HPV and cervical cancer epidemiology

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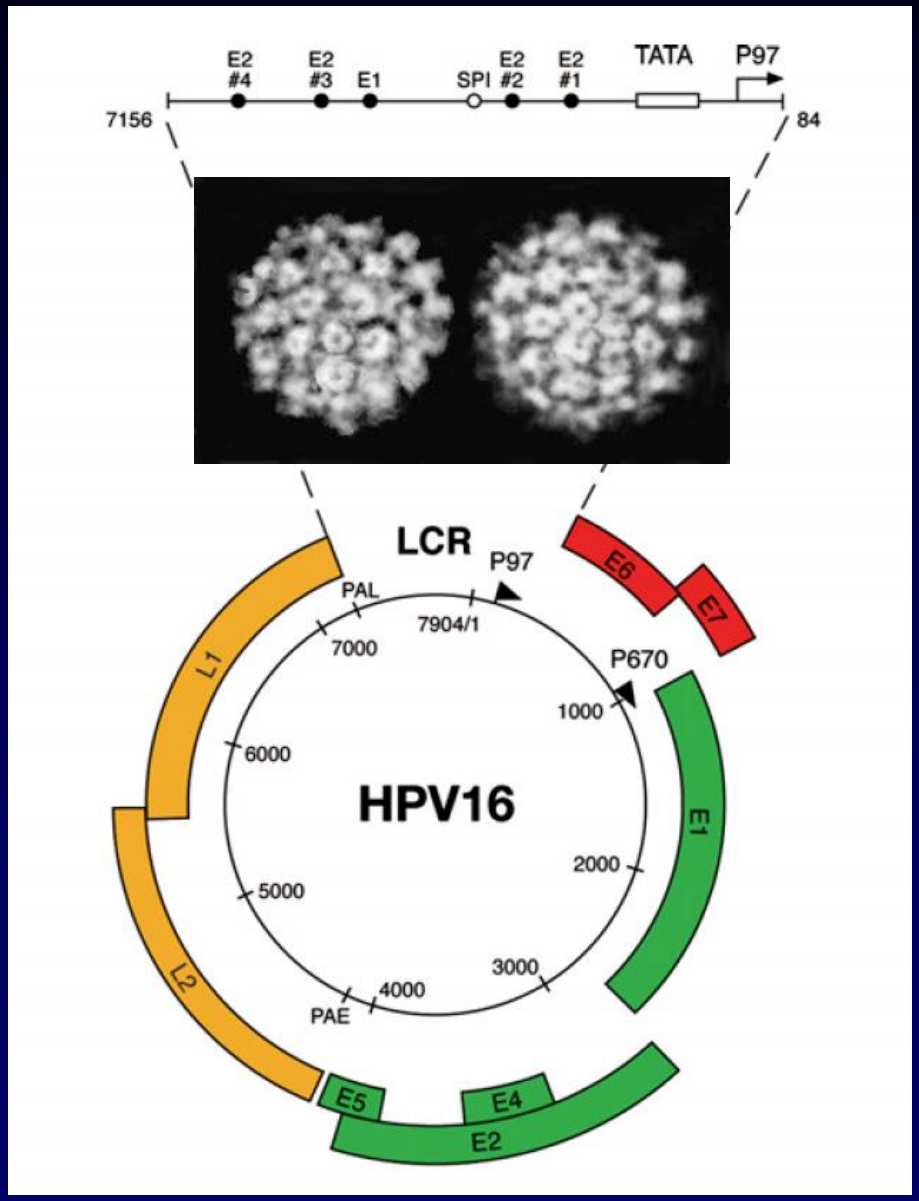
Human papillomaviruses (HPVs)

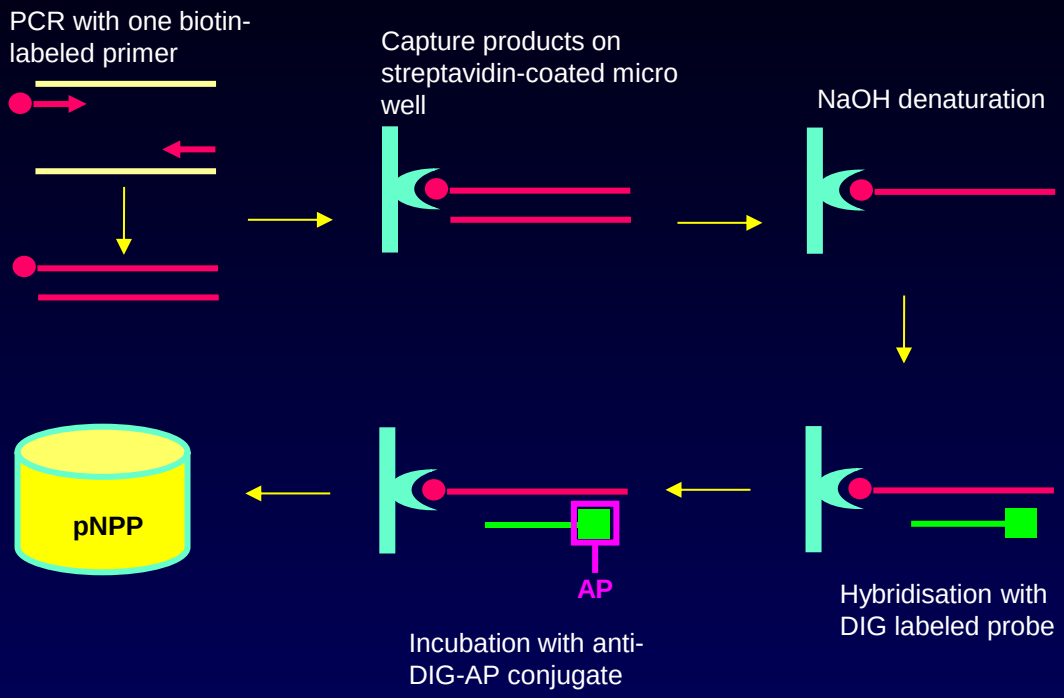
- Small DNA viruses
  - Circular, double stranded DNA genome (8 kb); 6 early ORFs (E1-E7), 2 late ORFs (L1, L2)
- More than 200 different HPV types identified; strictly epitheliotropic: cutaneous or mucosal
- More than 40 mucosal HPV types: low-risk or high-risk, depending on their association with benign or (pre)malignant lesions

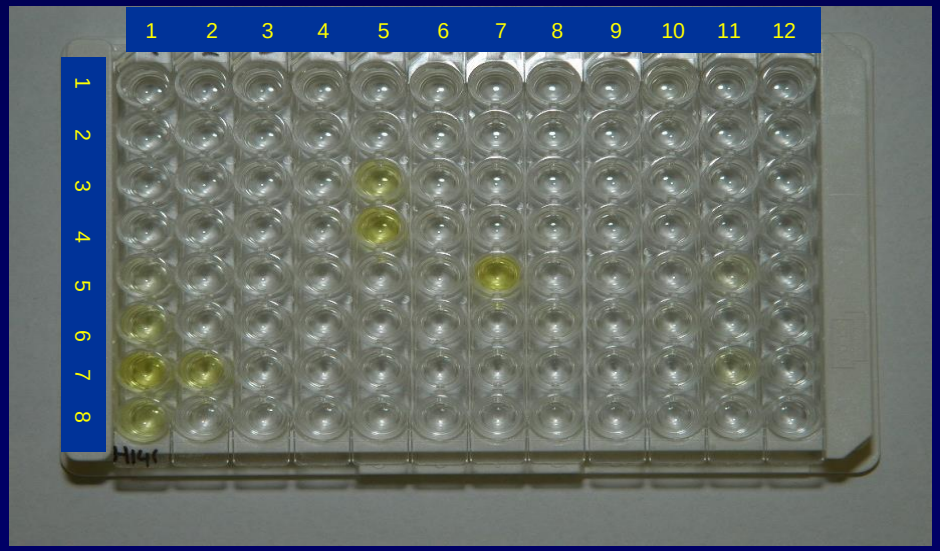


GP5+/6+ consensus PCR system (L1 region)

