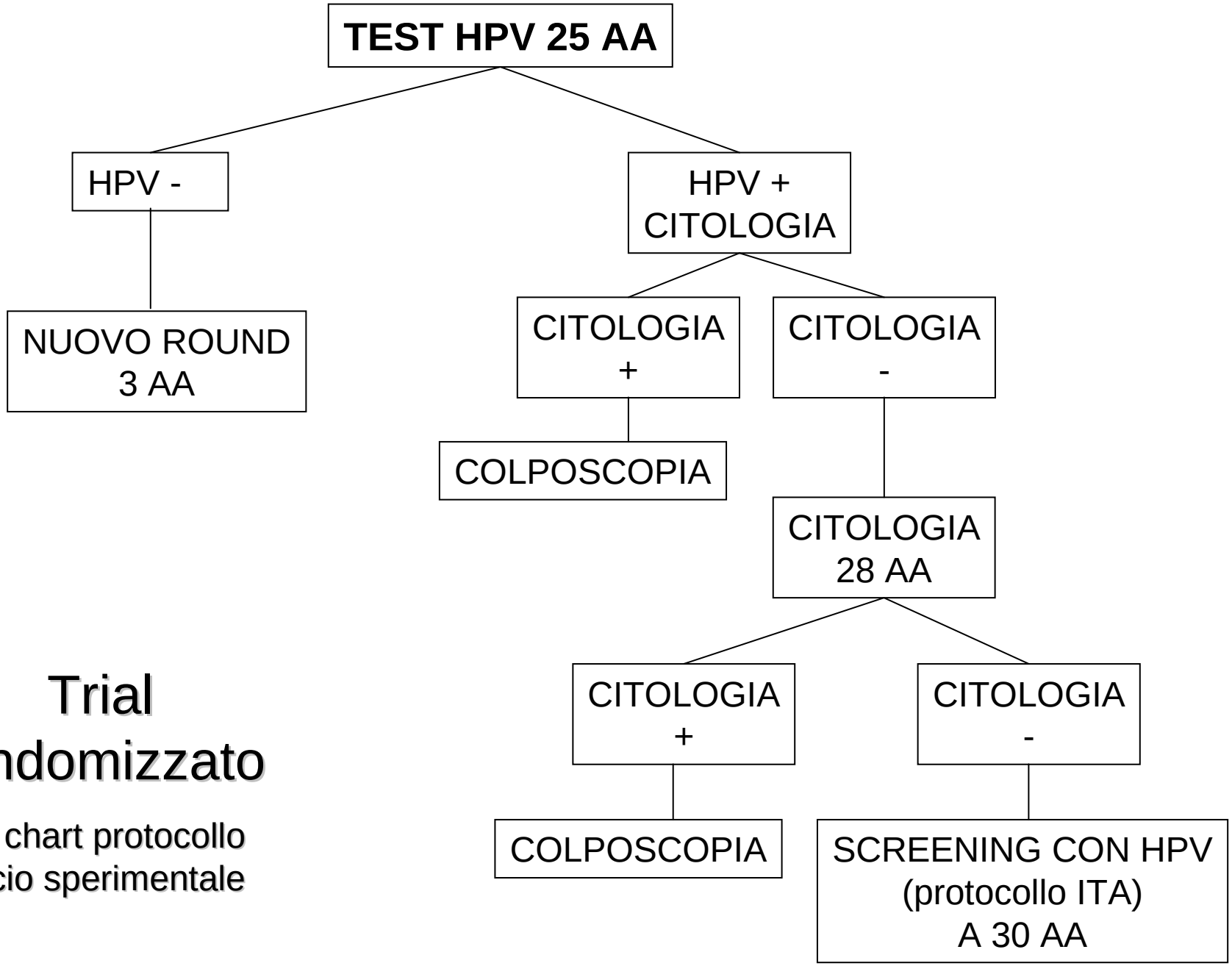
Ricerca e screening: i progetti di ricerca in corso

Guglielmo Ronco
CRPT
Città della Salute e della Scienza di Torino

STUDIO HPV GIOVANI
Background

- Screening con HPV non raccomandato sotto 30 aa di età
  - Uno studio (NTCC) ma non un altro (POBASCAM) indica maggiore sopradiagnosi di lesioni regressive nelle giovani con HPV **(Ronco et al Lancet Oncol 2010 Rijkaart et al Lancet Oncol 2012)**
  - Trattamento CIN legato a problemi in gravidanza **(Kyrgiou et al Lancet 2009)**
- Comunque sopradiagnosi rilevante anche con citologia (1/3 delle CIN3 progredisce a Ca in 30 anni, **McCredie et al. Lancet Oncol 2008**)
- Rischio di Ca entro 5.5 anni dopo test HPV- metà che rischio Ca entro 3.5 aa dopo test citologico negativo (**Ronco et al Lancet 2014**)

- Usare test HPV per selezionare a 25 anni le donne che hanno bisogno di screening fino a 30
- Si attende che sopradiagnosi e invio in colposcopia siano addirittura inferiori a quelli con screening citologico



