Impact of organized primary HPV-screening

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Prevention of cervical cancer is possible

- Primary prevention
  - vaccination (implemented recently)
- Secondary prevention
  - **screening** (used ~50 years)

POPULATION-BASED ORGANISED CANCER SCREENING PROGRAMMES - THE BEST RESULTS - so far

-Prevent cervical cancer mortality AND incidence

-Improve quality of life

Less aggressive treatments with early detection of precancer / (cancer) (sensitivity)

Limit adverse aspects of testing and management (specificity)

We screen healthy women!

Sens. and spec. are both important

Natural history of CIN and cancer: Important when designing screening

- Length of pre-cancer phase on average 10-12 years; typically between 5 and 15 years
- Progression rates of CIN to invasive cancer (Oortmassen & Habbema, 1991)
  - 16% in lesions in age 18-34 years
  - 60% in lesions in age 35-64 years
- Among 13 – 22 –years old girls and women up to 90 % of pre-cancer lesions regress naturally even in rather short-term follow-up (Moscicki et al. 2004)

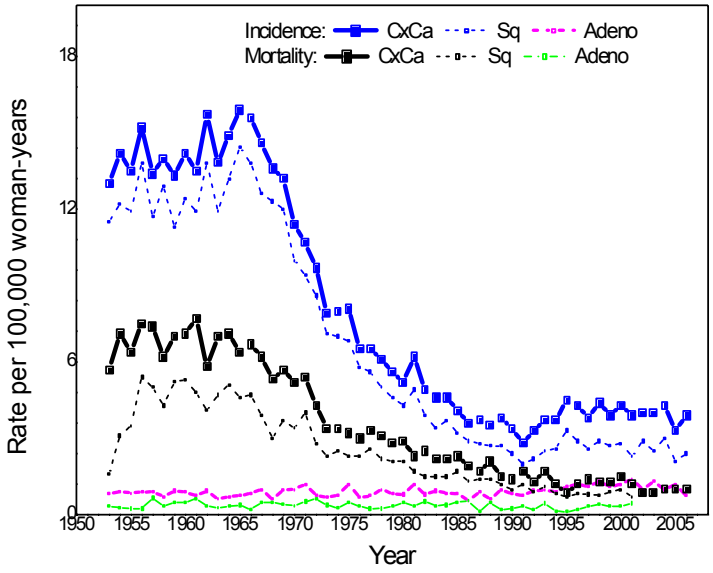
Cervical Cancer Screening Programme in Finland

- Organised programme from 1963, nationwide 1971
- Women aged 30-64 yrs. targeted nationally (25-69 y in some regions)
- Five-year interval
- Seven tests lifetime (regionally up to nine tests)
- Age-specific invitational coverage 98% in 2007; attendance rate at 72%

Organised cervical cancer screening programme in Finland in 2010

- Target population 1.3 million women
- ~ 260,000 women invited (98%)
- >180,000 screened (72%)
- Follow-up cytology (intensive screening) recommended: 5.4%
- Referral to colposcopy: 1.1%
- CIN2+ cases treated: 0.4% of screened women

Cervical cancer incidence and mortality rates in Finland during 1953-2006, adjusted for age to the world standard population (Finnish Cancer Registry, April 2008)



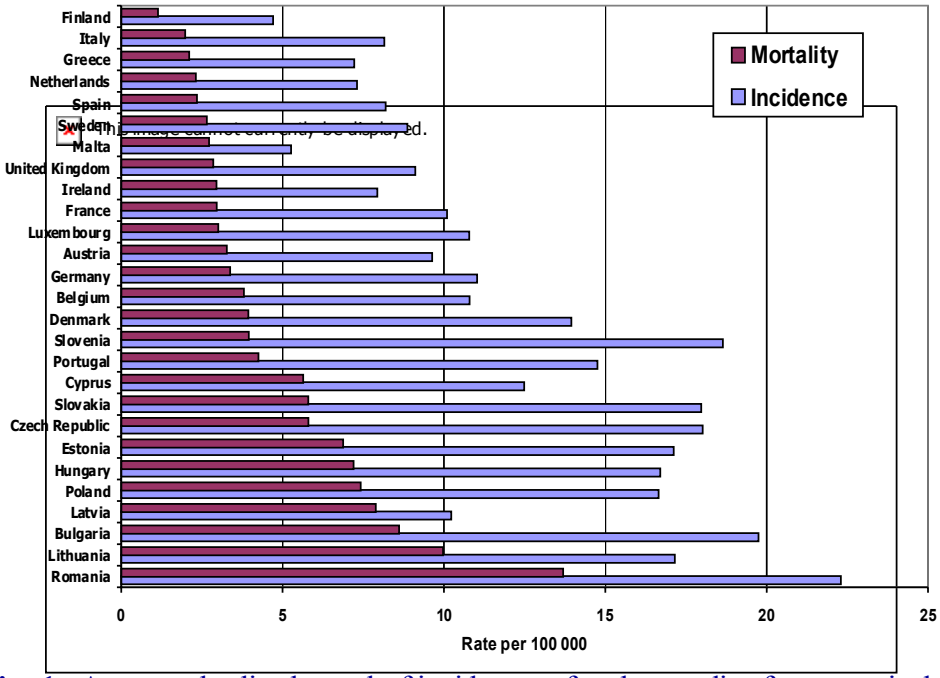
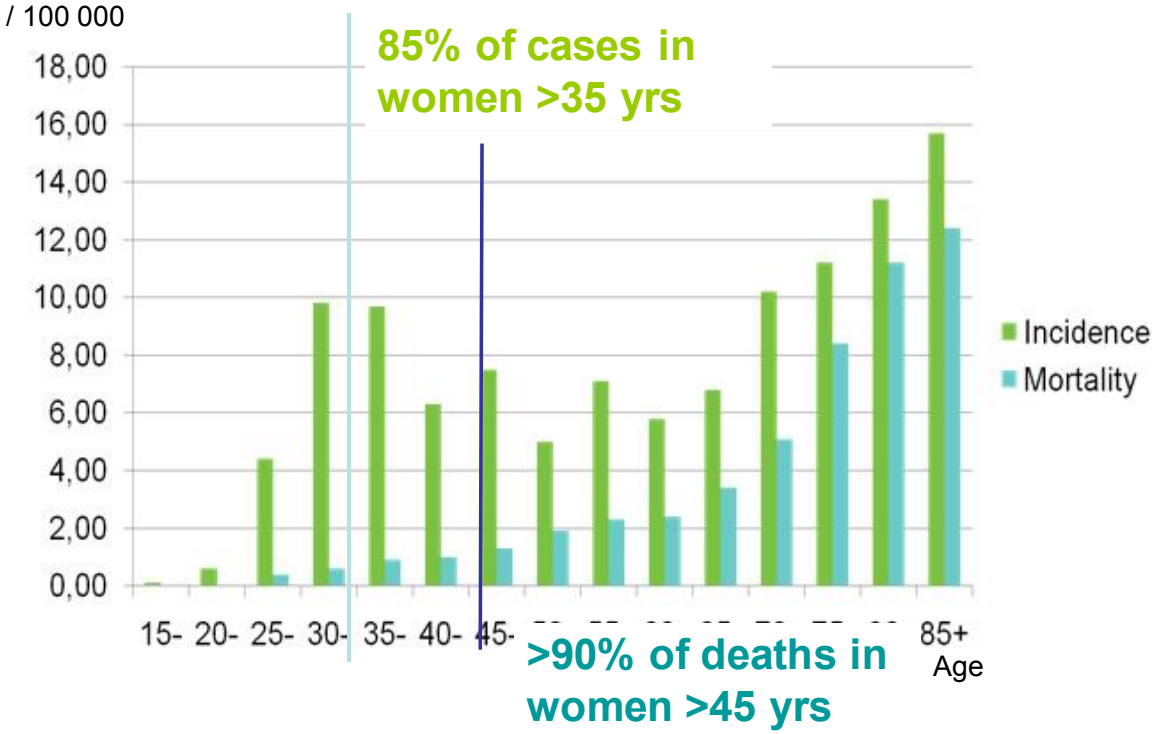