GP5+	5’- TTTGTTACTGTGGTAGATACTAC -3’	
GP6+	3’- CTTATACTAAATGTCAAATAAAAAG -5’	
HPV 16	TTTGTTACTGTTGTTGATACTAC (2)	CTTATACTAAATGTCAAATAAAAAG
HPV 18	TTTGTTACTGTGGTAGATACCAC (1)	CTTATACTAAACGTCAAATAAAAAG (1)
HPV 31	TTTGTTACTGTGGTAGATACCAC (1)	CTTAACTAAATGTTAAATATAAAG (3)
HPV 33	TTTGTTACTGTGGTAGATACCAC (1)	CTTATACTAGATGTCAAACAAAAAG (2)
HPV 35	TTTGTTACTGTAGTTGATACAAC (3)	CTTATACTAAATGTCAAATAAAAAG
HPV 39	TTTCTTACTGTTGTGGACACTAC (4)	CTCATACTAAATGTTAAATATAAAG (3)
HPV 45	TTTGTTACTGTAGTGGACACTAC (3)	CTTATACTAAATGTCAAATAAAAAG
HPV 51	TTTATTACCTGTGTTGATACTAC (6)	CTCATACTTAACGTTAAATAAAAAG (4)
HPV 52	TTTGTCACAGTTGTGGATACCAC (5)	CTTAAACTAAATGTTAAATAAAAAG (2)
HPV 56	TTTGTTACTGTAGTAGATACTAC (1)	CTTATACTTAATGTTAAACAAAAAG (3)
HPV 58	TTTGTTACCGTGGTTGATACCAC (3)	CTTATACTGAATGTCAAACAAAAAG (2)
HPV 59	TTTTTAACAGTTGTAGATACTAC (4)	CTTAAACTAAACGTCAAATATAAAG (3)
HPV 66	TTTGTTACTGTTGTGGATACTAC (2)	CTTATACTTGATGTCAAACACAAAG (4)
HPV 68	TTTCTTACTGTTGTGGATACCAC (4)	CTTATACTAAACGTTAAATATAAAG (3)

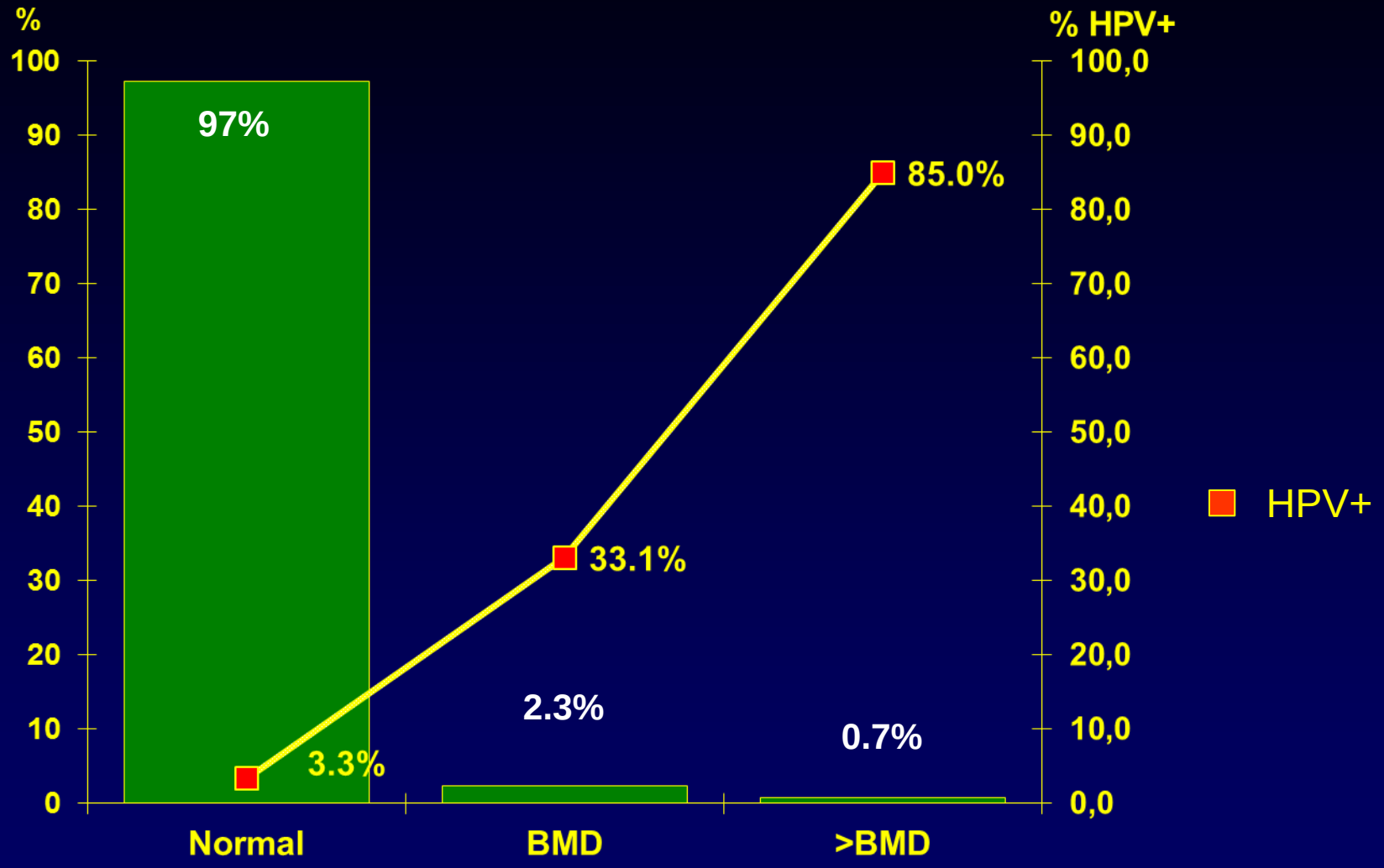
GP5+/6+-PCR read-out for high-througput analysis





Association with disease

High-risk HPV prevalence per cytology class



HPV prevalence increases proportional to disease severity

BMD= borderline or mild dyskaryosis (ASCUS/LSIL)

JOURNAL OF PATHOLOGY
J. Pathol. **189**: 12–19 (1999)

HUMAN PAPILLOMAVIRUS IS A NECESSARY CAUSE OF INVASIVE CERVICAL CANCER WORLDWIDE

JAN M. M. WALBOOMERS[1]*, MARCEL V. JACOBS[1], M. MICHELE MANOS[2], F. XAVIER BOSCH[3], J. ALAIN KUMMER[1], KEERTI V. SHAH[2], PETER J. F. SNIJDERS[1], JULIAN PETO[4], CHRIS J. L. M. MEIJER[1] AND NUBIA MUÑOZ[5]

The NEW ENGLAND JOURNAL of MEDICINE

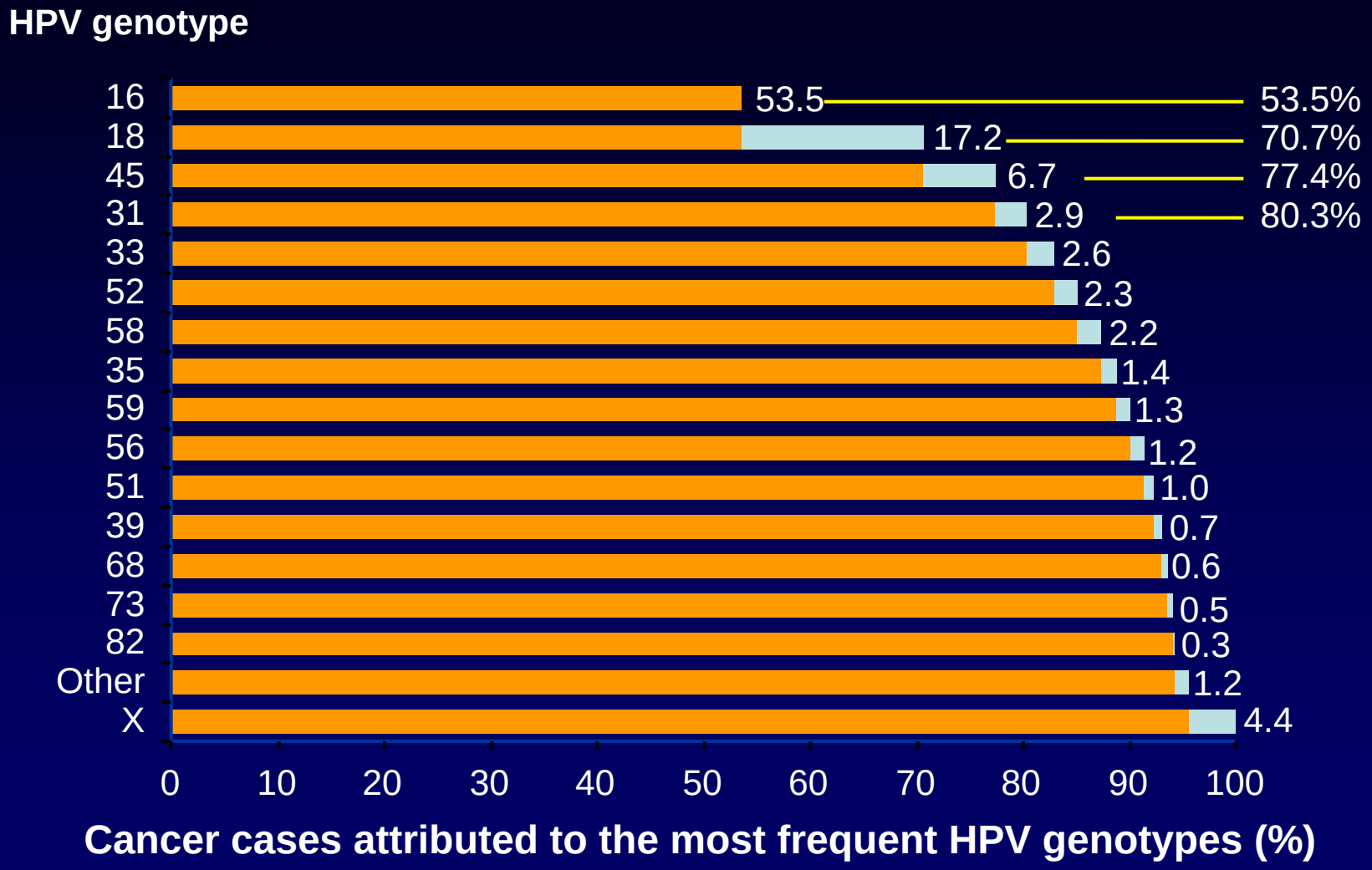
ORIGINAL ARTICLE

Epidemiologic Classification of Human Papillomavirus Types Associated with Cervical Cancer

