Razionale per l'uso clinico del test virale nel sistema di screening: studio italiano NTCC

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NTCC STUDY

- Multi-centre randomised Trial
- conventional (conventional cytology) vs. experimental (two phases)
  - experimental Phase 1: HPV (HC2) and liquid-based cytology (LBC)
  - experimental Phase 2: HPV only

Participating centres

Organised screening programmes in:

- ***Piemonte***: Torino
- ***Trentino***: Trento
- ***Veneto***:
  - Verona and Padova
- ***Emilia Romagna***:
  - Imola, Ravenna, Bologna
- ***Toscana***: Firenze
- ***Lazio***: Viterbo

Eligible women

- Age 25-60 years
- showing for a new screening episode - invited
- Excluded:
  - In follow-up after positive or unsatisfactory cytology or biopsy
  - Treated for cervical Ca or SIL in last 5 years
  - Hysterectomy at any time
- Individual randomisation after consent to enter the study

Protocol with HPV+

- **PHASE 1**
- If age 35-60 ⇒ colposcopy
- If age 25-34 ⇒ repeat both after 1 year if cytology normal (<ASCUS)
  - if HPV persisted or cytology + ⇒ colposcopy
  - Otherwise ⇒ standard interval
- **PHASE 2**
- colposcopy independently of age

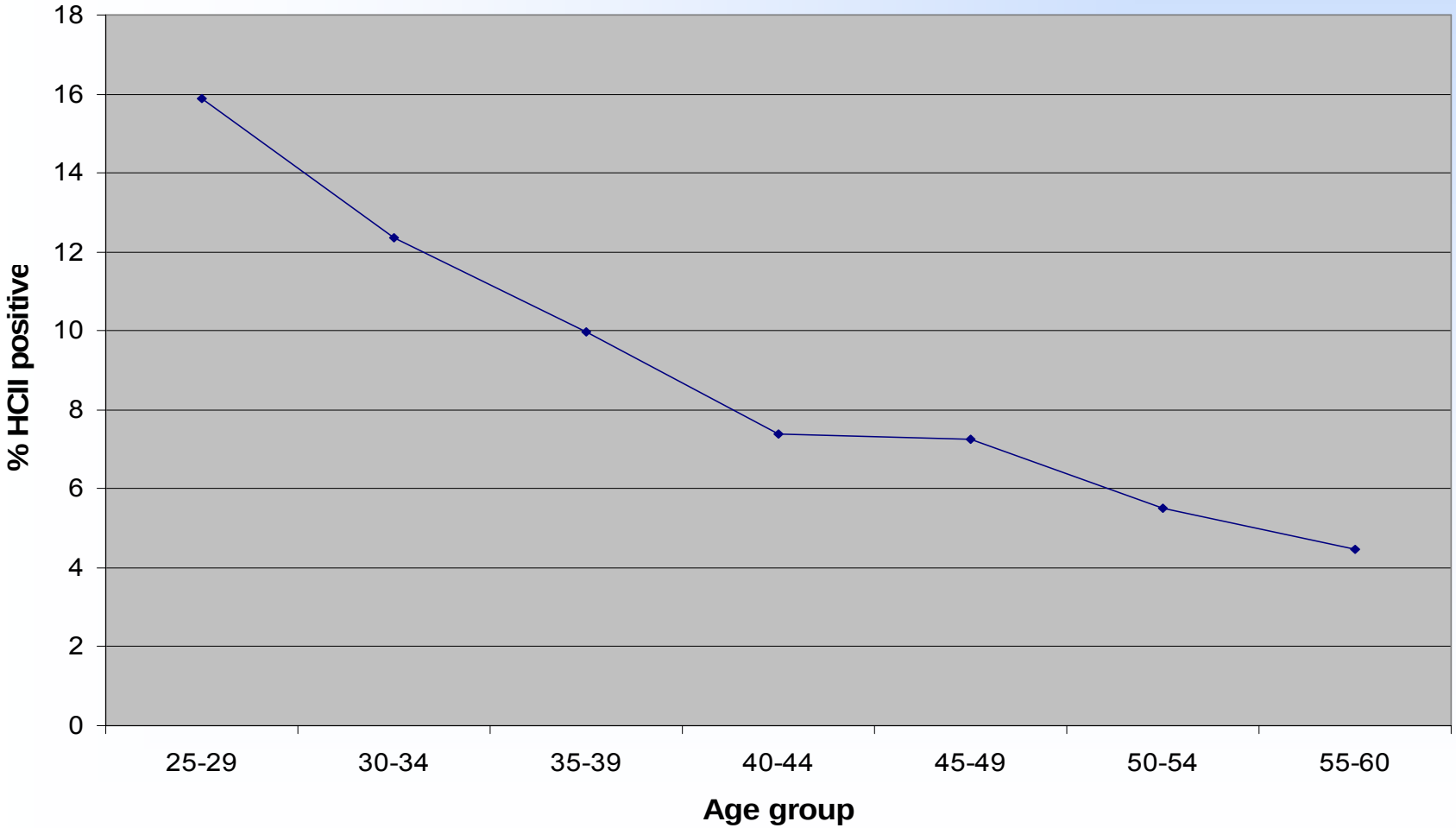
NTCC study phase 1
Randomised eligible women
45174