Trial randomizzato

Flow chart protocollo
braccio sperimentale

STUDIO HPV GIOVANI
Stato avanzamento

- Finanziato da Ministero Salute (Ricerca Finalizzata 2014)
- Data ufficiale avvio 1/12/2016
- Approvato da Comitato etico Città dalla Salute
- In attesa modifiche programma gestione screening

Screening nelle vaccinate

- Consensus conference nazionale (Giorgi-Rossi et al. Prev Med 2016)
- Previsto utilizzo dati da donne vaccinate a 16 anni per determinare prolungamento intervallo screening
- Reclutare coorti di donne vaccinate a 16 anni e negative per HPV a 25 anni
- Valutare detection rate di CIN3+ a 30 anni
- Se significativamente < 1/1000 donne screenate prolungare di 1 anno
- Iterare per prolungamenti ulteriori

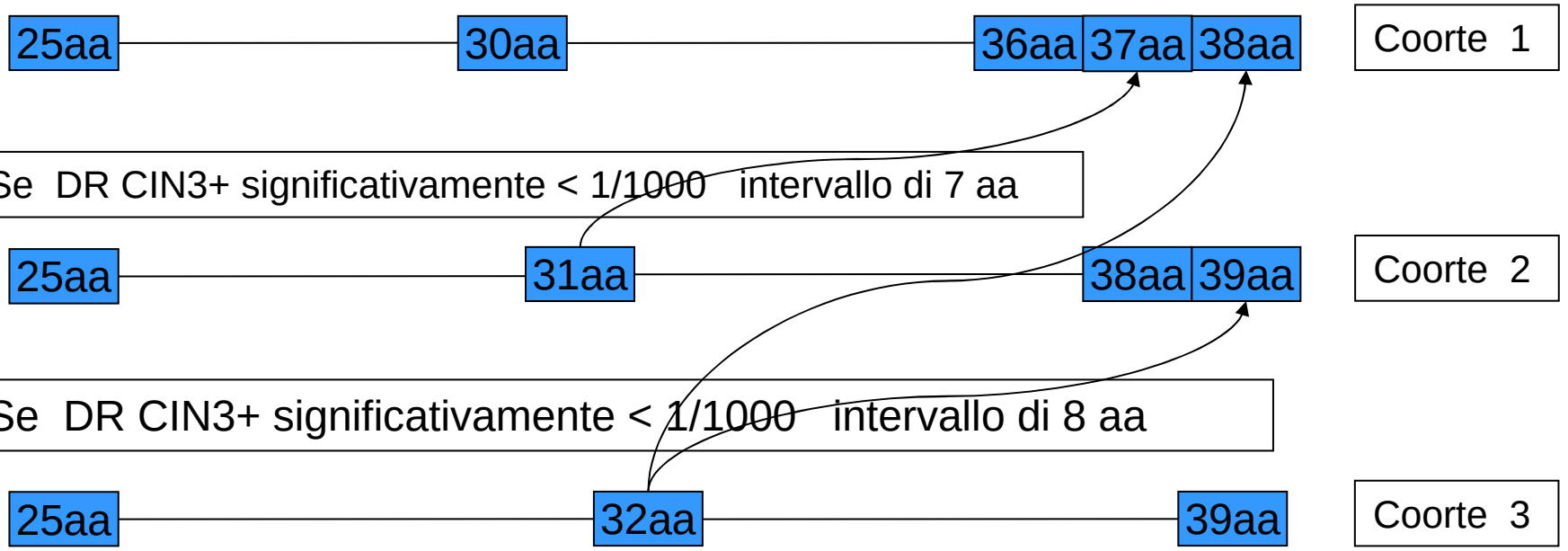
Screenate con HPV

Screenate con HPV e negative round precedente.

Calcolo DR CIN3+

donne vaccinate a 16 aa

Se DR CIN3+ significativamente < 1/1000 intervallo di 6 aa



Possibile anche confronto con coorte 00 di donne non vaccinate screenate con HPV a 25 aa

Altre valutazioni

- Associazione vaccinazione/partecipazione screening
- Riduzione prevalenza infezioni HPV (tipi vaccinali e non) e CIN2/3 nelle vaccinate (efficacia vaccino)
- Idem nelle non vaccinate di coorti vaccinate (herd effect)
- Type replacement
- VPP screening in vaccinate

Stato avanzamento

- Concesso finanziamento CCM per implementazione consensus conference (a cordata Regioni, capofila Toscana)
- Legato a progetto HPV giovani
- In attesa modifiche sistema informatico

Triage donne HPV+

- Uso combinato citologia, p16 e genotipizzazione — FP7
- Metilazione geni umani
- Metilazione geni virali — AIRC
- miRNA
- M-RNA e p16 — Ricerca finalizzata