Fig. 1. Age-standardised rated of incidence of and mortality from cervical cancer (/100,000 women-years) in the 27 member states of the European Union, estimates for 2004 (direct standardisation using the World reference population). (derived from Arbyn *et al.*, *Ann Oncol.* 2007b).

Cervical cancer by age group in Finland 2001-2007



Not without problems!

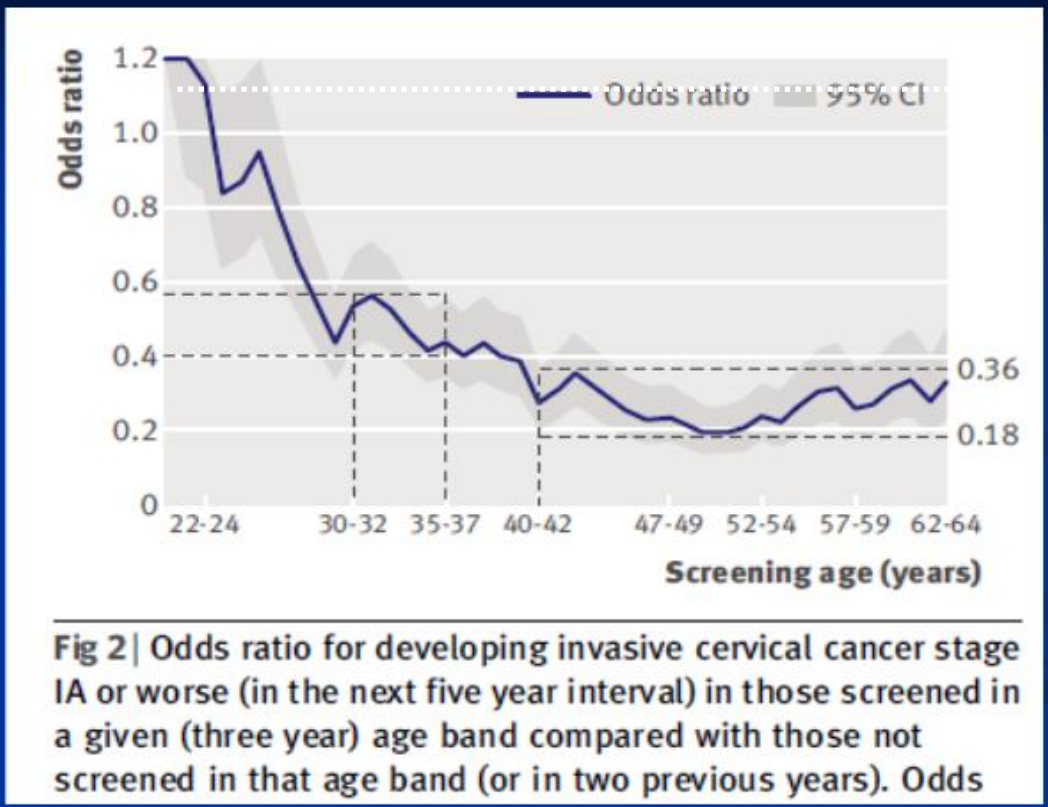


Fig 2 | Odds ratio for developing invasive cervical cancer stage IA or worse (in the next five year interval) in those screened in a given (three year) age band compared with those not screened in that age band (or in two previous years). Odds

Sasieni & Cuzick, BMJ 2009

Why organised screening works?

- Population based
- Defined target ages and groups
- Wide coverage (everybody invited)
  - mode of invitation (personal letter with time and place
- Good compliance (testing, treatment, F-U)
- Evaluation and development
  - screening and cancer registries

Problems in Finland and globally

- Cx Ca incidence is still increasing in many countries
- Among women under 40 years in Finland
  - Attendance rate for organised screening lower compared to older women?
  - Pap-smear not very effective
  - Smoking increased
  - HPV epidemic
- Number of cytotechnologists decreasing
- Organised Pap-smear screening not very common globally:
  - opportunistic screening not very effective.

New methods for screening?

- Pap-smear is not very sensitive
- HPV-test?

