

I Risultati dello studio NTCC

Guglielmo Ronco

CPO Piemonte

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

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

Participating centres

Organised screening programmes in:

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

NTCC STUDY

Women randomised by phase

- Phase 1: 45,307
- Phase 2: 49,196

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

NTCC STUDY phase 1 – all ages

Frequency of women with unsatisfactory cytology and with abnormal cytology by arm.

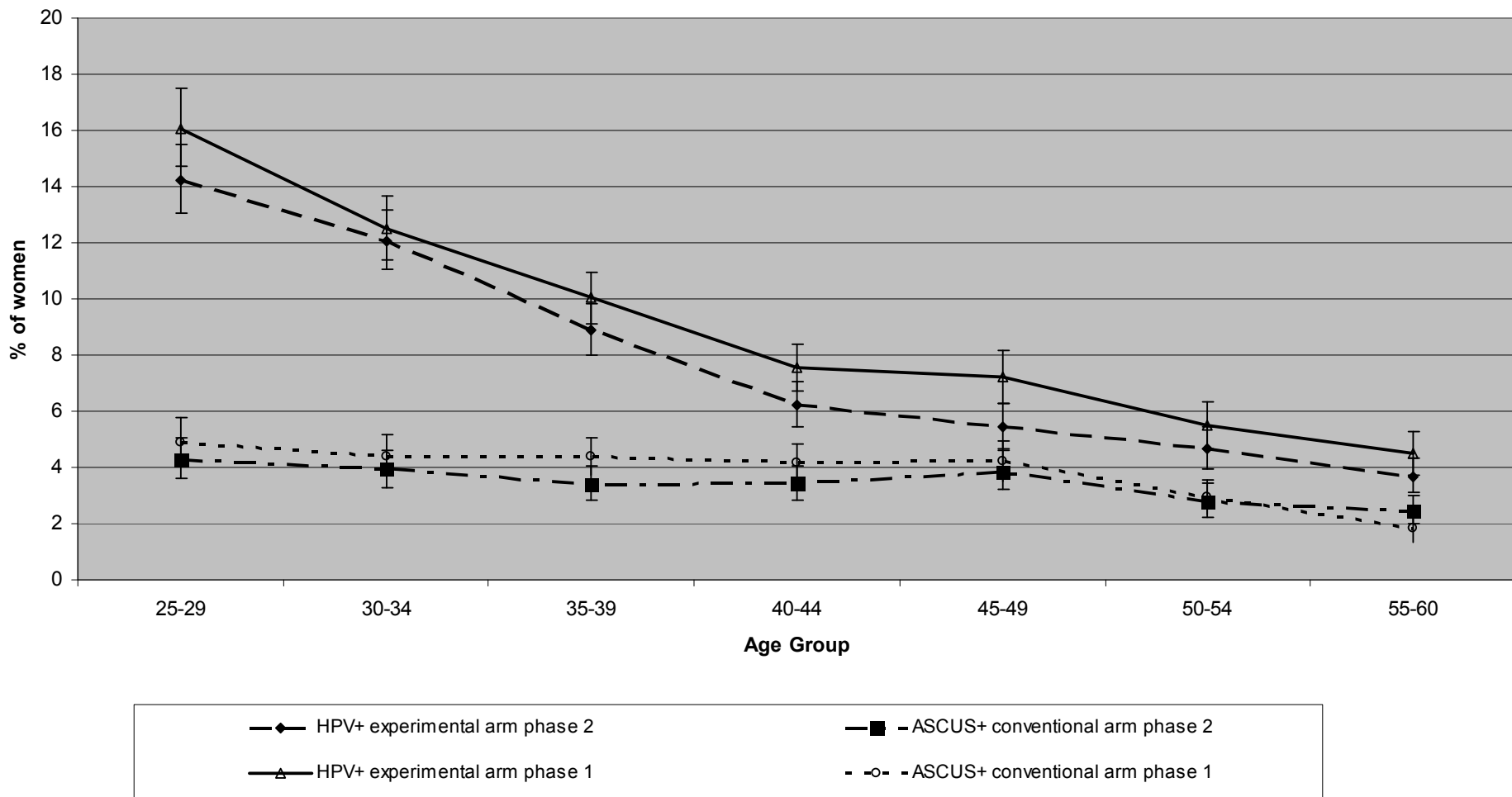
	% (n) Conventional arm	% (n) Experimental arm	Relative frequency* (95%CI)
At least one unsatisfactory cytology (any reason)	4.11 (923)	2.57 (583)	0.62 (0.56-0.69)
At least one unsatisfactory cytology (obscuring inflammation)	2.15 (483)	0.44 (100)	0.21 (0.17-0.25)
At least one unsatisfactory cytology (other reasons)	1.96 (440)	2.13 (483)	1.09 (0.96-1.23)

*experimental/conventional

Denominators are women randomised to the relevant arm. (22466 to conventional and 22708 to experimental)

NTCC study

Proportion of women HPV-positive and with abnormal cytology by age



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 \geq ASCUS

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

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 \geq 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 \geq 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 \geq 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.

