

Dialogue for Action Conference: Natural History and Epidemiology of Cervical Cancer

Philip E. Castle, PhD, MPH
Executive Director, Global Cancer Initiative
& Global Coalition against Cervical Cancer
March 20, 2013

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Always Beware of Observational Data!

BUT there are some things that you can't do prospective randomized controlled trials about, like global warming and prematurity after LEEP

proof of global warming



Courtesy of Walter Kinney

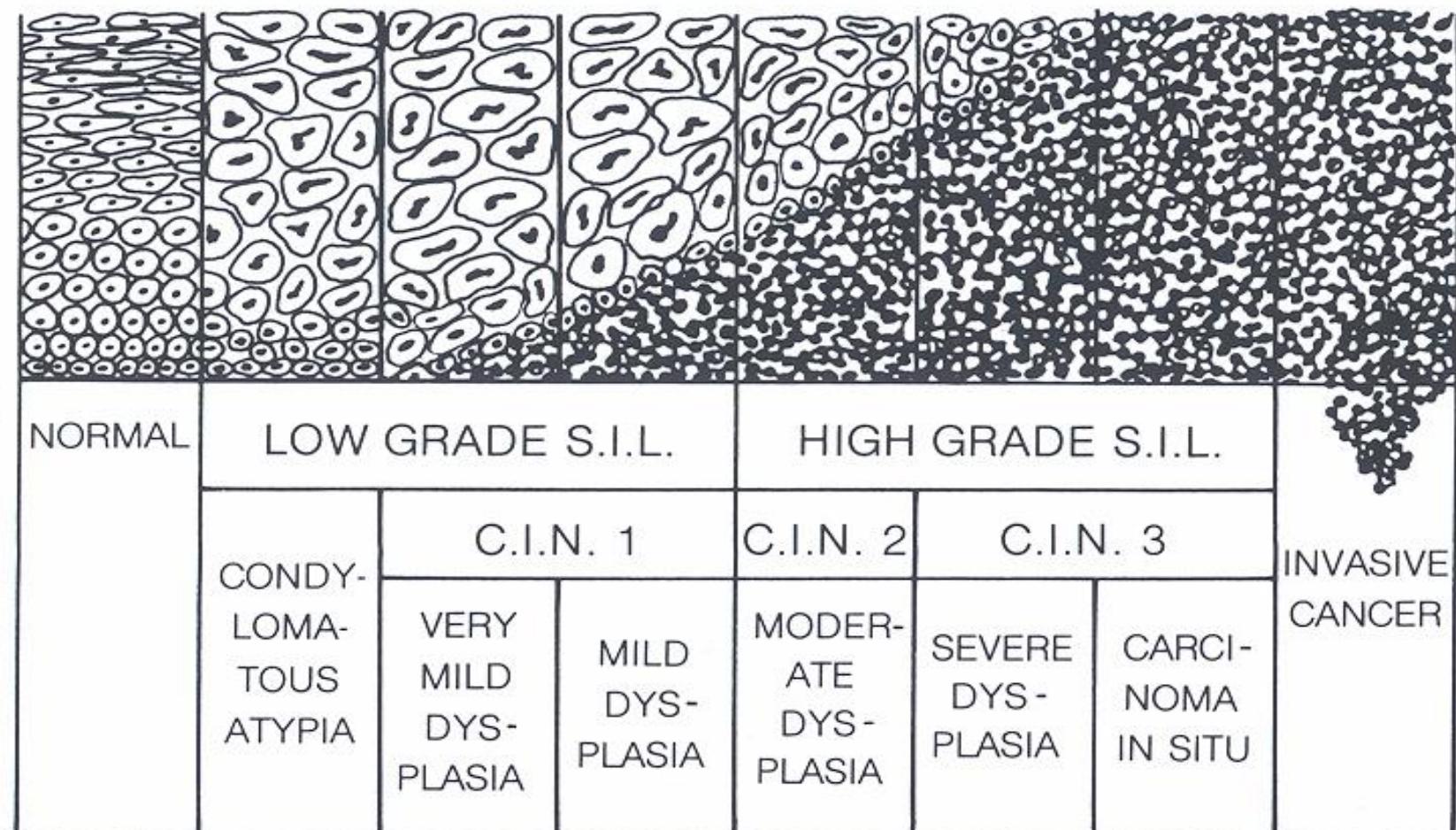
Today's Talk

1. Natural History of HPV: Rational Basis for Cervical Cancer Prevention
2. Vaccination and Screening
3. Global Cervical Cancer Prevention

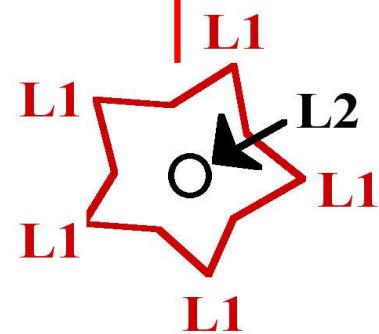
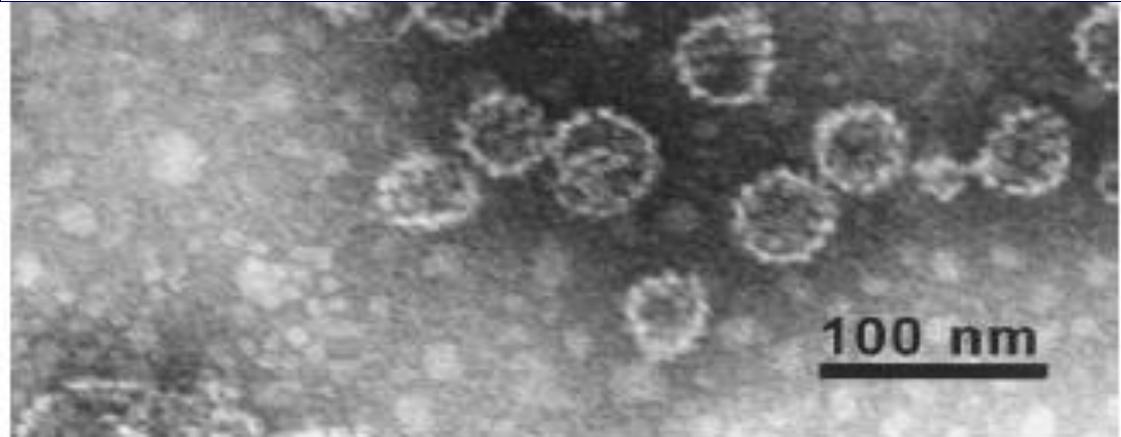
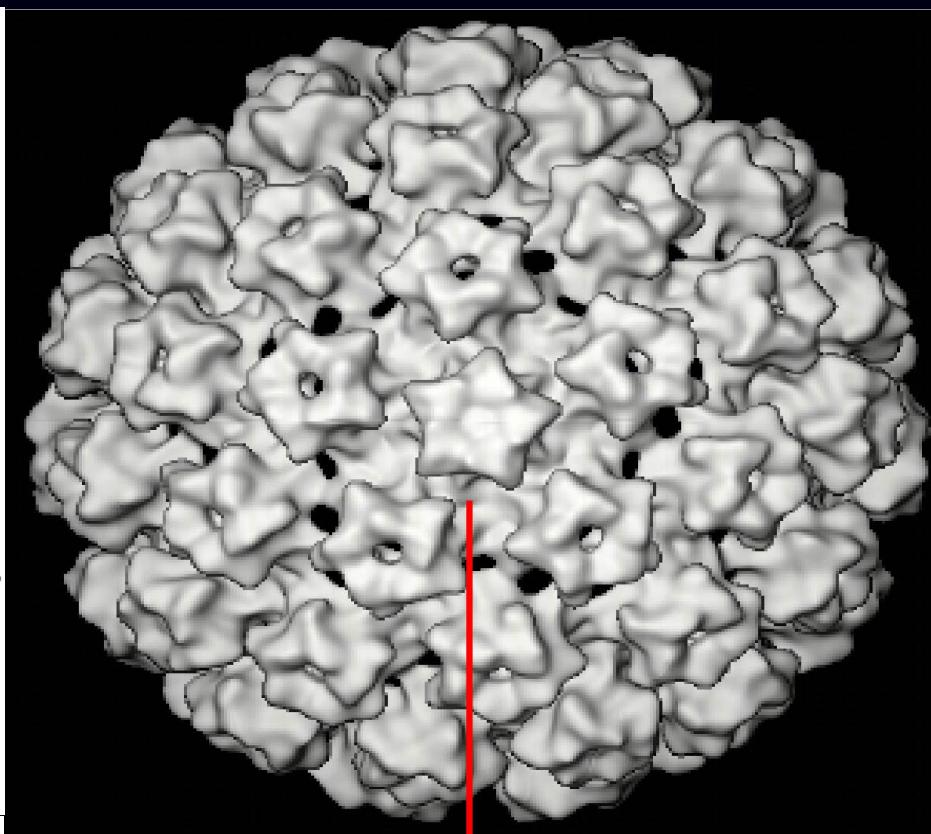
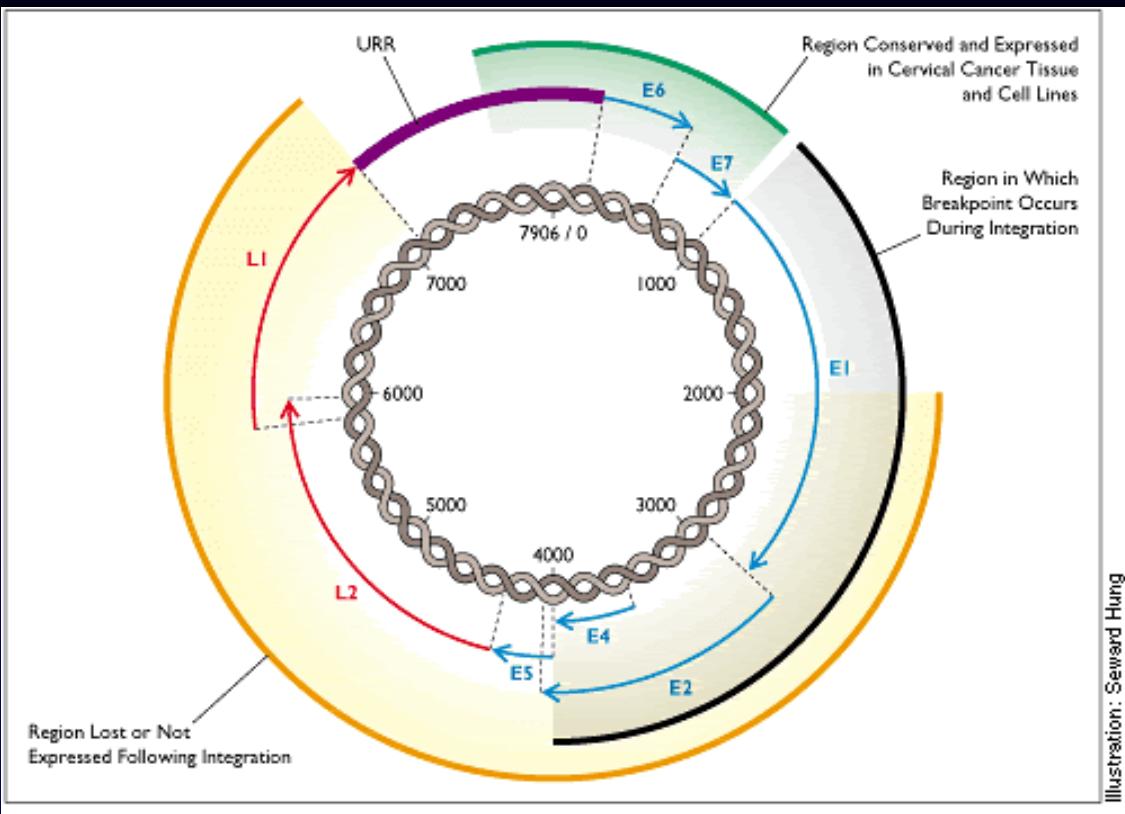
Cervical Cancer Continuum: The Old Model of Cervical Carcinogenesis