HPV-screening trial in Finland:

Objective:

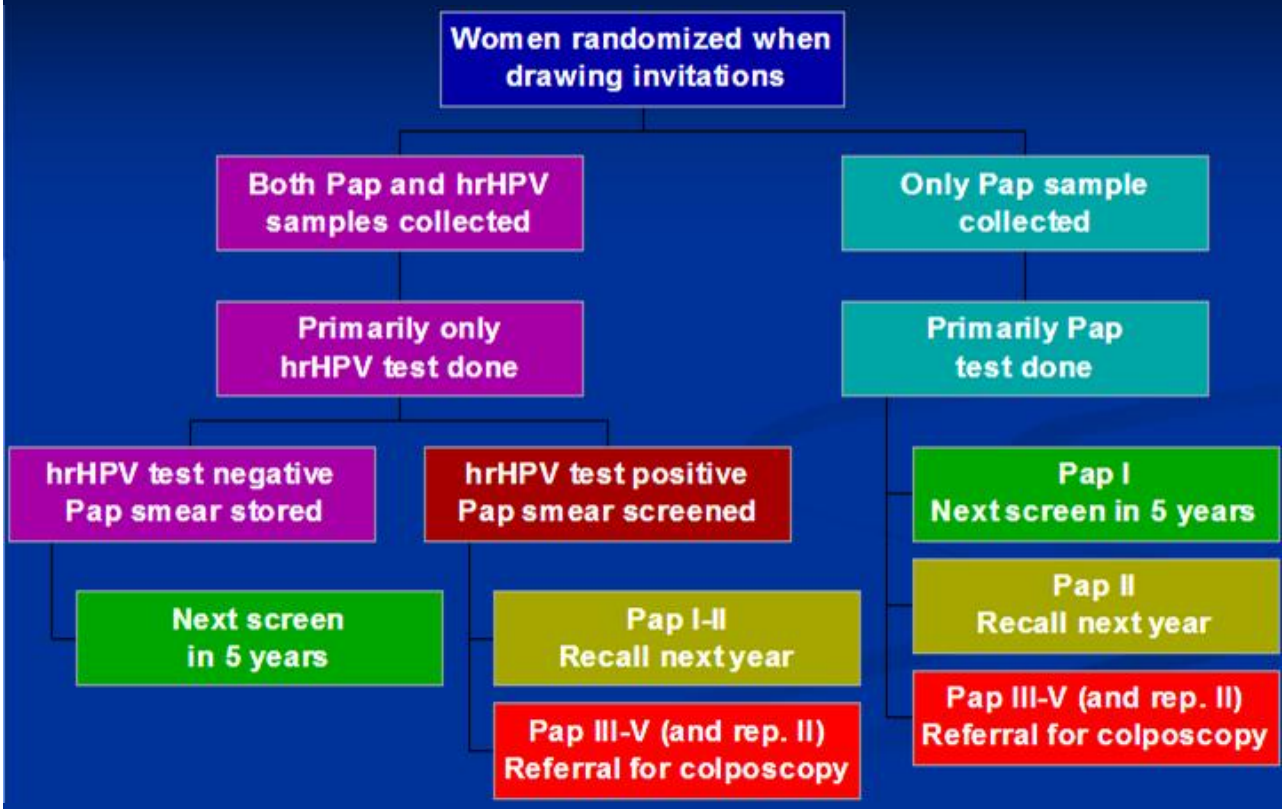
To assess performance of primary HPV-DNA screening in comparison with cytological screening within the context of the organised screening programme for cervical cancer

Started 2003

Other primary HPV screening trials

- Sweden (J. Dillner & al)
- Netherlands (C Meijer & al.)
- Italy (G Ronco & al)
- Canada (E Franco & al)
- India (Sankaranarayanan & al)

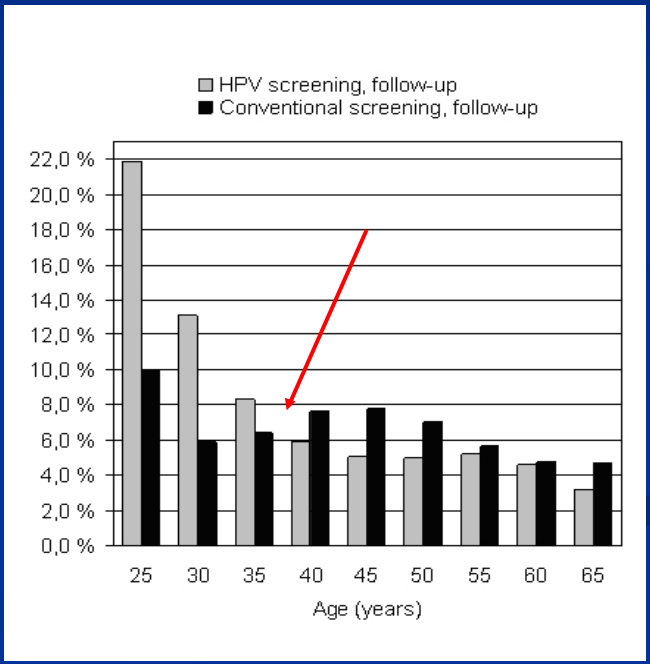
HPV screening protocol (simplified)



Frequency of recommendations for intensified screening

Leinonen, Nieminen et al. JNCI 2009

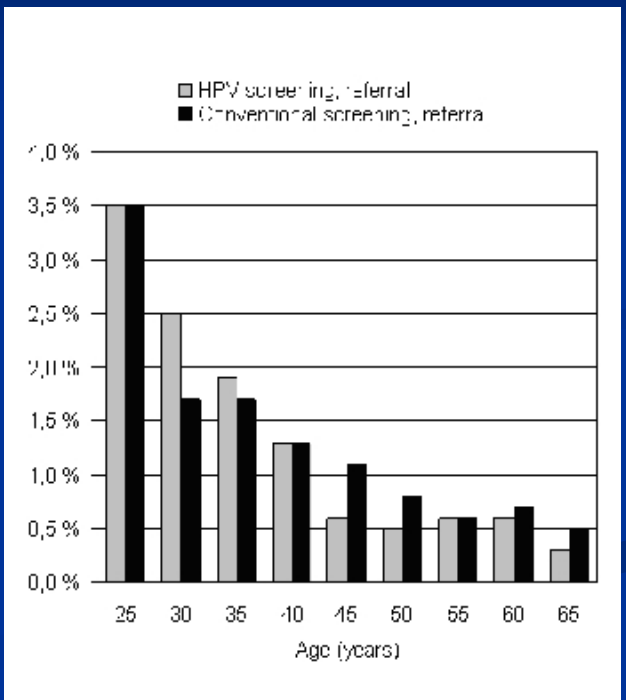
- Cross-sectional
- 2581 recommendations in the HPV arm, 2340 in the conventional arm
- 9% more recommendations in the HPV arm overall (95% CI 3-15%)
- From age 40 upwards, rate was constantly lower in HPV arm
- The rate was modified by age in both arms (p-value for age and for the interaction term 'age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