Nubia Muñoz, M.D., F. Xavier Bosch, M.D., Silvia de Sanjosé, M.D., Rolando Herrero, M.D., Xavier Castellsagué, M.D., Keerti V. Shah, Ph.D., Peter J.F. Snijders, Ph.D., and Chris J.L.M. Meijer, M.D., for the International Agency for Research on Cancer Multicenter Cervical Cancer Study Group*

Munoz N et al. 2003

HPV types in cervical cancer worldwide

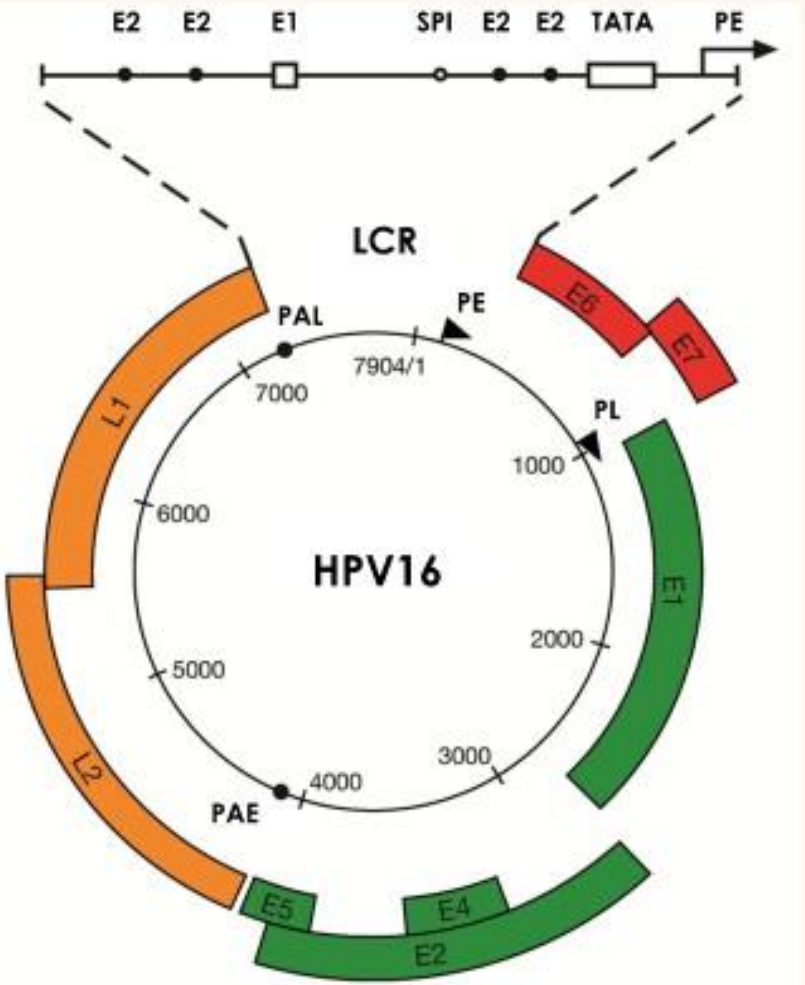


Munoz N et al. *Int J Cancer* 2004;111:278–85.

A

Genus + Species	Type	Invasive Cervical Cancer	IARC Category	Squamous Cell Carcinoma	Adeno Carcinoma	Tropism
Alpha 1	HPV32		3			mucosal
	HPV42					
Alpha 2	HPV3					
	HPV10					
	HPV28		3			
	HPV29		3			cutaneous
	HPV77		3			
	HPV94					
	HPV117					
	HPV125					
Alpha 3	HPV61	0.01	3			
	HPV62		3			
	HPV72		3			
	HPV81		3	0.4		
	HPV83		3	0.4		
	HPV84		3			mucosal
	HPV86		3			
	HPV87		3			
	HPV89		3			
	HPV102					
	HPV114					
Alpha 4	HPV2		3			
	HPV27		3			cutaneous
	HPV57		3			
Alpha 5	HPV26	0.37	2B	0.22		
	HPV51	1.25	1	0.75	0.54	
	HPV69	0.08	2B			
	HPV82	0.07	2B	0.26		
Alpha 6	HPV30	0.37	2B			
	HPV53	0.26	2B	0.04		
	HPV56	0.84	1	1.09		
	HPV66	0.08	2B	0.19		mucosal
Alpha 7	HPV18	10.28	1	11.27	37.3	
	HPV39	1.67	1	0.82	0.54	
	HPV45	5.68	1	5.21	5.95	
	HPV59	1.08	1	1.05	2.16	
	HPV68	1.04	2A	0.37		
	HPV70	0.11	2B			
	HPV85		2B			
	HPV97					
Alpha 8	HPV7		3		41.62	
	HPV40		3		1.08	cutaneous
	HPV43				0.54	(mucosal)
	HPV91	0.01	3		1.08	
Alpha 9	HPV16	61.35	1	54.38		
	HPV31	3.35	1	3.82	0.54	
	HPV33	3.83	1	2.06		
	HPV35	1.94	1	1.27		mucosal
	HPV52	2.71	1	2.25		
	HPV58	2.22	1	1.72		
	HPV67	0.31	2B			
Alpha 10	HPV6	0.11	3	0.07		
	HPV11	0.02	3	0.07		
	HPV13		3			mucosal
	HPV44	0.01	3			
	HPV74	0.01	3			
Alpha 11	HPV34	0.07				mucosal
	HPV73	0.52		0.49		
Alpha 12	HPV73					
Alpha 13	HPV54					
Alpha 14	HPV71					mucosal
	HPV90		3			
	HPV106		3			