Surface of epithelium

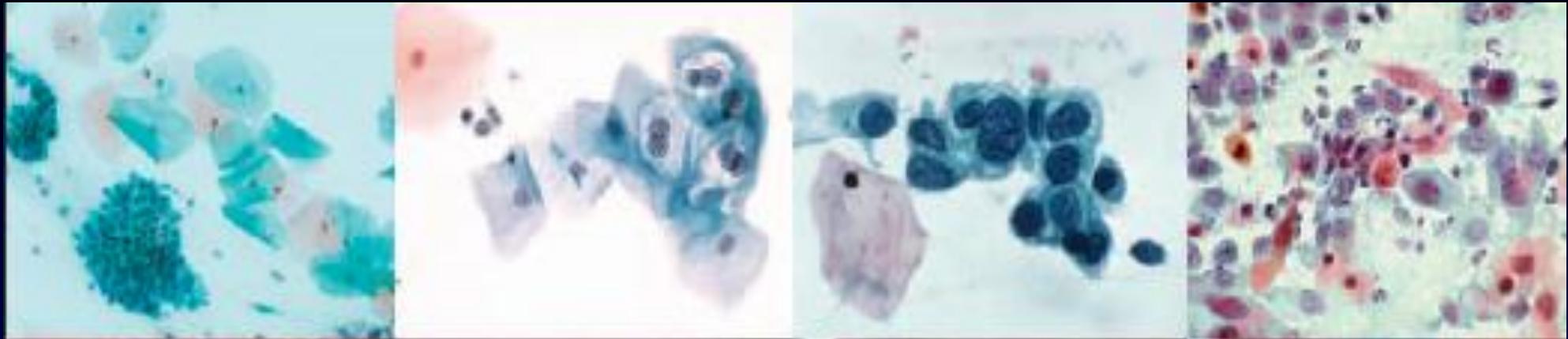
Basal epithelium



Human Papillomavirus (HPV)



New Model of Cervical Carcinogenesis



Transient infection

Persistent HPV

Normal
cervix

INFECTION

CLEARANCE

HPV-infected
cervix

PROGRESSION

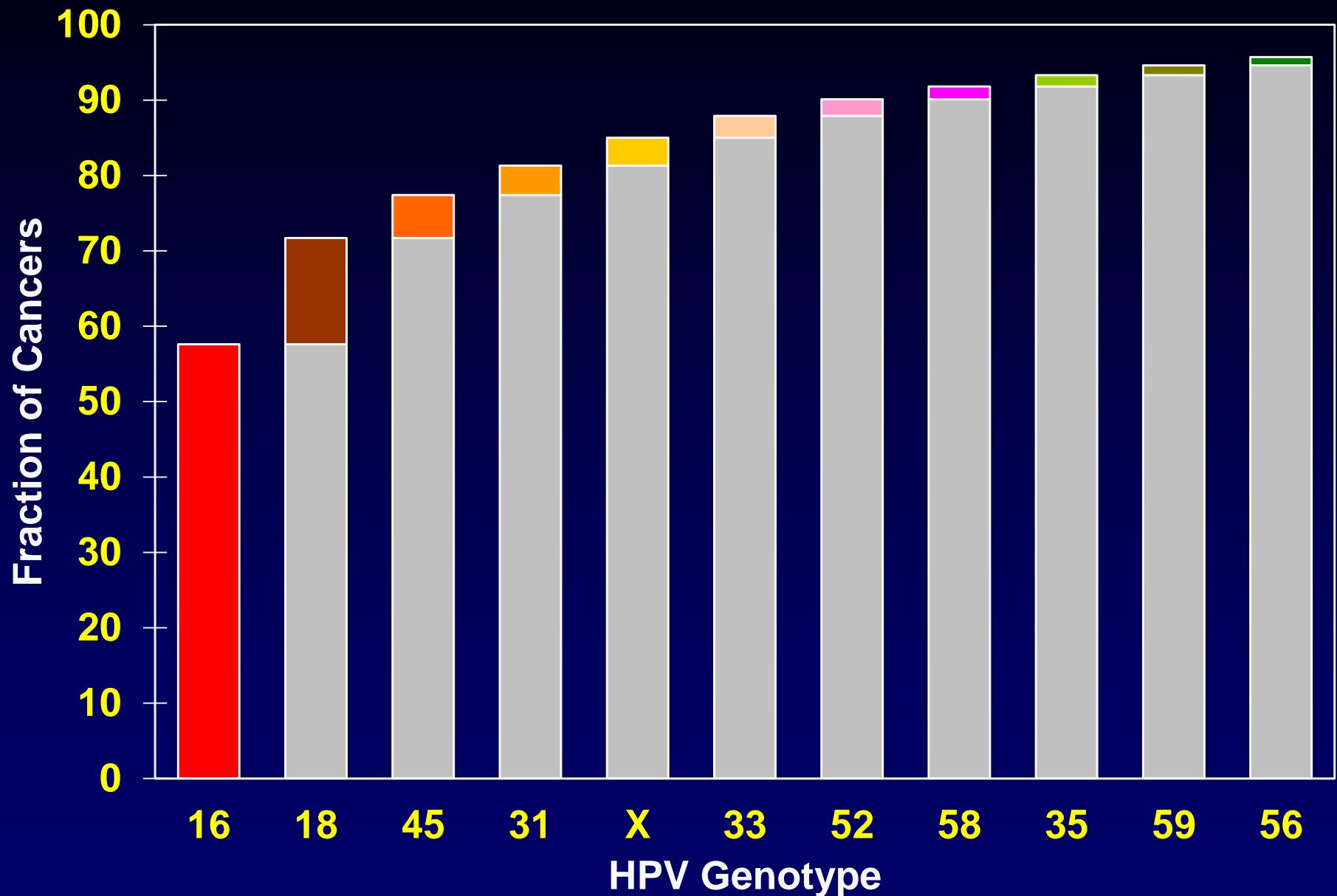
REGRESSION?