Frequency of referral for colposcopy

Leinonen, Nieminen et al. JNCI 2009

- Referral rate 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



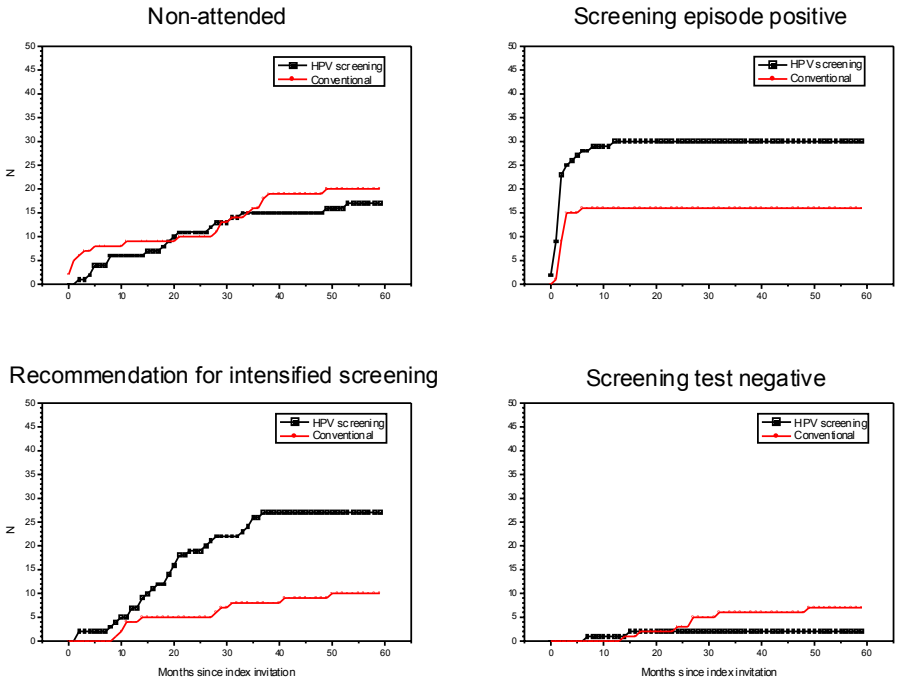
Follow-up information on HPV screening, cancer registry based: Number of women and woman-years at risk (Anttila, Nieminen et al BMJ 2010)

Screening group	HPV screening			Conventional screening		
	Women	Woman-years	%	Women	Woman-years	%
Invitees	29037	95553	100.0	29039	95666	100.0
Attendees	19449	64025	67.0	19221	63396	66.3
Non-attendees	9588	31528	33.0	9818	32270	33.7

Number of cervical cancer, CIN3 and AIS cases by study arm and screening result among attendees (Anttila, Nieminen et al. BMJ 2010).

	Number of cases		Comparison between arms	
Study group	HPV screening	Conventional screening	RR	95% CI
Screening test positive	**57**	**26**	**2.17**	**1.38-3.51**
Screening episode positive (~direct colposcopy)	**30**	**16**	**1.86**	**1.03-3.49**
Recommendation for intensified screening	**27**	**10**	**2.67**	**1.34-5.80**
Screening test negative	**2**	**7**	**0.28**	**0.04-1.17**

Cumulative number CIN3+ cases by months since invitation, screening result groups and study arm (Anttila et al. BMJ 2010)



Hazard rate of cervical lesion detection at index screen for women who attended organised cervical screening over one 5-year screening round (Leinonen et al , submitted 2012)

	No of cases age 25-34		No of cases age 35+		HR (95% CI)	HR (95% CI)	HR (95% CI)
	HPV test	Pap test	HPV test	Pap test	age 25-34	age 35+	Overall
Colposcopy referral							
ICC	1	1	8	6	0.72 (0.05-11.5)	1.43 (0.50-4.12)	1.21 (0.45-3.24)
CIN 3, AIS	37	20	80	54	**1.50 (0.87-2.58)**	**1.97 (1.39-2.78)**	**1.81 (1.35-2.43)**
CIN 2	85	59	106	85	1.17 (0.84-1.62)	1.66 (1.25-2.20)	1.52 (1.22-1.89)
CIN 1	47	26	70	52	1.46 (0.91-2.36)	1.79 (1.25-2.56)	1.72 (1.29-2.29)
Intensified screening							
ICC	-	-	3	-	0.00	0.00	0.00
CIN 3, AIS	23	2	32	14	**4.61 (1.09-19.6)**	**2.59 (1.38-4.86)**	**2.97 (1.70-5.18)**
CIN 2	64	11	70	15	2.33 (1.23-4.43)	5.29 (3.03-9.25)	4.45 (2.93-6.78)
CIN 1	34	6	49	21	2.27 (0.95-5.42)	2.65 (1.59-4.41)	2.66 (1.72-4.10)
Negative/normal							
ICC	-	1	5	1	0.00	4.93 (0.58-42.2)	2.50 (0.49-12.9)
CIN 3, AIS	2	10	4	9	**0.22 (0.05-1.00)**	**0.44 (0.13-1.42)**	**0.32 (0.13-0.79)**
CIN 2	6	15	14	16	0.44 (0.17-1.13)	0.86 (0.42-1.77)	0.65 (0.37-1.13)
CIN 1	7	11	19	11	0.70 (0.27-1.80)	1.70 (0.81-3.58)	1.18 (0.67-2.09)

