The future of cervical cancer screening

Pekka Nieminen, MD, PhD,
Associate Professor
Dept. Obst. & Gyn., Helsinki University Hospital, Finland

Contents of this presentation

• Prevention of cervical cancer
• HPV vaccines
  – principles
  – results of vaccine studies
• HPV primary screening
• Policy for HPV vaccination and screening in Finland

Prevention of cervical cancer

• Primary prevention is usually better than secondary prevention
• Cervical cancer screening is considered as secondary prevention, although the cancer itself can be prevented by treating the precancerous lesions
• Well organised screening can reduce cancer incidence and mortality about 80%
Primary prevention

• Deals with the causal factors
• HPV -infection prevention
• Immunizing with virus like particles (VLP)
• The structure is identical with real HPV
• Good antibody response

HPV vaccines

• Prophylactic (preventive)
  – two commercial vaccines
    • Gardasil, designed to be active against the high-risk HPV types 16 and 18, and low-risk types 6 and 11
    • Cervarix, designed to be active against the high-risk HPV types 16 and 18
• HPV 16 and 18 account for about 70% of all high-risk HPV type caused cervical cancers
• Possibly therapeutic vaccines in the future

Vaccine efficacy

• To prevent the development of cancer caused by high-risk HPV types (virus types contained in the vaccine), prophylactic vaccinations against HPV should be administered to adolescents before their exposure to HPV, i.e. before they become sexually active.
• No effect, if the woman has already that certain HPV infection
• Thus the real impact will happen 20-40 years after the vaccine is administered (Cx Ca peak at 30-50 years)
Results with the quadrivalent vaccine (Gardasil)

**Intention-to-treat (ITT)**
- ≥ 1 dose
- Case counting day after first dose
- Included women regardless of their baseline cytological, serological or HPV DNA status

**Per-protocol population (PPE)**
- Complied with protocol
- Received three doses
- Case counting 30 days after third dose
- Seronegative to relevant HPV type at baseline
- DNA negative for relevant HPV type at Day 1 and at Month 7

**Naïve to 14 HPV types**
- ≥ 1 dose
- Case counting day after first dose
- Normal cytology at enrolment
- HPV DNA negative and seronegative to HPV 6, 11, 16, 18 at enrolment
- DNA negative for 10 non-vaccine HPV types* at enrolment

**Modified intention-to-treat (MITT)**
- ≥ 1 dose
- Case counting 30 days after first dose
- MITT-3: Included women regardless of their baseline cytological, serological or HPV DNA status
- MITT-2: DNA negative for relevant HPV type at Day 1

**Restricted MITT-2 (RMITT)**
- ≥ 1 dose
- Case counting 30 days after first dose
- Normal cytology at baseline
- HPV DNA negative and seronegative to HPV 6, 11, 16, 18 at baseline
- DNA negative for 10 non-vaccine HPV types* at baseline

*10 non-vaccine HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59.

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**Gardasil®: Phase III study cohorts**

- **Naive to 14 HPV types**
  - ≥ 1 dose
  - Case counting day after first dose
  - Normal cytology at enrolment
  - HPV DNA negative and seronegative to HPV 6, 11, 16, 18 at enrolment
  - DNA negative for 10 non-vaccine HPV types* at enrolment

- **Per-protocol population (PPE)**
  - Complied with protocol
  - Received three doses
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- **Modified intention-to-treat (MITT)**
  - ≥ 1 dose
  - Case counting 30 days after first dose
  - MITT-3: Included women regardless of their baseline cytological, serological or HPV DNA status
  - MITT-2: DNA negative for relevant HPV type at Day 1

- **Restricted MITT-2 (RMITT)**
  - ≥ 1 dose
  - Case counting 30 days after first dose
  - Normal cytology at baseline
  - HPV DNA negative and seronegative to HPV 6, 11, 16, 18 at baseline
  - DNA negative for 10 non-vaccine HPV types* at baseline

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**Gardasil®: efficacy (modified ITT population-2) – Phase III trial (1.4 years)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine efficacy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16/18 CIN2/3+</td>
<td>97.2 (83.4–100.0)</td>
</tr>
<tr>
<td>HPV 16/18 CIN2</td>
<td>96.3 (77.4–100.0)</td>
</tr>
<tr>
<td>HPV 16/18 CIN3/AIS</td>
<td>100.0 (85.2–100.0)</td>
</tr>
</tbody>
</table>

Modified ITT population-2: women naïve to vaccine HPV types who received at least one vaccination.

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**Gardasil®**: overall vaccine efficacy against CIN2+ irrespective of HPV type in lesion (FUTURE I/II studies)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Cohort</th>
<th>Vaccine efficacy, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2+ irrespective of HPV type in lesion, DNA negative for all oncogenic HPV types at baseline</td>
<td>Generally naïve RMITT-2*</td>
<td>42.7±2</td>
<td>23.7–57.3</td>
</tr>
</tbody>
</table>

* RMITT-2 = at least one dose of vaccine, normal cytology, seronegative to vaccine HPV types and DNA negative for 14 oncogenic HPV types at baseline, case counting starts 30 days after 1st dose.