- **Conventional arm 22466**
- 25-34 yrs: 5808
- 35-60 yrs: 16658
- **Experimental arm 22708**
- 25-34 yrs: 6002
- 35-60 yrs: 16706

NTCC study phase 2
Randomised eligible women
49196

- **Conventional arm 24535**
- 25-34 yrs: 6788
- 35-60 yrs: 17747
- **Experimental arm 24661**
- 25-34 yrs: 6937
- 35-60 yrs: 17724

NTCC STUDY - Phase I
Proportion of women positive to HCII by age group
First test within woman



NTCC STUDY PHASE 1 WOMEN 35-60 YRS

Sensitivity and specificity of liquid-based cytology and human papillomavirus (HPV) in the experimental arm*

Not corrected for verification bias

Criterion	Sensitivity (95% CI)		Specificity (95% CI)	
	CIN2+	CIN3+	CIN2+	CIN3+
Liquid-based cytology ≥ASCUS	54/73=74.0% (62.4 to 83.6)	31/38=81.6% (65.7 to 92.3)	15,593/16,443= 94.8% (94.5 to 95.2)	15,605/16,478= 94.7% (94.4 to 95.0)
HPV ≥ 1pg/mL	73/75=97.3% (90.7 to 99.7)†	38/39=97.4% (86.5 to 99.9)‡	15,223/16,335= 93.2% (92.8 to 93.6)†	15,224/16,371= 93.0% (92.6 to 93.4)†
HPV ≥ 2pg/mL	72/75=96.0% (88.8 to 99.2)†	37/39=94.9% (82.7 to 99.4)	15,499/16,335= 94.9% (94.5 to 95.2)	15,500/16,371= 94.7% (94.3 to 95.0)

*Women (including 1 CIN2 and 1 CIN3+) without valid cytology (n=190) were excluded from computations for liquid-based cytology =ASCUS. Women (no CIN2+) were excluded from computations for HPV (n=296). Women (including 1 CIN2 and 1 CIN3+) without either valid test were excluded from computations of *P* values comparing tests (n=451).
ASCUS = atypical squamous cells of undetermined significance.
†*P*<.001 versus Liquid-based cytology =ASCUS (McNemar test) ‡*P*=0.034 versus Liquid-based cytology =ASCUS (McNemar test)

