

Progetti multicentrici: il Piemonte

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- Cluster randomised (anno nascita) vs. citologia
- Inizio 35 anni (prima citologia)
- Solo test HPV come primario (prelievo citologico fatto ma colorato solo se HPV+)
- Triage delle HPV+ con citologia e ripetizione HPV a 1 anno se cito<ASCUS.

Perché inizio a 35 anni

- HPV più frequente in donne giovani
- Specificità HPV aumenta con età
- età < 35 aa citologia 94.9% HPV 85.8%
- età >50 aa citologia 97.6% HPV 94.2%

analisi pooled studi EU e Nord America (Cuzick Int J Cancer 2006)

- American Cancer Society raccomanda dai 30 anni causa bassa specificità

NTCC STUDY

WOMEN AGE 25-34

DETECTION OF CIN3 or AIS BY STUDY PERIOD

Phase 1				
HPV group	6602 (5640)	23 (0.38%)	8 (0.14%)	31 (0.52%)
Cytology group	5808 (5721)	24 (0.41%)	6 (0.10%)	30 (0.53%)
RR (95%CI)		0.93 (0.52-1.64)	1.35 (0.47-3.90)	1.00 (0.61-1.65)
Phase 2				
HPV group	6937 (6395)	44 (0.63%)	2 (0.03%)	46 (0.66%)
Cytology group	6788 (6629)	11 (0.16%)	10 (0.15%)	21 (0.31%)
RR (95%CI)		3.91 (2.02-7.57)	0.21 (0.05-0.96)	2.14 (1.28-3.59)
<i>P heterogeneity between phases</i>		0.0009	0.037	0.036

NTCC STUDY

WOMEN AGE 25-34

DETECTION OF CIN 2 BY STUDY PERIOD

	Women enrolled (invited to round 2)	screening round1 N (%)	screening round2 N (%)	Total over both rounds N (%)
Phase 1				
HPV group	6602 (5761)	55 (0.92%)	3 (0.05%)	58 (0.97%)
Cytology group	5808 (5769)	13 (0.22%)	7 (0.12%)	20 (0.34%)
RR (95%CI)		4.09 (2.24-7.48)	0.43 (0.11-1.66)	2.81 (1.69-4.66)
Phase 2				
HPV group	6937 (6577)	71 (1.02%)	5 (0.08%)	76 (1.10%)
Cytology group	6788 (6714)	14 (0.21%)	8 (0.12%)	22 (0.32%)
RR (95%CI)		4.96 (2.80-8.79)	0.64 (0.21-1.95)	3.38 (2.11-5.43)
P heterogeneity between phases		0.65	0.66	0.60

NTCC STUDY WOMEN AGE 25-34

RELATIVE DETECTION OF CIN 2 – CIN3 BY AGE AT RECRUITMENT

	Screening round 1	Screening round 2	Total over both rounds
CIN2			
25-29 years at recruitment	8.81 (3.39-13.68)	0.50 (0.15-1.68)	3.84 (2.26-6.52)
30-34 years at recruitment	3.41 (2.02-5.75)	0.58 (0.17-1.97)	2.61 (1.65-4.13)
<i>P heterogeneity age</i>	0.11	0.88	0.28
CIN3			
25-29 years at recruitment			
Phase1	0.61 (0.24-1.58)	1.00 (0.25-4.00)	0.71 (0.32-1.53)
Phase 2	3.72 (1.39-9.96)	0.51 (0.09-2.79)	2.29 (1.05-4.99)
<i>P heterogeneity phase</i>	0.0071	0.55	0.033
30-34 years at recruitment			
Phase1	1.20 (0.58-2.48)	2.00 (0.37-10.91)	1.30 (0.66-2.53)
Phase 2	4.07 (1.67-9.91)	0.00 (p=0.015)	2.04 (1.02-4.04)
<i>P heterogeneity phase</i>	0.0329	0.015	0.35
<i>P het. age within phase 1</i>	0.27	0.53	0.24
<i>P het. age within phase 2</i>	0.89	0.12	0.83
CIN2/3			
25-29 years at recruitment	3.46 (2.23-5.38)	0.63 (0.29-1.39)	2.35 (1.63-3.37)
30-34 years at recruitment	2.74 (1.88-3.98)	0.54 (0.23-1.27)	2.10 (1.51-2.91)
<i>P heterogeneity age</i>	0.43	0.78	0.81

- Sotto i 35 anni i dati di NTCC indicano sopradiagnosi di CIN2 che sarebbero regrediti spontaneamente
 - Sia con invio diretto che con triage
 - Sia 25-29 che 30-34.
- Non evidente negli altri RCTs ma non fatta analisi stratificata (diluizione)
- Utile analisi pooled RCT
- Nel frattempo prudentiale inizio screening con HPV a 35 anni

Perché randomizzato

- Stimare direttamente effetto su compliance (non valutato in NTCC)
- Paragonare effetto protocollo adottato (studiato solo in RCT Finlandese) con citologia in termini di Detection Rate, PPV, referral rate, esami necessari
 - ➔ stima corretta costi relativi.
- Potenziale valutazione intervalli, età termine ecc.

