Epidemiologia delle infezioni da HPV e delle malattie ad esse correlate.

Guglielmo Ronco

CPO Piemonte

IARC classification

Group 1 Carcinogenic to humans

Group 2A Probably carcinogenic hum.

Group 2B Possibly carcinogenic hum.

Group 3 Not classifiable

Bouvard et al. Lancet Oncol 2009

Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
3	6, 11	..
Beta HPV types		
2B	5 and 8	Limited evidence for skin cancer in patients with epidermodysplasia verruciformis
3	Other beta and gamma types	..

Estimated number of new cancer cases occurring in 2012 attributable to HPV by anatomic site and gender worldwide (de Martel et al, 2017)

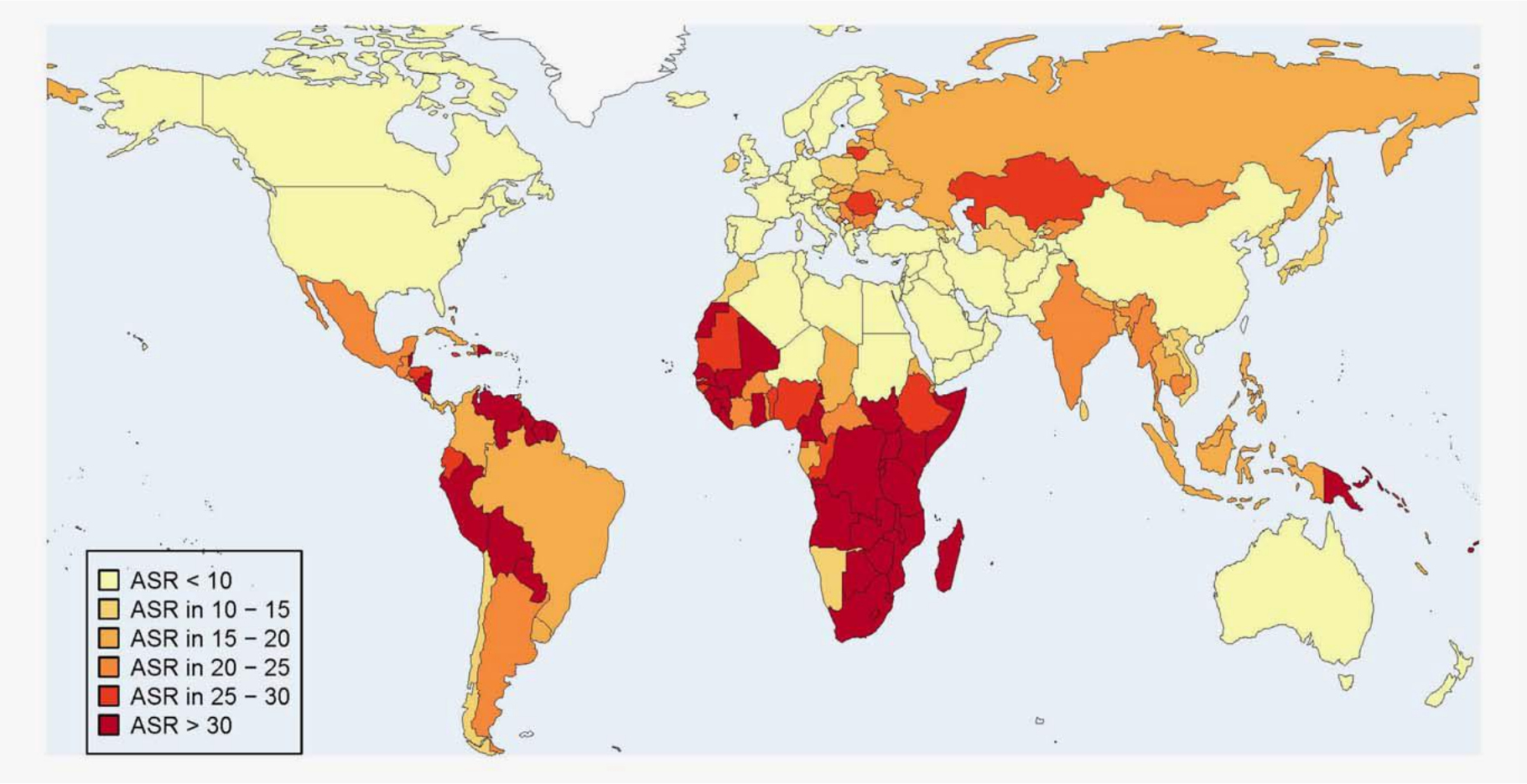
HPV RELATED CANCER SITE	Number of incident cases	Number attributable to HPV	AF (%)	Number attributable to infection by gender	
				Males	Females
Cervix uteri	530,000	**530,000**	**100**	0	530,000
Anus	40,000	**35,000**	**88.0**	17,000	18,000
Vulva	34,000	**8,500**	**24,9**	0	8,500
Vagina	15,000	**12,000**	**78.0**	0	22,000
Penis	26,000	**13,000**	**50.0**	13,000	0
Oropharynx	96,000	**29,000**	**30.8**	24,000	5,500
Oral cavity	200,000	**4,400**	**2.2**	2,900	1,500
Larynx	160,000	**3,800**	**2.4**	3,300	460
TOTAL HPV RELATED SITES	**1,200,000**	**630.000**	**54,0**	**60,000**	**570,000**

Tassi di incidenza 2003-7 stand. età Friuli Venezia Giulia

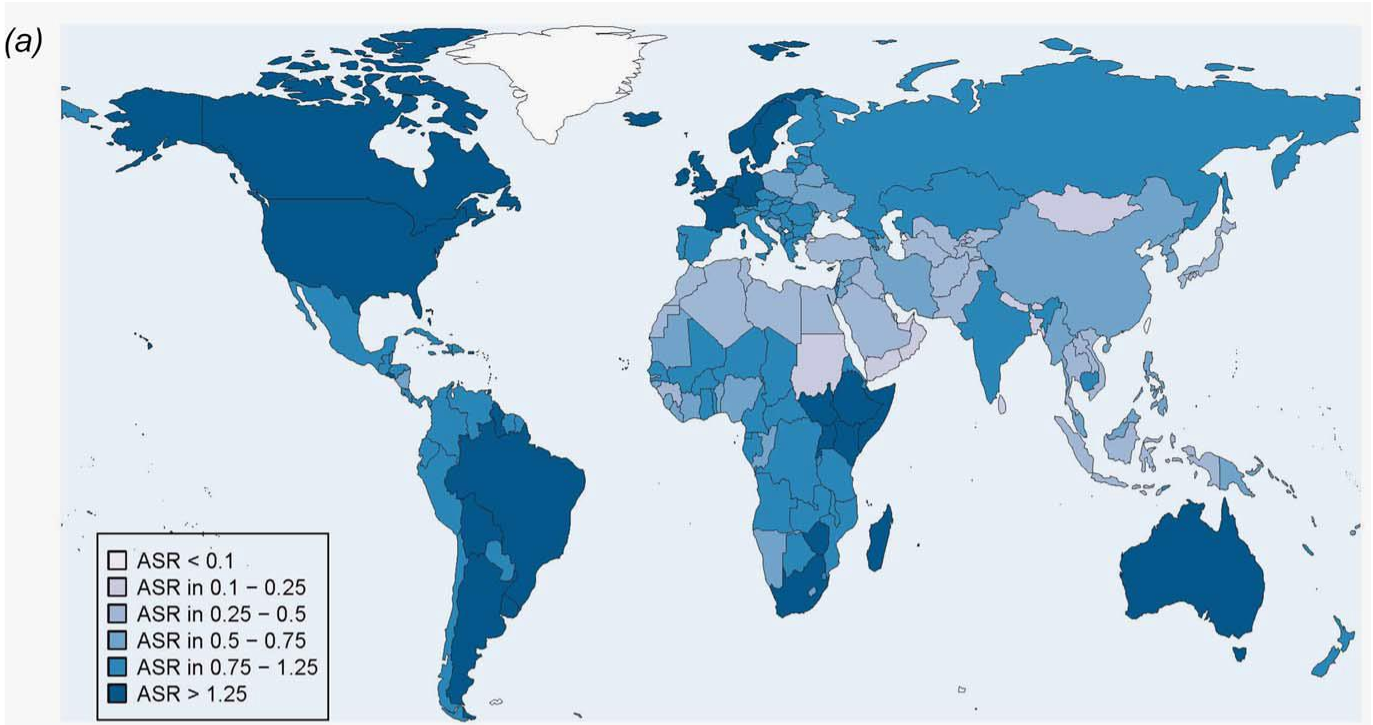
fonte AIRTUM ITACAN

	Femmine	Maschi
Cervice	7.6	-
Vulva e vagina	2.1	-
Pene	-	1.2
Bocca	1.7	5.3
Orofaringe	0.6	3.2
Laringe	1.8	13.1

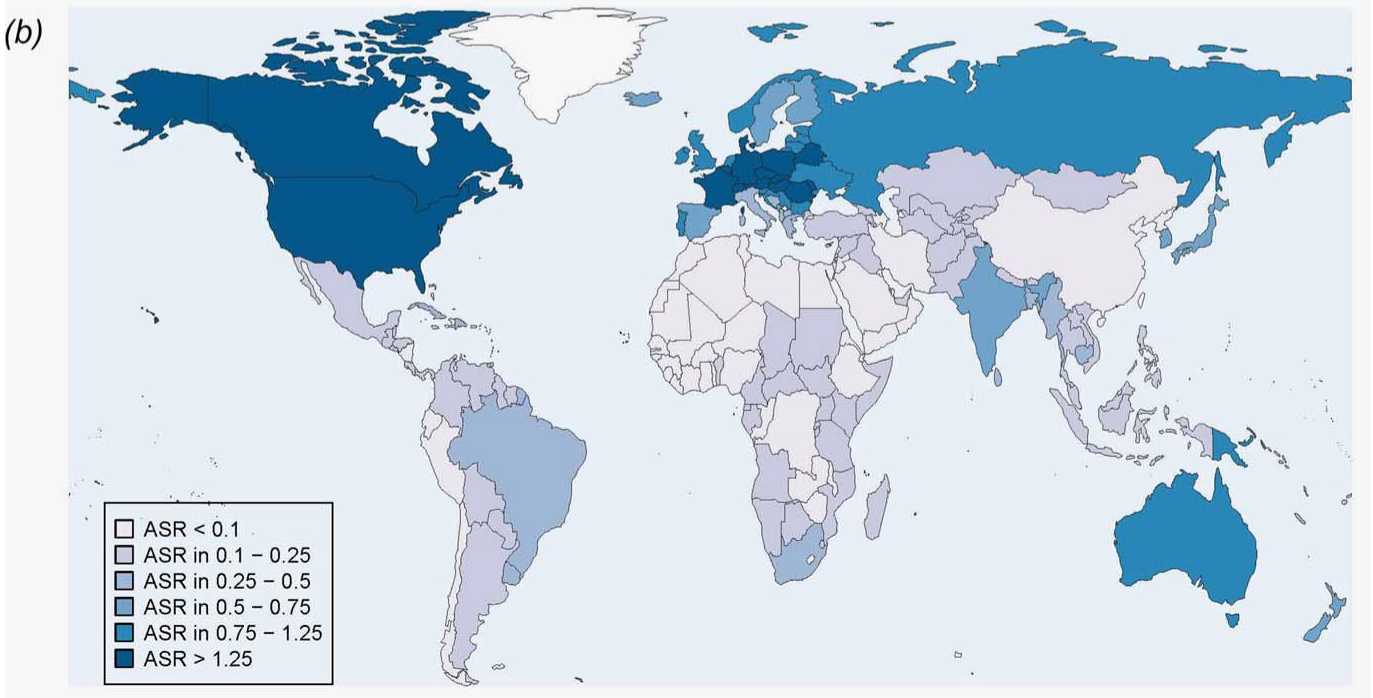
Age standardized (world) incidence rates (per 100,000) of cervical cancer cases attributable to HPV in 2012.