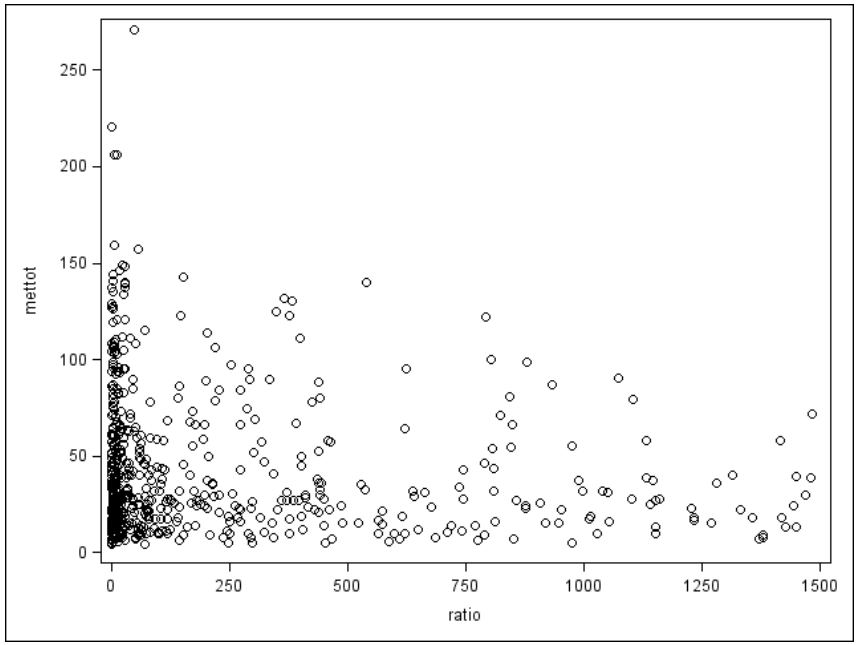
Cross-sectional accuracy for combinations of cytology, p16 immunostaining and HPV genotypes for HPV positive woman

	HSIL+	HSIL+ or HPV16/18	HSIL+ or HPV33/16/35/59/31+	HSIL+ or p16+	HSIL+ or p16+ or HPV16/18	HSIL+ or p16+ or HPV33/16/35/59/31+
N(%)[1]	80 (7.33%)	428 (39.23%)	522 (47.85%)	474 (43.45%)	679 (62.24%)	747 (68.47%)
Endpoint CIN2+						
N	49/92	70/92	81/92	82/92	87/92	90/92
Sensitivity	53.26 (42.56, 63.74)	76.09 (66.06, 84.37)	88.04 (79.61, 93.88)	89.13 (80.92, 94.66)	94.57 (87.77, 98.21)	97.83 (92.37, 99.74)
Specificity	96.90 (95.62, 97.88)	64.16 (61.10, 67.14)	55.86 (52.71, 58.96)	60.76 (57.65, 63.80)	40.74 (37.67, 43.86)	34.23 (31.29, 37.27)
PPV	**61.25** (49.70, 71.94)	**16.36** (12.98, 20.21)	**15.52** (12.52, 18.91)	**17.30** (14.00, 21.01)	**12.81** (10.39, 15.56)	**12.05** (9.80, 14.60)
1-NPV	4.25 (3.09, 5.69)	3.32 (2.09, 4.98)	1.93 (0.97, 3.43)	1.62 (0.78, 2.96)	1.21 (0.40, 2.81)	0.58 (0.07, 2.08)
Endpoint CIN3+						
N	24/40	34/40	37/40	38/40	39/40	39/40
Sensitivity	**60.00** (43.33, 75.14)	**85.00** (70.16, 94.29)	**92.50** (79.61, 98.43)	**95.00** (83.08, 99.39)	**97.50** (86.84, 99.94)	**97.50** (86.84, 99.94)
Specificity	94.67 (93.14, 95.95)	62.51 (59.51, 65.45)	53.85 (50.78, 56.90)	58.52 (55.47, 61.51)	39.11 (36.14, 42.13)	32.64 (29.81, 35.56)
PPV	30.00 (20.26, 41.28)	7.94 (5.56, 10.92)	7.09 (5.04, 9.64)	8.02 (5.74, 10.84)	5.74 (4.12, 7.77)	5.22 (3.74, 7.07)
1-NPV	**1.58** (0.91, 2.56)	**0.90** (0.33, 1.96)	**0.53** (0.11, 1.53)	**0.32** (0.04, 1.17)	**0.24** (0.01, 1.34)	**0.29** (0.01, 1.61)

Rischio di CIN3 nelle negative estremamente basso consente richiamo ad intervallo molto lungo.
PPV per CIN2+ >10%

Metilazione virale

Methylation significantly decreases with increasing ln(RLU Ratio)