PILOTA TORINO – PRIMISSIMI DATI - ADESIONE

22/03-30/04	NUMERO INVITI	ADERENTI INVITO	%ADESIONE ALL'INVITO	% FATTO TEST HPV	% RICHIESTA CITOLOGIA
BRACCIO HPV	989	567	57.3%	47.1%	(101*) 10.2%
BRACCIO CITO	553	256	46.2%		

* 27 straniere

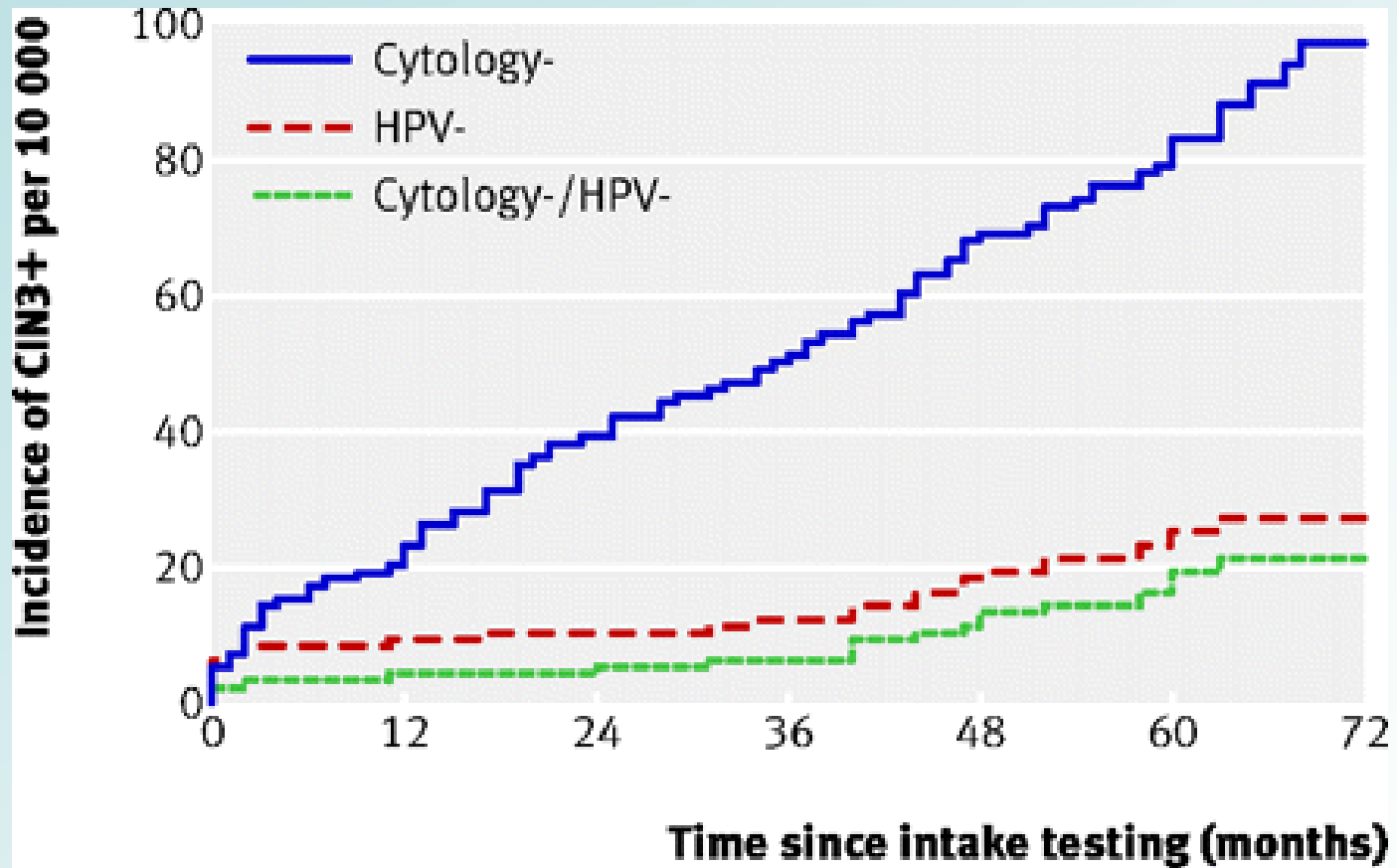
Randomised controlled trials

Detection ratio of CIN3 between HPV and cytology group in 2° screening round

Study	Screening interval	Detection ratio CIN3 (HPV vs. cytology)
Sweedscreen ¹	3	0.53
POBASCAM ²	5	0.45
ARTISTIC ³	3	0.53
NTCC 35-60yrs ⁴	3	0.48

Relative Positive Predictive Value of colposcopy referral (HPV vs. cytology)

- Stand-alone HPV plus “cytological triage” (Finnish trial¹): **1.34 (1.04-1.72)**
- Stand alone HPV with direct referral (NTCC PHASE 2²): **0.80 (0.55-1.18)**
- Combined testing with direct referral NTCC PHASE 1³): **0.34 (0.21-0.54)**



Dillner, J. et al. BMJ 2008;337:a1754

PHASE I

45174 women

CONVENTIONAL ARM

22466 women

Conventional cytology

Routine protocol

EXPERIMENTAL ARM

22708 women

Thin layer cytology + hrHPV DNA test

Referral to colposcopy with cytology ASCUS or more severe

With normal cytology but HPV positive(1 pg/ml):
- *if age 35 years or more. referral to colposcopy*
- *If age < 35 years retesting for HPV and cytology and referral if still HPV positive or cytology became ASCUS+*

PHASE 2

49196 women

CONVENTIONAL ARM

24535 women

Conventional cytology

Routine protocol

EXPERIMENTAL ARM

24661 women

hrHPV DNA test

Referral to colposcopy if positive at 1 pg/mL cutoff.