Precancer

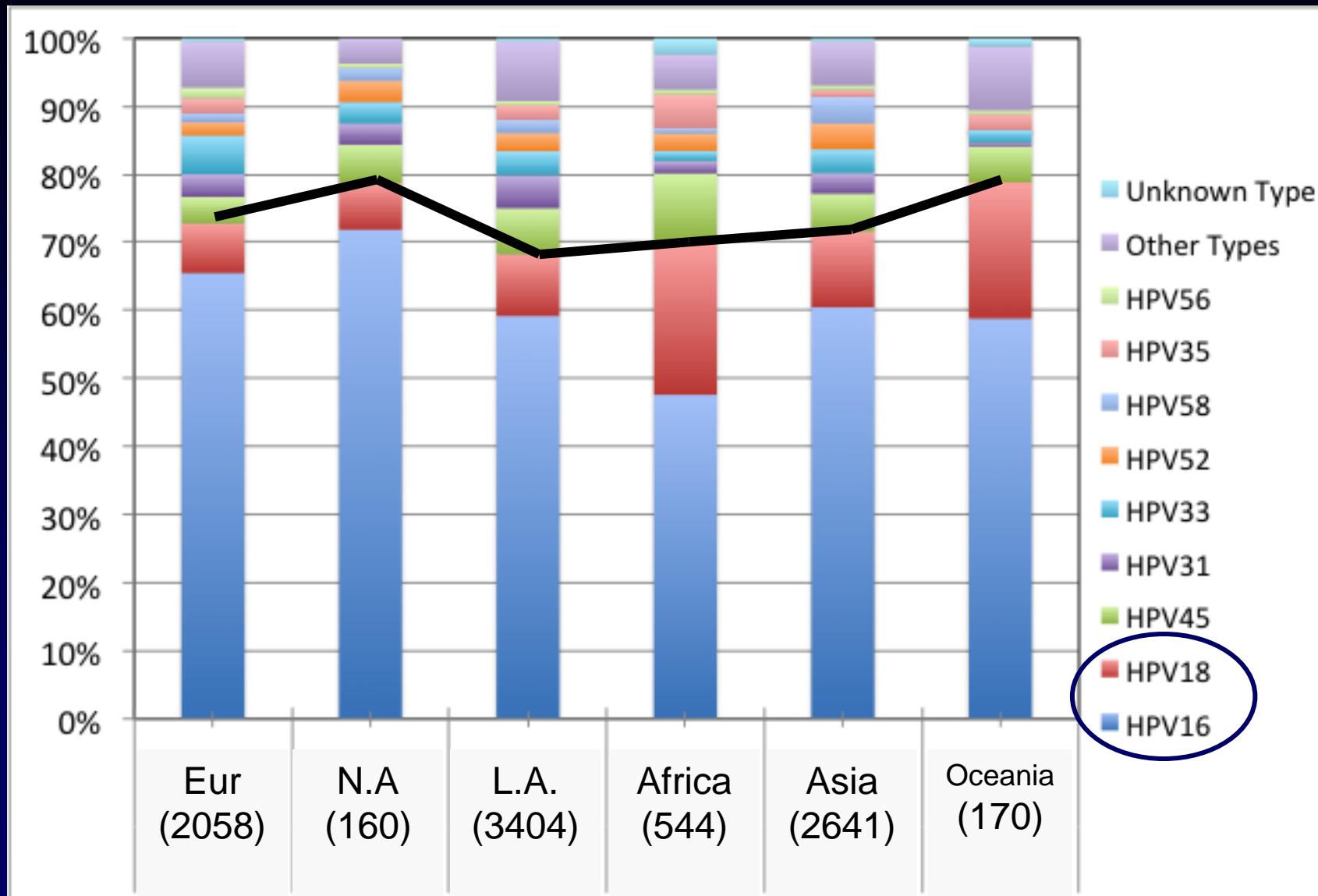
INVASION

Cancer

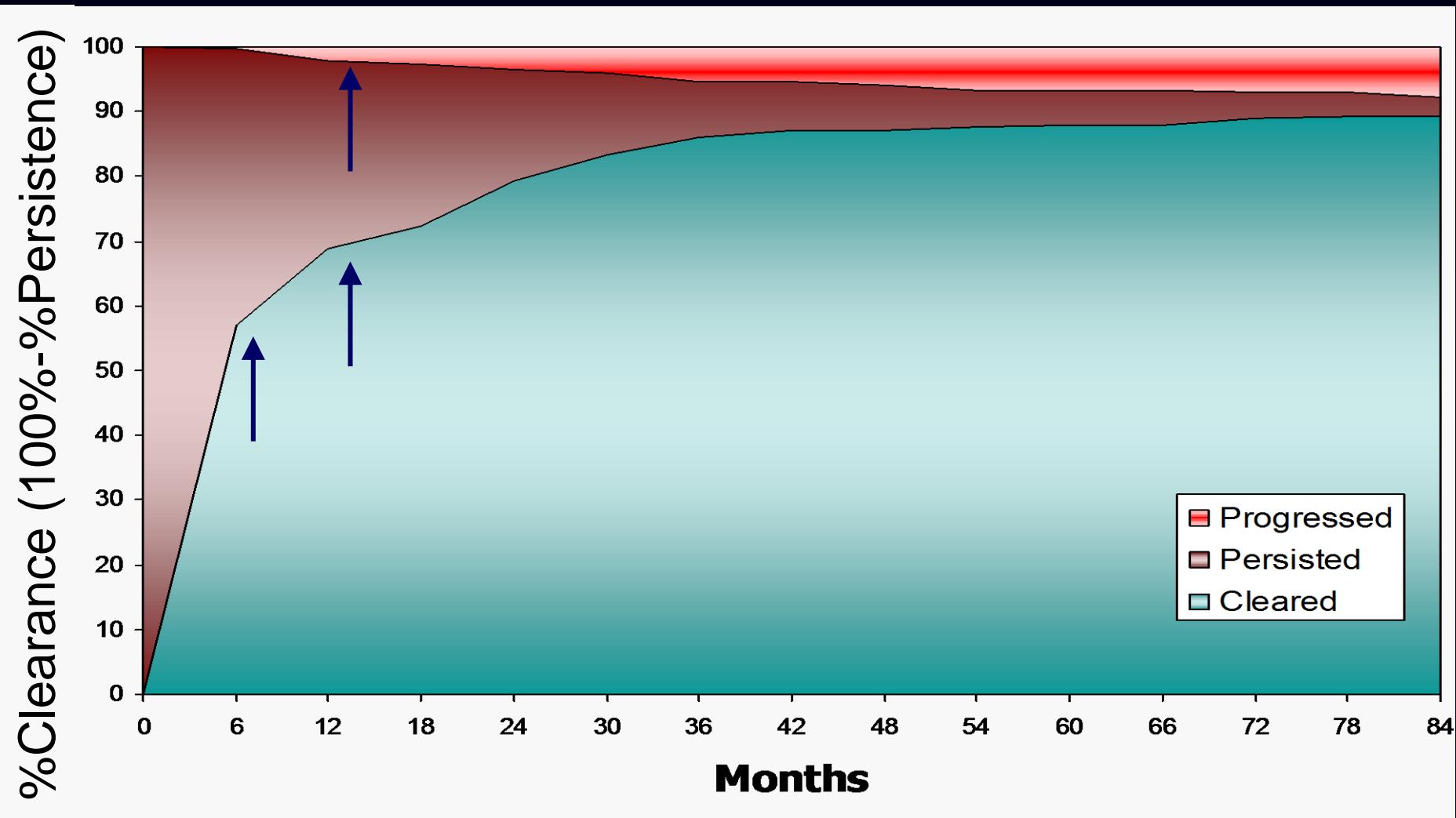
Etiologic Contribution of HPV Genotypes



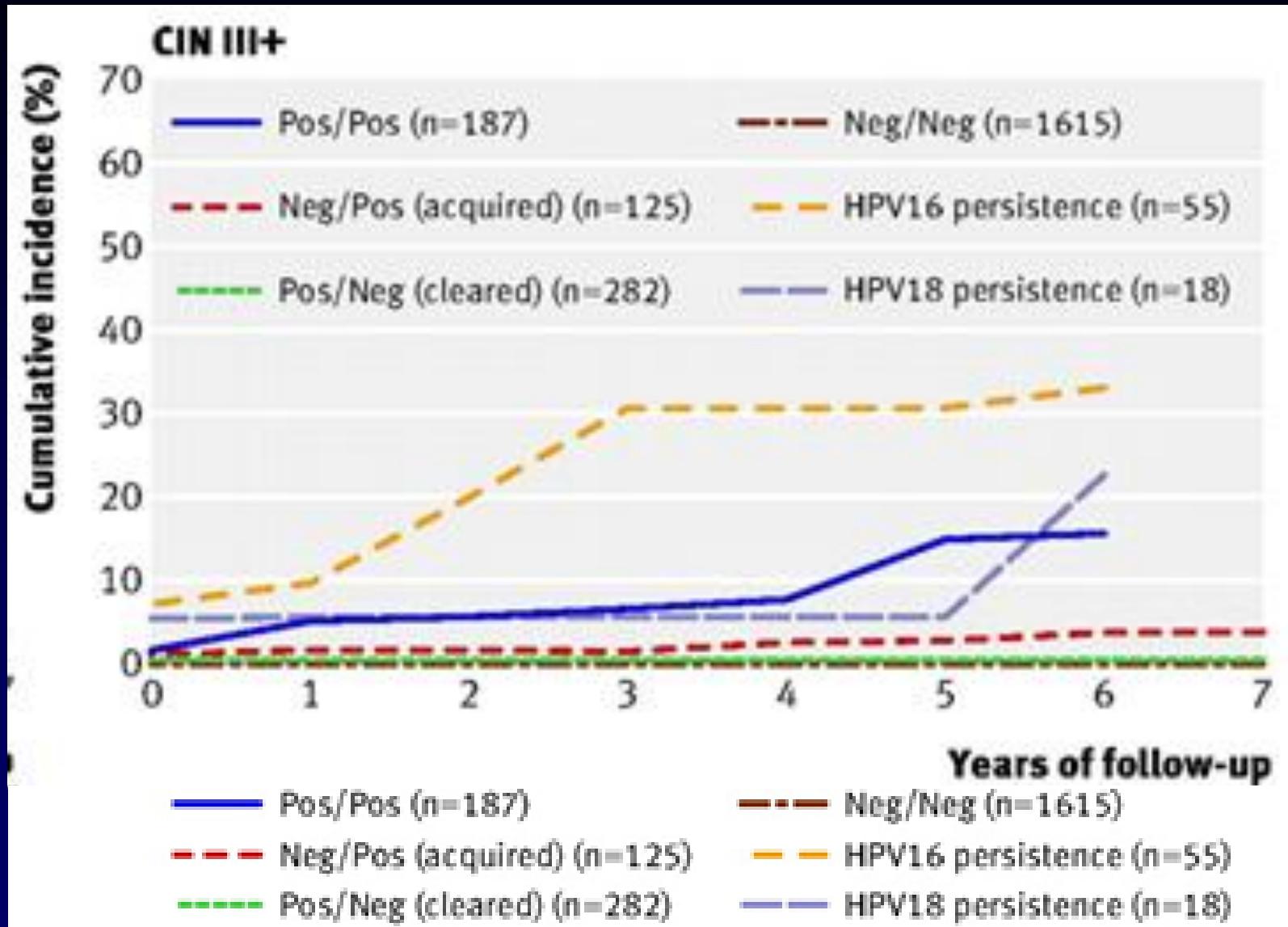
Variation of HPV Genotypes in CxCa



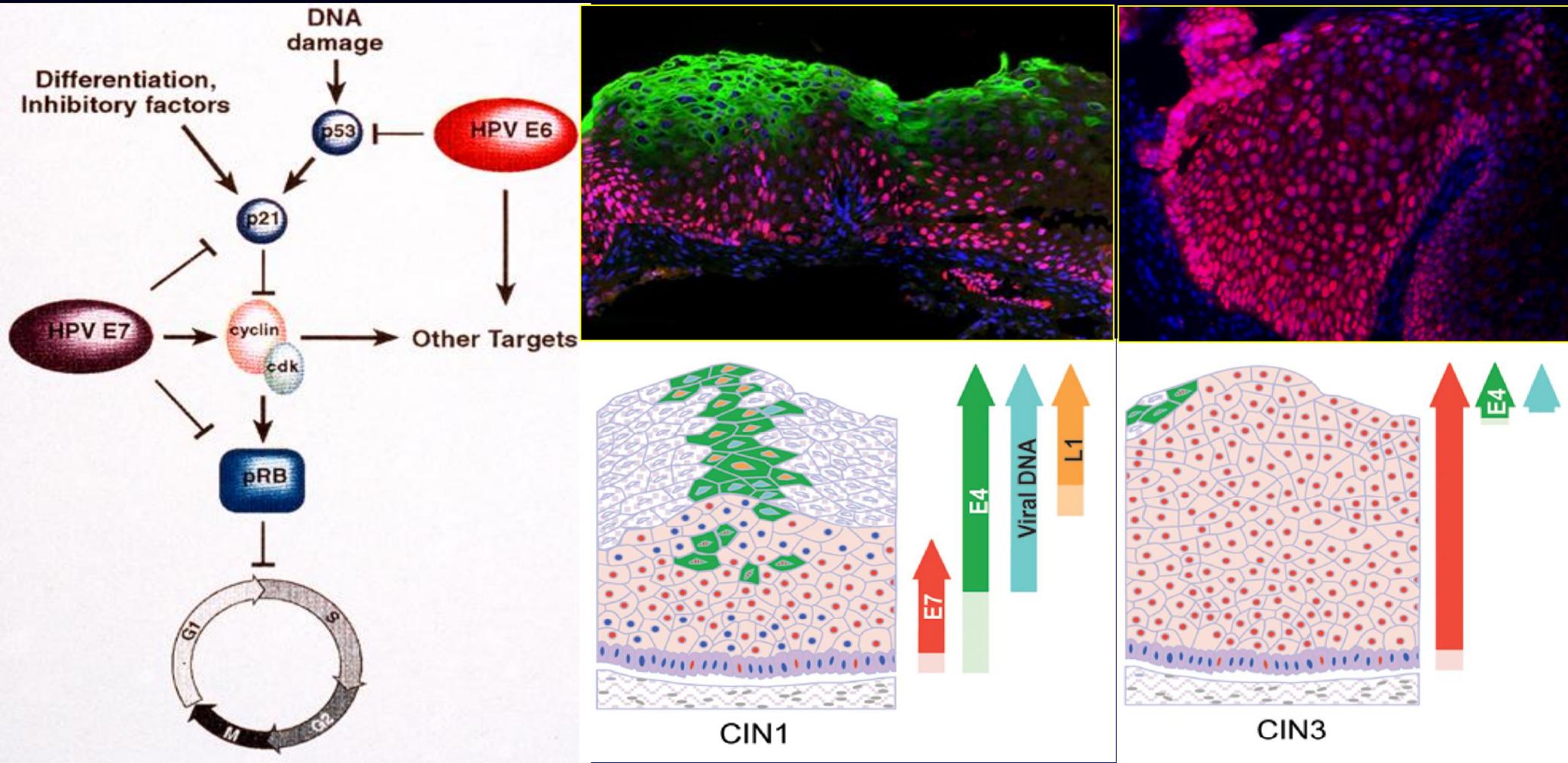
Natural History Profile of Prevalent HPV