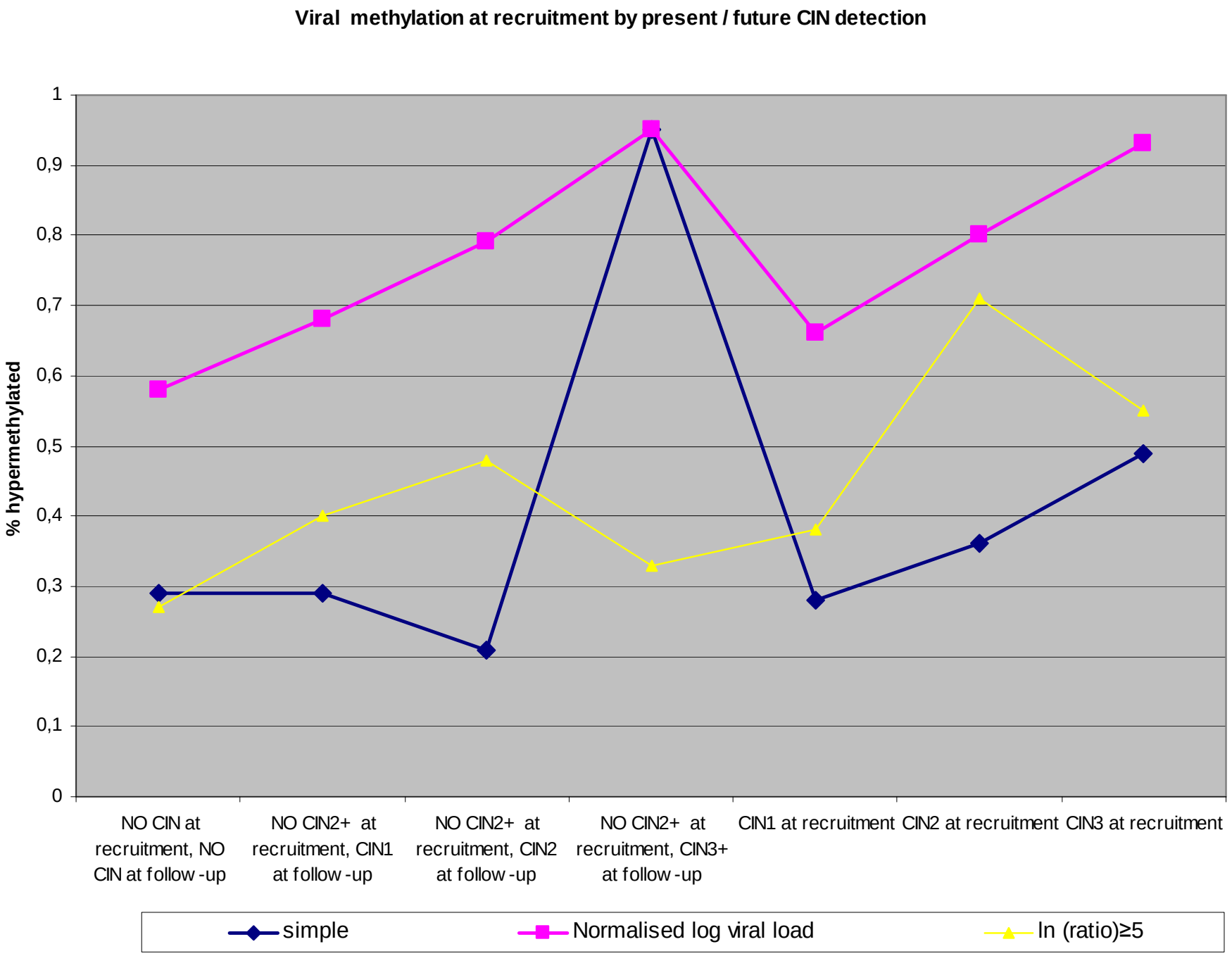


Methylation levels rapidly decrease with increasing viral load. Stable low levels above RLU ratio 200-250

Overall methylation in women with no CIN at baseline nor f.u.

- Beta for ln(RLU ratio) = -2.23 ($p<0.0001$) Type-adjusted
- Linear effect of viral load not significant: Beta for 100 RLU ratio = -0.022 ($p=0.23$) Type-adjusted

- "ratio normalized" methylation computed as methylation x ln(ratio)

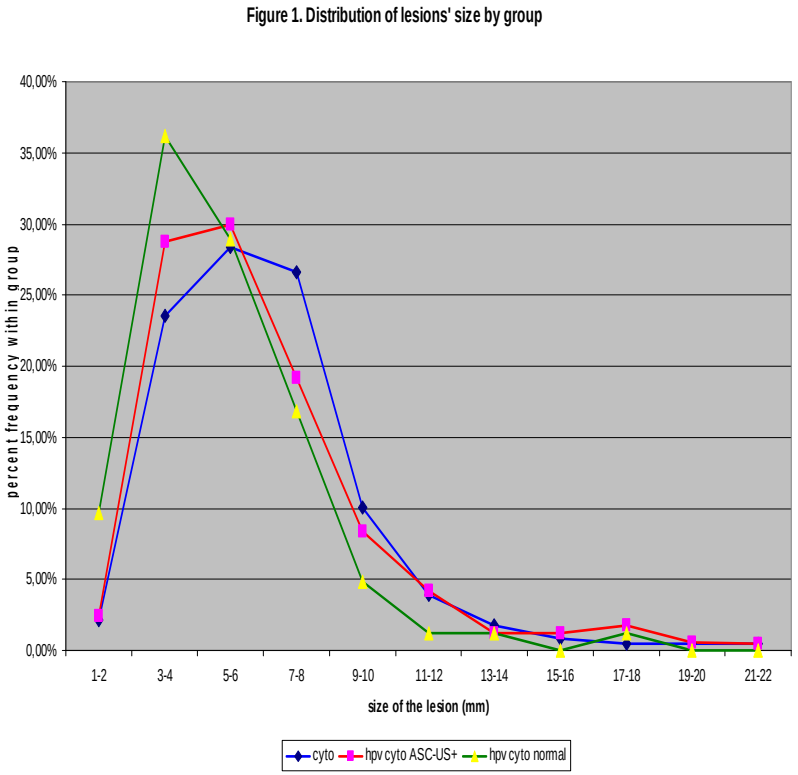

Viral methylation at recruitment by present / future CIN detection
% hypermethylated
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
NO CIN at recruitment, NO CIN at follow-up
NO CIN2+ at recruitment, CIN1 at follow-up
NO CIN2+ at recruitment, CIN2 at follow-up
NO CIN2+ at recruitment, CIN3+ at follow-up
CIN1 at recruitment
CIN2 at recruitment
CIN3 at recruitment
simple
Normalised log viral load
ln (ratio)≥5