Comparison with other studies

- Women with a negative test result have shown 70% lower CIN3+ incidence (Dillner et al., BMJ 2008)
- First round finds ~70% more CIN3+ cases than cyto, and the CIN3+ incidence is ~50% lower in the next round (Naucler et al., 2008; Bulkmans et al.,2008; Ronco et al. 2010)
- Risk of invasive cervical cancer is less after HPV-screening than after cyto screening (Ronco et al., 2010)
- Sankaranarayanan et al. (NEJM 2009): even after a single HPV-test incidence of advanced Cx cancers as well as mortality from them is decreased

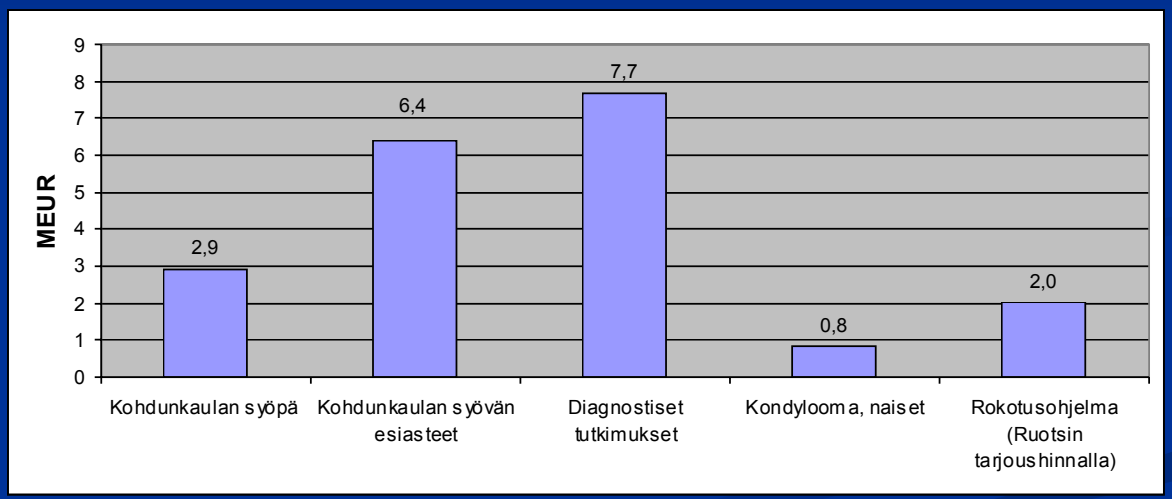
New means to prevent HPV disease burden

- National Institute for Health and Welfare (THL) in Finland established a working group in 2008.
- Modelling the best strategies to prevent HPV diseases in Finland by combining vaccination and screening
- Novel screening techniques
- HPV vaccines

HPV-disease burden: yearly costs in Finland

- Population of Finland is 5,3 mill.
- 500 000 Pap-tests
- 16 300 colposcopies
- 6 400 condyloma patients
- 2 800 CIN cases
- 150 cervical carcinomas
- Total costs about. 41 mill. €