Short-Term HPV Persistence



HPV Oncoproteins Block Tumor Suppressor Genes p53 and rB



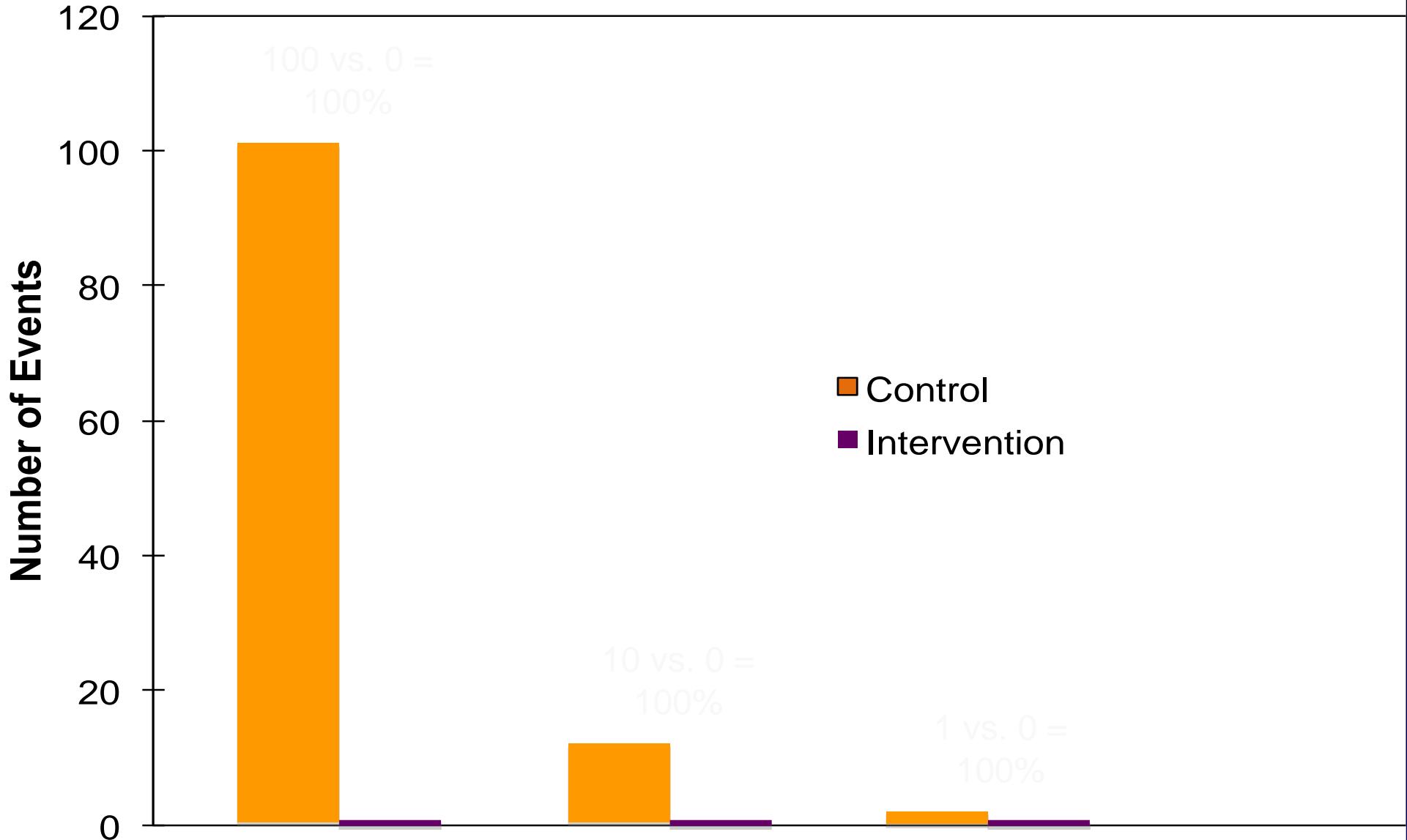
Risk Factors for Cervical Cancer

Risk Factor	Association	Absolute Risk
Having a cervix	Infinite	Low
Having sex	Infinite	Low
Exposure to HPV, Lifetime	Infinite	Low
HPV16 Detection	500	High
HR-HPV (pooled) Detection	100	Medium
HPV56, 68 Detection	25-50	Medium
Abnormal Pap	25-50	Medium
AIDS	10-20	Medium
HIV	5-10	Medium
Parity (vs. none)	2-4	Low
Oral Contraceptive Use (vs. none)	2-4	Low
Smoking	2-5	Low
Immunogenetics (HLA)	2-5	Low

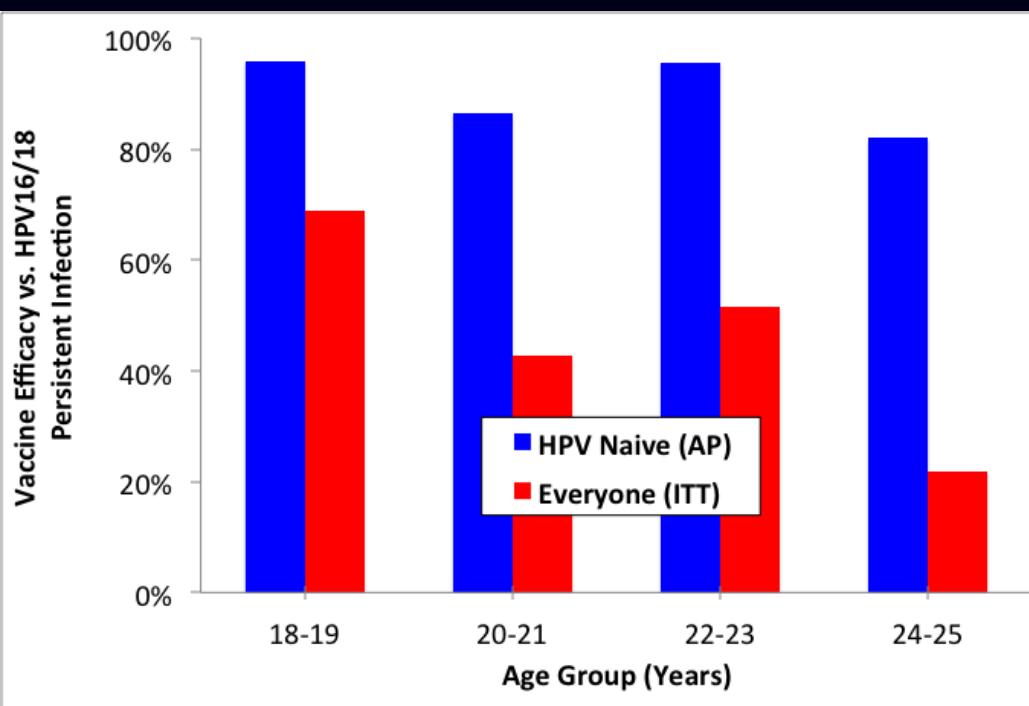
Today's Talk

- 1. Natural History of HPV: Rational Basis for Cervical Cancer Prevention**
- 2. Vaccination and Screening**
- 3. Global Cervical Cancer Prevention**