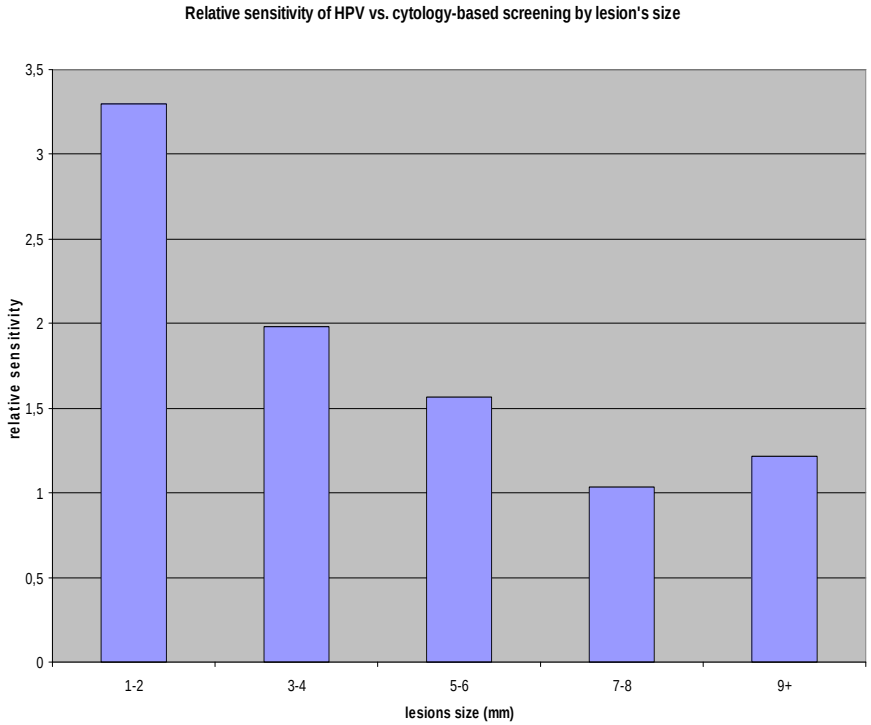
Conclusions

- Hyper-methylation (and low viral load) seems very early marker to identify infections imprinted to result in CIN3
- Proportion hypermethylated strongly reduced (and viral load increased) in women who already have a CIN3. Ratio-normalised methylation has good cross-sectional sensitivity for CIN3.
- Process seems concluded when CIN3 become detectable. Samples taken close to CIN3 detected at f.u. (recently arisen) not different from those taken close to CIN3 detected at baseline (possibly long-lasting).
- Women with current CIN2 intermediate between those with current CIN3 and currrent CIN1. Data do not support that lesions initially oriented to CIN1/2 change orientation to CIN3.

Dimensioni CIN2/3 identificate mediante citologia

o mediante test HPV





Confronto con quelle trovate da sola citologia

Lesioni HPV+ cito+ :dimensioni simili

Lesioni trovate perché HPV+ persistente: dimensioni ridotte

Calcolata sensibilità relativa HPV vs. cito secondo dimensioni lesione (funzione esponenziale negativa)

Linkage colposcopies and cancer registry Torino 1992-2012

	IRR vs. never abnormal cytology adj. age	
	All cancers	Detected > 6 months from 1st colposcopy
Never abnormal cytology	1	1
Abnormal cytology no colposcopy	**46.30** (25.12-85.34)	37.14 (19.12-72.18)
1st colposcopy without biopsy referral cytology not HSIL/ASC-H	**9.25** (3.39-25.22)	7.21 (2.28-22.81)
1st colposcopy without biopsy, referral cytology ≥HSIL/ASC-H	**441.51** (139.20-1400)	324.76 (79.59-1325)
1st colposcopy with biopsy<CIN2	**5.60** (2.27-13.75)	3.39 (1.07-10.73)