HPV-diseases yearly management costs 17,8 M€

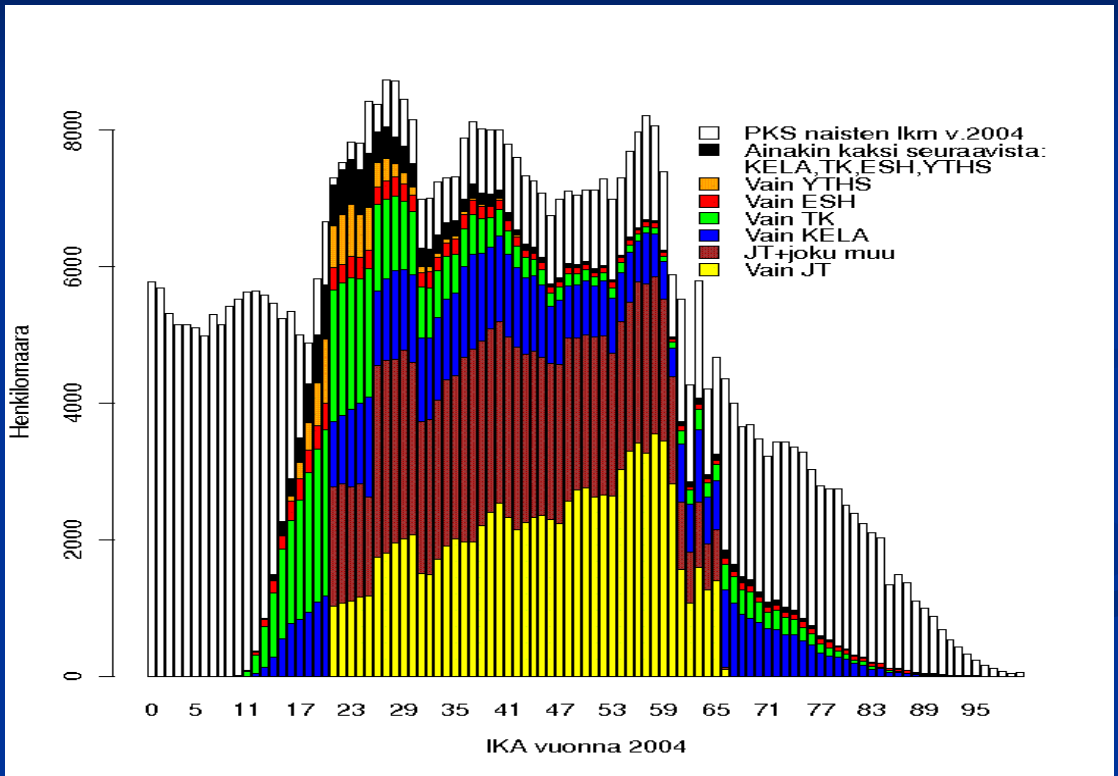


Ca CIN dgn. colpos etc. condyloma women vaccination programme

Screening smears (organised and opportunistic) yearly costs 23 M€

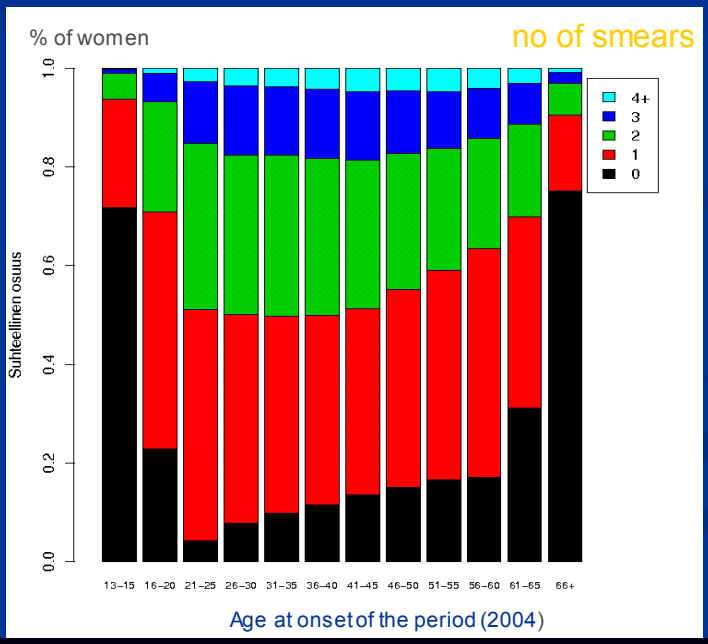
organised screening | private, reimbursed | health care centers | hospitals | student health care

Smears in Helsinki region (2004-08) (THL:n HPV-tautitaakkatyöryhmä)



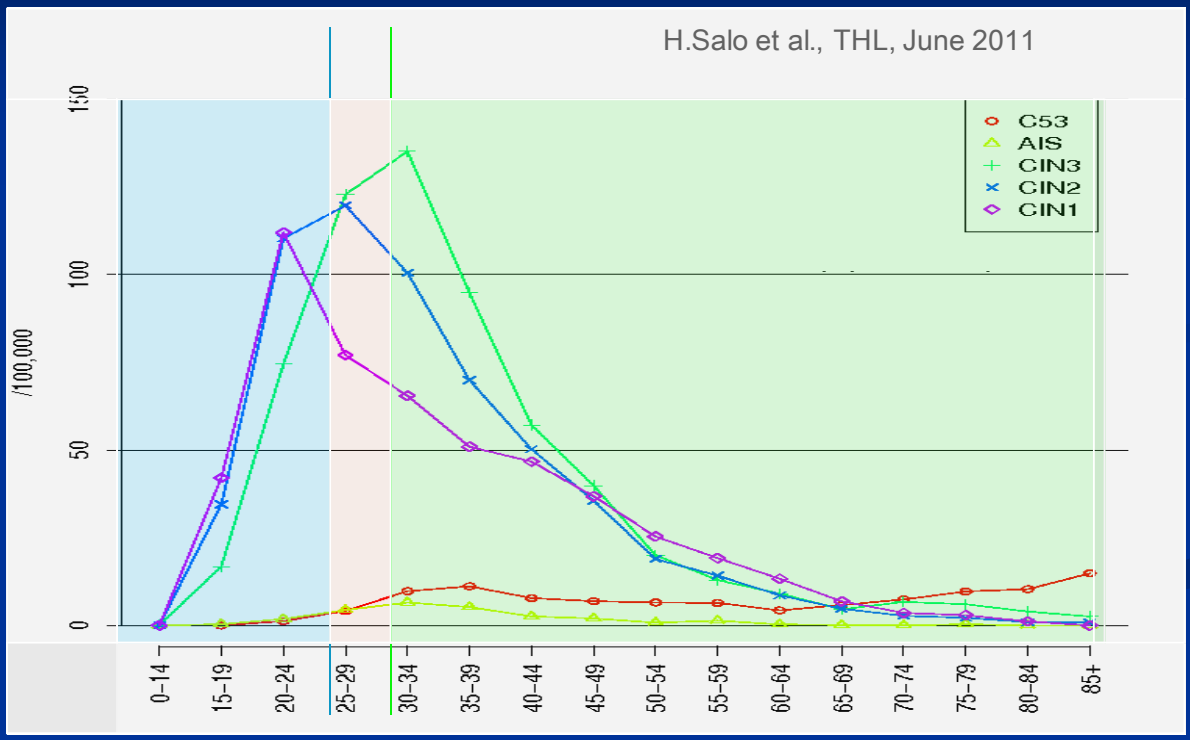
Proportion of women with any Pap smear test at least once in 5 yrs. Organised and opportunistic screening

(H.Salo, P Nieminen et al. THL, June 2011)