De Martel et al. 2017



Anogenital non-cervix

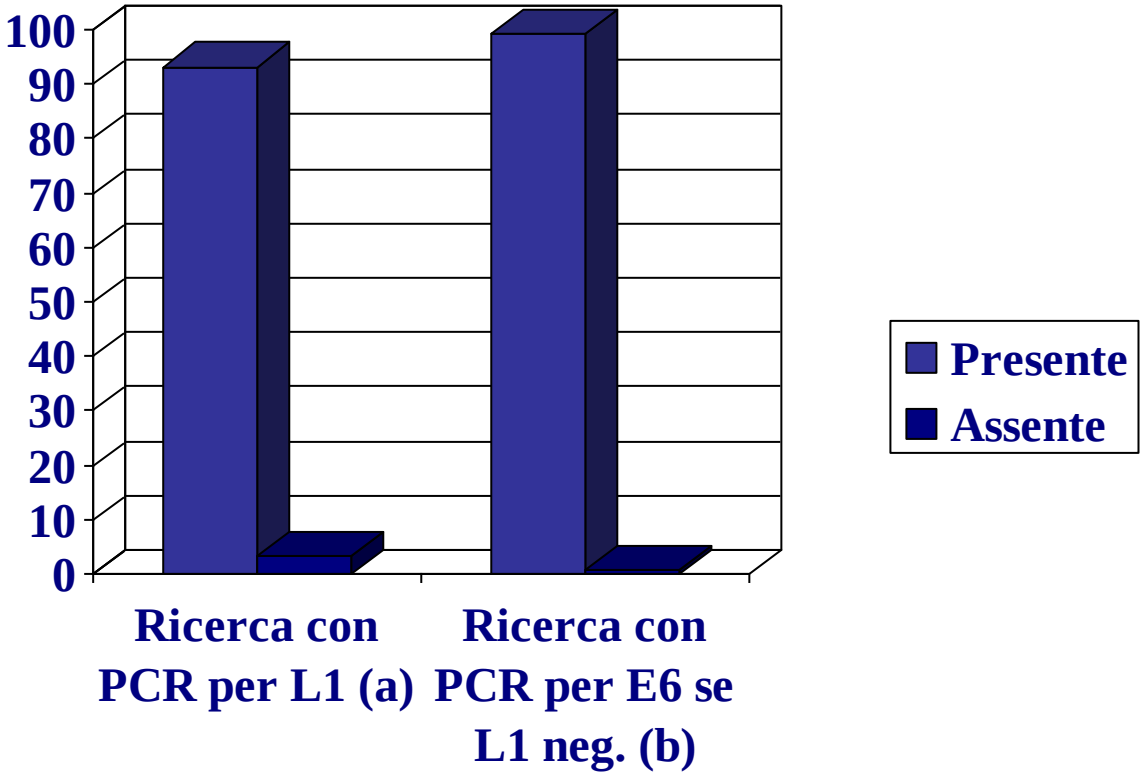


Head and neck

Cervice uterina

Presence of HPV (any type)

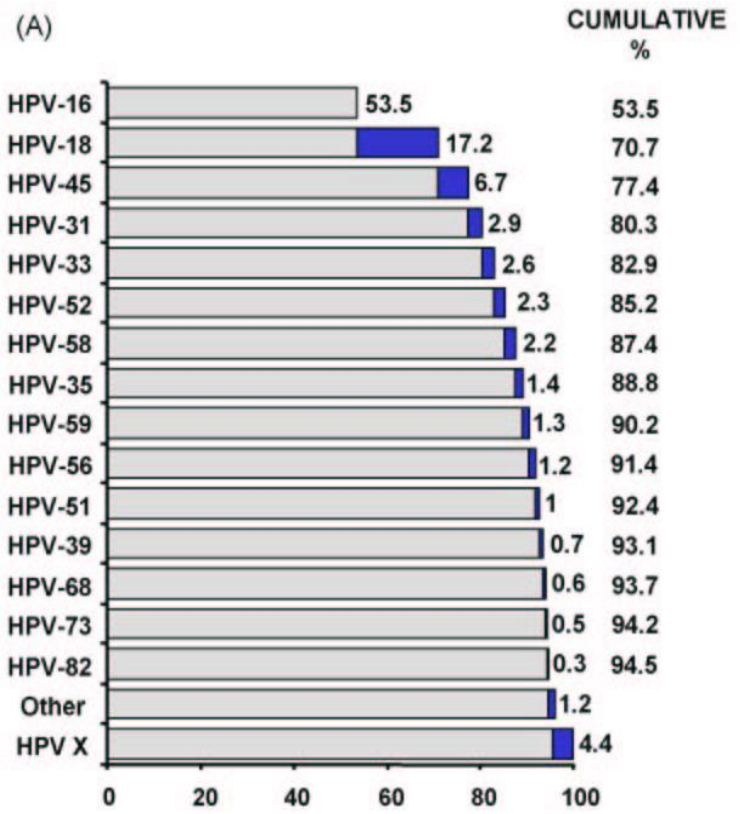
in 932 invasive cervical cancers



(a) Bosch et al - J.Natl Cancer Inst. 1995, 87:796-802

(b) Walboomers et al. - J. Pathol. 1999; 189:12-9

% cervical cancer attributed to the most frequent HPV types worldwide



Munoz et al. Int J Cancer 2004;111:258-85.

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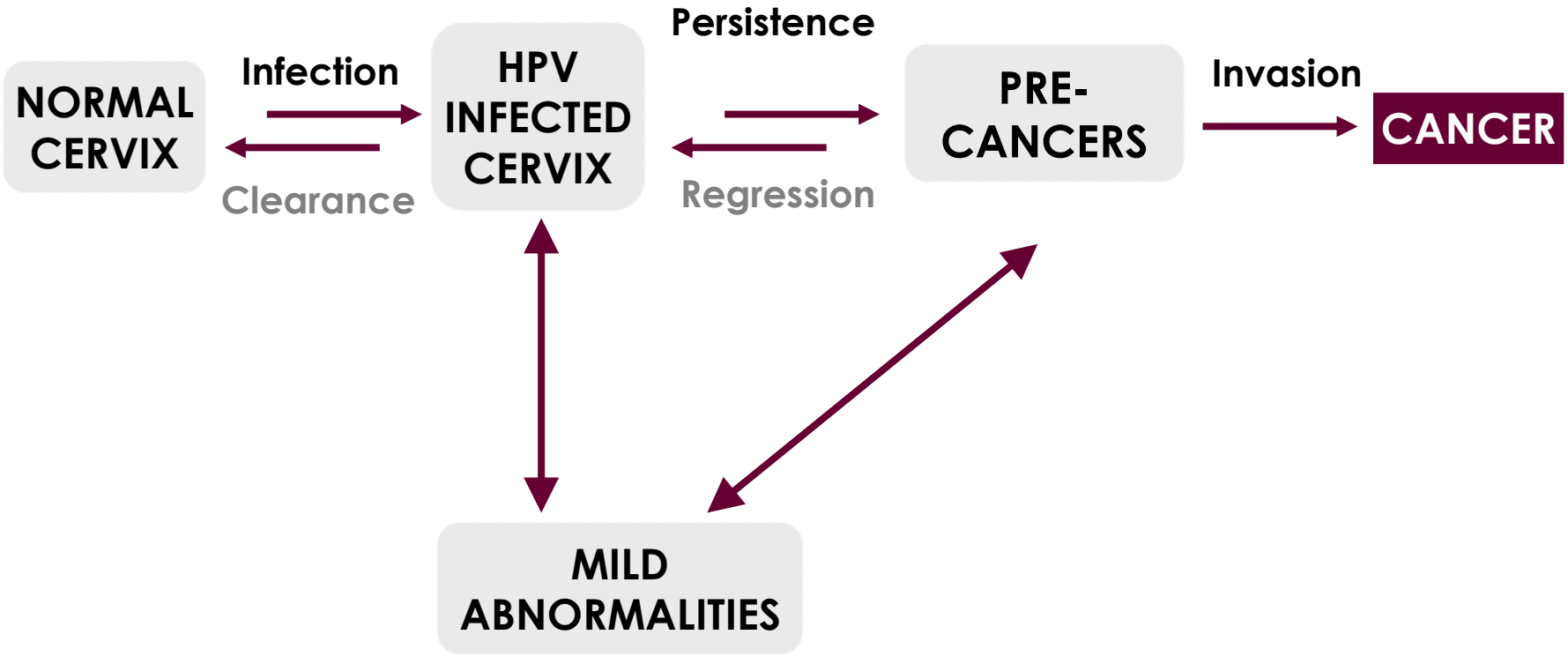
MAJOR STEPS IN CERVICAL CARCINOGENESIS

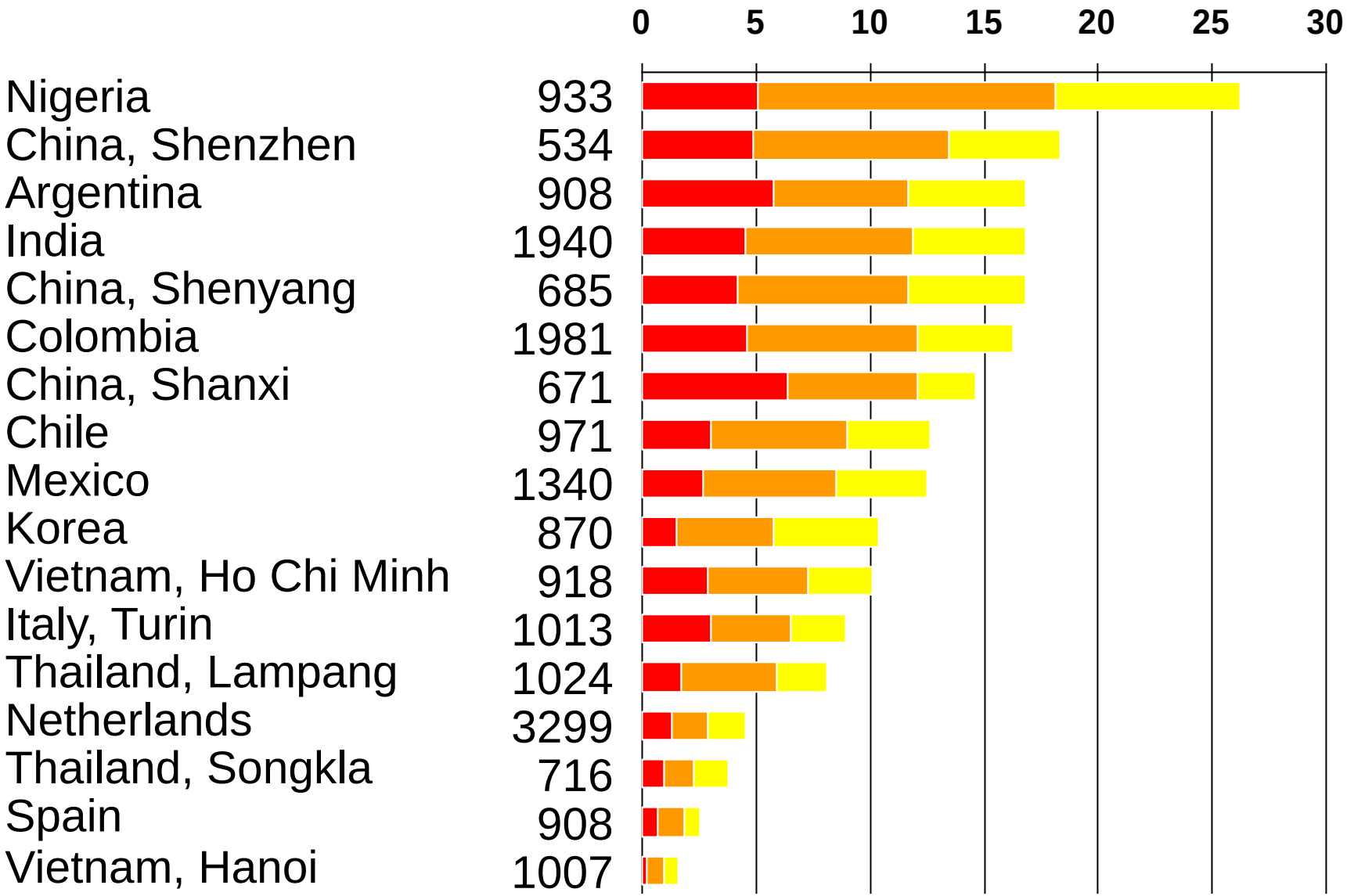


Schiffman M *et al.* J Natl Cancer Inst Monogr 2003 Modif.