B

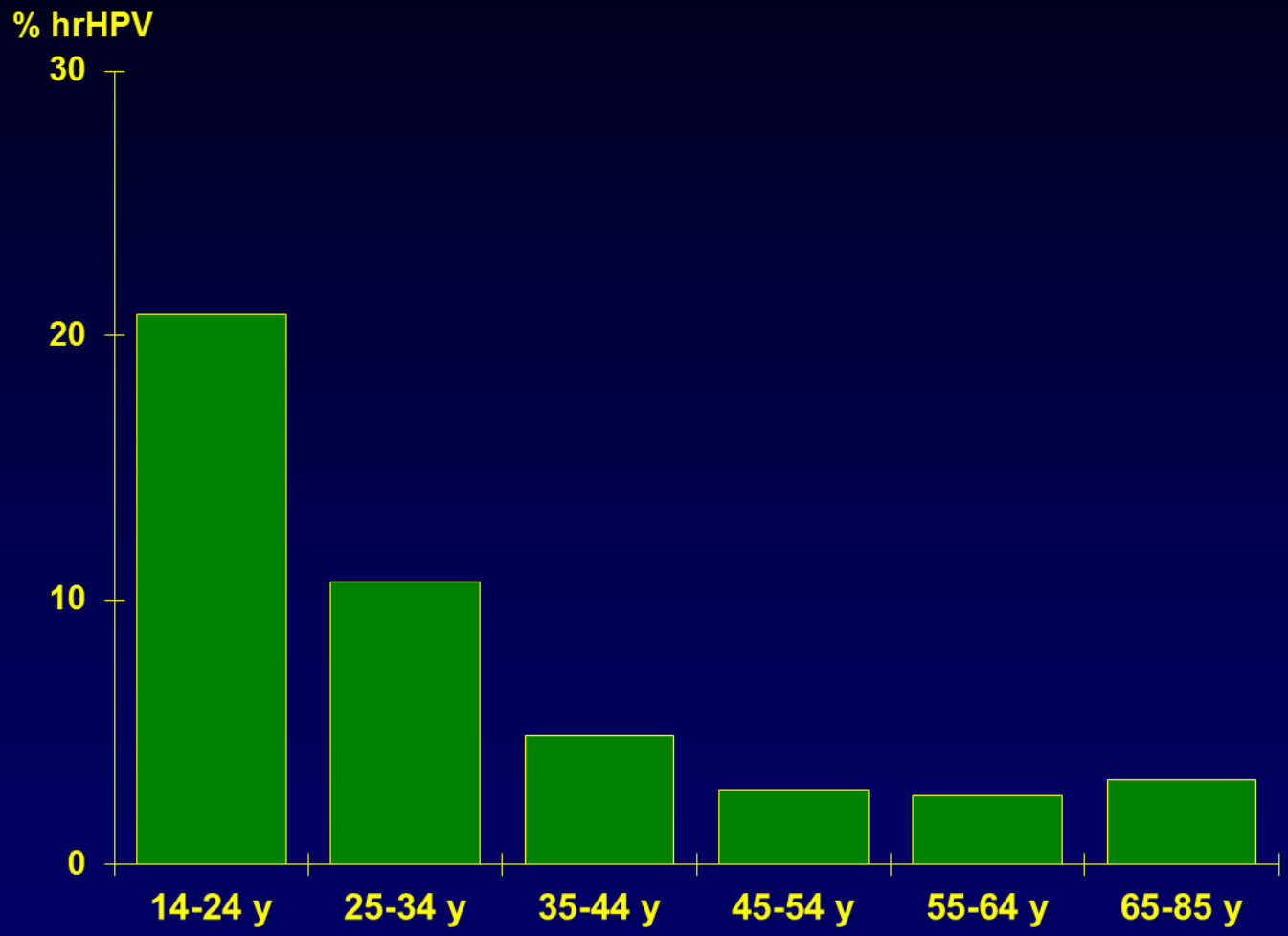


IARC category 1=carcinogenic, 2A=possibly carcinogenic, 2B= possibly carcinogenic because of phylogenetic relationship with 1 or 2A, 3=non-carcinogenic

Doorbar: Vaccine suppl 2013

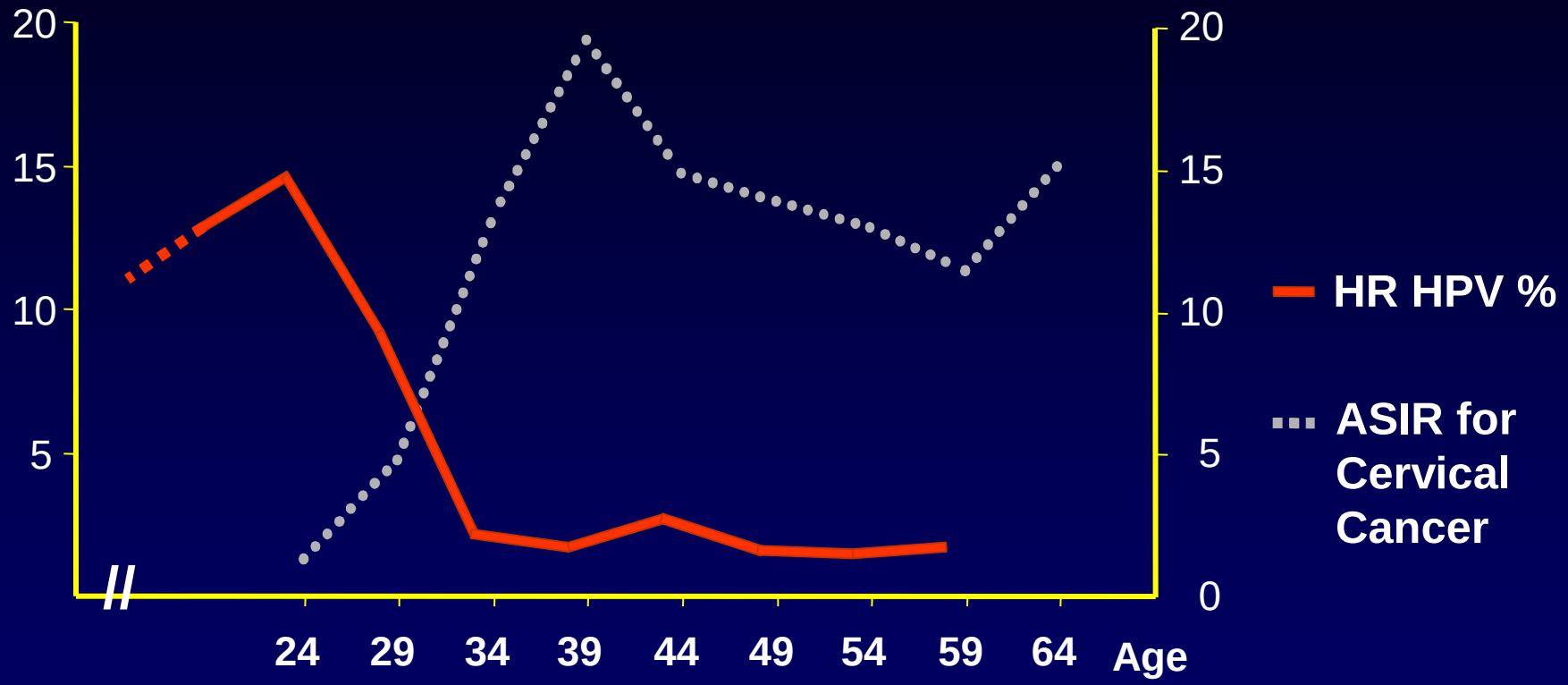
Temporality: does hrHPV infection precede lesion development?

HPV prevalence according to age



HPV prevalence age-dependent: peak prevalence below 20 years of age

Age specific prevalence of hrHPV-DNA and ASIR cervical cancer in the Netherlands



Peak HPV prevalence precedes that of ASIR cervical cancer

Bosch FX et al. 2002

Incident CIN3 is preceded by hrHPV infection

Case	*Age (years)*	*Routine screening (Pap)*	*NNS (Pap)*	*High risk HPV*	*Follow up time (years)*	*CIN*
1	34	1	1	Yes	2.1	3
2	35	2	3a2	Yes	2.6	3
3	35	1	1	Yes	3.4	3
4	35	2	2	Yes	2.6	3
5	35	1	1	Yes	5.7	3
6	36	1	1	Yes	2.9	3
7	38	1	3a2	Yes	3.0	3
8	38	1	2	Yes	1.5	3
9	38	1	1	Yes	7.9	3
10	42	1	1	Yes	5.1	3
11	42	1	2	Yes	8.9	3
12	53	2	3a1	Yes	0.9	3
13	41	2	1	No*	4.7	3

13 Incident CIN3 from 2250 with normal/ very mildly abnormal Pap enrolled
* Acquired hrHPV two years following enrolment

Rozendaal et al., 1996; 1999

Is hrHPV persistence related to disease progression?

Follow-up of women with abnormal cytology in relation to HPV status: progression/regression

- 353 women referred because of abnormal smear between 1990-1992

- Monitoring: every 3-4 months by cytology, colposcopy and hrHPV testing
- Primary endpoint: clinical progression
  - Colposcopical impression of CIN3 over ≥ 3 quadrants and/or
  - Cytology suspected of invasive carcinoma (Pap5)
- Secondary endpoint: histology CIN3 at the end of the study or when reaching primary endpoint.
- Cytological regression: abnormal cytology returned to normal cytology for at least two consecutive cervical smears
- HPV clearance: none of the hrHPV types from the previous visit were detected at the next visit
- Mean age: 32 years (range 18-15)
- Median follow up time: 33 months (3-74)

Nobbenhuis et al Lancet 1999, 354:20-25, Lancet 2001;358:1782-3

hrHPV status during study and risk for end histology of CIN3

HPV status during study	Number of women	Clinical progression (n=33)		No clinical progression (n=320)				OR for CIN3 histology (95% CI)
		CIN3 (n=32)	CIN2 (n=1)	CIN3 (n=71)	CIN2 (n=29)	CIN1 (n=64)	Normal (n=156)	
HPV persistence	122	32	1	66	7	6	10	327 (42-2468)
HPV clearance or acquisition	150	-	-	4#	15	35	96	2.9 (0.2-20)
Negative	81	-	-	1	7	23	50	1.0

Two women cleared their infection and acquired another infection persisting for 24 and 32 months, respectively
Two women tested negative at baseline but acquired an infection that persisted for 32 months