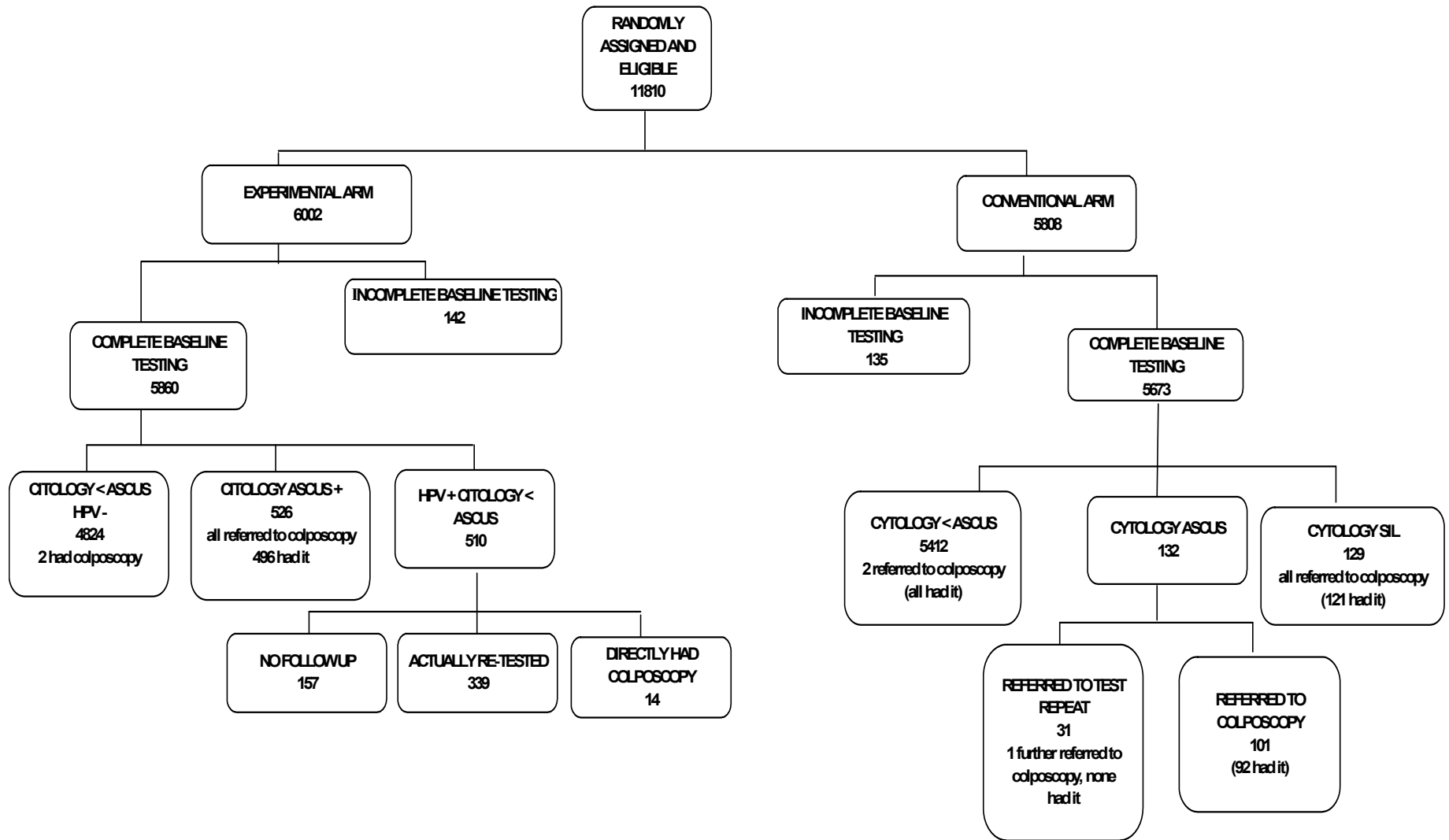
[†]P<.001 versus Liquid-based cytology =ASCUS (McNemar test) [‡]P=0.034 versus Liquid-based cytology =ASCUS (McNemar test)

Relative sensitivity and relative PPV(95% CI) for CIN2+ of HPV testing (1 RLU) vs. conventional cytology \geq ASCUS women age 35-60

	Phase 2	Phase1	Combined	P heterogeneity between phases
Relative sensitivity				
Experimental arm HPV \geq 1pg/ml	1.92 (1.28-2.87)	1.43 (1.00-2.04)	1.63 (1.25-2.12)	0.28
Experimental arm HPV \geq 2pg/ml	1.81 (1.20-2.72)	1.41 (0.98-2.01)	1.57 (1.20-2.06)	0.37
Relative Positive Predictive Value				
Experimental arm HPV \geq 1pg/ml	0.80 (0.55-1.18)	0.58 (0.33-0.98)	0.67 (0.52-0.87)	0.22
Experimental arm HPV \geq 2pg/ml	0.99 (0.67-1.46)	0.75 (0.45-1.27)	0.85 (0.66-1.09)	0.28

NTCC study Phase 1

women age 25-34



NTCC STUDY - Phase I
Women age 25-34
HPV clearance at re-testing
Women previously HPV+ cytology-

Interval (days)	N women	N HPV negative	% clearance (95% ci.i)
180-365	118	59	50.0% (40.7-59.3)
366-547	196	78	60.2% (53.0-67.1)
>547	13	9	69.2% (38.6-90.9)
All	327	186	56.9% (51.3-62.3)

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

Relative sensitivity and relative PPV vs. conventional cytology \geq ASCUS.