CIN: Cervical intraepithelial neoplasia

Prevalence of cervical HPV DNA in sexually active women

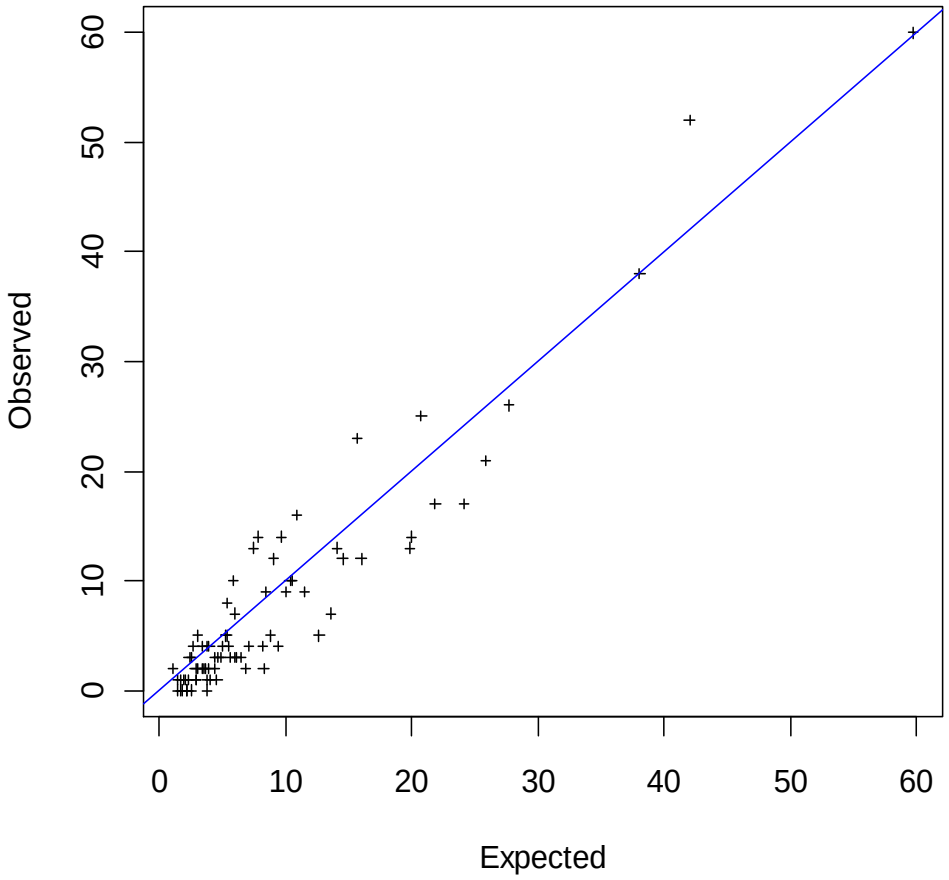
IARC Multi-centre HPV Prevalence Survey, 1995-2002



Clifford et al. Lancet 2005;366:991-98 modif.

- Prevalenza HPV cervice in generale maggiore in paesi in via di sviluppo.
- HPV 16 genotipo più frequente quasi ovunque ma differenza mix genotipi tra continenti
- Differente mix anche a in diverse aree italiane (cfr dati NTCC **Carozzi et al. J.Clin Virol 2014**)

Studio NTCC. Occorrenza attesa e osservata delle combinazioni di 13 genotipi di HPV.



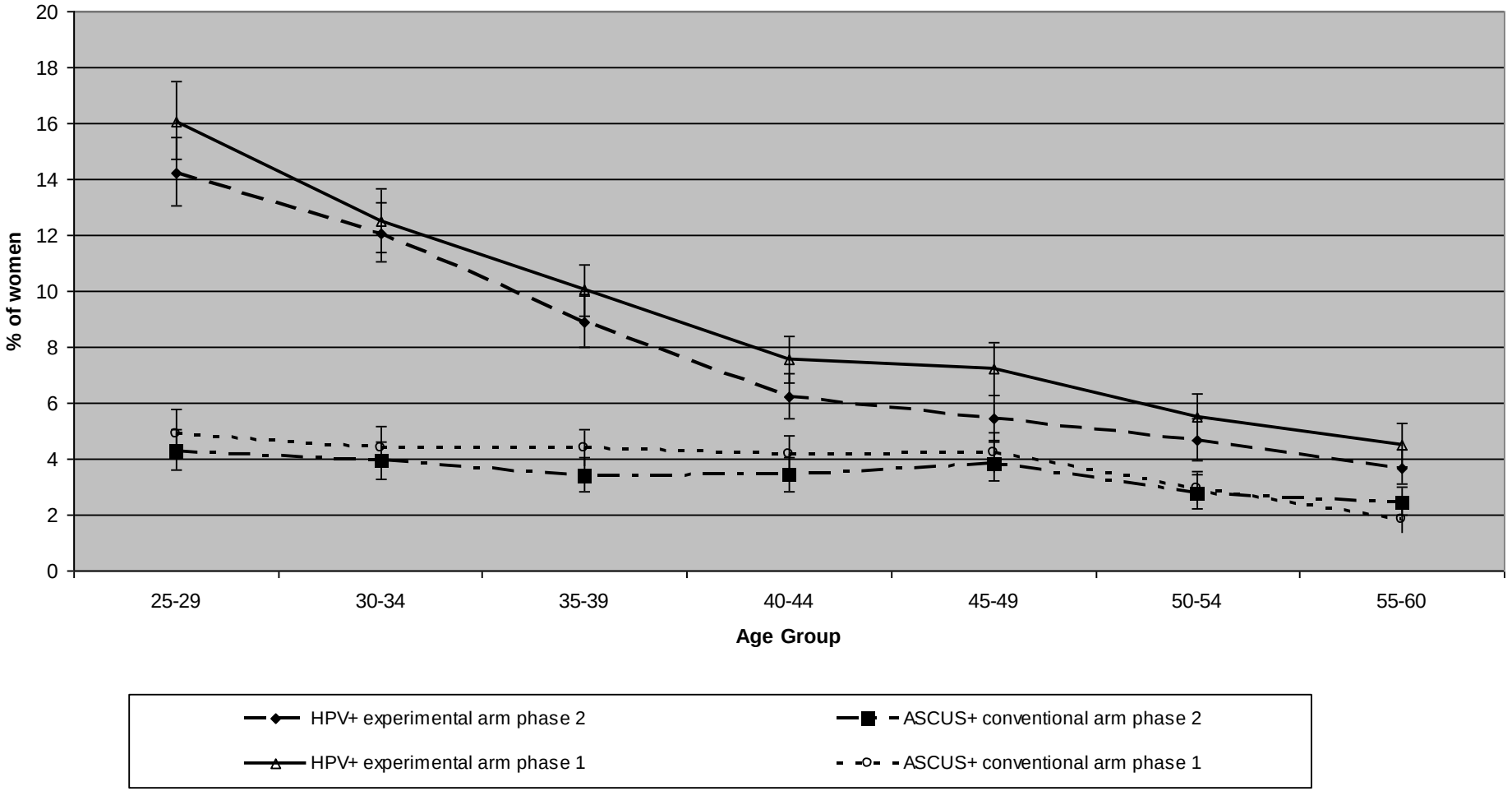
Associazione positiva dovuta a fattori di rischio comuni corretta mediante modello con effetto casuale individuo

Nessuna associazione significativa, né positiva né negativa, con $p<0.01$

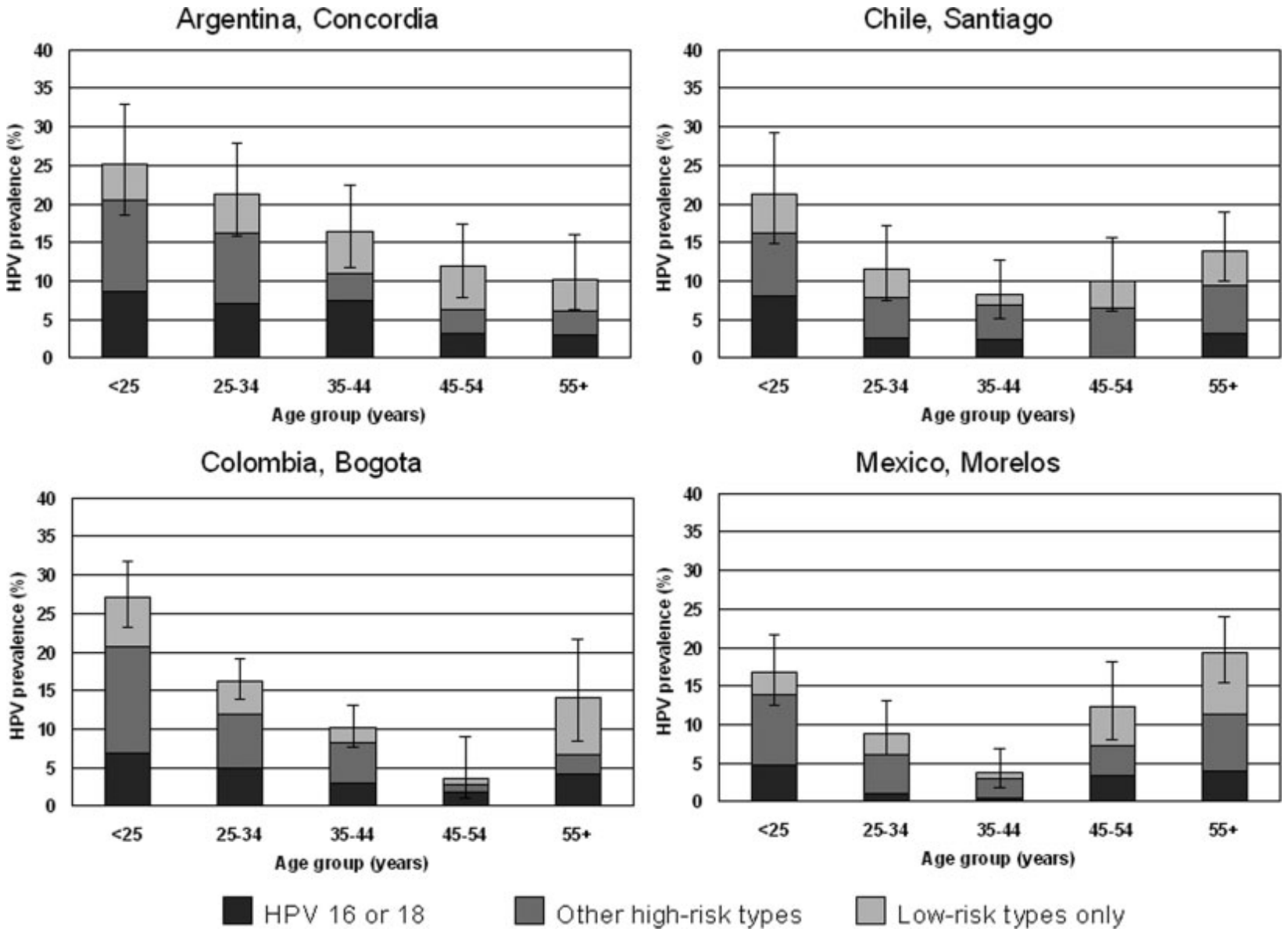
Carozzi et al. Eur.J.Cancer 2011

NTCC study

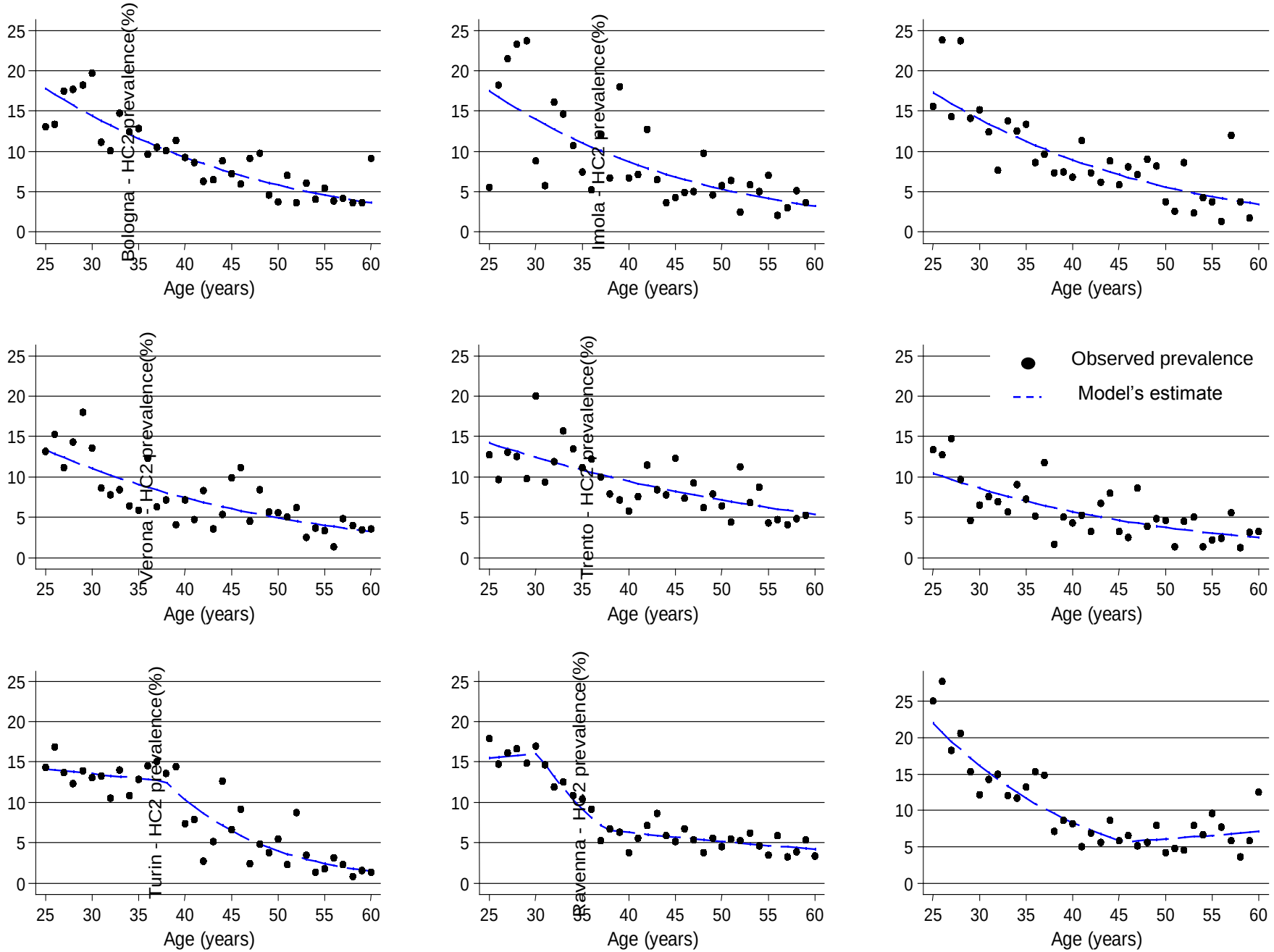
Proportion of women HPV-positive and with abnormal cytology by age