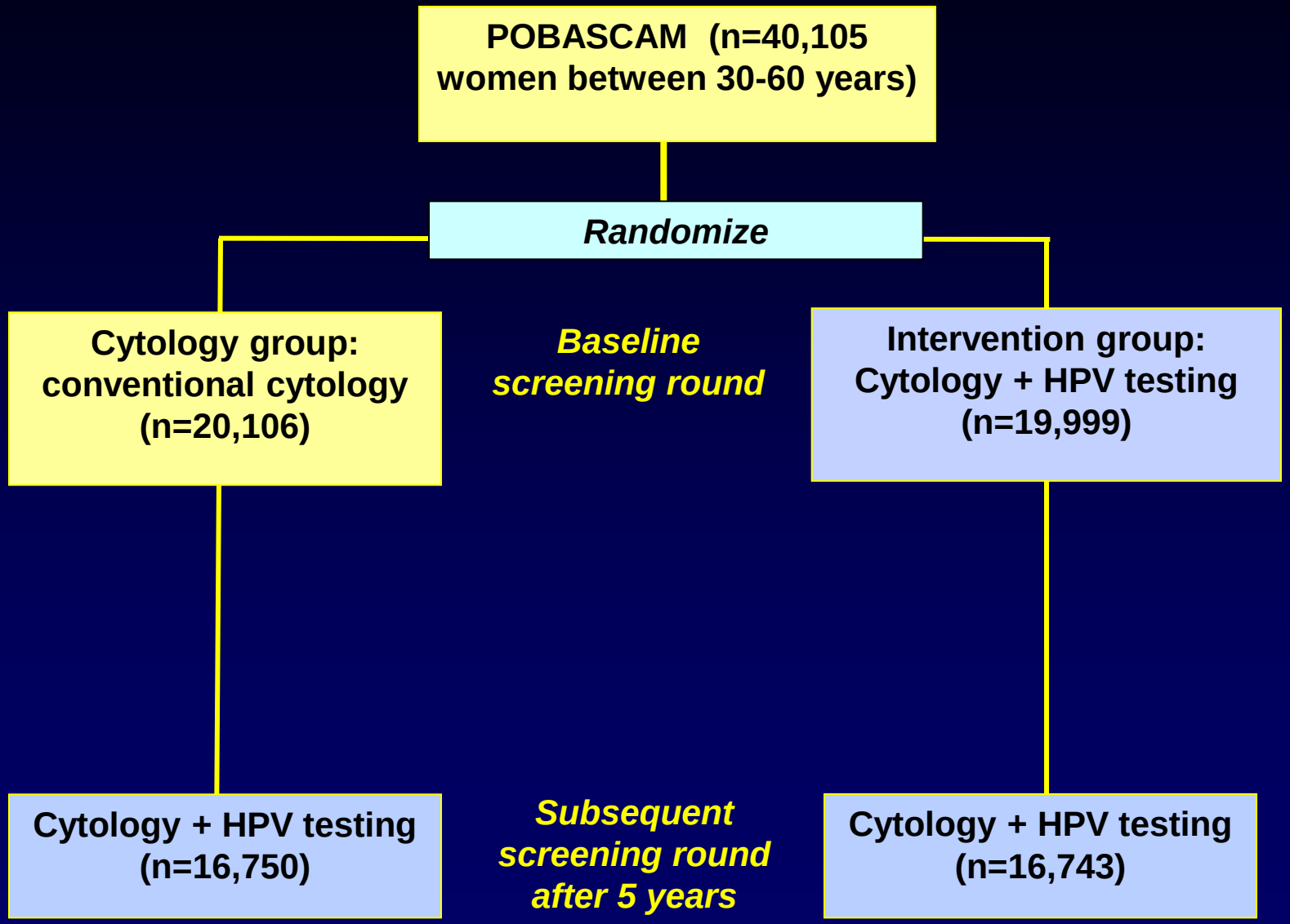
Nobbenhuis et al Lancet 1999

Large Dutch screening studies

POBASCAM: 44,102 women (RCT)
Setting : regular screening program (5 year interval)
Randomised: HPV + cytology vs Cytology (HPV blinded)
Follow-up 5+ years (incl. subsequent screening round)
HPV test: GP5+/6+ PCR EIA
Primary endpoint: nr of CIN3+ in each arm

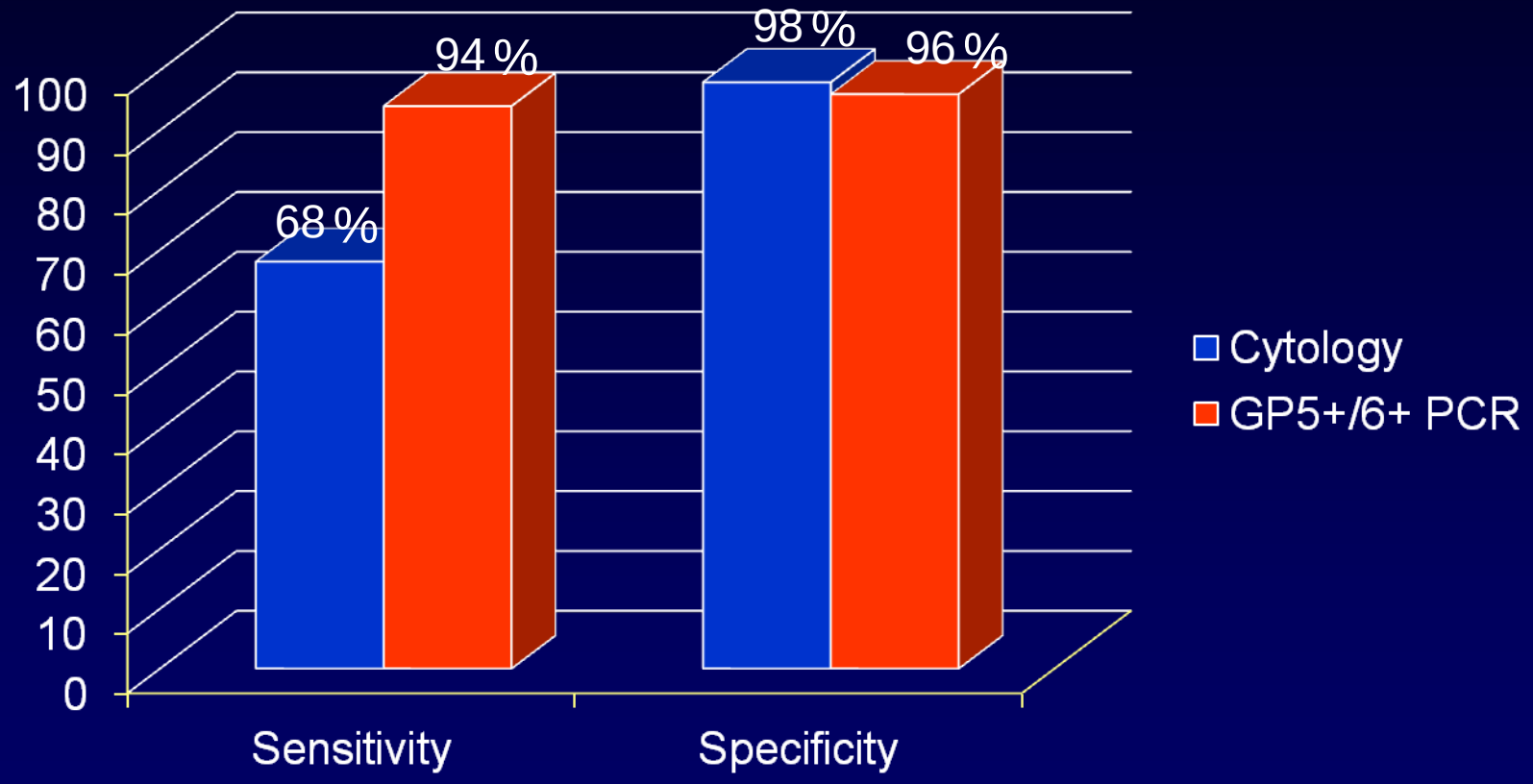
VUSA-SCREEN: 25,871 women (cohort study)
Setting : regular screening program (5 year interval)
HPV + cytology
Follow-up 2 years (2004-2007)
HPV test: Hybrid capture 2 (hc2)
Primary endpoint: CIN 3+

