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)
P heterogeneity between phases		**0.0009**	**0.037**	**0.036**

Ronco et al. Lancet Oncol 2010 modif

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**

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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)
P heterogeneity age	**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)
P heterogeneity phase	**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)
P heterogeneity phase	**0.0329**	**0.015**	**0.35**
P het. age within phase 1	**0.27**	**0.53**	**0.24**
P het. age within phase 2	**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)
P heterogeneity age	**0.43**	**0.78**	**0.81**

Ronco et al. Lancet Oncol 2010 modif

- 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 prudenziale 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 betweeen HPV and cytology group in 2° screening round

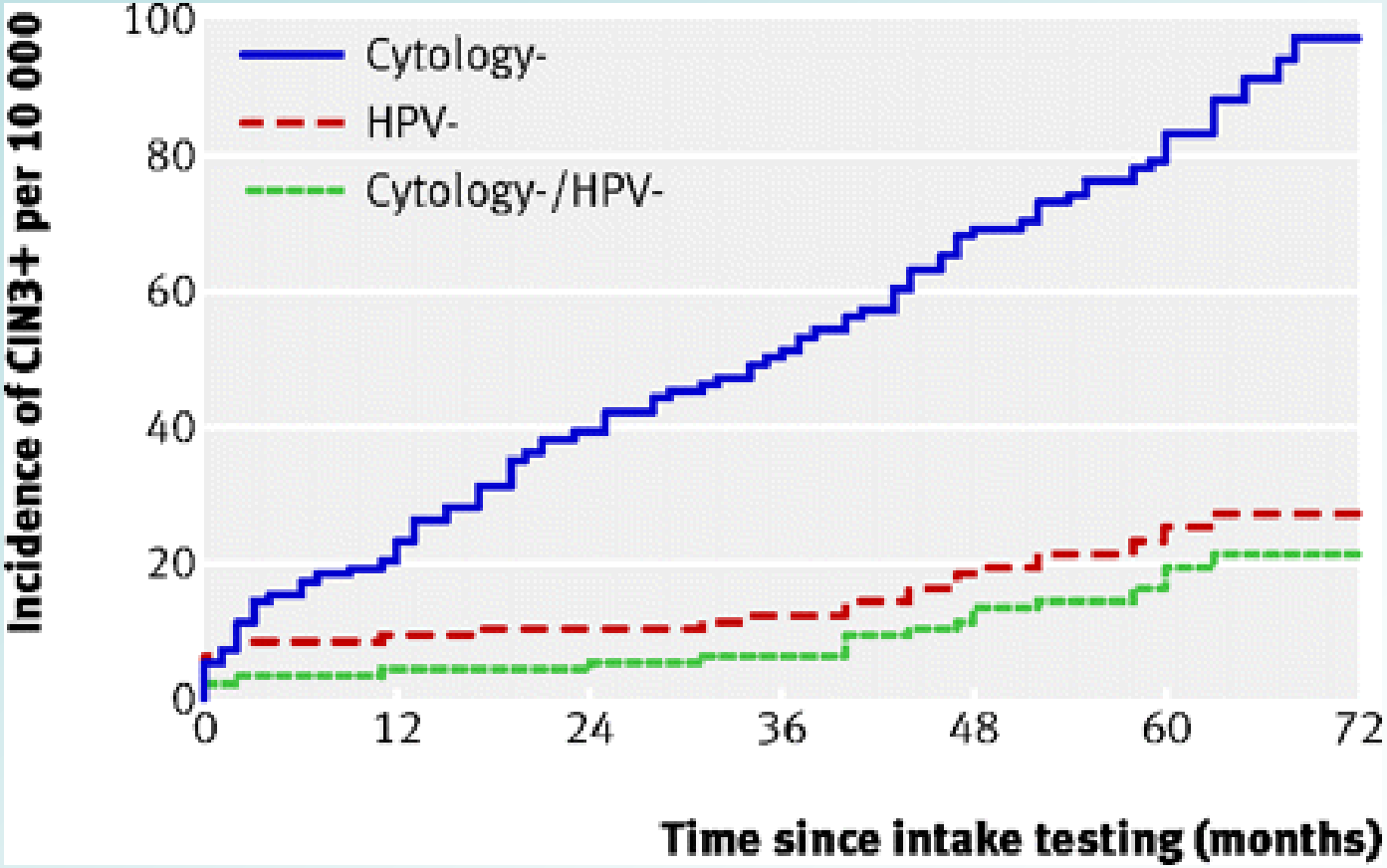
Study	Screening interval	Detection ratio CIN3 (HPV vs. cytology)
Sweedscreen[1]	3	0.53
POBASCAM[2]	5	0.45
ARTISTIC[3]	3	0.53
NTCC 35-60yrs[4]	3	0.48

1 Naucler et al 2007 2 Bulkmans et al. 2007 3 Kitchener et al 2009 4 Ronco et al. 2010

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

- Stand-alone HPV plus “cytological triage” (Finnish trial[1]): 1.34 (1.04-1.72)
- Stand alone HPV with direct referral (NTCC PHASE 2[2]): 0.80 (0.55-1.18)
- Combined testing with direct referral NTCC PHASE 1[3]): 0.34 (0.21-0.54)

1. Leinonen et al JNCI 2009 2. Ronco et al JNCI 2008 3.Ronco et al JNCI 2006



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

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