Estimated worldwide prevalence of HPV 16/18 in CIN2+ is 52%†

† Prevalence varies by region: Asia 45%, Europe 53%, North America 55%, Central America 44%.*

Overall efficacy is aligned with what would be expected from a vaccine that protects against HPV 16/18

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**Gardasil®**: efficacy against CIN2–3 or AIS associated with the most frequent non-vaccine oncogenic HPV types (subjects naïve to 14 HPV types, FUTURE I/II studies)

<table>
<thead>
<tr>
<th>HPV type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>Vaccine efficacy, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 31/45</td>
<td>Vaccine</td>
<td>4,616</td>
<td>11</td>
<td>58.7</td>
<td>(14.1–81.5)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4,680</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 31/33/45/52/58</td>
<td>Vaccine</td>
<td>4,616</td>
<td>44</td>
<td>32.5</td>
<td>(−0.3–55.0)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4,680</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 31/33/35/39/52/58</td>
<td>Vaccine</td>
<td>4,616</td>
<td>62</td>
<td>32.5</td>
<td>(6.0–51.9)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4,680</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All species (HPV 31/33/35/39/52/58)</td>
<td>Vaccine</td>
<td>4,616</td>
<td>44</td>
<td>35.4</td>
<td>(4.4–66.8)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4,680</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All species (HPV 31/33/35/52/58)</td>
<td>Vaccine</td>
<td>5,449</td>
<td>11</td>
<td>47.0</td>
<td>(15.0–76.9)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5,436</td>
<td>21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Subjects naïve to 14 HPV types, women received at least one dose of vaccine, had normal cytology, and were seronegative for vaccine HPV types and DNA negative for 14 oncogenic HPV types at baseline.


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Results with the bivalent vaccine (Cervarix®)
PATRICIA (HPV-008): study population

Total Vaccinated Cohort (TVC)
N = 18,644
- ≥1 dose
- Case counting day after first dose
- Included women regardless of their baseline cytological, serological or HPV DNA status

ATP-E
N = 16,162 (87% of TVC)
- Complied with protocol
- Received three doses
- Case counting day after third dose
- Normal or low-grade cytology at Month 0
- Includes women not HPV naïve

TVC-naïve: approximates the primary target population for organized vaccination programmes i.e. adolescent girls before sexual debut

TVC-naïve
N = 11,641 (62% of TVC)
- ≥1 dose
- Case counting day after first dose
- At Month 0:
  - normal cytology
  - HPV DNA negative for 14 high-risk types*
  - seronegative for HPV 16 and 18

Vaccine
n = 5,822
Control
n = 5,819


* 14 high-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Cervarix®: efficacy in TVC-naïve – final analysis of Phase III trial (39.4 months post-dose 1)

<table>
<thead>
<tr>
<th>Endpoint (TVC-naïve)</th>
<th>Group</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2+ HPV 16/18</td>
<td>Vaccine</td>
<td>5,440</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5,438</td>
<td></td>
</tr>
</tbody>
</table>

The TVC-naive approximates adolescent girls pre-exposure

Cervarix®: efficacy in final analysis of Phase III trial (39.4 months post-dose 1)

<table>
<thead>
<tr>
<th>TVC-naïve</th>
<th>Vaccine</th>
<th>Control</th>
<th>Vaccine efficacy, % (96.1% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colposcopy referrals</td>
<td>304</td>
<td>478</td>
<td>28.3 (14.7–36.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cervical excision procedures</td>
<td>26</td>
<td>83</td>
<td>68.8 (50.0–81.2)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>TVC</th>
<th>Vaccine</th>
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<td>Reduction</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colposcopy referrals</td>
<td>1,107</td>
<td>1,235</td>
<td>10.4 (2.3–17.8)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Cervical excision procedures</td>
<td>180</td>
<td>240</td>
<td>24.7 (7.4–38.9)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

Overall vaccine efficacy of Cervarix® against CIN2+ irrespective of HPV type in the lesion

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine n</th>
<th>Control n</th>
<th>Vaccine efficacy, %</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2+</td>
<td>33</td>
<td>110</td>
<td>79.2 (54.7–80.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant

Estimated worldwide prevalence of HPV 16/18 in CIN2/3 is 52%.4

- Efficacy beyond what would be expected from a vaccine that protects against HPV 16/18 alone

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<td>HPV-31/45</td>
<td>100</td>
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<td>&lt;0.0001</td>
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<td>68.2</td>
<td>40.5–84.1</td>
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<td>HPV-31/33/35/39/45/52/51/56/58/59</td>
<td>66.4</td>
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<td>All species (HPV-31/33/35/52/58)</td>
<td>66.1</td>
<td>37.3–82.6</td>
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<td>77.3</td>
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<td>77.7</td>
<td>63.5–87.0</td>
<td>&lt;0.0001</td>
</tr>
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Cervarix® efficacy against CIN2+ associated with non-vaccine oncogenic HPV types

* Prevalence varies by region: Asia 45%, Europe 53%, North America 55%, Central America 44%.