POBASCAM screening study



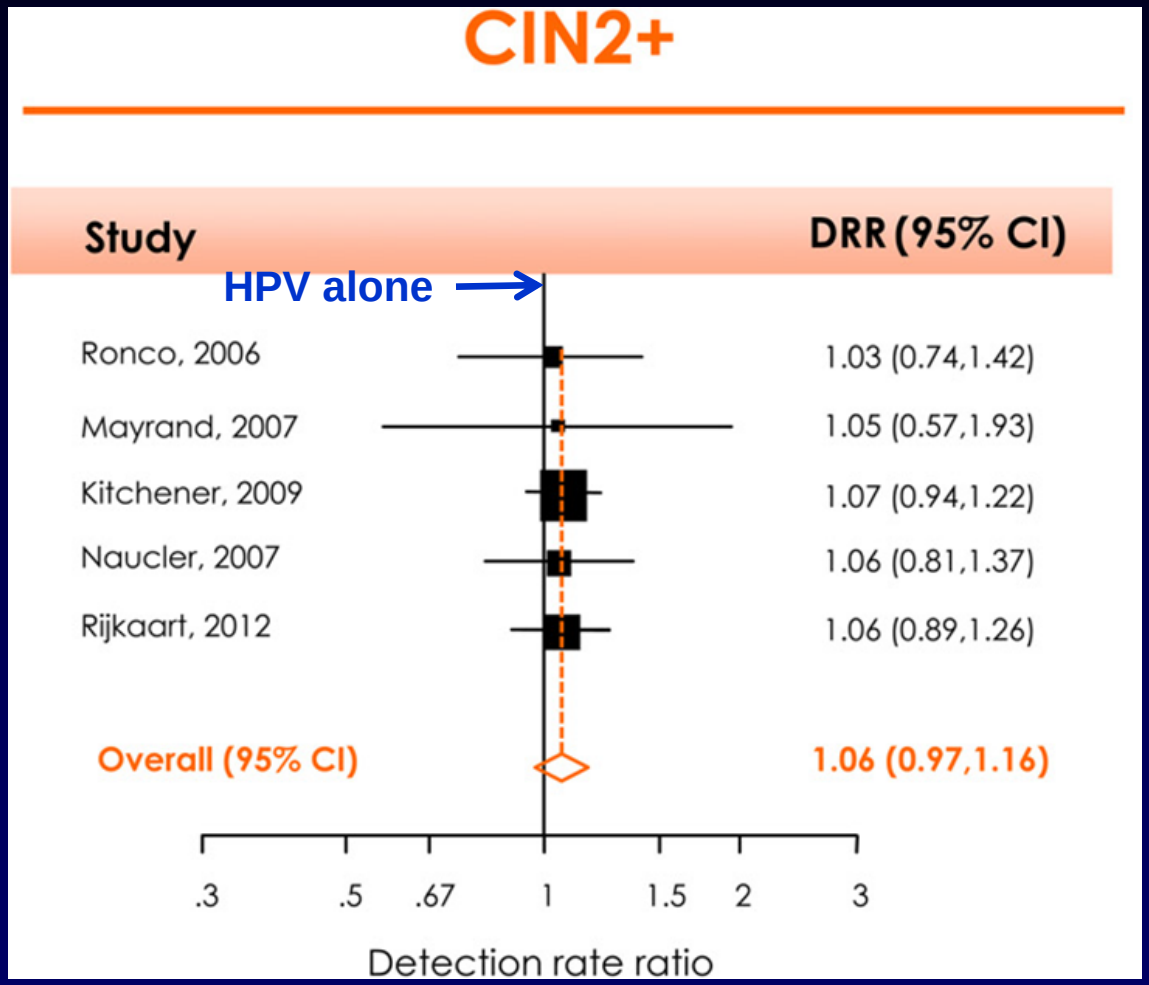
Bulkmans et al. IJC 2004; Lancet 2007

Cross-sectional sensitvity/specificity for CIN2+ of HPV test versus cytology



Bulkmans et al. Int J Cancer 2007

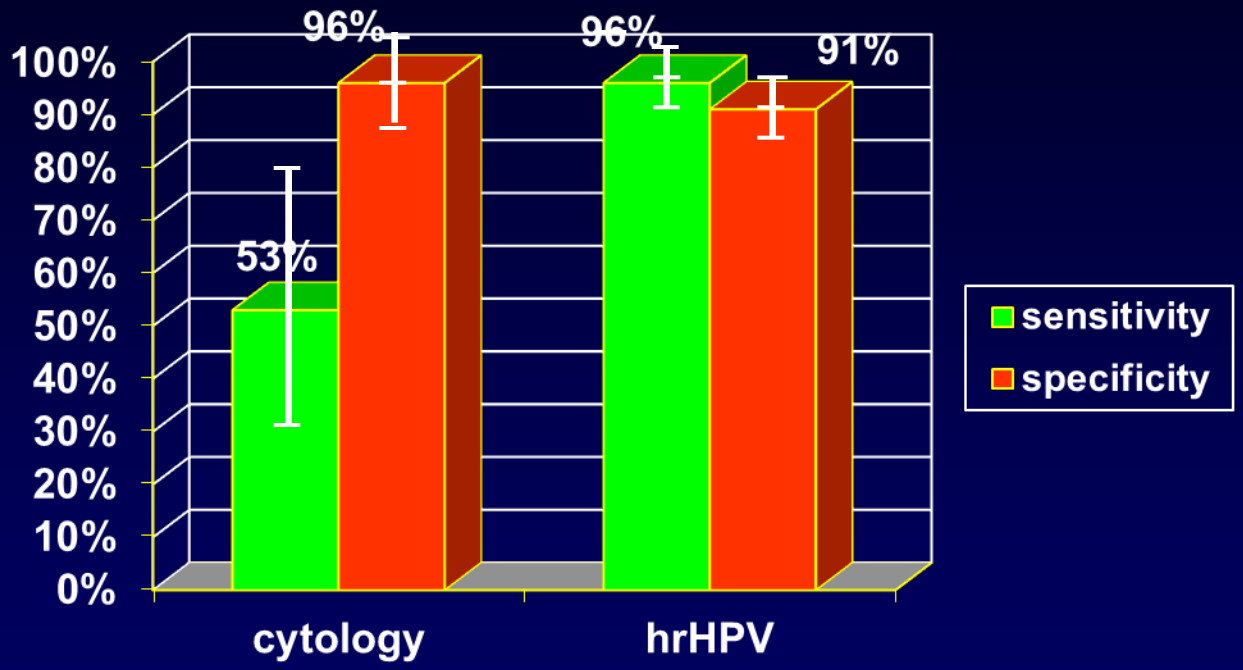
Performance HPV & Pap (combo) vs HPV test alone



Sensitivity of HPV&Pap is not higher than solely HPV testing

Arbyn et al., Vaccine 2012

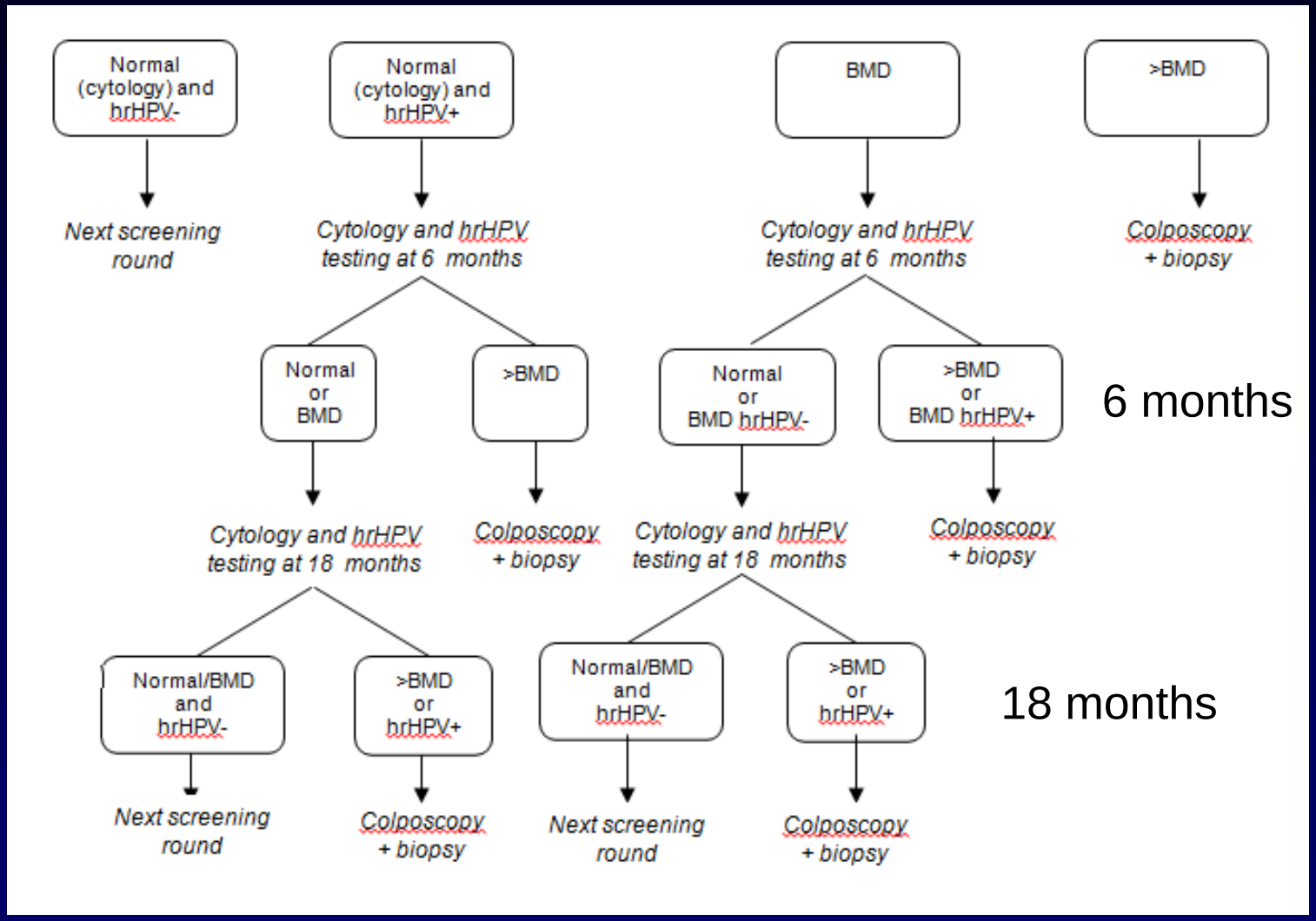
Sensitivity and specificity for CIN2+: HPV testing vs Cytology in cross-sectional studies



Overview of European and North American studies (n=~ 60,000)

Cuzick et al. Int.J.Cancer 2006

Management of women in the intervention group at the baseline and subsequent round and the control group at the subsequent round