225,186 women
2,443,551 years of f.u
155 ICC

IRR biopsy vs. no biopsy at 1st colposcopy

Adjusted age and referral for HSIL/ASC-H cytology

Cancers detected >6 months from 1st colposcopy

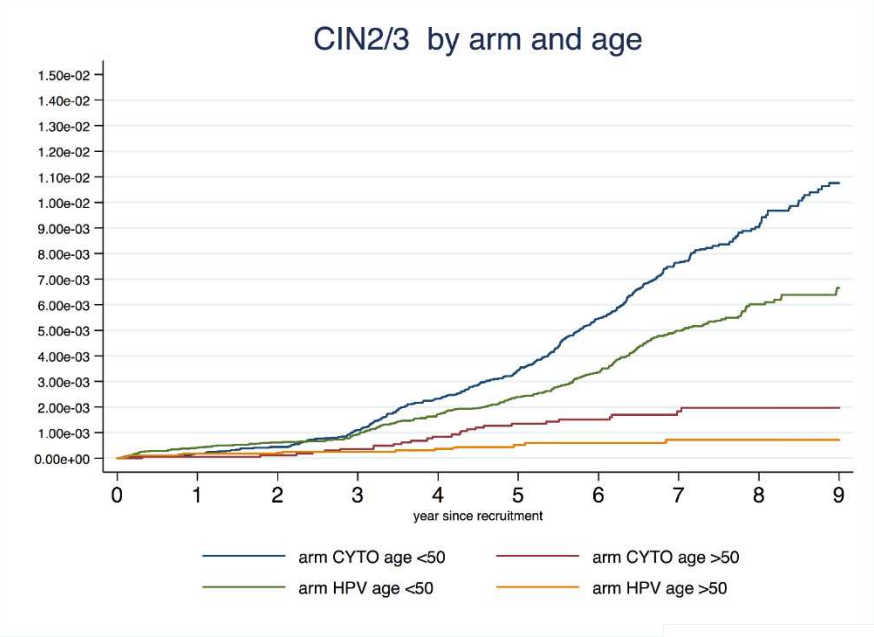
0.34 (0.10-1.18)

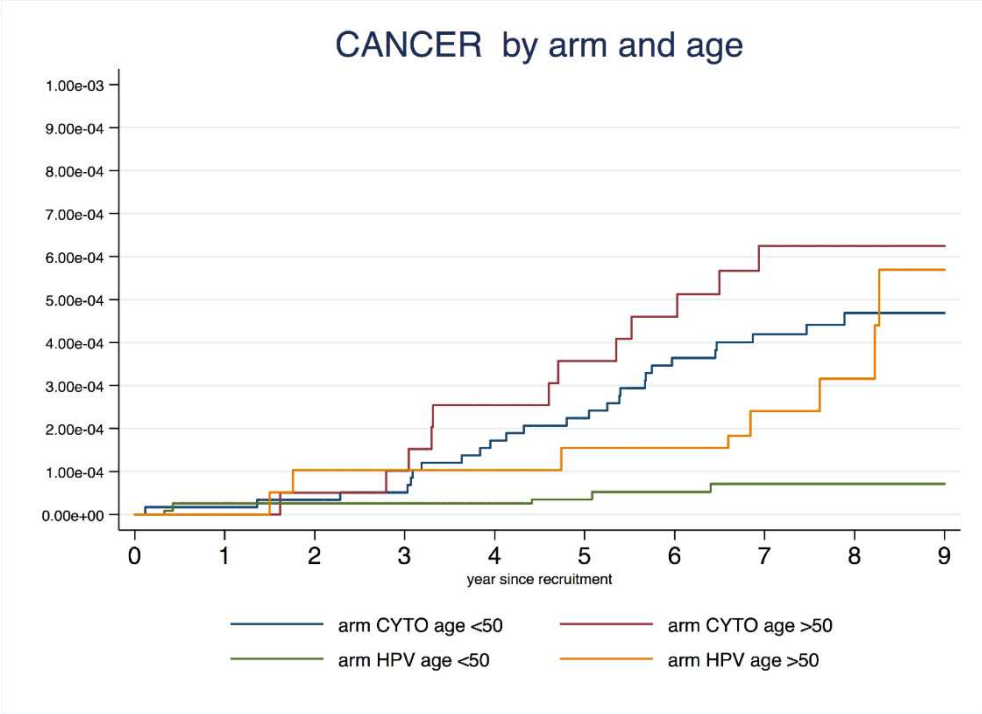
Screening in older women

Pooled analysis of the 4 EU RCTs (cfr Ronco et al Lancet 2014) by age <50 vs. ≥50

Both after negative cytology and negative HPV test

- Detection of CIN2/3 **decreases** in women age ≥50 years
- Risk of invasive cervical cancer (ICC) **increases** in women age ≥50 years


CIN2/3 by arm and age
1.50e-02
1.40e-02
1.30e-02
1.20e-02
1.10e-02
1.00e-02
9.00e-03
8.00e-03
7.00e-03
6.00e-03
5.00e-03
4.00e-03
3.00e-03
2.00e-03
1.00e-03
0.00e+00
0
1
2
3
4
5
6
7
8
9
year since recruitment
arm CYTO age <50
arm CYTO age >50
arm HPV age <50
arm HPV age >50


CANCER by arm and age
1.00e-03
9.00e-04
8.00e-04
7.00e-04
6.00e-04
5.00e-04
4.00e-04
3.00e-04
2.00e-04
1.00e-04
0.00e+00
0
1
2
3
4
5
6
7
8
9
year since recruitment
arm CYTO age <50
arm CYTO age >50
arm HPV age <50
arm HPV age >50

Why do CIN2/3 decrease and ICC increase?