Criteria for referral (retrospectively applied)	Detection Rate per 1000	Endpoint CIN2+ Relative sensitivity (95%CI)	PPV %	Relative PPV (95%CI)
EXPERIMENTAL ARM				
HPV ≥ 1 pg/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 ≥ 2 pg/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

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.

Relative sensitivity and relative PPV(95% CI) for CIN2+ of HPV testing (1 RLU) vs. conventional cytology \geq ASCUS

women age 25-34

	Phase 2	Phase1	P heterogeneity between phases
Relative sensitivity			
Experimental arm HPV\geq1pg/ml	3.50 (2.11-5.82)	1.58 (1.03-2.44)	0.019
Experimental arm HPV\geq2pg/ml	3.45 (2.08-5.74)	1.58 (1.03-2.44)	0.021
Relative Positive Predictive Value			
Experimental arm HPV\geq1pg/ml	0.89 (0.55-1.44)	0.78 (0.52-1.16)	0.67
Experimental arm HPV\geq2pg/ml	0.99 (0.62-1.62)	0.84 (0.56-1.25)	0.58

STUDIO NTCC

- **Principali risultati finora:**
 - Citologia liquida non più sensibile che citologia convenzionale
 - Test per DNA di HPV oncogeni più sensibile che citologia convenzionale per neoplasia intraepiteliale (CIN) di alto grado.
 - Associare la citologia al test HPV per lo screening primario migliora solo marginalmente sensibilità ma diminuisce di molto specificità
 - L'invio diretto in colposcopia delle donne HPV positive di età <35aa porta plausibilmente a sopradiagnosi di lesioni regressive e sopratrattamento. Necessario "trriage" con citologia.
 - HPV come test primario con "trriage" pare strategia migliore anche in età 35+
- **Risultati attesi:**
 - Capacità del test HPV di individuare in anticipo CIN persistenti
 - Possibilità di utilizzare intervalli di screening prolungati
 - Ruolo della tipizzazione nel processo di screening

Number of CIN3+ and CIN2+ detected

	CIN2	CIN3	ACIS	AdCa	SCC	CIN3+	CIN2+
Intervention group							
Baseline round (n=8575)	30	60	3	1	4	68(0.8,0.6-1.0)	98(1.1,0.9-1.4)
Subsequent round (n=8413*)	15	22	0	0	2	24(0.3,0.2-0.4)	39(0.5,0.3-0.6)
Both rounds (n=8575)	45	82	3	1	6	92(1.1,0.9-1.3)	137(1.6,1.4-1.9)
Control group							
Baseline round (n=8580)	23	37	1	1	1	40(0.5,0.4-0.6)	63(0.7,0.6-0.9)
Subsequent round (n=8456*)	20	44	3	2	5	54(0.6,0.5-0.8)	74(0.9,0.7-1.1)
Both rounds (n=8580)	43	81	4	3	6	94(1.1,0.9-1.3)	137(1.6,1.4-1.9)

Table 2. Relative Rates of Detection of Cervical Intraepithelial Neoplasia (CIN) or Cancer.*

Variable	Lesions Detected during Entire Study		Lesions Detected by Prevalence Screening†			Lesions Detected by Incidence Screening‡		
	Intervention Group	Control Group	Intervention Group	Control Group	Relative Rate (95% CI)	Intervention Group	Control Group	Relative Rate (95% CI)
	no. (%)					no. (%)		
CIN grade 2 or 3 or cancer	139 (54)	119 (46)	114 (60)	76 (40)	1.51 (1.13-2.02)	25 (37)	43 (63)	0.58 (0.38-1.90)
CIN grade 3 or cancer	88 (51)§	85 (49)	72 (57)	55 (43)	1.31 (0.92-1.87)	16 (35)§	30 (65)	0.53 (0.38-0.98)
CIN grade 2 only	53 (61)	34 (39)	42 (67)	21 (33)	2.01 (1.19-3.40)	11 (46)	13 (54)	0.85 (0.38-1.90)

* CI denotes confidence interval.

† Prevalence screening denotes screening at enrollment and associated follow-up.

‡ Incidence screening denotes screening taking place after the prevalence screening.

§ In two women, grade 2 lesions were detected by prevalence screening and grade 3 lesions were subsequently by incidence screening in the next round

Detection of precancerous lesions by screening round according to test used

