The future of cervical cancer screening

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Contents of this presentation

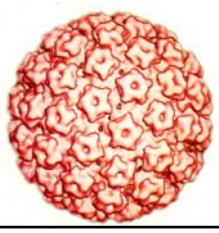
- Prevention of cervical cancer
- HPV vaccines
  - principles
  - results of vaccine studies
- HPV primary screening
- Policy for HPV vaccination and screening in Finland

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

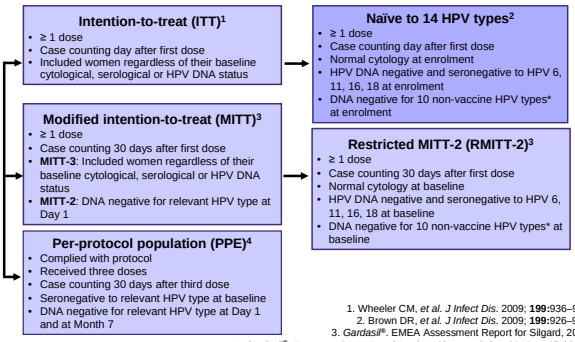
- Prophylactic (preventive)
  - two commercial vaccines
    - Gardasil, designed to be active against the high-risk HPV types 16 and 18, and low-risk types 6 and 11
    - Cervarix, designed to be active against the high-risk HPV types 16 and 18
- HPV 16 and 18 account for about 70% of all high-risk HPV 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)

Gardasil®: Phase III study cohorts



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

1. Wheeler CM, *et al. J Infect Dis*. 2009; **199:**936–944;
2. Brown DR, *et al. J Infect Dis*. 2009; **199:**926–935;
3. *Gardasil*®. EMEA Assessment Report for Silgard, 2008;
4. *Gardasil*®. European Summary of Product Characteristics, 2010. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/emea-combined-h703en.pdf (accessed February 2010).

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

Endpoint	Vaccine efficacy, % (95% CI)
HPV 16/18 CIN2/3+	**97.2** (83.4–100.0)
HPV 16/18 CIN2	**96.3** (77.4–100.0)
HPV 16/18 CIN3/AIS	**100.0** (85.2–100.0)

Modified ITT population-2: women naïve to vaccine HPV types who received at least one vaccination.
n = 6,082 (vaccine group); 6,075 (placebo).

EMEA. Gardasil Scientific Discussion. Available at: http://www.emea.europa.eu/ (accessed February 2010).

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

Endpoint	Cohort	Vaccine efficacy, %	95% CI
CIN2+ irrespective of HPV type in lesion, DNA negative for all oncogenic HPV types at baseline	Generally naïve RMITT-2*	**42.7**[1,2]	**23.7–57.3**

* 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 first dose.

Estimated worldwide prevalence of HPV 16/18 in CIN2/3 is 52%[†3]

† Prevalence varies by region: Asia 45%, Europe 53%, North America 55%, Central America 44%.[4]

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

1. EMEA. *Silgard Assessment Report*. London: EMEA, July 2008;
2. *Gardasil*® Summary of Product Characteristics, February 2010;
3. Smith JS, *et al. Int J Cancer* 2007; **121:** 621–632;
4. WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer. Available at: http://www.who.int/hpvcentre/statistics (accessed February 2010).

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)