Rijkaart et al. Lancet Oncol. 2012

POBASCAM trial: cumulative 18-month risk CIN3+

- Overall hrHPV+ (95%CI)
  - Normal 6% (4-9)
  - BMD 20% (16-25)
- HPV16+
  - Normal 14% (9-21); p<.0001
  - BMD 37% (28-48); p<.0001

After excl. HPV16:

- HPV18+
  - Normal 9% (2-23); p=.031
  - BMD 11% (3-27); p=.883
- HPV31+
  - Normal 7% (2-16); p=.049
  - BMD 27% (14-46); p=.016
- HPV33+
  - Normal 10% (0-33); p=.087
  - BMD 22% (9-44); p=.025

Berkhof et al. CEBM 2006

Summary 18-months risk CIN2+/CIN3+

- HPV 16+ confers an increased risk of CIN2+/CIN3+ both in women with normal cytology and BMD
- In the subset of women without HPV 16:

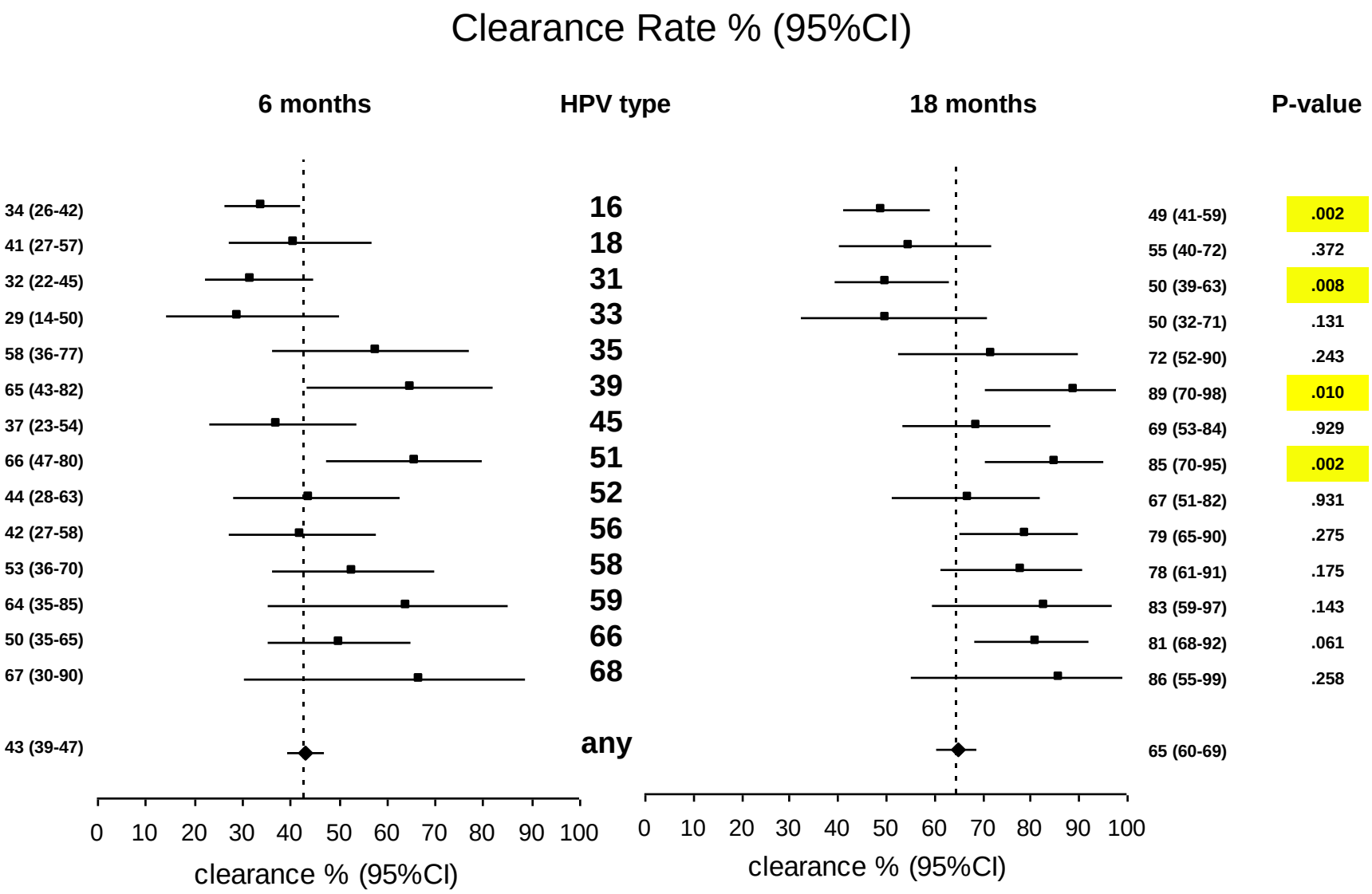
  - HPV 18, 31 and/or 33: increased risk in women with normal cytology and/or BMD

- After repetitive normal smears:
  - Only HPV 16 and HPV 18 were associated with an increased risk of high-grade CIN (p=0.028)
    - HPV 16/18+ : 9% (4-48)
    - Non-HPV 16/18: 2% (0-6)

- Opens possibilities for algorithms with HPV16/18 genoyping incorporated to triage women with normal cytology