Ronco et al. J. Natl Cancer Inst. 2008



Franceschi et al. Cancer Epidemiol Biomarkers Prev. 2006

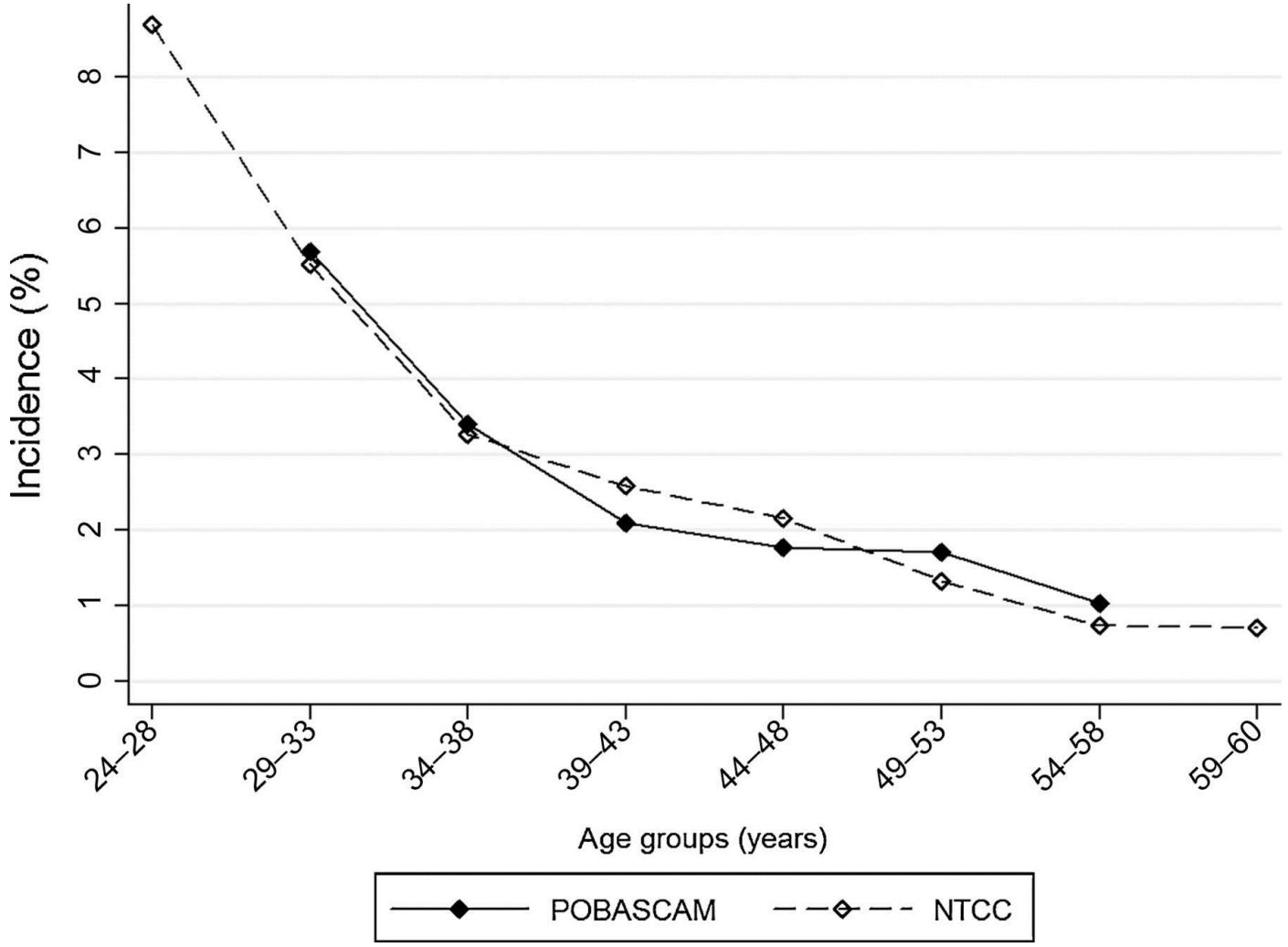


Baussano et al. BMC Infect.Dis 2013

Profilo età-specifico prevalenza infezione

- Profilo più comune decrescita con aumento età
- In alcuni paesi, specie Sud America secondo picco età avanzata.
- Effetto coorte? Riaccensione infezioni latenti?
- Variabilità profili anche in Italia (effetto coorte + migrazione)

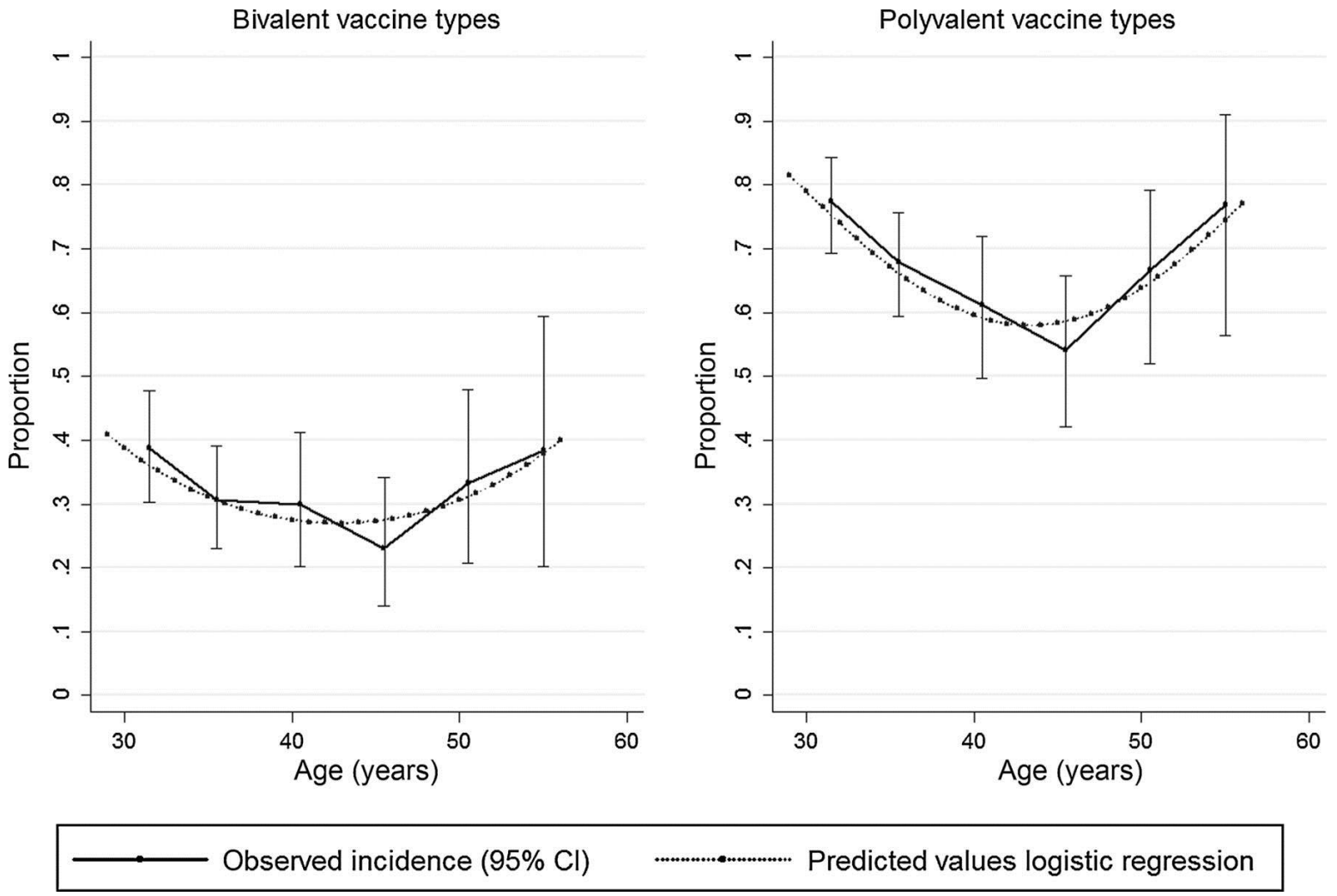
The incidence of screen-detected hrHPV.



Veldhuijzen et al. Cancer Epidemiol Biomarkers Prev 2015

AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

HPV vaccine-type positivity among women with single hrHPV incident infection.



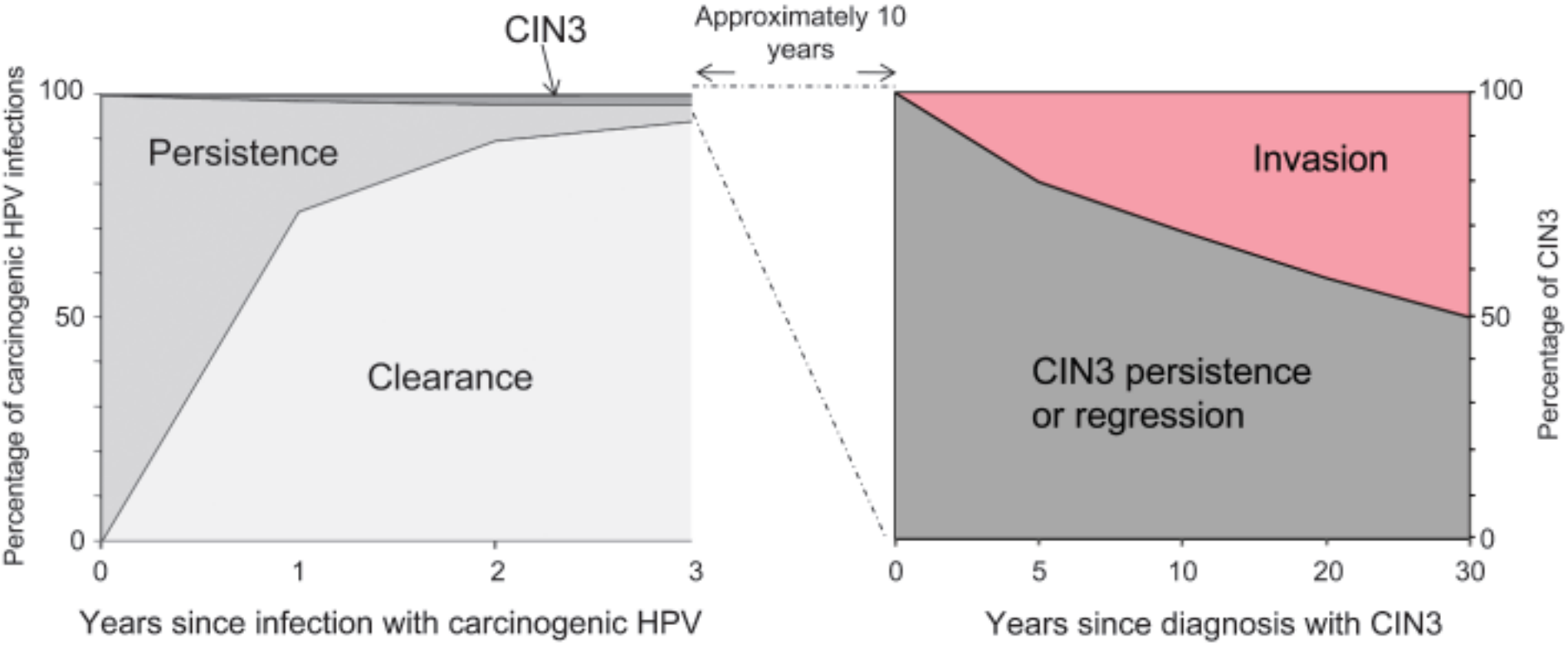
Veldhuijzen et al. Cancer Epidemiol Biomarkers Prev 2015;24:111-118

AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

- Curva incidenza simile a curva prevalenza (durata media breve)

- Forma curva diversa per genotipo (tipi più comuni/aggressivi più frequenti età estreme) . Suggerisce componenti biologiche.