Ronco et al. J. Natl.Cancer. Inst. 2006; 98: 765-74

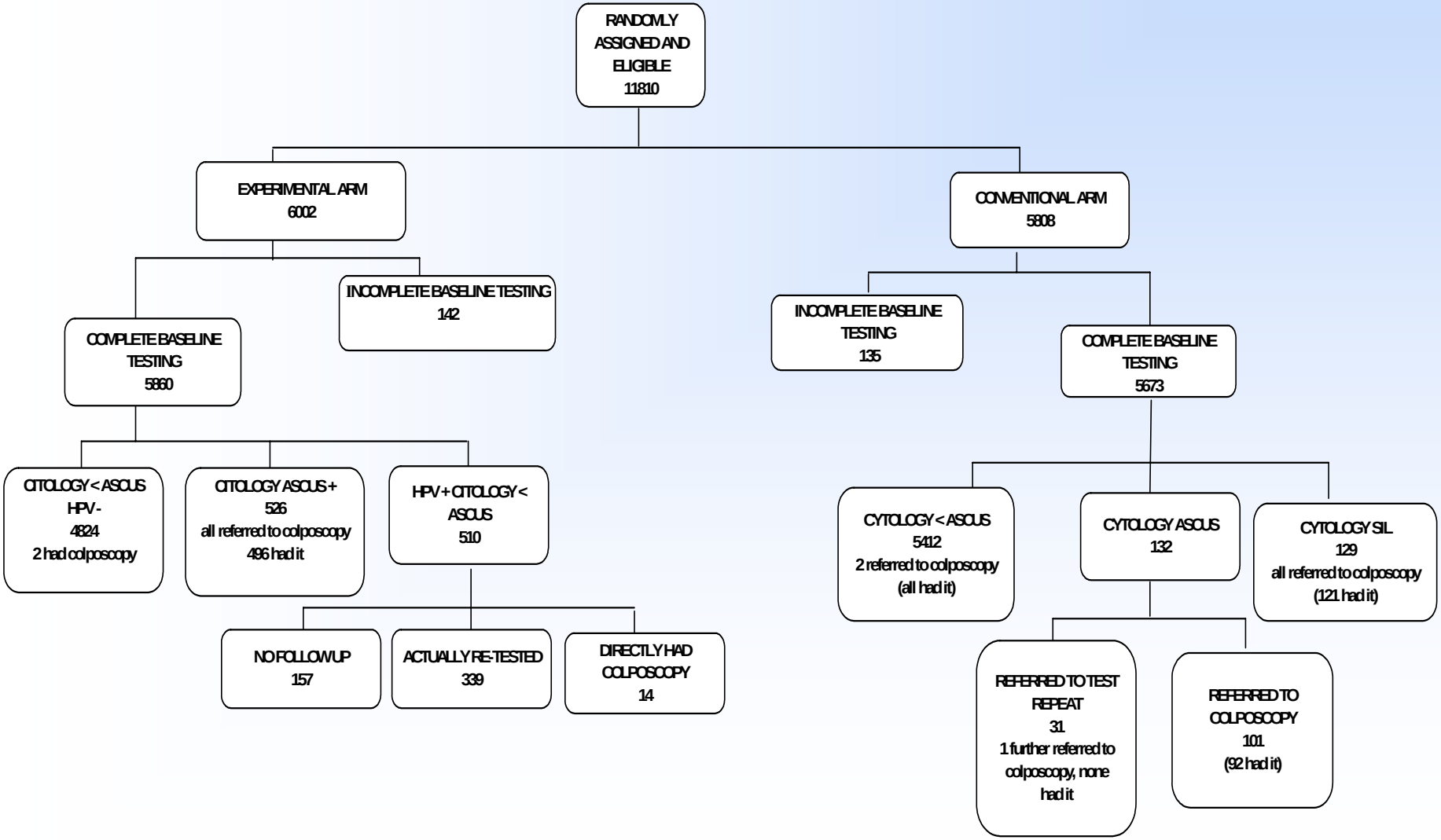
NTCC STUDY PHASE 1 YRS 35-60 YRS

Detection rate, positive predictive value (PPV), relative sensitivity and relative PPV for histology-confirmed CIN2+ vs conventional cytology ≥ASCUS

	Endpoint CIN2+			
	Detection Rate per 1000	Relative sensitivity (95% CI)	PPV %	Relative PPV (95% CI)
	Experimental arm			
HPV ≥ 1pg/mL	4.37	1.43 (1.00 to 2.04)†	6.6	0.58 (0.33 to 0.98)
HPV ≥ 2pg/mL	4.25	1.41 (0.98 to 2.01)	8.5	0.75 (0.45 to 1.27)
Liquid-based cytology ≥ ASCUS or HPV ≥1pg/mL	4.49	1.47 (1.03 to 2.09)	4.5	0.40 (0.23 to 0.66)
	Conventional arm			
Conventional cytology ≥ ASCUS	3.06	1.00 (referent)	11.4	1.00 (referent)

Ronco et al. J. Natl.Cancer. Inst. 2006; 98: 765-74 modified

NTCC study Phase 1
women age 25-34



Ronco et al. Lancet Oncol 2006; 7:547-55

NTCC STUDY PHASE 1 - WOMEN 25-34 yrs

Positivity to Hybrid Capture 2 at re-testing among women HPV+ but cytologically normal at baseline.

	HPV-/HPV+ at re-testing	% HPV+ at re-testing	OR (95% CI) (1)
Interval from baseline testing			
<1year	56/56	50.0	1
≥1 year	134/88	39.6	0.66 (0.41-1.05)
RLU at baseline			Chi2 (4df)= 16.63; p=0.0023 (2)
1-1.99	41/12	22.6	1
2.0-3.99	24/13	35.1	1.88 (0.74-4.80)
4.0-9.99	29/18	38.3	2.10 (0.87-5.04)
10.0-99.99	55/54	49.5	3.38 (1.60-7.14)
≥100.00	41/47	53.4	3.91 (1.81-8.46)
Age			
25-29	92/72	43.9	1
30-34	98/72	42.3	0.99 (0.63-1.55)

(1) Adjusted for the other variables in the table by unconditional logistic regression

(2) P value for the overall effect in classes, obtained by the likelihood ratio test

Ronco et al. Lancet Oncol 2006; 7:547-55

NTCC STUDY PHASE 1 - WOMEN 25-34 yrs

Cytology at 1-year repeat among women previously HPV+ and cytology normal

- HPV+ at repeat : 58% ASCUS+
- HPV- at repeat : 11% ASCUS+
- Note: HPV- at baseline: 4% ASCUS+ ($p<0.0001$)

NTCC STUDY PHASE 1 - WOMEN 25-34 yrs

Sensitivity and specificity for histologically confirmed CIN2+ within the experimental arm.