- TVC-naïve cohort

Cervarix®的功效针对CIN2+的非疫苗相关 oncogenic HPV类型

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Cervical cancer screening

- Organised screening gives the best results
- Only proven method yet
Cervical cancer incidence and mortality rates in Finland in 1953-2004, age-standardised (WSP), Finnish Cancer Registry

Organised screening in the future

- HPV based screening
  - sole HPV testing
  - combined HPT test and Pap smear
  - HPV test with triage
    - Pap
    - molecular markers
    - HPV typing
- Trials ongoing

Primary screening with HPV-test in Finland

Näytteenotto

Laboratorio

Osaan testimäärä:
Papan ja HPV-testi

Eräääänä:
Testaa HPV-testi

Papa-raja

HPV-test NEUTRAALI

Papaa ei analysoida, uusia testaatioita

PAPA ANALYYSIDÄÄN

PAPA ANALYYSIDÄÄN

Ei sota

Sota

Teho
töö

Käytä uunia

Käytä uunia

Käytä uunia

Käytä uunia

Toiminta

Toiminta

Toiminta

Toiminta

Nieminen P. The future of cervical cancer screening.
108,425 invitations to a routine cervical cancer screening
54,207 invitations randomized to HPV DNA screening
18,370 did not attend
18,718 did not attend
35,500 women attended (65.5%) 35,475 scr with primary cytology 25 scr with primary HPV DNA test
18,718 did not attend
33,185 prim scr test negative 30,472 HPV negative* 2,737 cytology negative†
35,078 prim scr test negative 35,055 cytology negative† 23 HPV test negative*
424 referred to colposcopy
420 cytology positive referred
2 HPV DNA test positive
211 no CIN or not available
213 histologically confirmed diagnosis‡
67 CIN 1
104 CIN 2
42 CIN 3+
266 no CIN or not available
154 histologically confirmed diagnosis
46 CIN 1
74 CIN 2
34 CIN 3+

Frequency of recommendations for intensified screening (Leinonen et al. JNCI 2009)

- 2581 recommendations in the HPV arm, 2340 in the conventional arm
- 9% more recommendations in the HPV arm overall (95% CI 3-15%)
- From age 40 onwards, rate was constantly lower in HPV arm
- The rate was modified by age in both arms (p-value for age, and for the interaction term ‘age x arm’ < 0.001)

Frequency of referral to colposcopy (Leinonen et al. JNCI 2009)

- Rate of referral was 1.2% overall, no difference between arms (RR 1.00; 95% CI 0.87-1.14)
- Among women < 35 years, slightly more referrals in the HPV arm?
- P-value for age < 0.001, no systematic interaction over age
Conclusions

• HPV primary testing with cytology triage is better than conventional Pap-smear screening in women 35 years and older
• Among women under 35 years HPV screening is unspecific and causes adverse effect.
• Triage may solve the problem.

Policy for HPV vaccination and screening in Finland
Situation in Finland

• HPV-vaccines are not yet in the National Vaccination Programme
• Only spontaneous vaccination activities in Finland (few thousand vaccines given)
• Together 6500 finnish girls vaccinated in phase III trials
• Large phase IV study ongoing in Finland involving 45 000 young girls and boys

What is happening?

• National Public Health Institute of Finland (KTL) appointed in May 2008 a national expert group.

• Aims of the group:
  – To review and evaluate the role of screening and vaccination together, for the national decision making on control of cervical cancer
  – To make proposals for national action for KTL and Ministry of Health.
  – The proposal should be given by October 2010
  – The chair of this group is P Nieminen.

To be considered within the group

• Screening and vaccination together, not independently
  – pros and cons, e.g.
    - vaccine effects
    - screening effects with present and novel methods
  – total cost-efficiency
  – organisation
  – target age groups
  – girls and boys?
  – etc.
If vaccination is included into the programme

- National vaccination programme
  - free for the participants
  - coverage ~100 %
  - state funded

Why not in programme yet?

- We are not in a hurry in Finland
- Good screening results, 80% reduction in incidence and mortality already
- Theoretically max. 70-80% reduction with vaccines!
- Vaccination benefits fully only after 30 years
- Impact on cytological abnormalities and CIN quite modest
- Over 99% of imminent cervical cancers prevented by treating of CIN (Kalliala et al, BMJ 2005)

Screening & vaccination

- No changes yet in the organised screening programme, except trials on new screening techniques incorporated in the routine (automation, primary HPV screening)
- HPV primary screening with cytology triage is probably the future in the screening era
  - promising results
  - with vaccination the PPV and sensitivity decreases
- Screening has to exist and be of high quality at least for 50 years