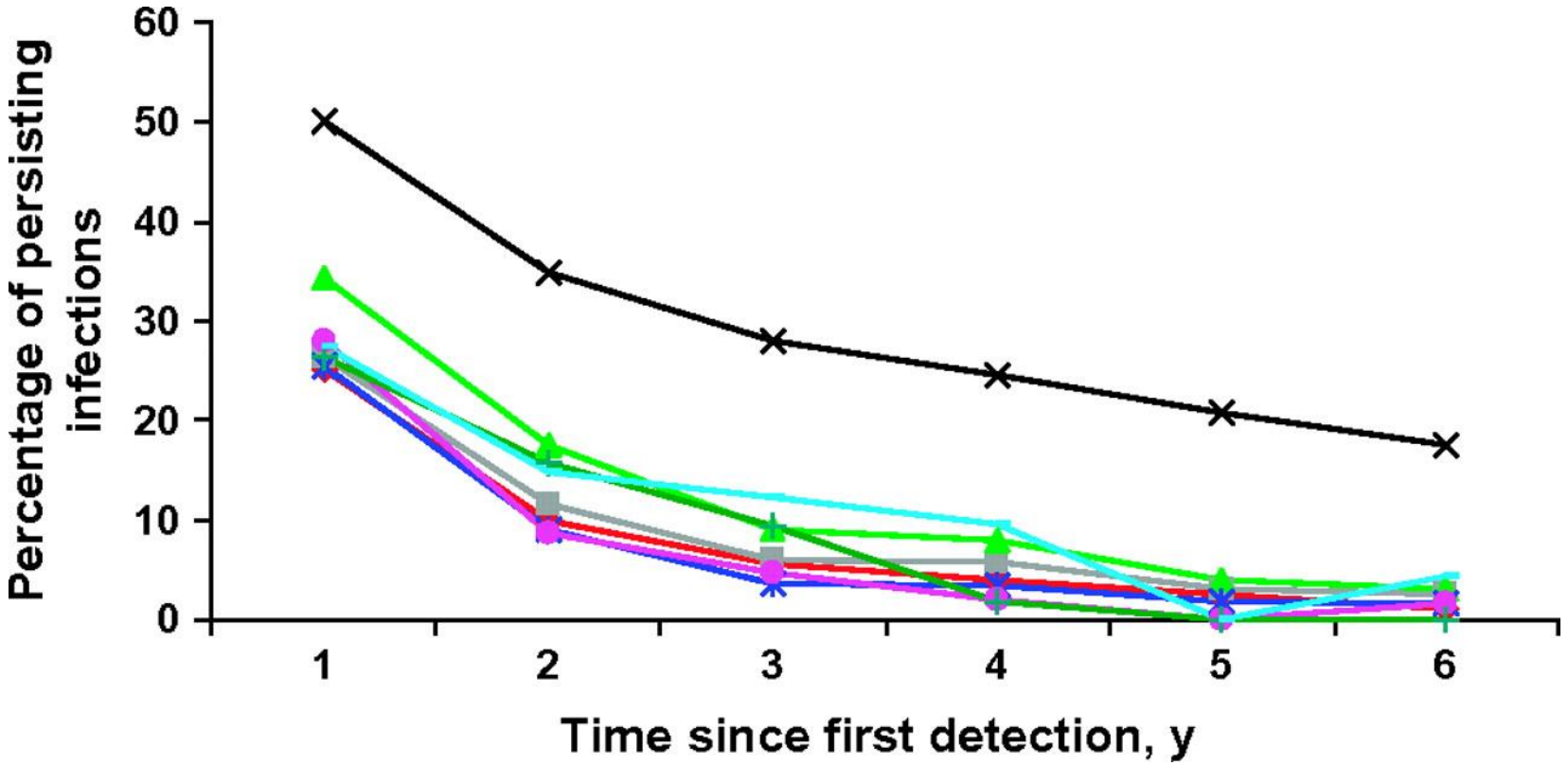
Evoluzione delle infezioni da HPV



- **Metà delle infezioni da HPV scompare dopo 6-12 mesi**
- **Il 90% scompare dopo 2-3 anni**

Mark Schiffman et al. J Natl Cancer Inst 2011;103:368–383

Persistence of baseline-detected and newly detected carcinogenic genotypes of human papillomavirus (HPV) infection by age group.



Rodríguez A C et al. JNCI J Natl Cancer Inst 2010

JNCI

- La grandissima maggioranza delle infezioni da HPV regredisce spontaneamente
- Circa metà regredisce nel corso di 1 anno
- Clearance inizialmente più rapida poi si riduce
- Le nuove infezioni scompaiono più rapidamente di quelle già esistenti
- Tra le nuove infezioni non differenza per età

High-risk human papillomavirus status during study and risk for end histology of CIN3

HPV status during study	Number of women	CIN 3 (n=71)	Odds ratio for end histology CIN 3 (95% CI)
Persisitent infection	122	66	327 (42-2468)
Clearance and acquisition	150	4	2.9 (0.2-20)
Negative	81	1	1.0

Nobbenhuis et al. Lancet 1999; 354:20-25 (modified)

Guanacaste cohort

Risk of CIN3+ in the first 3 years of active follow-up after infection detection

Age (yrs)	Prevalent infections	Newly appearing infections
18-25	**4.0**	**2.7**
26-33	**3.1**	**4.4**
34-41	**6.0**	**0.0**
≥42	**5.3**	**1.0**

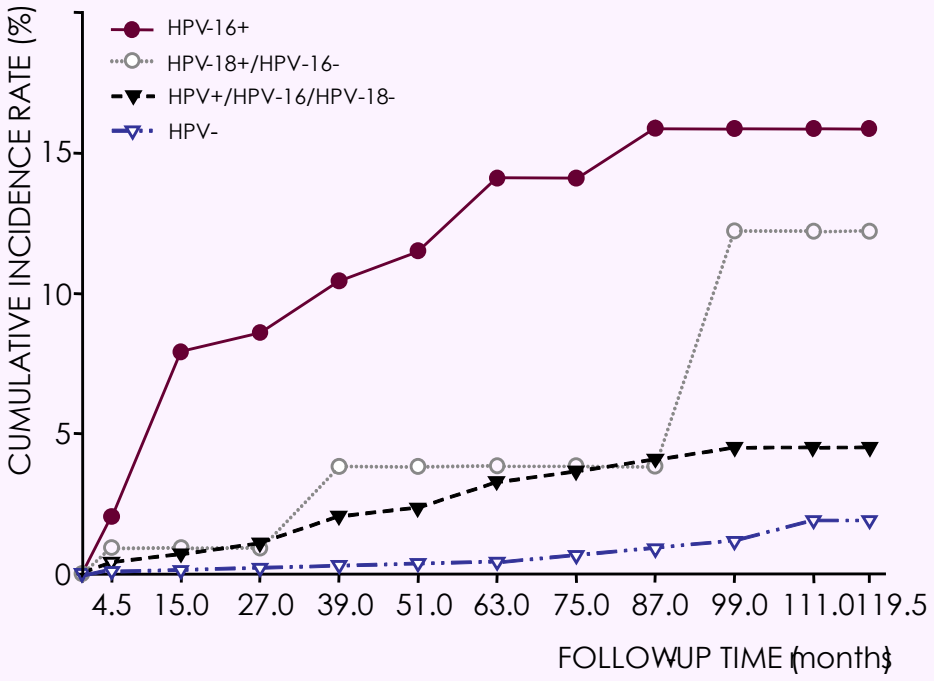
Risk of CIN3 from newly appearing infections:

Age 18-33: 11/312 (3.5%) Age 34+: 1/182 (0.5%)
p=0.06

Rodriguez et al JNCI 2010

CUMULATIVE INCIDENCE OF CIN-3 OR GREATER OVER A 10-YEAR PERIOD ACCORDING TO ONCOGENIC HPV STATUS AT ENROLLMENT

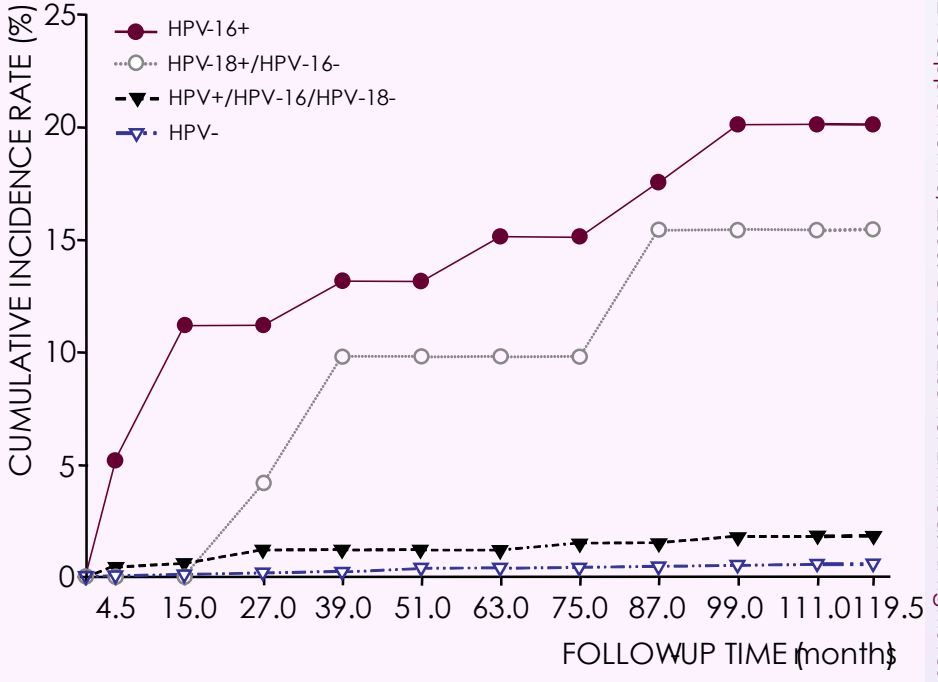
(A) 7,285 WOMEN < 30 YEARS OF AGE



(A) NO. OF WOMEN SEEN DURING FOLLOW-UP INTERVAL

HPV-16+	339	184	140	99	84	68	61	49	57	21	1
HPV-18+/HPV-16-	110	62	50	34	26	26	26	21	23	13	1
HPV+/HPV-16/HPV-1	,249	663	514	407	352	312	261	228	229	112	7
HPV-	5,498	2,896	2,349	1,957	1,695	1,493	1,285	1,214	1,083	543	23

(B) 13,229 WOMEN ≥30 YEARS OF AGE



(B) NO. OF WOMEN SEEN DURING FOLLOW-UP INTERVAL

HPV-16+	116	63	50	45	41	44	33	35	32	14	2
HPV-18+/HPV-16-	44	23	24	17	17	15	10	16	12	3	0
HPV+/HPV-16/HPV-1	962	545	502	455	403	389	339	300	318	144	10
HPV-	11,893	6,863	6,323	5,856	5,441	4,986	4,675	4,337	4,195	2,078	133

Reprinted from Khan MJ, *et al.* J Natl Cancer Inst 2005;97(14):1072–9 with permission from Oxford University Press.