Age-specific rates of cervical cancers and pre-cancers in Finland

Finnish Cancer Registry and Hospital/Outpatient Treatment Register 2004-2008



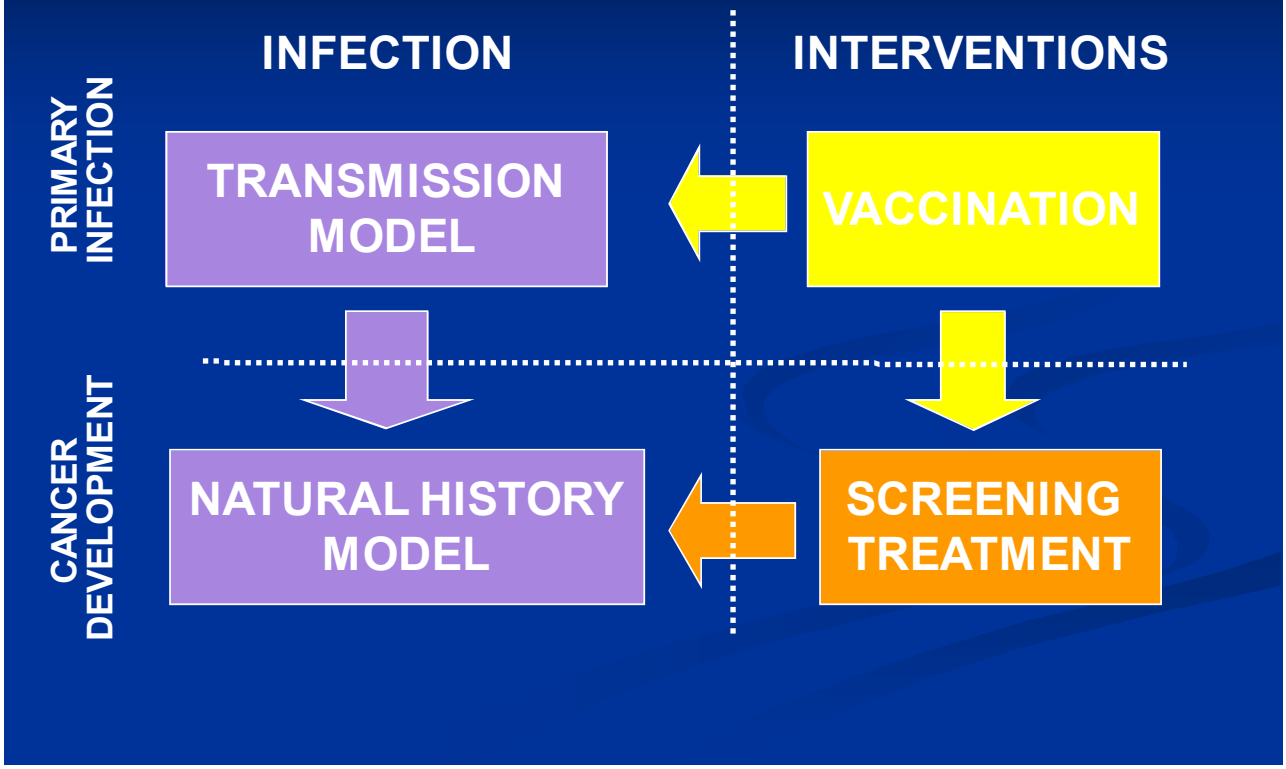
A clear need to rationalize!

- Improve organised screening
  - methods
  - target age groups
- Strongly reduce opportunistic screening
  - non-optimal target groups
  - produces adverse effects

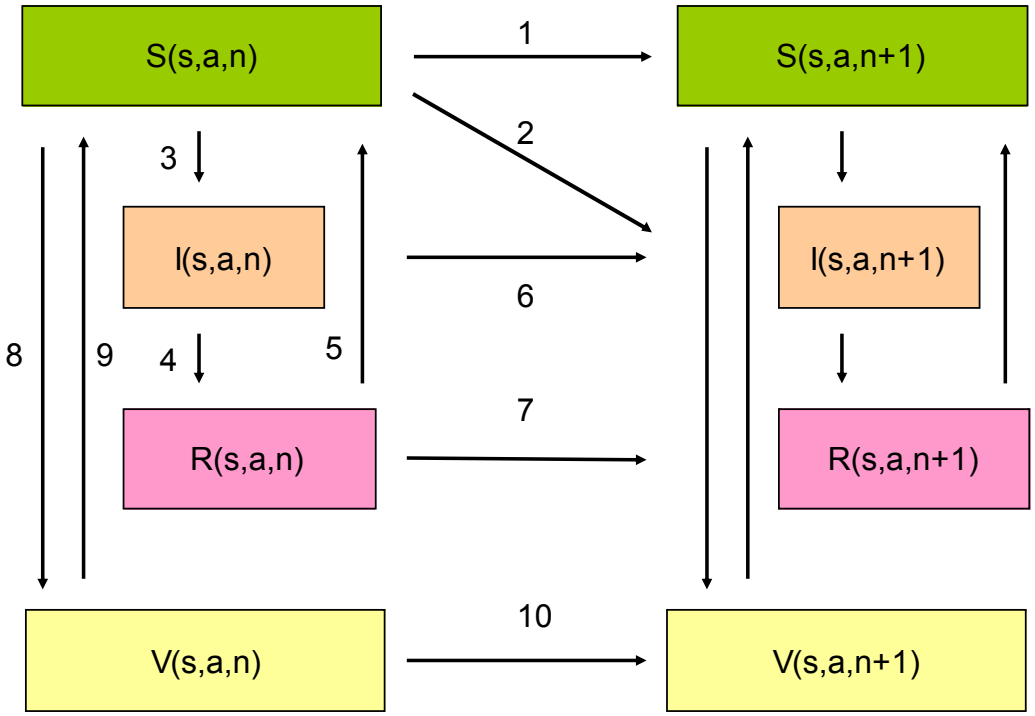
Mathematical modelling of HPV disease burden in Finland

- Data collected from every registries available
  - Cancer registry
  - Screening registry
  - Diagnosis and procedures registry
  - Other registries in health care
- Modelling with dynamic methods (National Institute of Health and Welfare 2011):
  - screening
  - vaccination
- **To find cost-effective methods for prevention**

