country</th>
<th>Cumulative number of incident cases, 1961-2010</th>
<th>ASR (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Projected</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>95% CI</td>
</tr>
<tr>
<td>Denmark</td>
<td>25,704</td>
<td>53,210</td>
</tr>
<tr>
<td>Finland</td>
<td>9,410</td>
<td>15,133</td>
</tr>
<tr>
<td>Norway</td>
<td>15,146</td>
<td>24,603</td>
</tr>
<tr>
<td>Sweden</td>
<td>24,556</td>
<td>42,777</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• Without screening, current rates in the Nordic countries would have been **3-to-5 times higher** that those observed, i.e., comparable to rates in low-income countries.

• Screening programs might have prevented over **60,000 cases** of cervical cancer in the Nordic countries, i.e., **nearly half** of the cases expected in a no-screening scenario.
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