Efficacy vs. Public Health Benefit

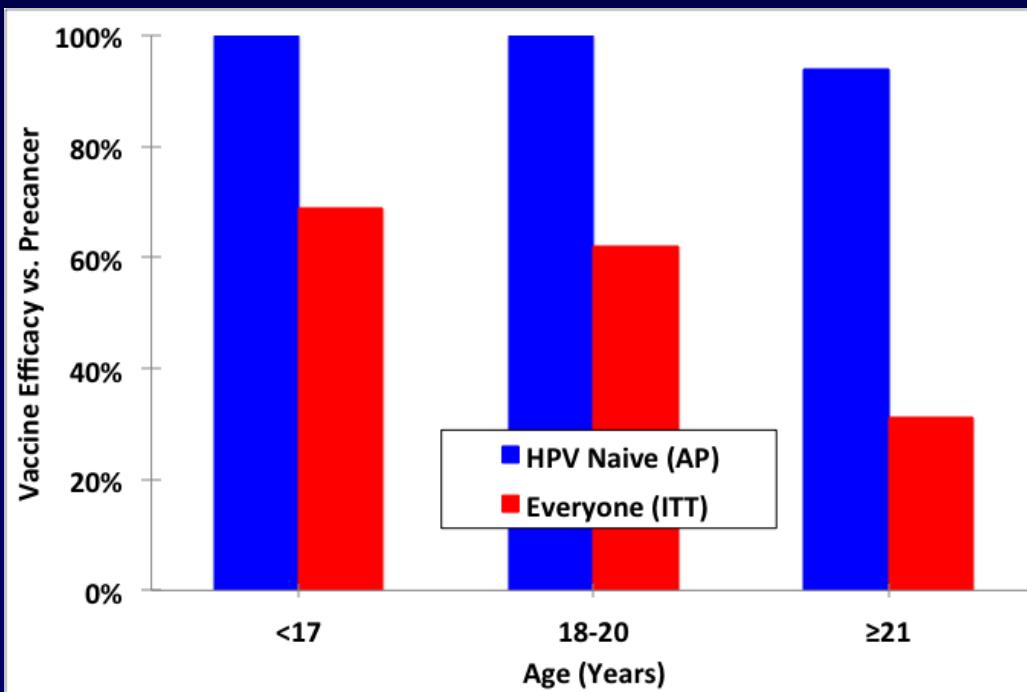


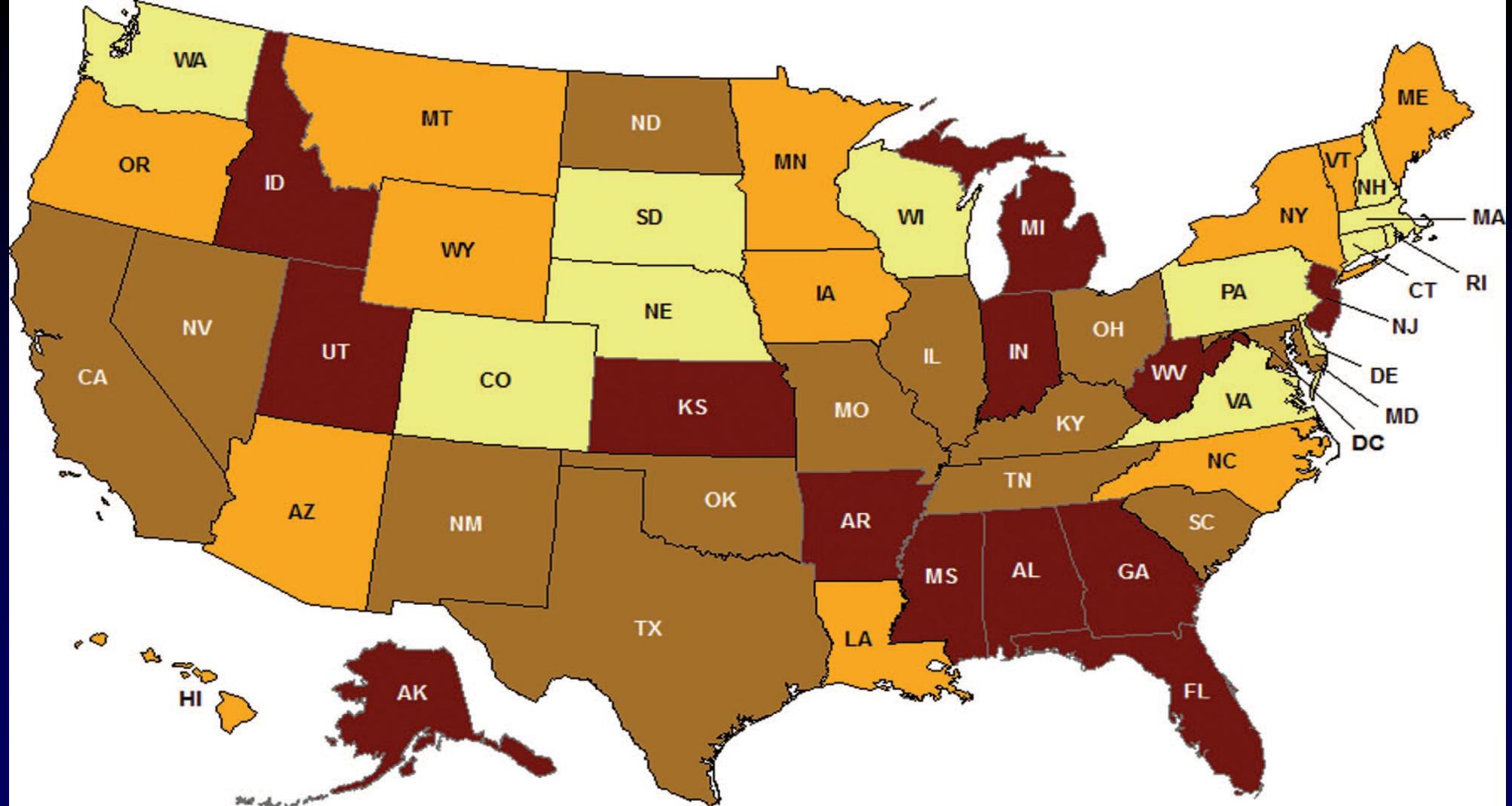
Impact of Age on Vaccine Efficacy



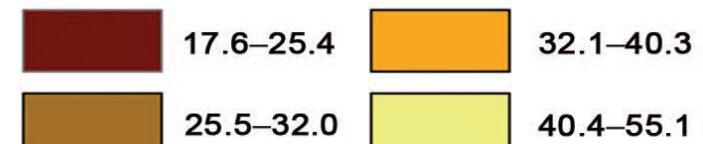
Herrero *et al.*, Cancer Discov, 2012

Kjaer, Cancer Prev Res, 2009

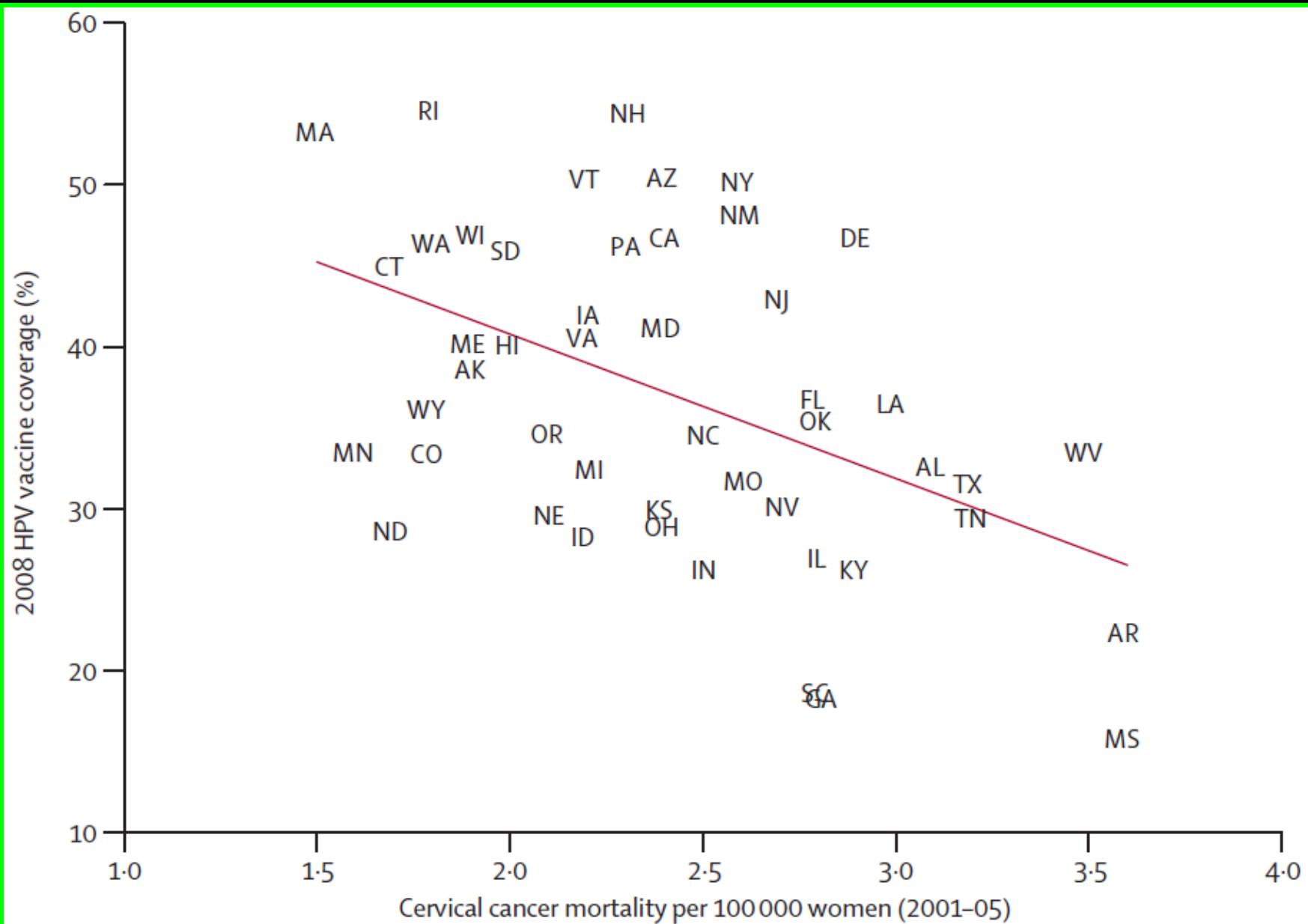




Percentage of adolescent girls who received 3 doses of HPV vaccine



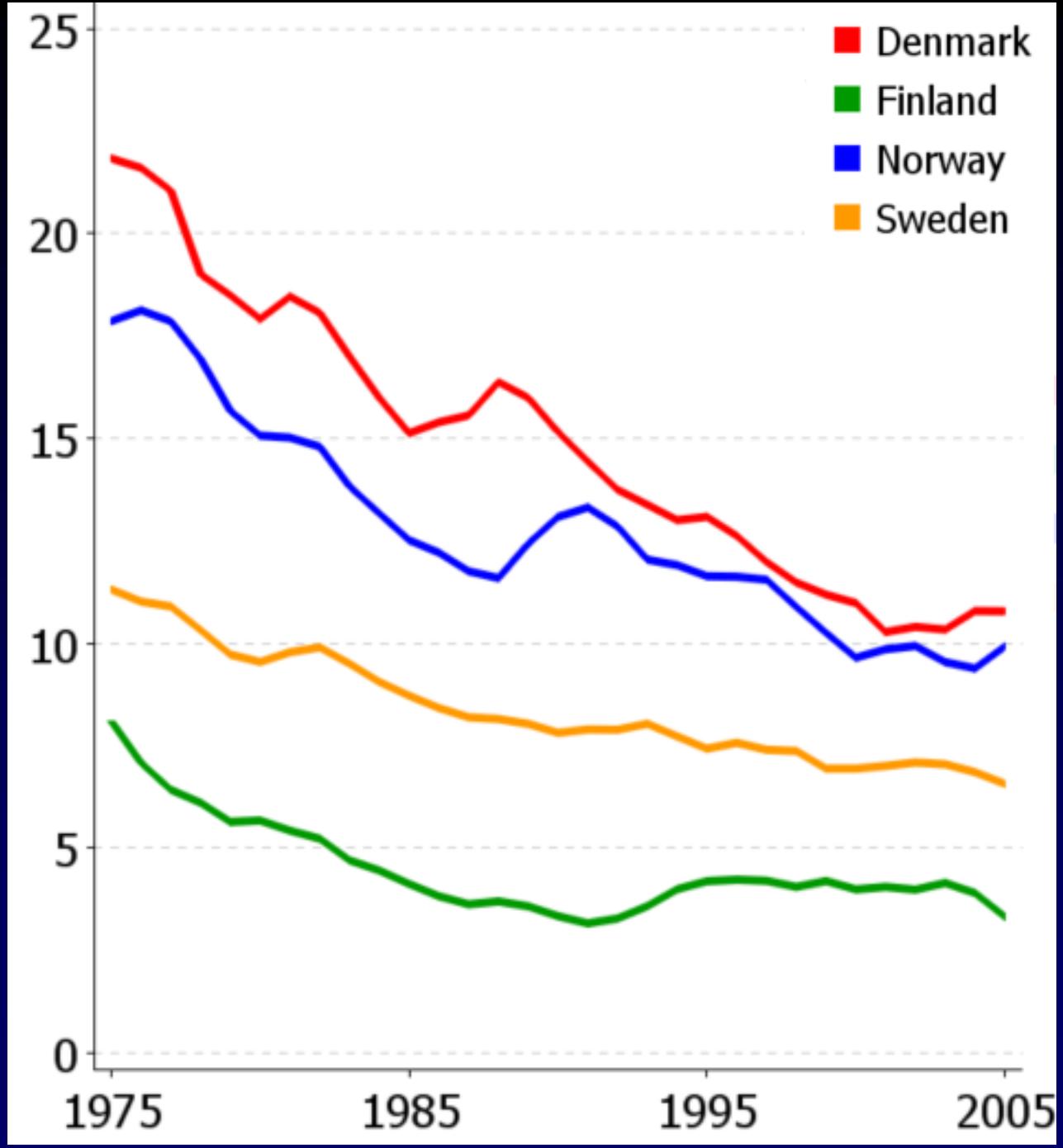
Increasing Cancer Health Disparities



George Papanicolaou (1883-1962): Inventor of the Pap Smear



TIME TRENDS IN AGE- STANDARDIZED (WORLD) CERVICAL CANCER INCIDENCE IN FOUR NORDIC COUNTRIES



Sensitivity: CIN2+