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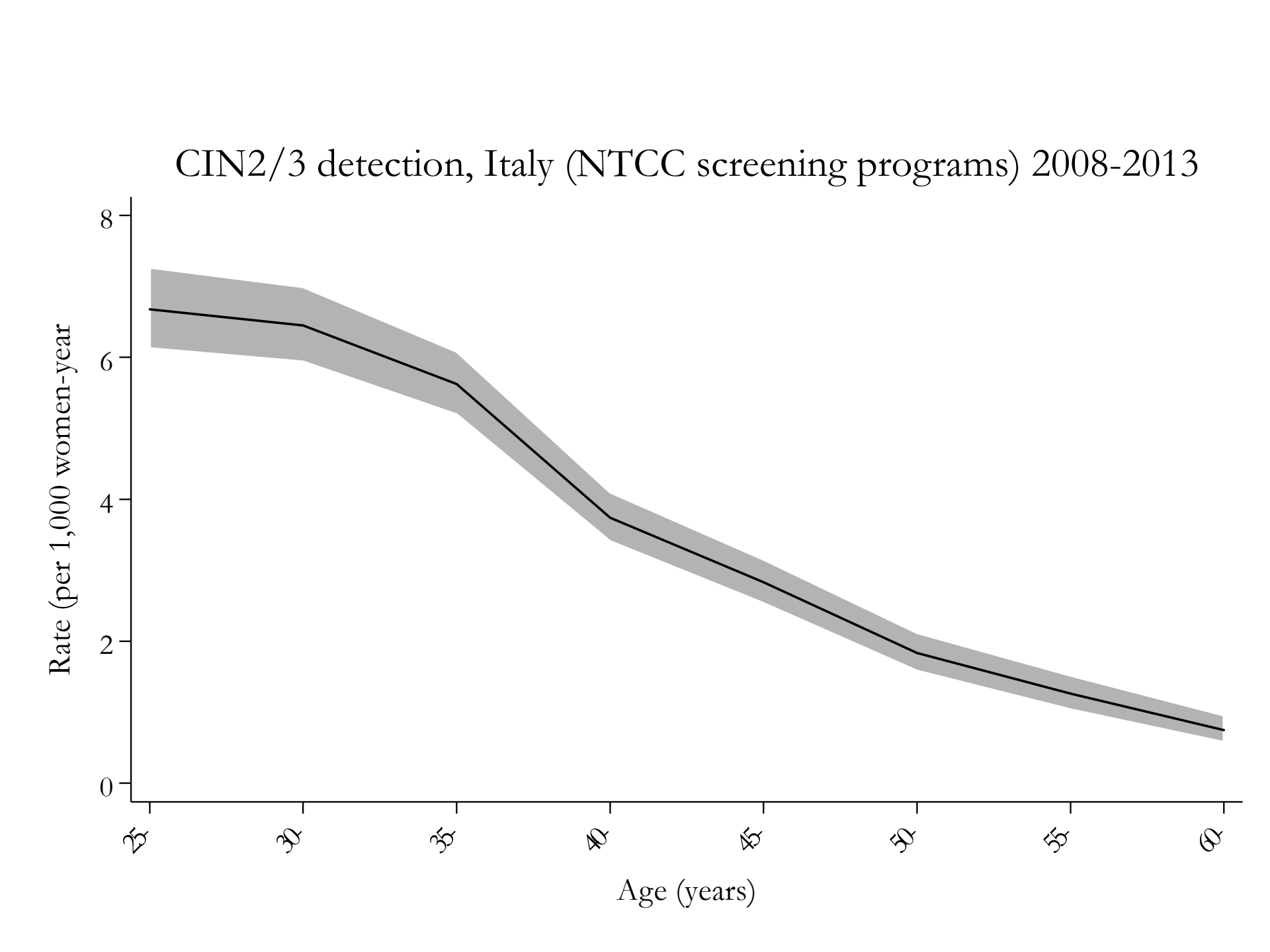
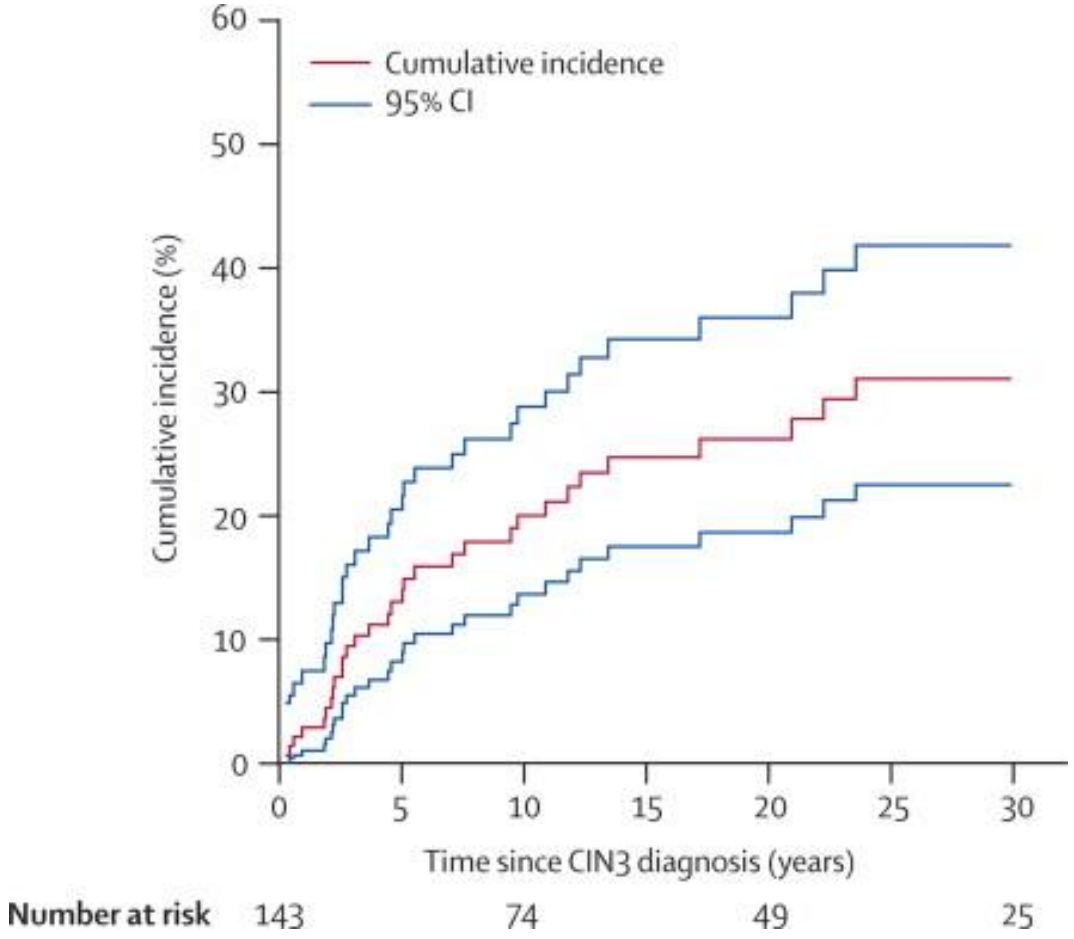
Vaccine, Vol 24 Supplement 3, 2006. Chapter 05, Figure 3


CIN2/3 detection, Italy (NTCC screening programs) 2008-2013
Rate (per 1,000 women-year
0
2
4
6
8
25
30
35
40
45
50
55
60
Age (years)

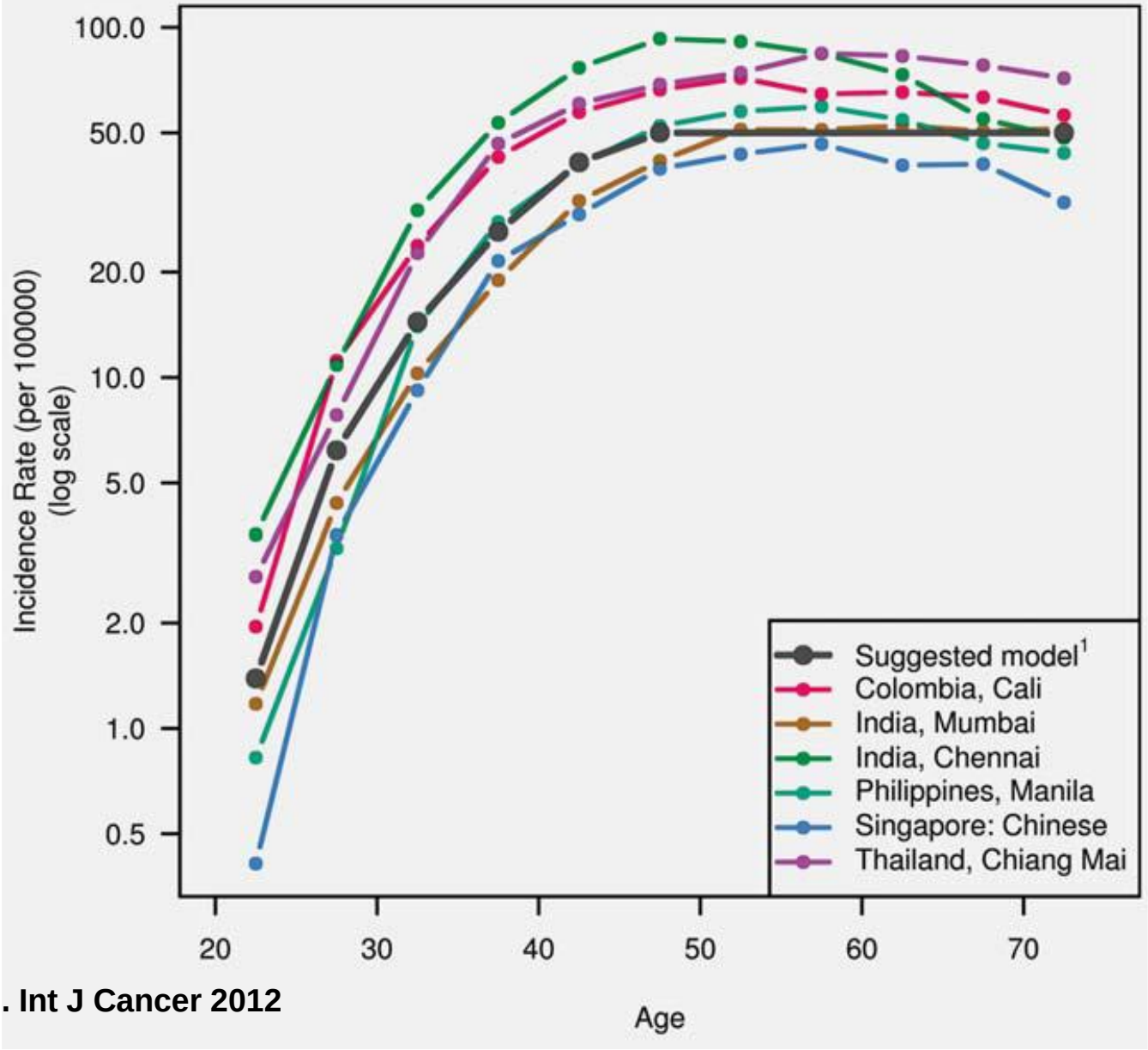
- Solo una piccola quota di infezioni progredisce a CIN2/3
- Necessaria persistenza infezione (inattivazione funzionale di prodotti di p53 ed RB da parte dei prodotti dei geni virali E6 ed E7).
- Intervallo da infezione dipende da come si cercano le CIN (plausibilmente mesi)
- Progressione più rapida con HPV16
- Donne già sottoposte a screening, dati recenti: profilo per età segue quello incidenza/prevalenza infezione (ritardato).

Cumulative incidence of cancer of the cervix or vaginal vault in women with minimum disturbance of the CIN3 lesion