Criteria for referral (retrospectively applied)	CIN2 + detected	Sensitivity (95%CI)	Specificity (95%CI)
LBC ≥ASCUS alone §	45/55	81.8 (69.1-90.9)	91.7 (91.0-92.4)
HPV **≥1pg/ml** with LBC triage of those positive; if cytology <ASCUS repeat both tests and refer if **either** is positive $	54/55	98.2 * (90.3-99.95)	92.5*** (91.8-93.2)
HPV **≥2pg/ml** with LBC triage of those positive; if cytology <ASCUS repeat both tests and refer if **either** is positive $	54/55	98.2 * (90.3-99.95)	93.1*** (92.4-93.8)
HPV **≥1pg/ml** with LBC triage of those positive; if cytology <ASCUS repeat both tests and refer if **both** are positive $	53/55	96.4 ** (87.5-99.6)	94.3 *** (93.7-94.7)
HPV **≥2pg/ml** with LBC triage of those positive; if cytology <ASCUS repeat both tests and refer if **both** are positive $	53/55	96.4 ** (87.5-99.6)	94.6 *** (94.0-95.2)

* p=0.0067 vs. LBC ≥ASCUS ** p=0.0114 vs. LBC ≥ASCUS *** p<0.0001 vs. LBC ≥ASCUS
Specificity significantly increased (p<0.0001) both with 2pg vs. 1pg cut-off and with "both tests" vs. "either test" referral criterion at follow-up.

Ronco et al. Lancet Oncol 2006; 7:547-55

NTCC STUDY PHASE 1 - WOMEN 25-34 yrs
Relative sensitivity and relative PPV vs. conventional cytology ≥ ASCUS.

Criteria for referral (retrospectively applied)	Endpoint CIN2+ Detection Rate per 1000	Relative sensitivity (95%CI)	PPV %	Relative PPV (95%CI)
EXPERIMENTAL ARM				
HPV **≥1pg/ml**; triage HPV+ by cytology; if cytology <ASCUS repeat both tests and refer if **either** is positive	**9.00**	**1.58 (1.03-2.44)**	**12.1**	**0.78 (0.52-1.16)**
HPV **≥2pg/ml**; if cytology <ASCUS repeat both tests and refer if **both** are positive	**8.83**	**1.55 (1.01-2.40)**	**15.8**	**1.02 (0.69-1.52)**
Experimental procedure	**9.16**	**1.61 (1.05-2.48)**	**8.5**	**0.55 (0.37-0.82)**
CONVENTIONAL ARM				
Conventional Cytology ≥ASCUS	**5.68**	**1.00**	**15.5**	**1.00**

Ronco et al. Lancet Oncol 2006; 7:547-55 modif

NTTC STUDY PHASE 1 – all ages

Relative Sensitivity and relative PPV of experimental (LBC) vs. conventional arm (conventional cytology)

	Histological endpoint		
	CIN1+	CIN2+	CIN3+
Positive if Cytology ≥ASCUS			
% Detection Rate (N cases) conventional arm	0.82 (184)	0.37 (84)	0.24 (53)
% Detection Rate (N cases) experimental arm &	1.38 (313)	0.44 (99)	0.20 (45)
Relative Sensitivity* (95%c.i.)	1.68 (1.40-2.02)	1.17 (0.87-1.56)	0.84 (0.56-1.25)
% PPV conventional arm	27.84	12.7	8.02
%PPV experimental arm&	23.41	7.4	3.37
Relative VPP* (95%c.i.)	0.84 (0.72-0.98)	0.58 (0.44-0.77)	0.42 (0.29-0.62)

& only CIN cases detected by cytology considered * experimental/conventional

Ronco et al. *BMJ* 21 May 2007 (e-pub ahead of print).

Main Outcome: Relative Detection Rate (CIN2+) after 3 years

- In both arms conventional cytology after 3 years
- Among women negative at recruitment provides information about the safety of longer screening intervals
- Overall (# of lesions detected at recruitment + new round) provides information about regression of excess lesions detected by HPV at recruitment

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