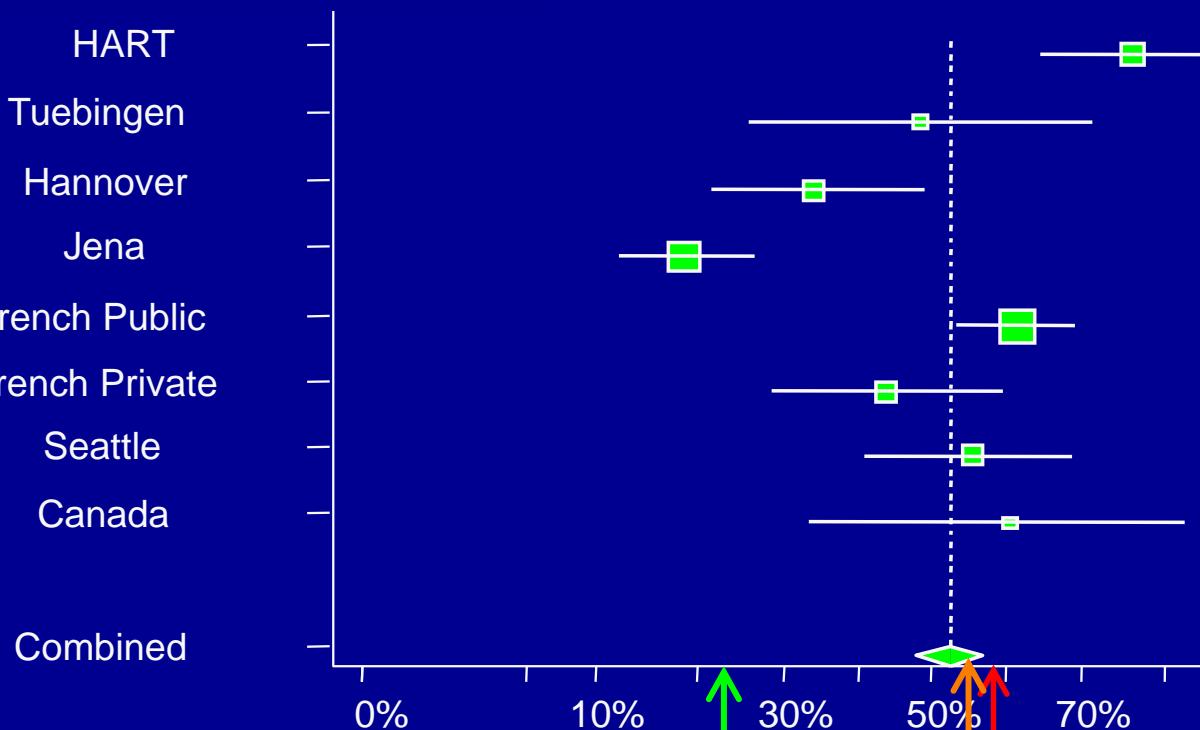
Cuzick *et al.*, IJC, 2006

Mayrand *et al.*, NEJM, 2007

Castle *et al.*, LO, 2011

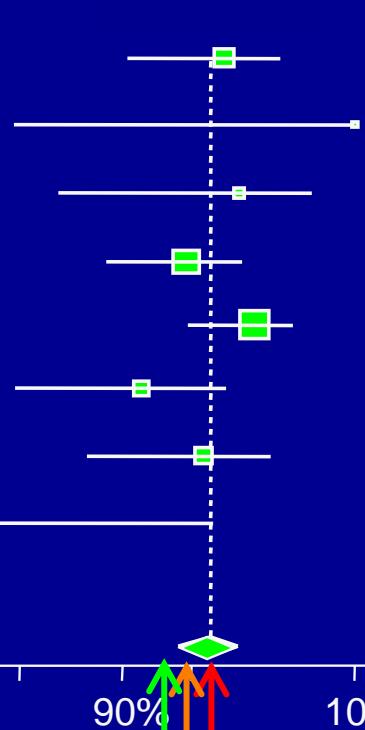
Ferreccio *et al.*, IJC, 2012

CIN2+



Cytology/Pap

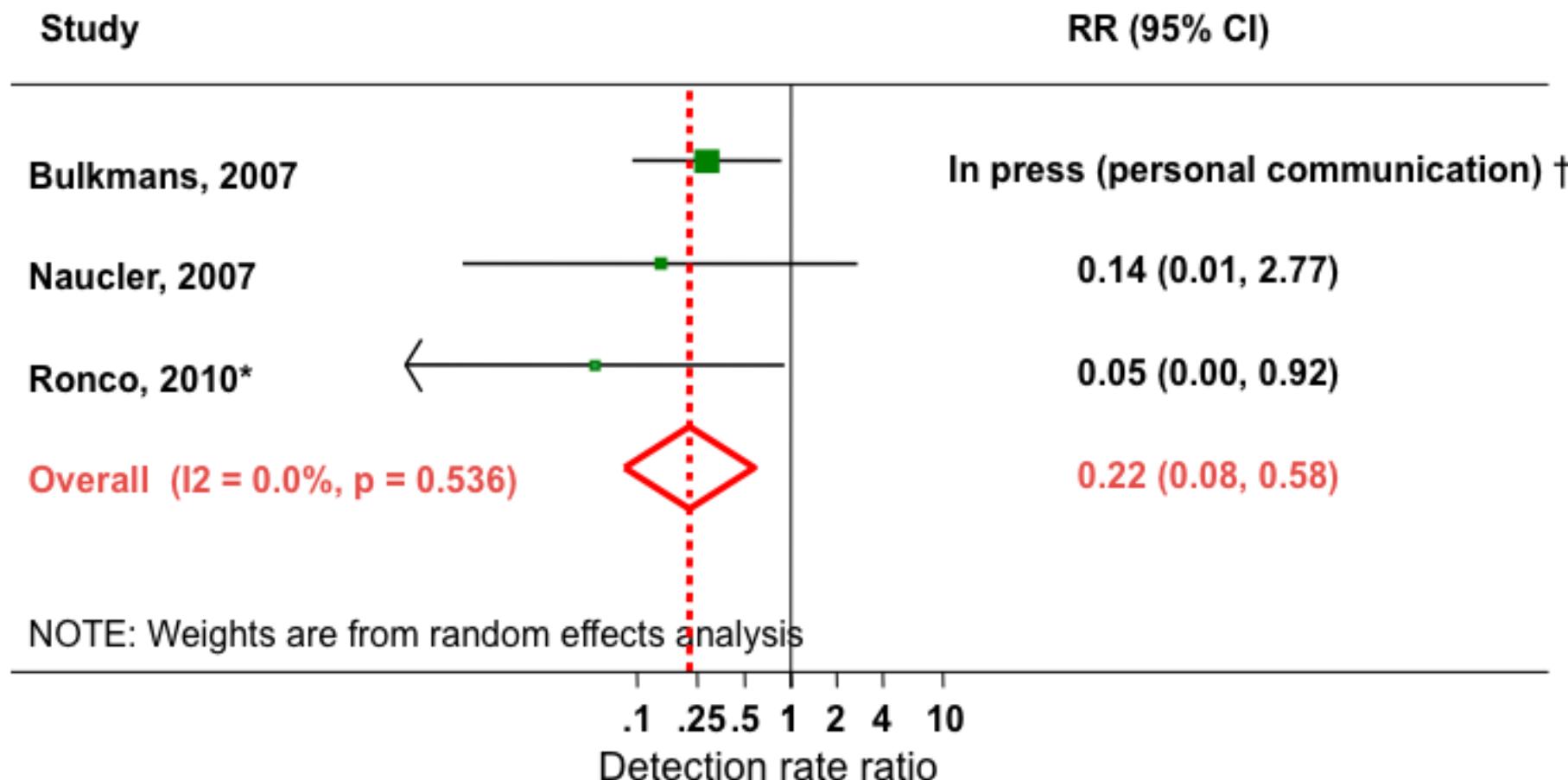
CIN2+



HPV Testing

Cancer Risk Reduction: HPV vs. Cytology

CxCA in 2nd round among women with negative screen test at baseline



† C. Meijer: data in press;

*Continuity correction ($k=0.5$) applied, since 0 cases in HPV-negative group

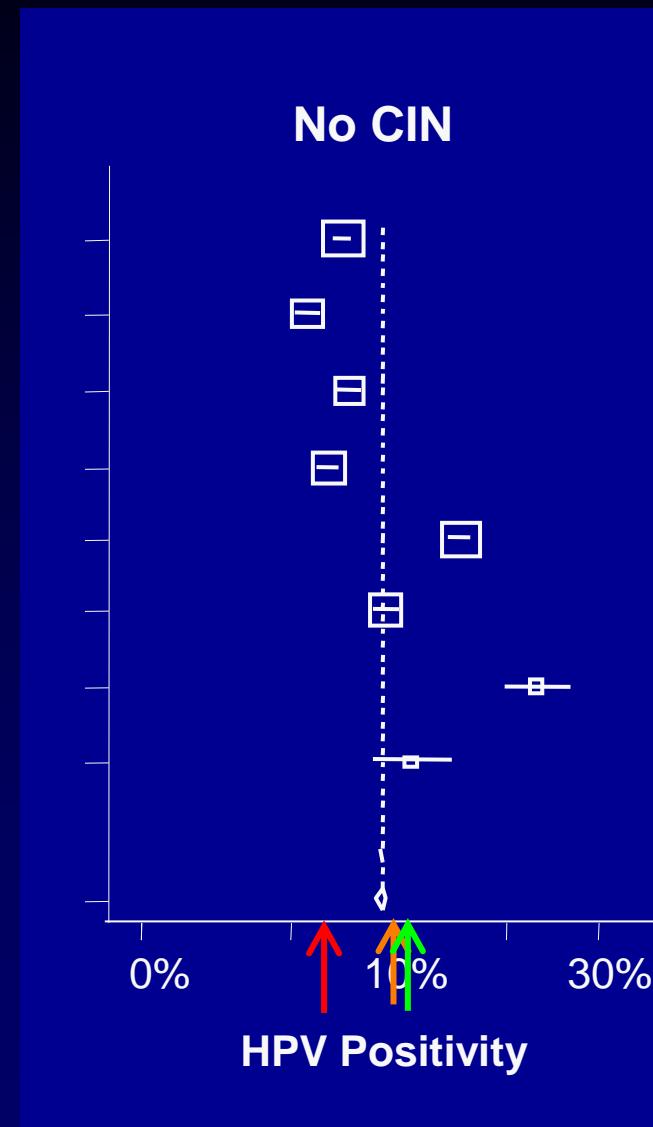
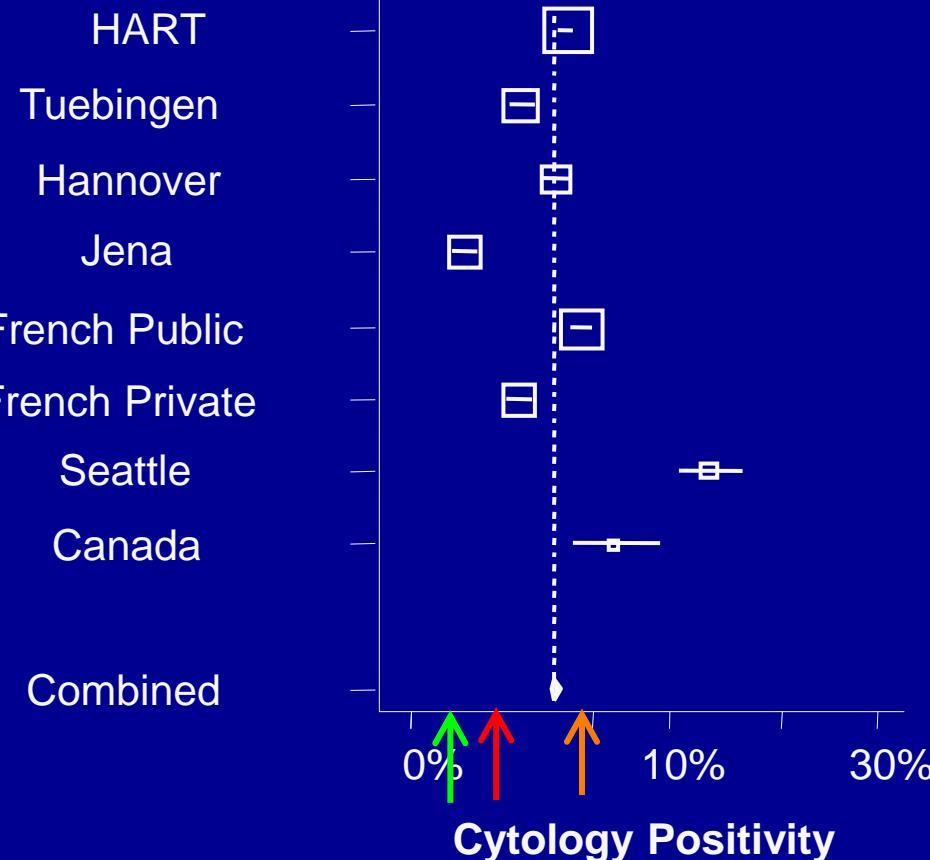
%Cytology and HPV Positive: No CIN