Hypothesis: Cytology has low sensitivity for a subset of precancerous lesions

HYPOTHESIS TESTED BY MATEMATICAL MODEL

- Models with and without HGCIN difficult to detect by cytology (sensitivity 5%).
- 3-year ICC risk after negative cytology by age predicted
- Different models represent different theories
- Theory predictions compared with observations (above)

HGCIN,among women cytology negative at baseline:

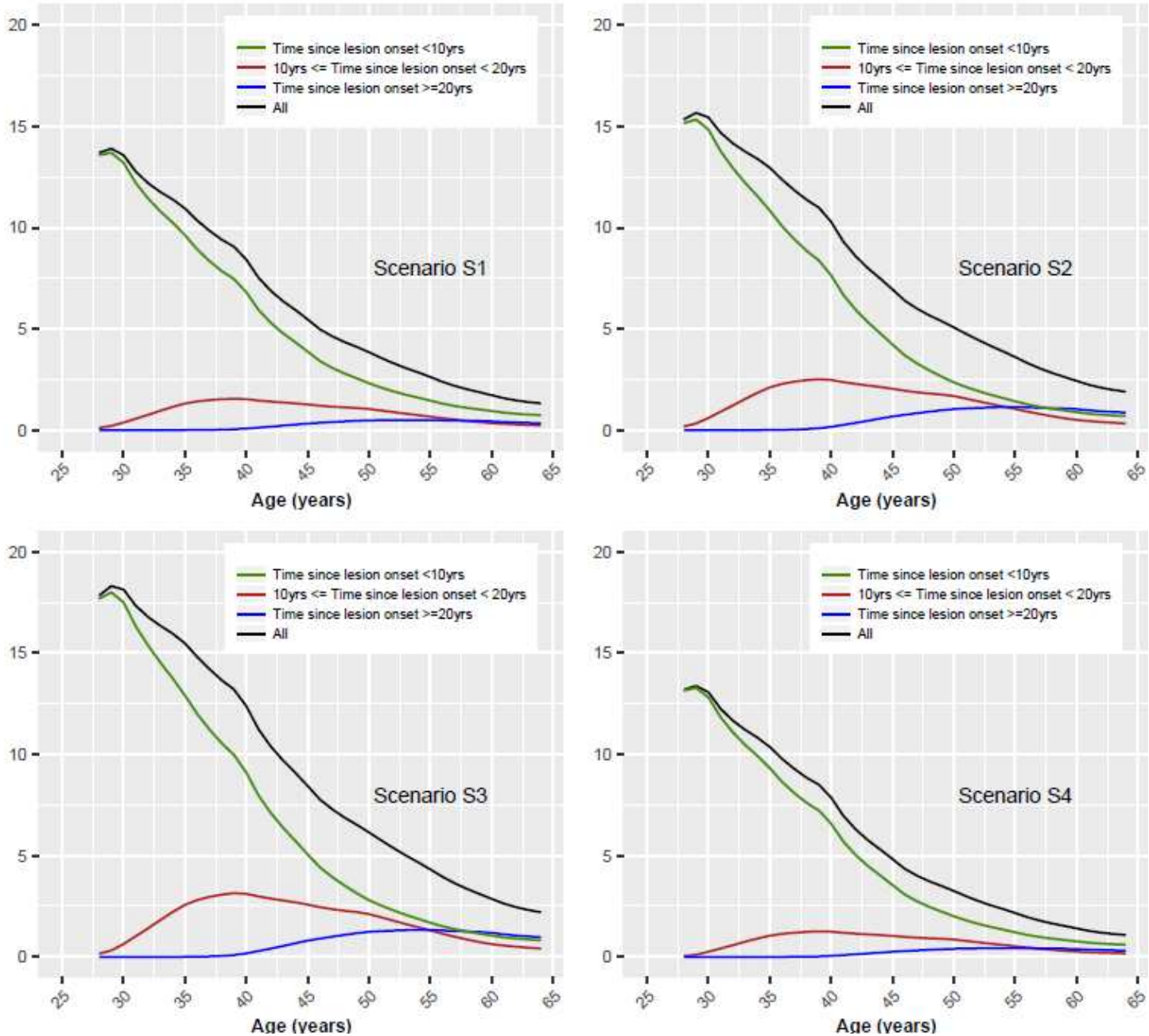
- In the models with difficult-to-detect 3-year risk of ICC **INCREASES** from 25-49 to 50+
- In the models without difficult-to-detect 3-year risk of ICC **DECREASES** from 25-49 to 50+
- CIN2/3 detection decreases in women 50+ with all models

		3-year cumulative detection of CIN2/3 (per 1000)				3-year cumulative cervical cancer incidence (per 100,000)			
Scenario	N*	25-49 years		50-64 years		25-49 years		50-64 years	
Two types of lesion		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
S1	133	4,02	(3,86 - 4,18)	0,93	(0,82 - 1,03)	8,97	(7,48 - 10,45)	10,74	(9,99 - 11,48)
S2	30	3,99	(3,89 - 4,09)	0,92	(0,83 - 1,00)	10,38	(8,74 - 12,01)	13,91	(12,75 - 15,07)
S3	35	4,02	(3,91 - 4,14)	0,95	(0,87 - 1,04)	11,46	(9,67 - 13,24)	16,33	(15,00 - 17,66)
S4	68	4,05	(3,95 - 4,15)	0,94	(0,83 - 1,04)	7,82	(6,39 - 9,26)	8,46	(7,77 - 9,14)
S5	117	4,27	(4,10 - 4,44)	1,19	(1,10 - 1,29)	10,68	(9,18 - 12,19)	15,23	(13,67 - 16,80)
One type of lesion									
S10	16	4,11	(4,08 - 4,14)	1,05	(0,95 - 1,15)	6,00	(5,34 - 6,66)	2,97	(2,74 - 3,20)
S11	5	4,10	(4,10 - 4,11)	0,97	(0,97 - 0,98)	6,58	(5,89 - 7,27)	4,12	(3,83 - 4,41)
S12	2	4,16	(4,15 - 4,17)	1,05	(1,04 - 1,05)	7,15	(6,05 - 8,24)	4,77	(4,66 - 4,87)