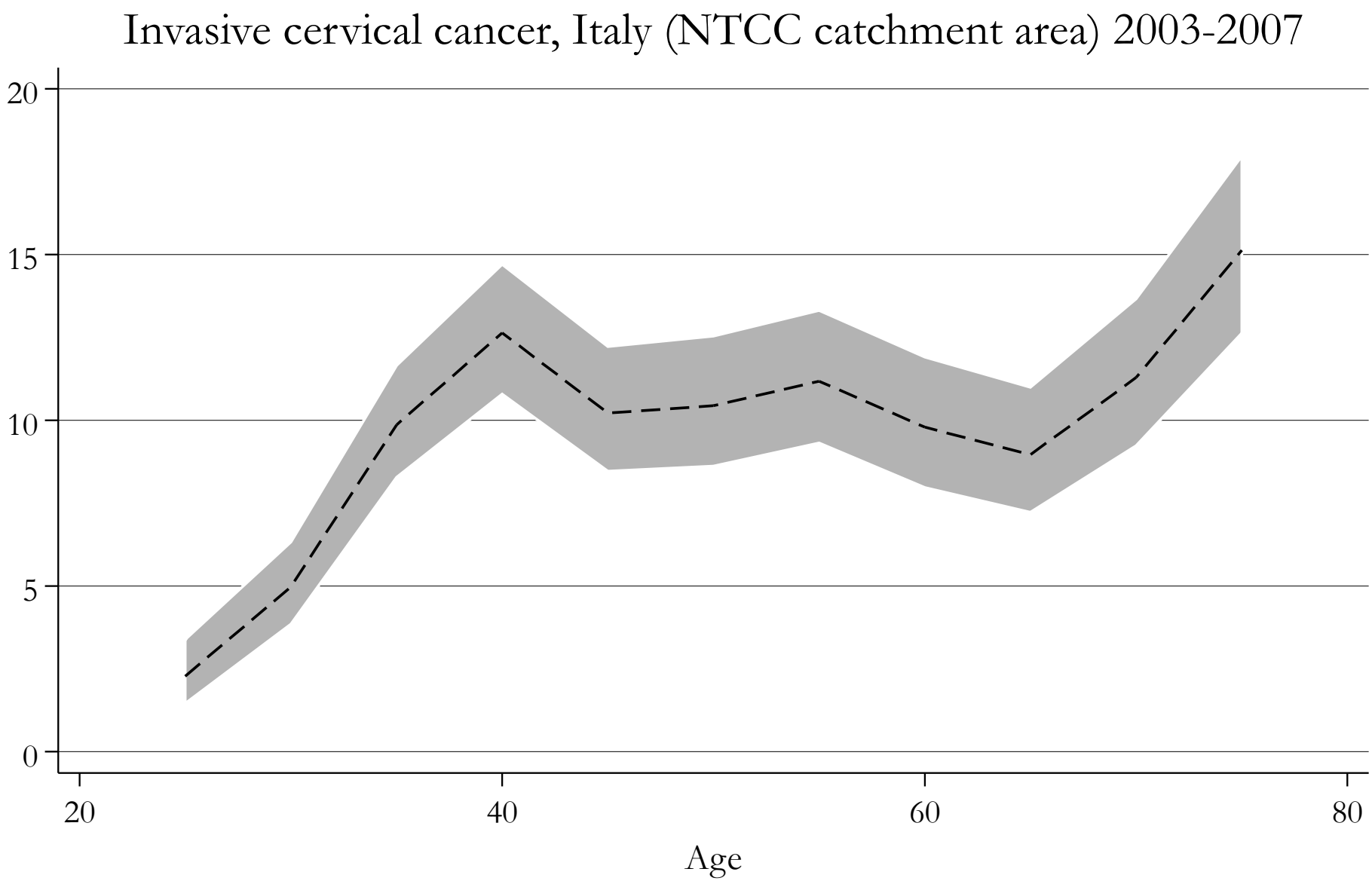


Mc Credie et al Lancet Oncol 2008

Age dependence of cervical cancer incidence in largely unscreened populations in calendar years 1971–2001 from an age-cohort model. The age-specific rates displayed are fitted values for the 1950–1954 birth cohort.



Plummer et al. Int J Cancer 2012


Invasive cervical cancer, Italy (NTCC catchment area) 2003-2007
20
15
10
5
0
20
40
60
80
Age

- Dati NZ: circa 1/3 delle CIN3 progredisce a Ca in 30 anni da individuazione
- CIN trovate 40 anni fa. Ora plausibilmente trovate prima, quindi intervallo da individuazione CIN a Ca più lungo.
- Incidenza Ca in assenza di screening non aumenta dopo i 45 aa.
- In presenza di screening due picchi. Effetto screening su coorte (donne nate prima non hanno fatto screening o hanno iniziato dopo). Altro?

In conclusione, Ca cervice complicanza rara di infezione molto comune

Cervical Cancer Screening.
IARC Handbooks on Cancer Prevention 2005

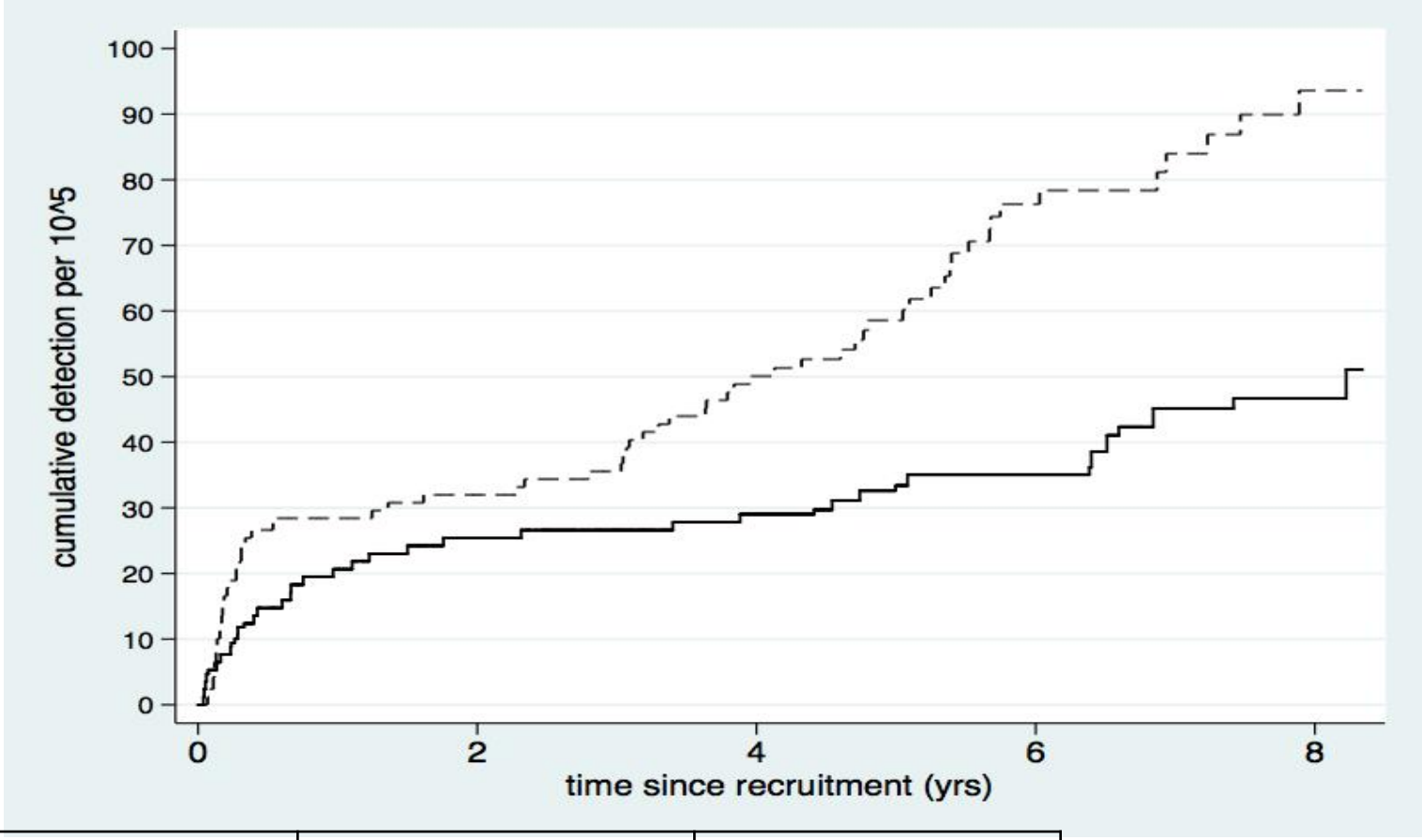
There is sufficient evidence that screening for cancer precursors every 3-5 years between the ages 35 and 64 years by conventional cytology in a high-quality programme reduces the incidence of invasive cancer by 80% or more among the women screened

Pooled analysis of Swedescreen, POBASCAM, NTCC and ARTISTIC

Cumulative incidence of ICC by arm. All recruited women

Solid lines:HPV group.

Dotted lines: cytology group



	Overall	≤2.5 yrs from enrolment	>2.5 yrs from enrolment
Pooled RR	**0.60** (0.40-0.89)	**0.79** (0.46-1.36)	**0.45** (0.25-0.81)

Ronco et al. Lancet 2014 modif.

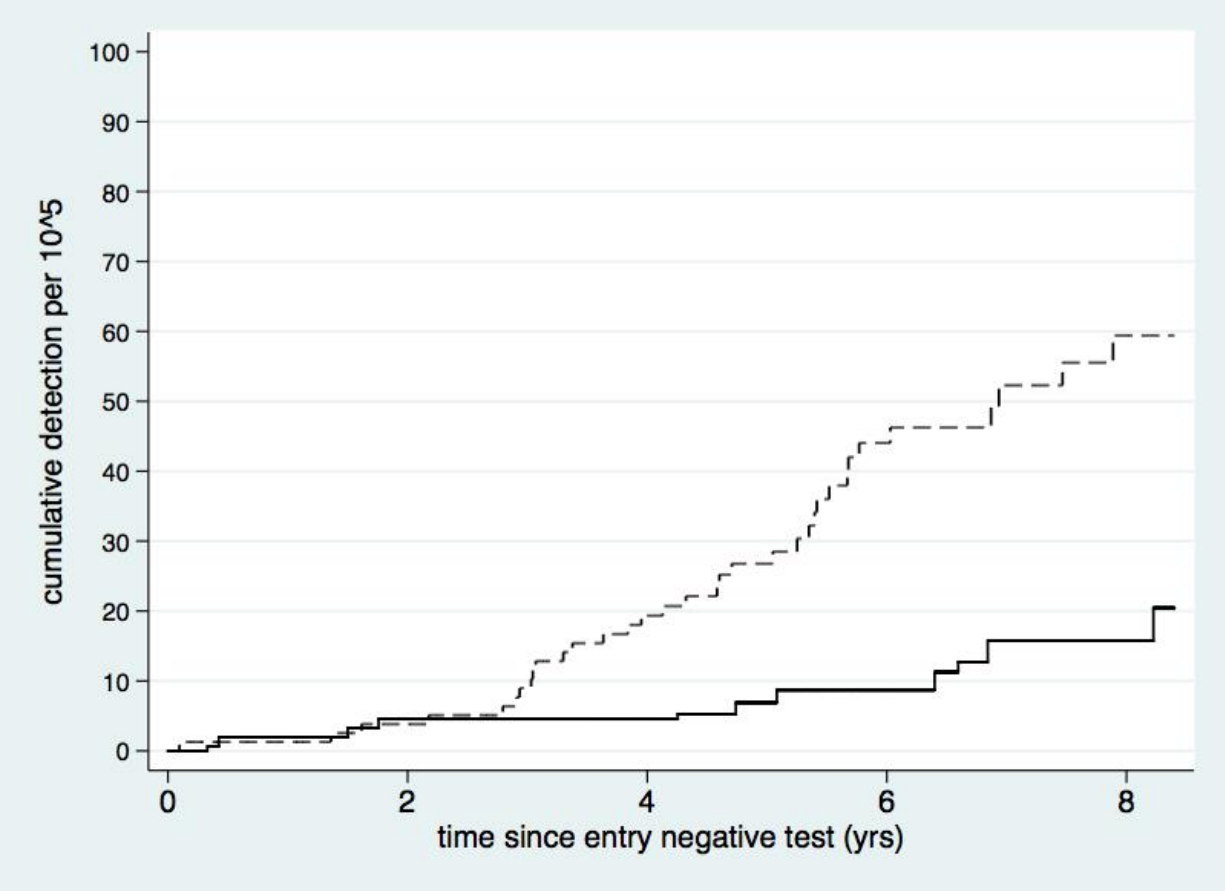
Risk of invasive carcinoma after a negative entry test (HPV- in HPV arm and cytology- in cytology arm)

Solid lines: HPV group.

Dotted lines: cytology group

Pooled RR

0.30 (0.15-0.60)



	3.5 years	5.5 years
cytology	15.4 (CI 7.9-27.0)	36.0 (23.2-53.5)
HPV	4.6 (1.1-12.1)	8.7 (3.3-18.6)

Ronco et al. Lancet 2014 modif.