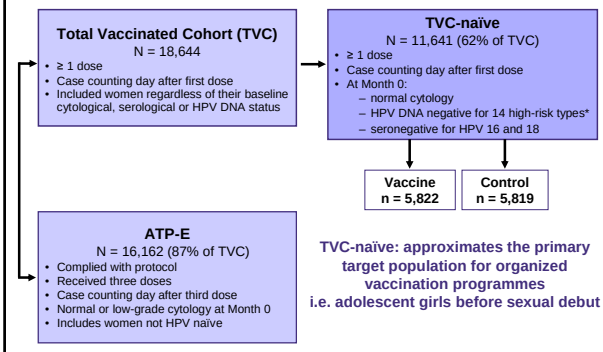
HPV type	Group	N	n	Vaccine efficacy, %	96.1% CI
HPV 31/45 *2 most frequent non-vaccine types*	Vaccine	4,616	11	**58.7**	(14.1–81.5)
	Control	4,680	27		
HPV 31/33/45/52/58 *5 most frequent non-vaccine types*	Vaccine	4,616	44	**32.5**	(-0.3–55.0)
	Control	4,680	66		
HPV 31/33/35/39/45 /51/52/56/58/59 *10 most frequent non-vaccine types*	Vaccine	4,616	62	**32.5**	(6.0–51.9)
	Control	4,680	93		
A9 species (HPV 31/33/35/52/58)	Vaccine	4,616	44	**35.4**	(4.4–56.8)
	Control	4,680	69		
A7 species (HPV 39/45/59/68)	Vaccine	5,449	11	**47.0**	(-15.0–76.9)
	Control	5,436	21		

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.

Brown DR, *et al. J Infect Dis* 2009; **199:**929–935.

Results with the bivalent vaccine (*Cervarix*®)

PATRICIA (HPV-008): study population



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

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

Paavonen J, *et al. Lancet* 2009; **374:**301–314.

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

Primary analysis (TVC-naïve)

Endpoint	Group	N	n	Vaccine Efficacy (96.1%CI)			
				%	LL	UL	*p*-value
CIN2+ HPV 16/18	Vaccine	5,449	1	**98.4**	90.4	100.0	< 0.0001
	Control	5,436	63				

Endpoint	Group	N	n	Vaccine Efficacy (96.1%CI)			
				%	LL	UL	*p*-value
CIN3+ HPV 16/18	Vaccine	5,449	0	**100.0**	64.7	100.0	< 0.0001
	Control	5,436	13				

The TVC-naïve approximates adolescent girls pre-exposure

Paavonen J, *et al. Lancet* 2009; **374:**301–314.

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

TVC-naïve

Reduction in	Vaccine N = 5,449	Control N = 5,436	Vaccine efficacy, % (96.1% CI)	*p*-value
Colposcopy referrals	354	476	**26.3** (14.7–36.4)	< 0.0001
Cervical excision procedures	26	83	**68.8** (50.0–81.2)	< 0.0001

TVC

Reduction in	Vaccine N = 8,667	Control N = 8,682	Vaccine efficacy, % (96.1% CI)	*p*-value
Colposcopy referrals	1,107	1,235	**10.4** (2.3–17.8)	0.0055
Cervical excision procedures	180	240	**24.7** (7.4–38.9)	0.0035

Paavonen J, *et al. Lancet* 2009; **374:**301–314.

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

TVC-naïve[1]

	Vaccine, n	Control, n	Vaccine efficacy, % (96.1% CI)	*p*-value
CIN2+	33	110	**70.2** (54.7–80.9)	<0.0001

Statistically significant

Estimated worldwide prevalence of HPV 16/18 in CIN2/3 is 52%[2]*

* Prevalence varies by region: Asia 45%, Europe 53%, North America 55%, Central America 44%.[3]

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

1. Paavonen J, *et al. Lancet* 2009; **374:**301–14; 2. Smith JS, *et al. Int J Cancer* 2007; **121:** 621–632; 3. WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer. Available at: http://www.who.int/hpvcentre/statistics (accessed February 2010).