*Number of simulations with acceptable fit to population data

Trial Simulation

Cin23 Prevalence at second round per 1000 enrolled women



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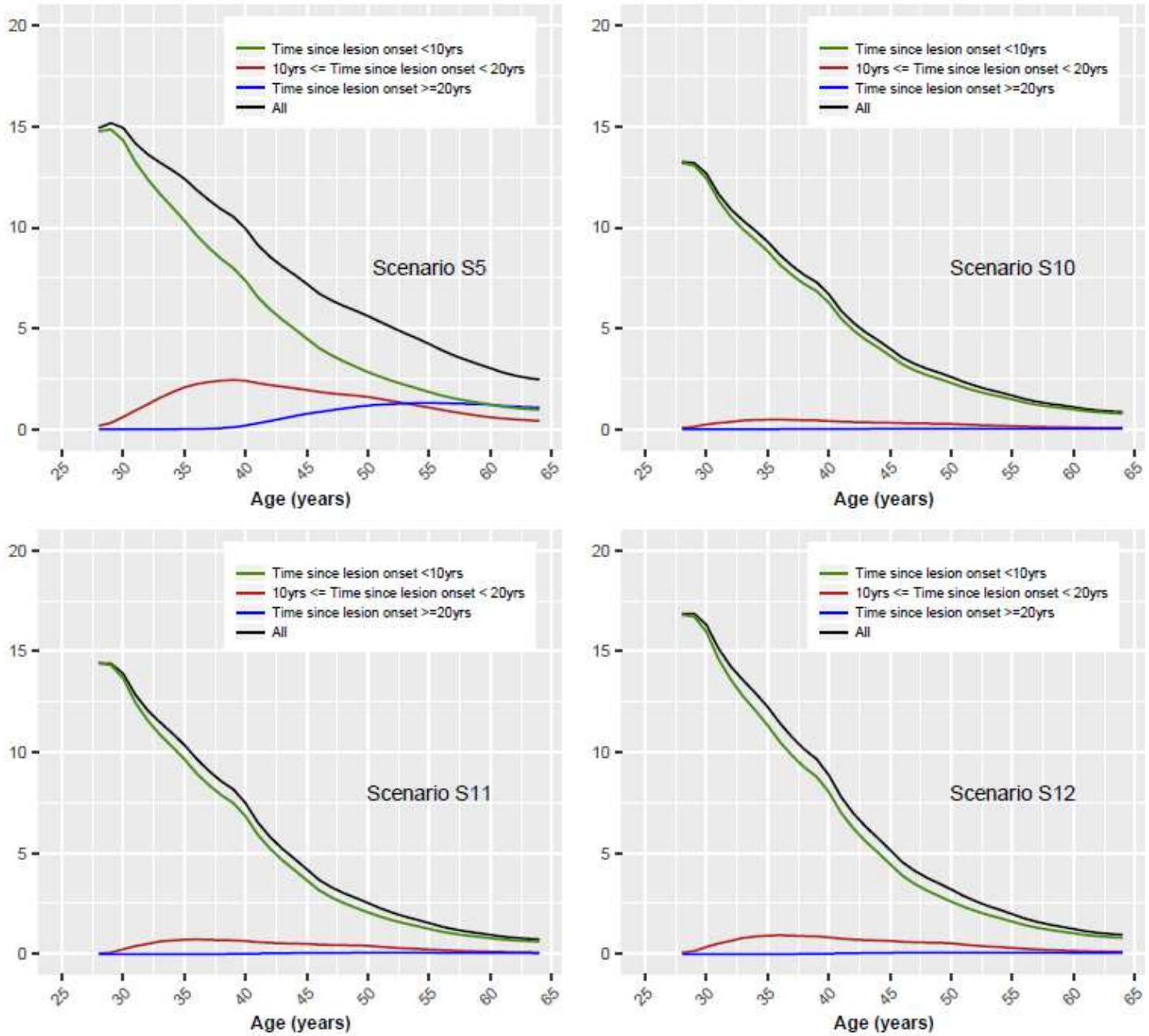

Conclusions

- The sensitivity of cytology for a sub-group of HGCIN is very low
- This results in an accumulation of long-lasting lesions at high risk of invasion in women aged ≥50 years
- This causes higher ICC risk after negative cytology in women aged ≥50 than in those <50
- The same happens, at lower absolute level also after a first negative HPV test
- HPV testing removes these lesions (KPNC cohort)
- Effect expected to disappear after repeated HPV screening rounds allowing longer intervals at older age