Testa e collo

Chaturvedi et al, J. Clin Oncol 2011

Observed and projected incidence rates for HPV+ oropharyngeal cancer (OPSCC) among men and women & cervical cancers

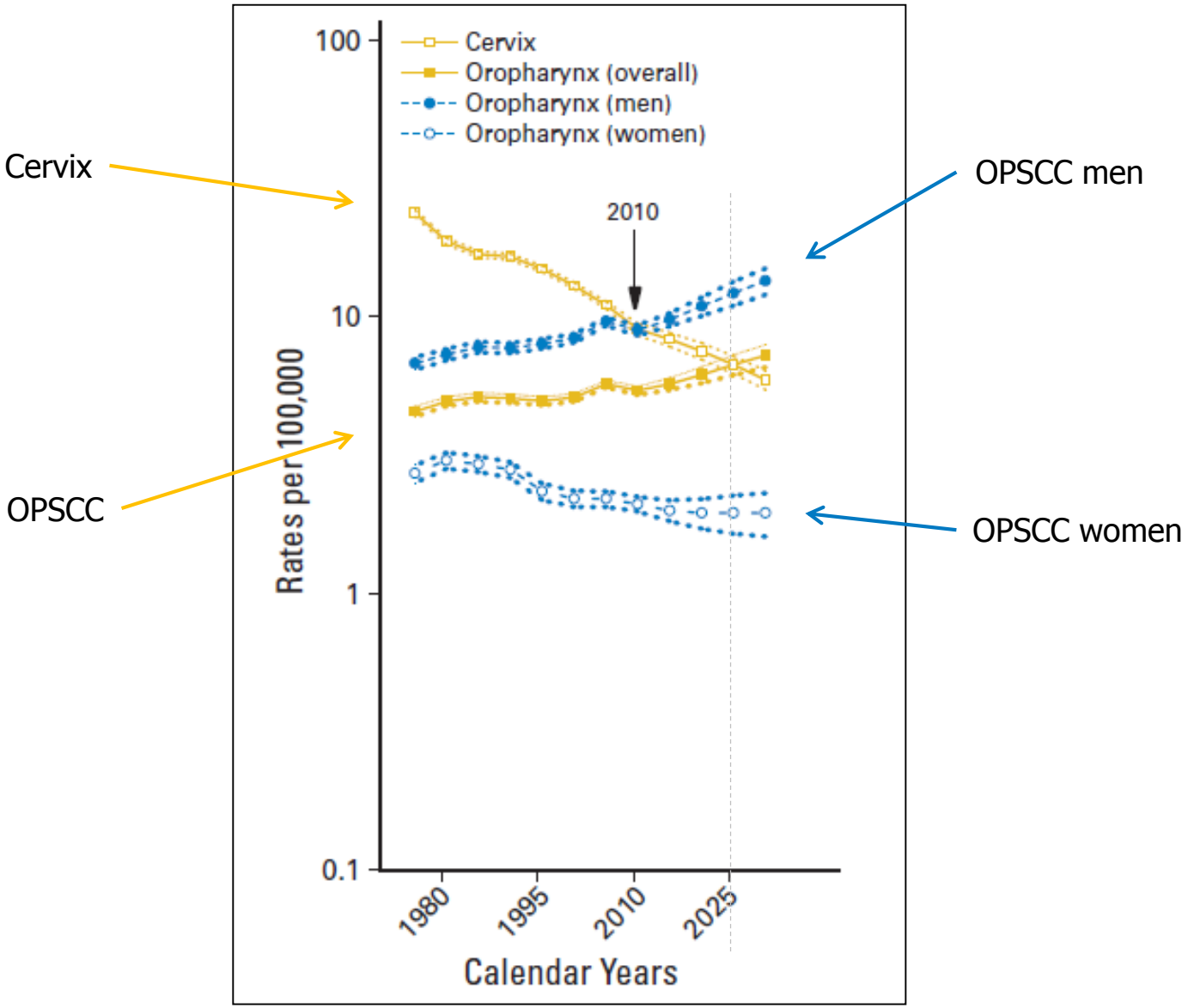


Table 1
Prevalence of human papillomavirus in head and neck cancer (HNC) by cancer site and region,[a] adapted from Kreimer et al. [16].

Site region	*n* Studies	*n* Cases	Overall HPV prevalence (95% CI)	HPV16 prevalence (95% CI)
Oral cavity				
Europe	15	744	16.0 (13.4–18.8)	10.8 (8.6–13.2)
North America	8	577	16.1 (13.2–19.4)	10.1 (7.7–12.8)
Asia	13	1 133	33.0 (30.3–35.8)	22.3 (20.3–25.2)
Other[b]	2	188	18.1 (12.9–24.3)	14.9 (10.1–20.8)
Total	35[c]	2 642	23.5 (21.9–25.1)	16.0 (not reported)
Oropharynx				
Europe	17	529	28.2 (24.4–32.2)	23.8 (20.2–27.7)
North America	7	285	47.0 (41.1–53.0)	42.1 (36.3–48.1)
Asia	4	54	46.3 (32.6–60.4)	35.2 (22.7–49.4)
Other[b]	2	101	36.6 (27.3–46.8)	33.7 (24.6–43.8)
Total	27[c]	969	35.6 (32.6–38.7)	30.9 (not reported)
Larynx[d]				
Europe	19	799	21.3 (18.5–24.3)	13.8 (11.5–16.4)
North America	7	297	13.8 (10.1–18.3)	10.1 (7.0–14.1)
Asia	8	306	38.2 (32.8–43.9)	26.5 (21.6–31.8)
Other[b]	1	33	48.5 (30.8–66.5)	45.5 (28.1–63.6)
Total	35[c]	1 435	24.0 (21.8–26.3)	16.6 (not reported)

Abbreviations: HPV = human papillomavirus; CI = confidence interval.

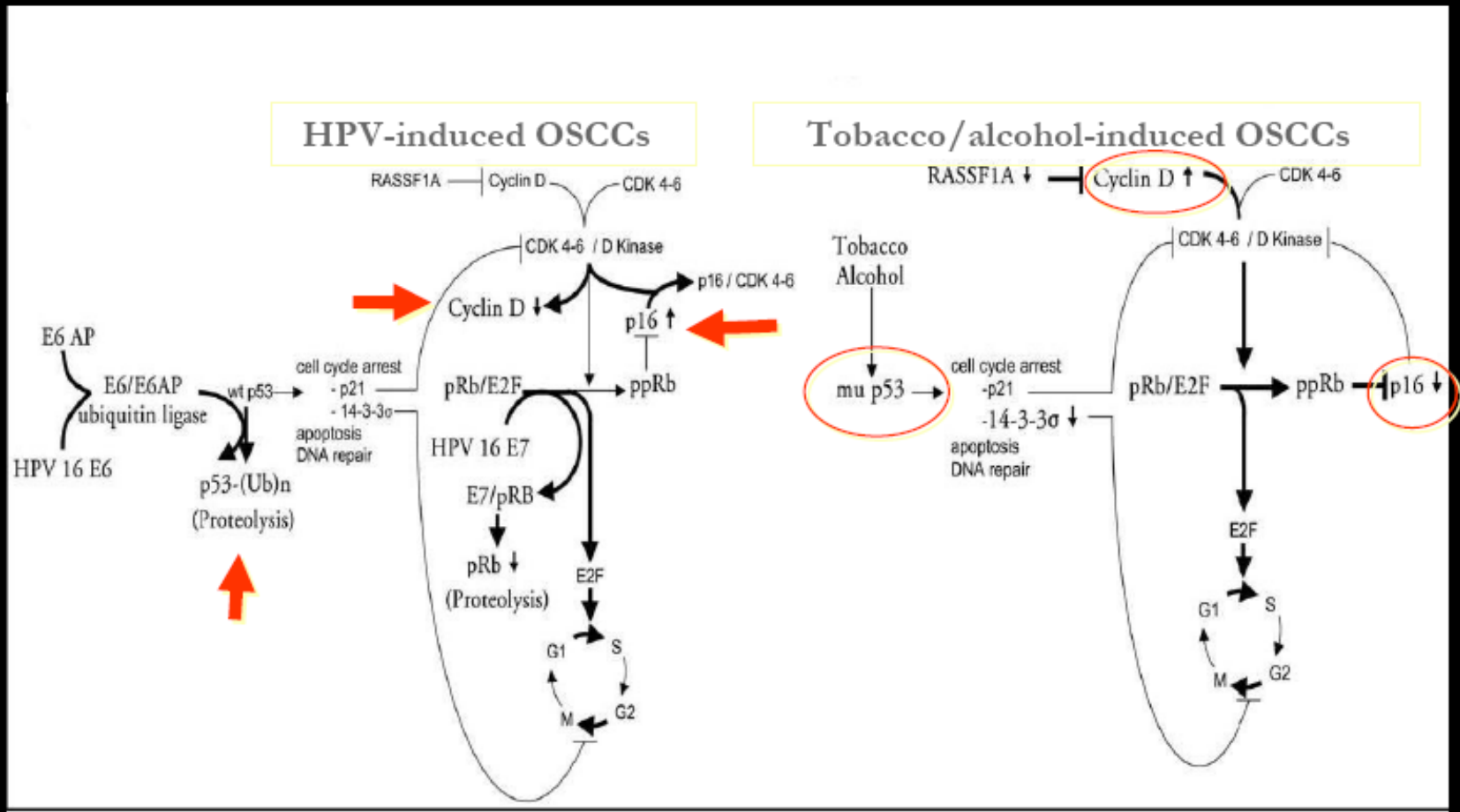
[a] The inclusion criteria were (a) type-specific HPV results from cancer tissue biopsies, (b) HPV results on a minimum of 40 cases of HNC or 20 cases of an individual HNC, and (c) clearly described PCR-based HPV testing methods. Studies included were published between 1990 and 2004.

[b] Includes Central and South America, Australia, and Africa.

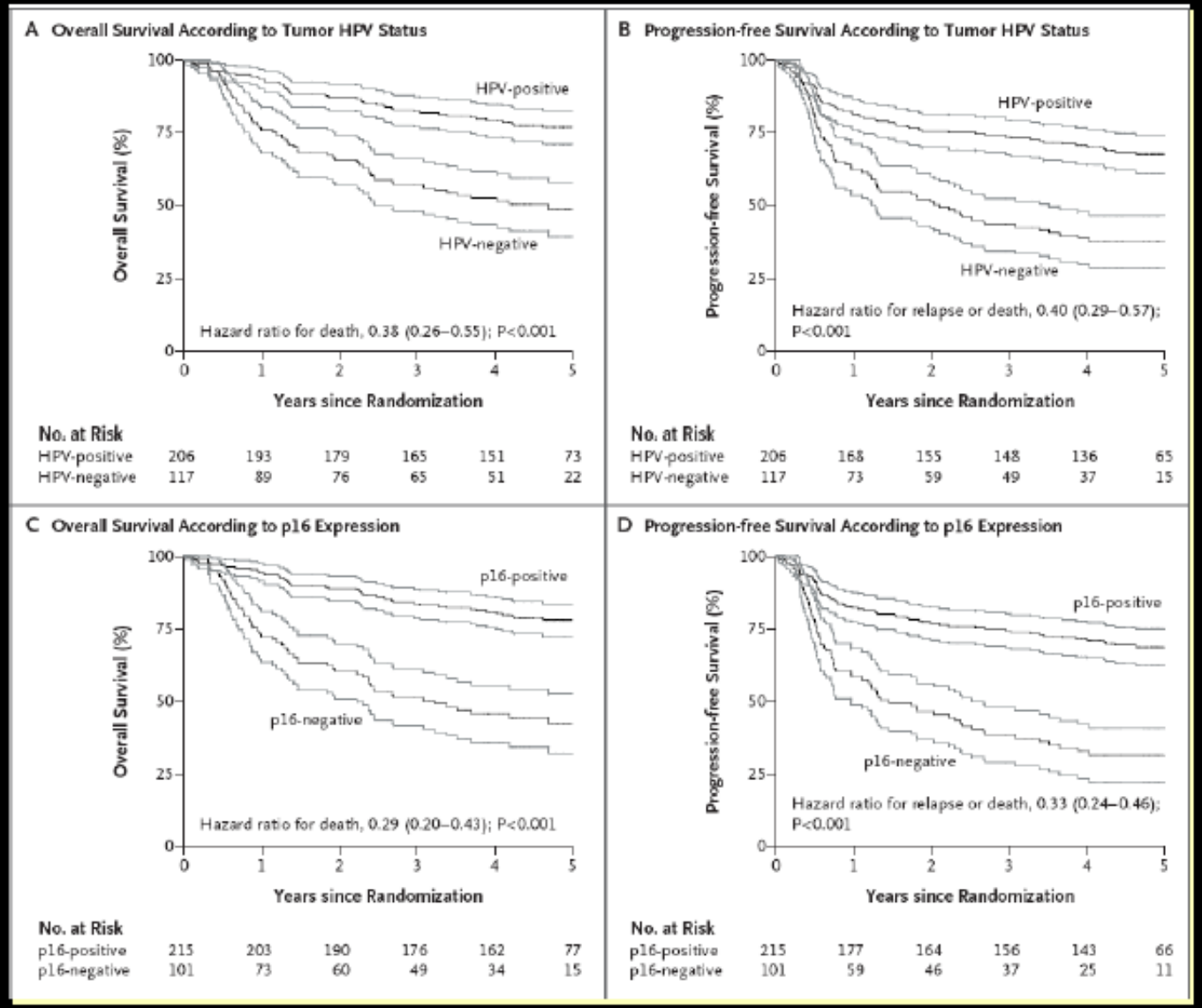
[c] Does not add up to the total number of studies because some studies investigated multiple sites.

[d] Larynx includes cases of the hypopharynx.

Combes & Franceschi 2013



Gillison ML. Seminars in Oncology, 2004



Ang NEJM 2010

Relative contribution of HPV 16/18 or HPV6/11/16/18/31/33/45/52/58 to HPV-associated cancers by site and by gender; world, 2012

	Cervix	Anus	Vulva	Vagina	Penis	Head & neck	Tot. men	Tot women
16/18	70.8	87.0	72.6	63.7	70.2	84.9	71.4	82.3
9valent	89.5	95.9	87.1	85.3	84.6	89.7	89.6	90.4

De Martel et al. 2017