Cervarix® efficacy against CIN2+ associated with non-vaccine oncogenic HPV types

Endpoint	Vaccine efficacy		P-value
	%	96.1% CI	
HPV-31/45	**100**	**82.2–100**	<0.0001
HPV-31/33/45/52/58	**68.2**	**40.5–84.1**	<0.0001
HPV-31/33/35/39/45/52/51/56/58/59	**68.4**	**45.7–82.4**	<0.0001
A9 species (HPV-31/33/35/52/58)	**66.1**	**37.3–82.6**	<0.0001
A7 species (HPV-39/45/59/68)	**77.3**	**36.0–93.7**	0.0009
14 oncogenic HPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68)	**77.7**	**63.5–87.0**	<0.0001

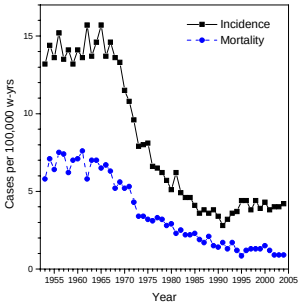
- **TVC-naïve cohort**

Paavonen J et al. Lancet 2009; 374 (9686): 301 - 314; Adapted from Skinner SR et al. 25th International Papillomavirus Conference (Abstract O-29.01), 2009.

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

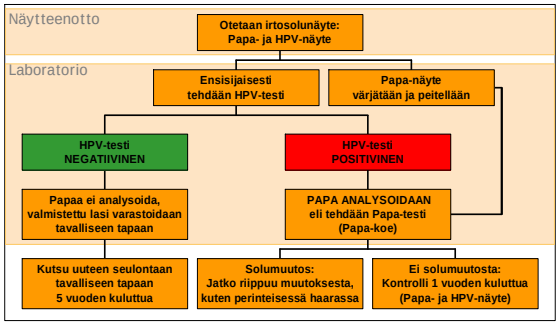


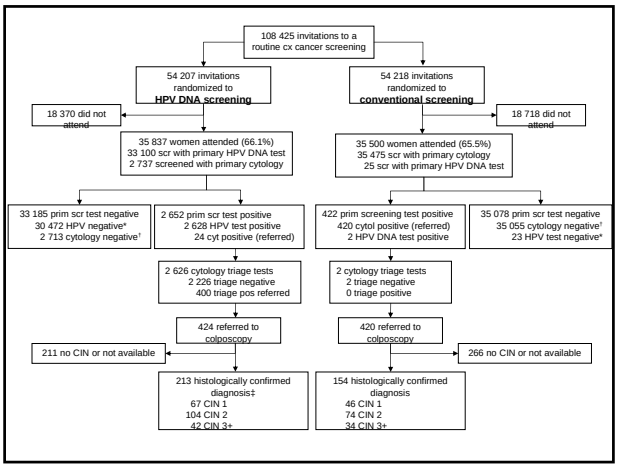
80% reduction in incidende and mortality

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

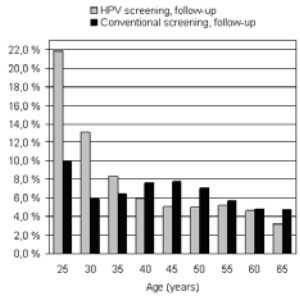
Primary screening with HPV-test in Finland





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

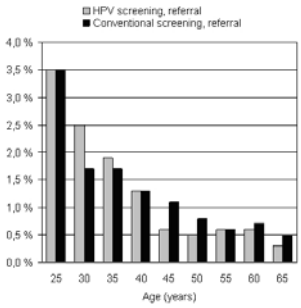
- 2581 recommendations in the HPV arm, 2340 in the conventional arm
- 9% more recommendations in the HPV arm overall (95% CI 3-15%)
- From age 40 onwards, rate was constantly lower in HPV arm
- The rate was modified by age in both arms (p-value for age, and for the interaction term 'age x arm' < 0.001)



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



CIN3+ incidence after screening (Dillner ym., BMJ 2008)

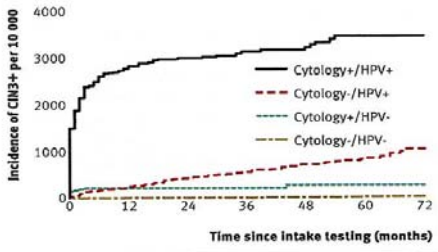


Fig 1 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in the first 72 months of follow-up in all seven countries

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 propably 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