Cuzick *et al.*, IJC, 2006

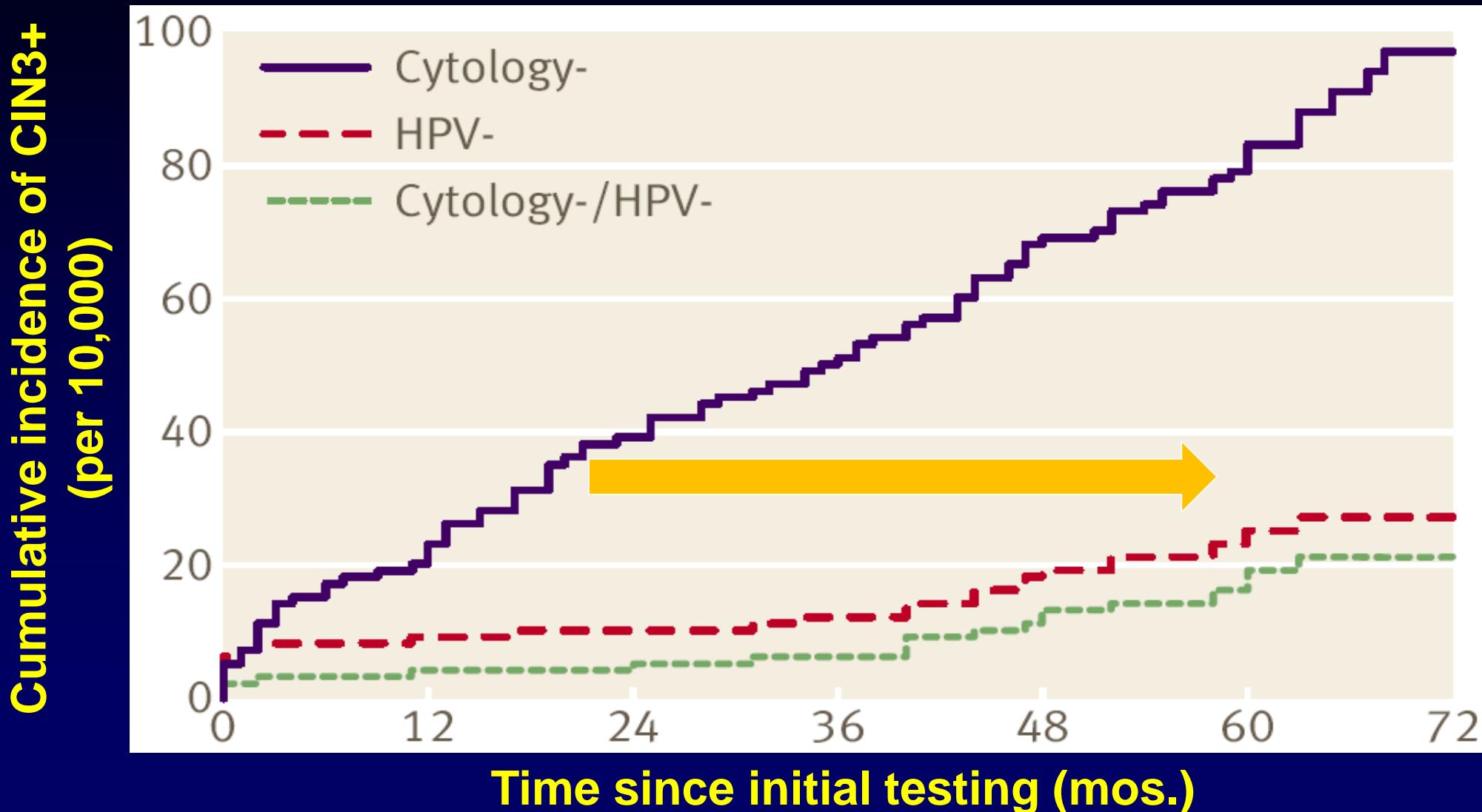
Mayrand *et al.*, NEJM, 2007

Castle *et al.*, LO, 2011

Ferreccio *et al.*, IJC, 2012



CIN3+ Risk Following a Negative Screening Test



Benefits vs. Harms

	Benefits	Harms
Actual	❖ Cervical cancer prevention	<ul style="list-style-type: none">➤ Anxiety associated with a positive screening test➤ Potential stigmatization from the diagnosis of a sexually transmitted infection➤ Discomfort from additional diagnostic and treatment procedures➤ Bleeding from treatment➤ Increased risk of pregnancy complications such as preterm delivery due to treatment.
Surrogate	Early detection of CIN3	Number of colposcopic referrals

Current ACS-ASCP-ASCCP Cervical Cancer Screening Guidelines (2012)

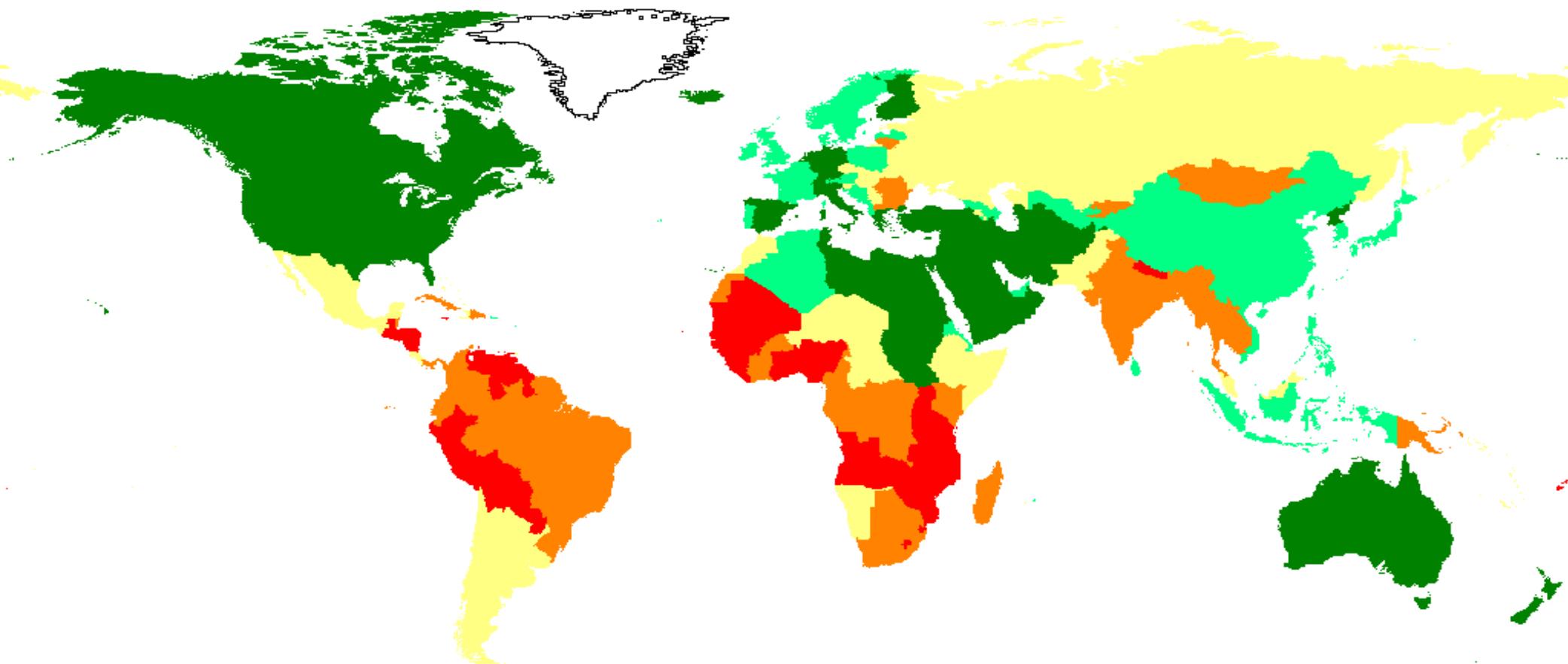
<u>Age (Years)</u>	<u>Recommended Screening</u>
<21	No Screening!!!!
21-29	Cytology (3 Year)
30-64	HPV and Cytology Cotesting (5 Year) (Preferred) Cytology (3 Year) Acceptable
65 and Older	No Screening with a 10-Year Negative Screening History

Today's Talk

- 1. Natural History of HPV: Rational Basis for Cervical Cancer Prevention**
- 2. Vaccination and Screening**
- 3. Global Cervical Cancer Prevention**

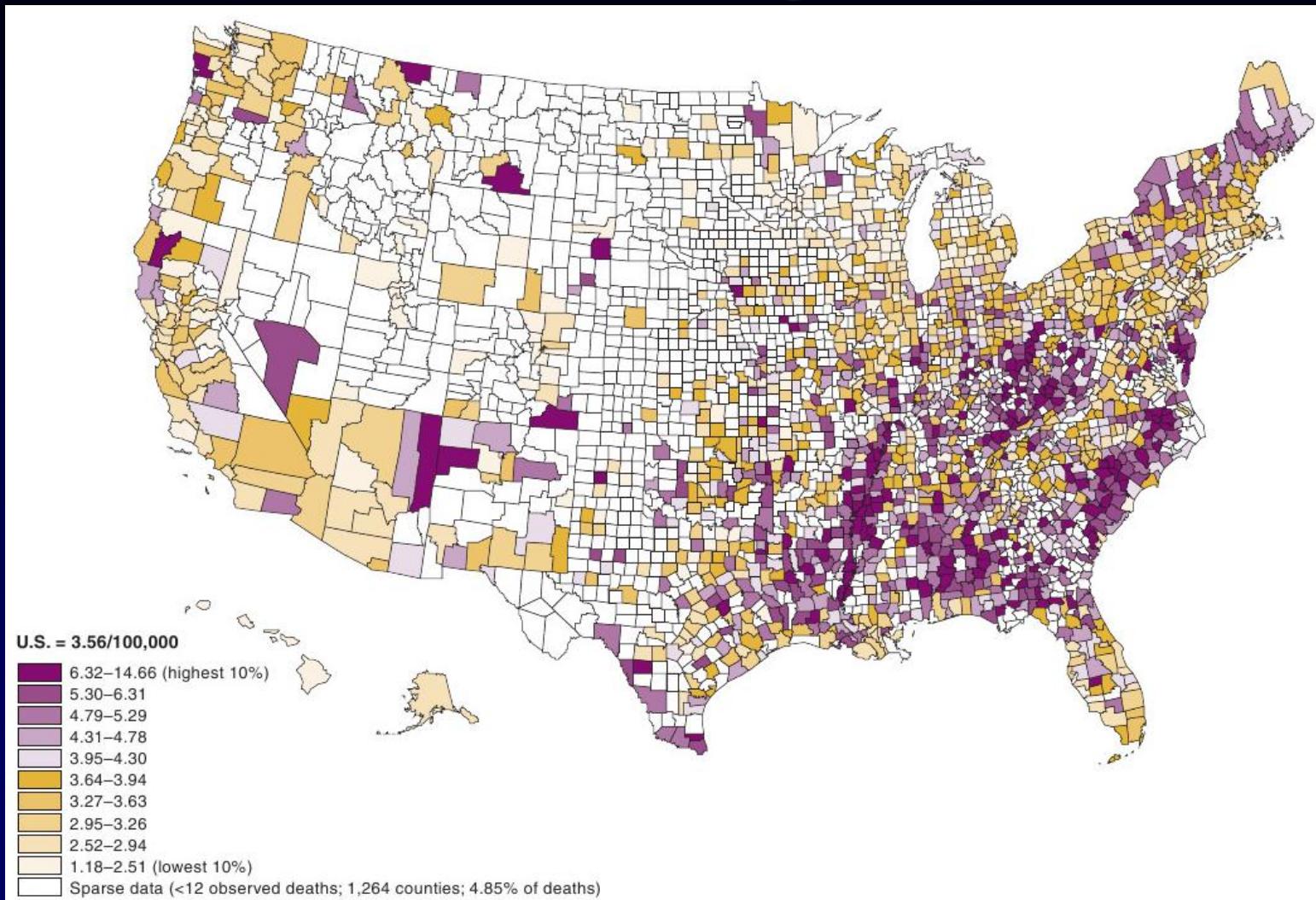
Estimated age-standardised incidence rate per 100,000