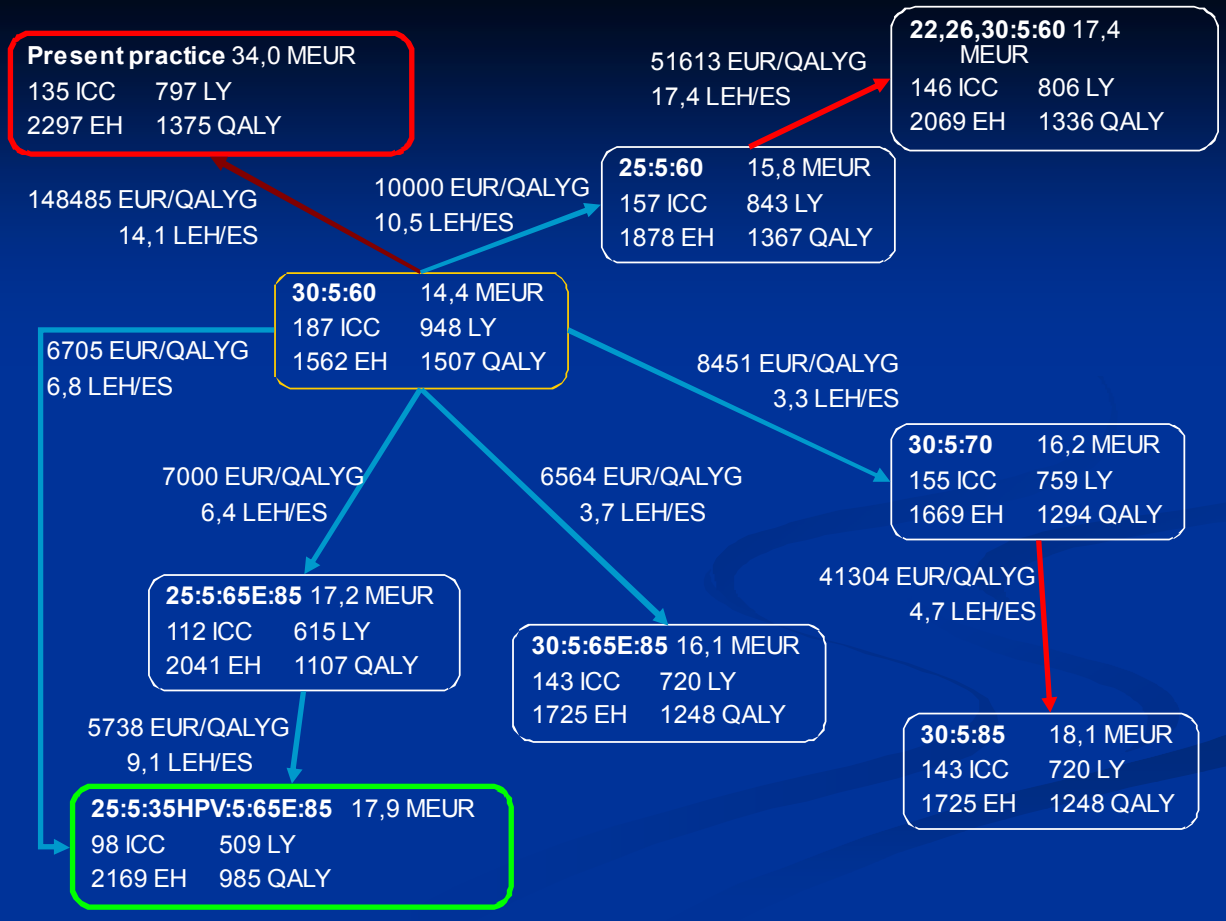
Model structure



Transmission model states – one HPV type



The optimal way to do screening?

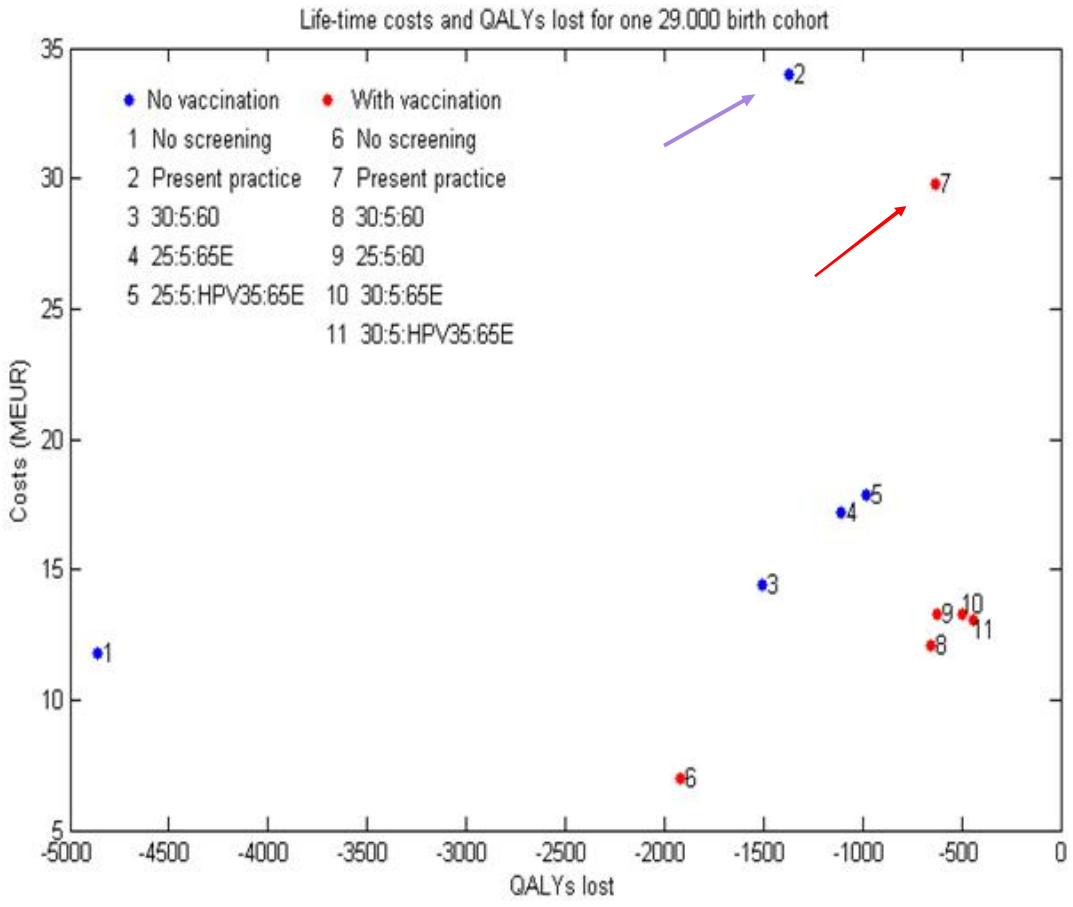


New recommendation for screening:

25-65 –years old women, 5-year interval, HPV-test instead of Pap-test for women 35-years and older

	Present		New recommendation	Change
	2008	model population*		
Carcinomas	**150**	**135**	**98**	**-27 %**
CIN	**2800**	**2300**	**2170**	**-6 %**
Lost life years	**1000**	**800**	**510**	**-36 %**
M€	**41,0**	**34,0**	**17,9**	**-47 %**

*Model population, age cohort of 29 000 girls



Screening & vaccination

- Vaccination does not replace organised screening
- Improving and developing organised screening is necessary
- There are obvious synergies between screening and vaccination
  - Vaccination prevents CIN3+ cases of younger women, (<35 years), sooner, while screening is not very effective in those age groups
  - older women protected effectively by screening