Berkhof et al. CEBM 2006

hrHPV type-specific clearance rates: women with normal cytology

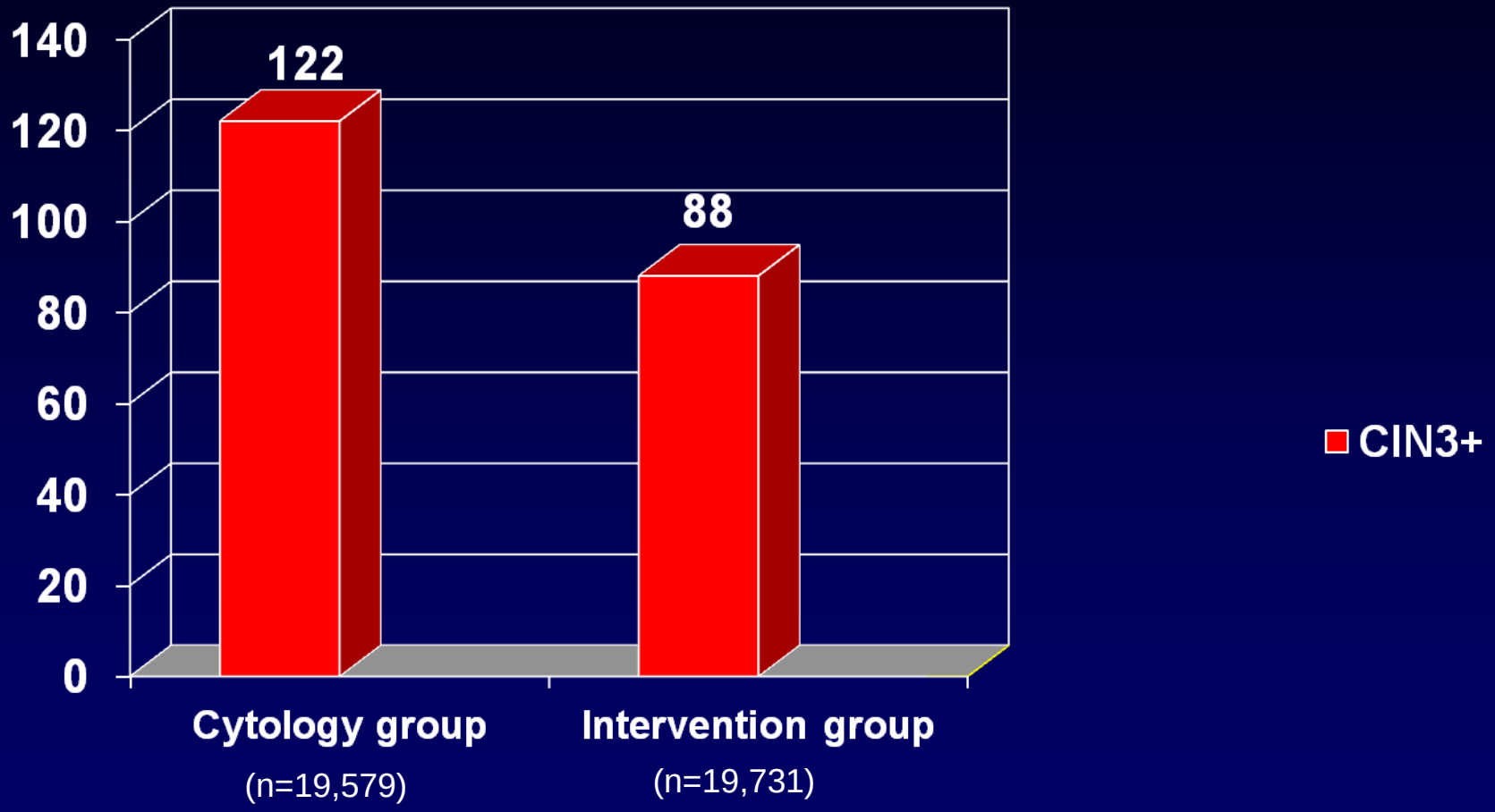


Differential risks at least in part attributable to differential clearance rates

Bulkmans et al Br J Cancer 2007

POBASCAM results subsequent screening round

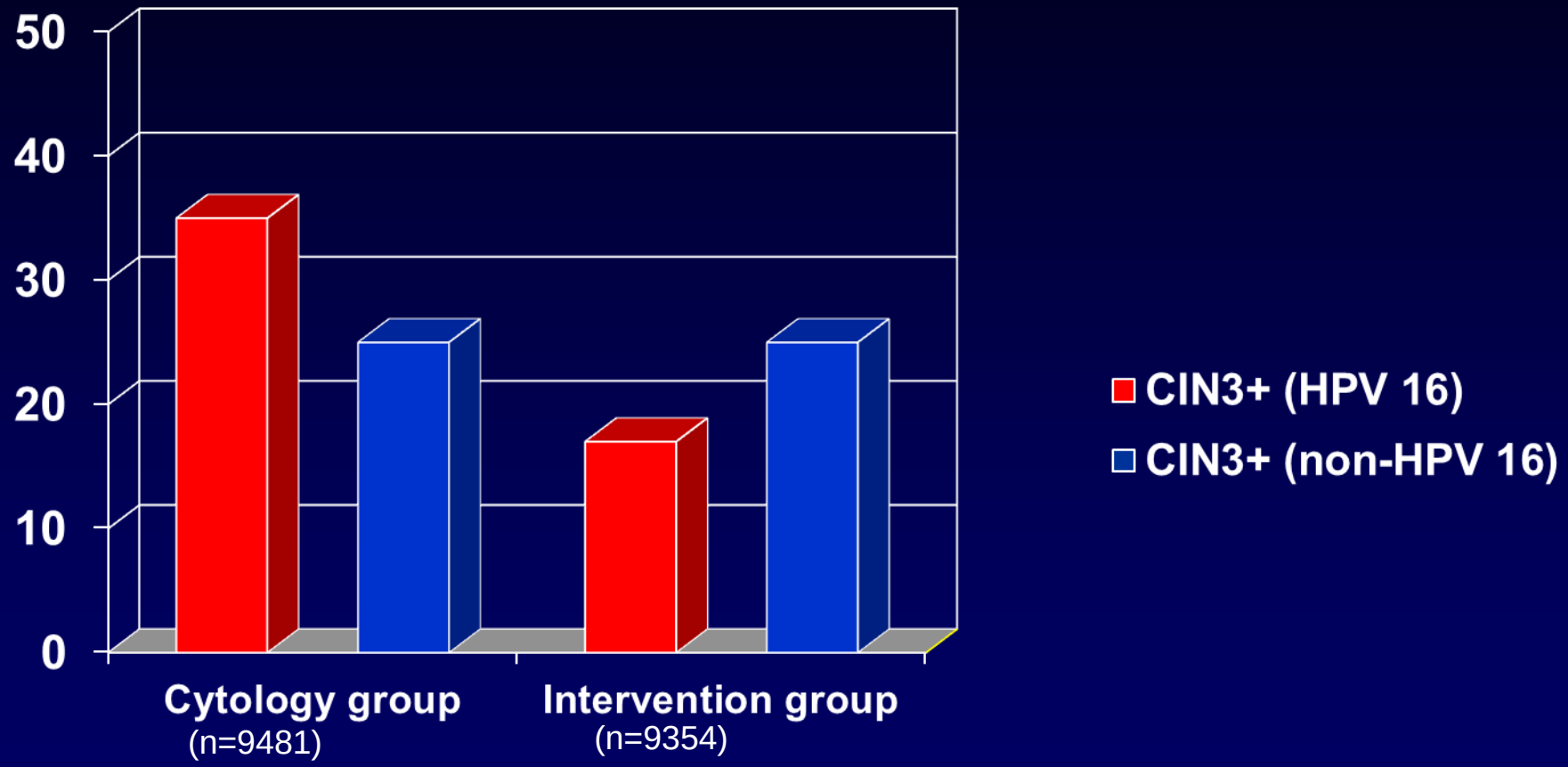
Final results POBASCAM at subsequent screening round (after 5 years)



27% less CIN3+ in HPV group (p=.02)

Rijkaart et al. Lancet Oncol. 2012

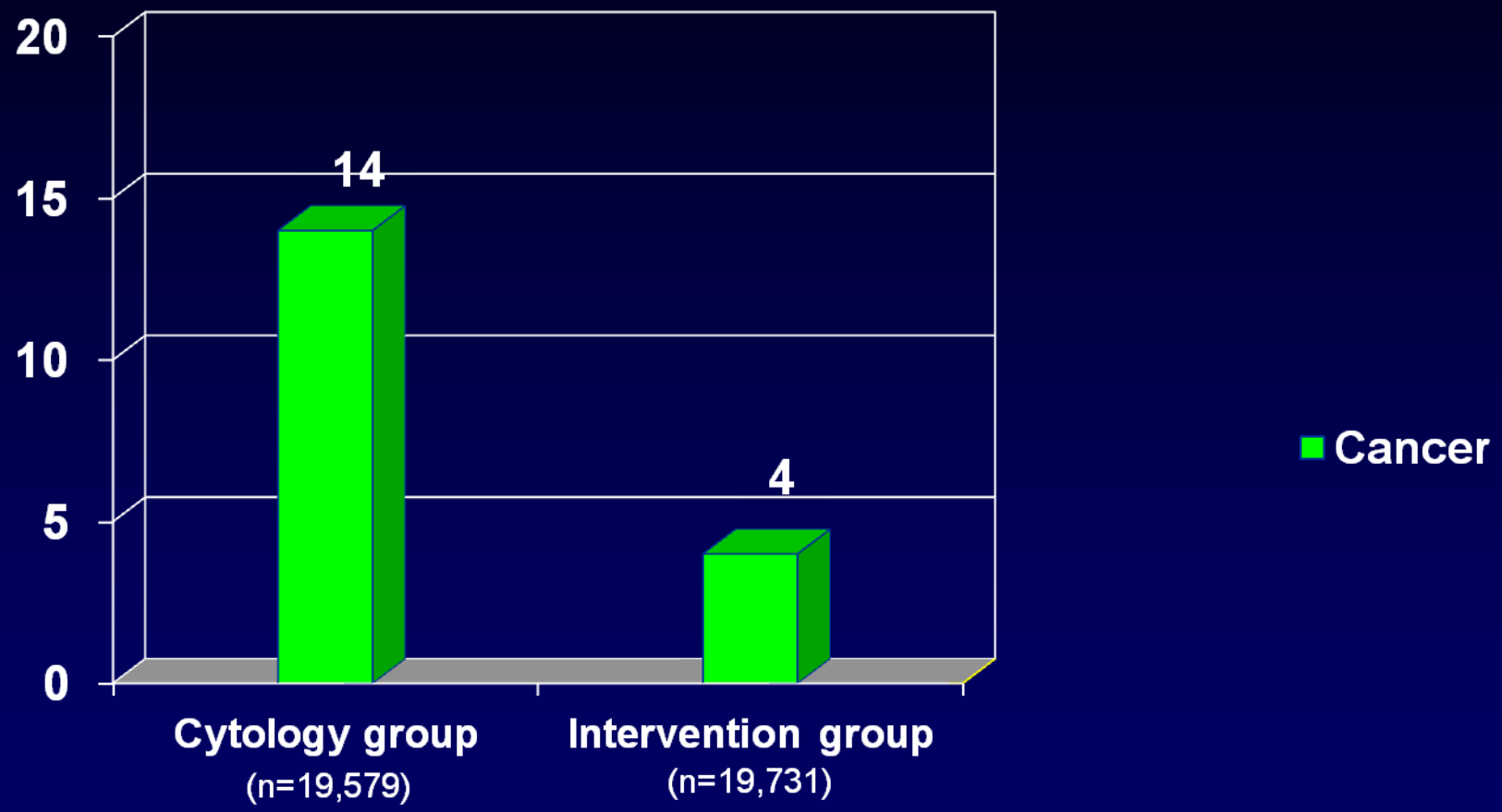
Final results POBASCAM at subsequent screening round (after 5 years)



Protective effect largely attributable to HPV16

Rijkaart et al. Lancet Oncol. 2012

Final results POBASCAM at subsequent screening round (after 5 years)



71% less cancer in HPV group (p=.03)

Rijkaart et al. Lancet Oncol. 2012

Conclusion

- hrHPV is necessary for development of premalignant cervical disease and progression towards carcinoma

Implications for screening:

- HPV testing allows *earlier* detection of clinically relevant CIN2+ lesions and consequently better prevents invasive cervical cancer than cytology

- This permits extension of the screening interval without increasing interval risk

- HPV test valuable as primary screening test (cytology as triage test for HPV positive women)

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