Cervix uteri, all ages



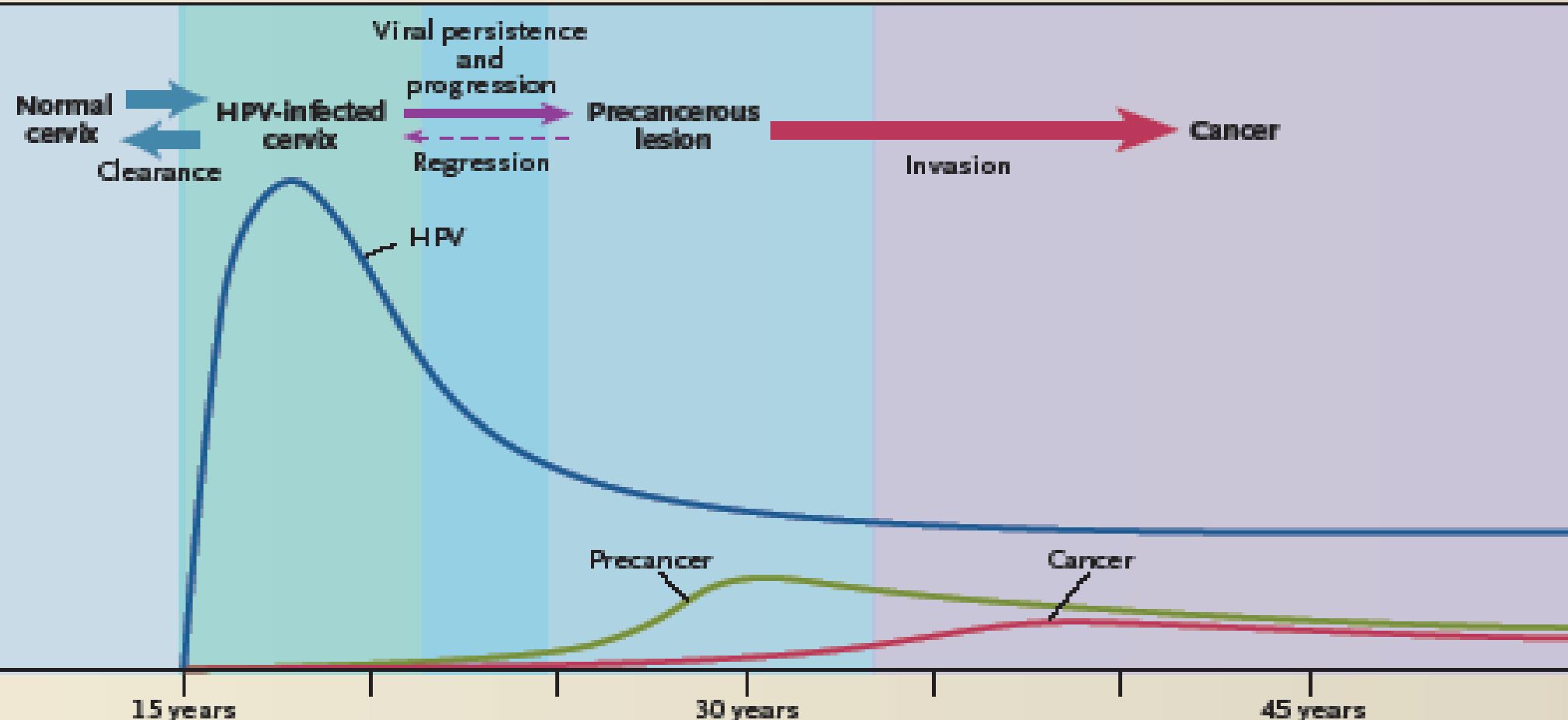
■ < 7.0 ■ < 12.9 ■ < 20.3 ■ < 29.8 ■ < 56.3

Cervical Cancer Mortality Map for The U.S.



Freeman HP, Wingrove BK. Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities. Rockville, MD: National Cancer Institute, Center to Reduce Cancer Health Disparities, May 2005. NIH Pub. No. 05–5282.

The Promise of Cervical Cancer Prevention

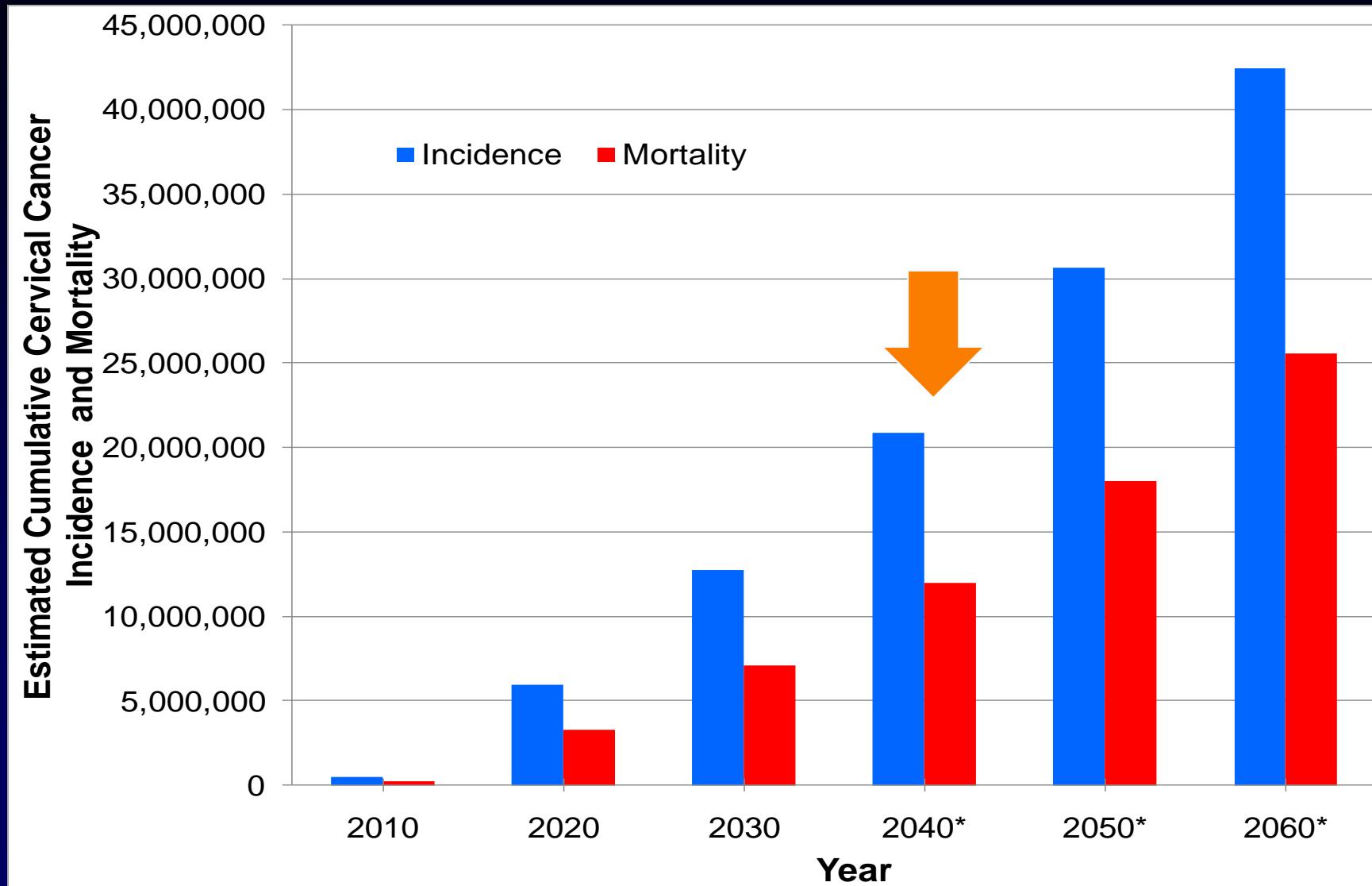


Schiffman & Castle, NEJM, 2005

The Menu of Options

STEPS	OPTIONS	STRENGTHS	ISSUES/LIMITATIONS
Sampling	Clinician Self @ home Self @ clinic	Better Se and SP Logistically easier Help available (vs. @ home)	Requires most personnel, disposables, clinic time and space; transportation Specimen transport & acceptability Clinic time and space; transportation
Testing	Pap VIA HPV DNA Biomarkers (E6; p16)	Well-accepted; considered standard of care Lowest cost; well suited to screen&treat strategy Best Se; proven with self-collection May provide a good tradeoff of Se and Sp; Triage	Difficult to establish and maintain; facility; chemicals Detects on the most large and obvious lesions; reliability? More expensive than VIA; laboratory needed; disposables Large-scale validation needed; more specific, less long-term impact
Management	Colposcopy Triage to Colposcopy Treatment Triage to Treatment	Well-accepted; diagnostic confirmation Reduces colposcopy; more specific Limits losses to follow-up Reduces over-treatment	Requires trained personnel and equipment: colposcopy misses small precancerous lesions Requires a more Sp test that still has reasonably high Se; losses to follow-up Over-treatment Reduces over-treatment; losses to follow-up in triage-negative women
Treatment	Excision Cryotherapy	Most efficacious (90-95%) Can be implemented by any health worker	Requires trained personnel; Excessive bleeding Selected population; risk of HIV infection?; acceptability; CO ₂ ?

The Forecast Calls For Pain



Conclusions

1. Cervical infections by certain HPV types cause cervical cancer everywhere in the world. HPV does not discriminate by race, ethnicity, or creed.
2. Persistent HPV infection and lack of access to preventative interventions are the key determinants for who gets cervical cancer
3. The discovery of HPV has led to the development of new technologies that can benefit populations in a cost-effective manner if used in an age-appropriate manner.
4. If we are serious about reducing the burden of cancer globally, there is no cancer for which we have a better chance of success than cervix. Investment in cervix will build capacity for the prevention, control, and care for other cancers and other diseases.