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Epidemiology and natural history of HPV cervical cancer: New opportunities for prevention

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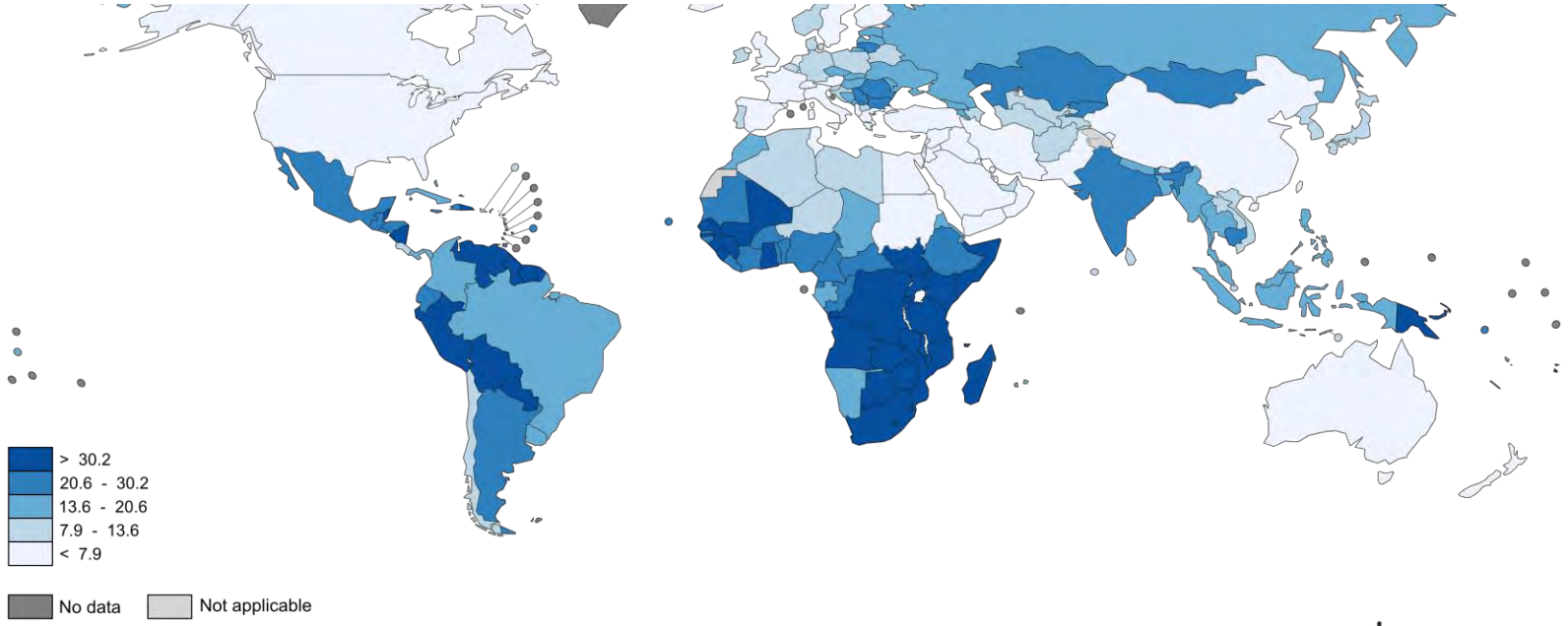
Cervical Cancer

Cervical cancer is the 4th most common cancer in women worldwide

528,000 new cases and 266,000 deaths globally (2012)

12,820 new cases and 4,210 deaths in the US (2017)

Estimated Cervical Cancer Incidence Worldwide in 2012



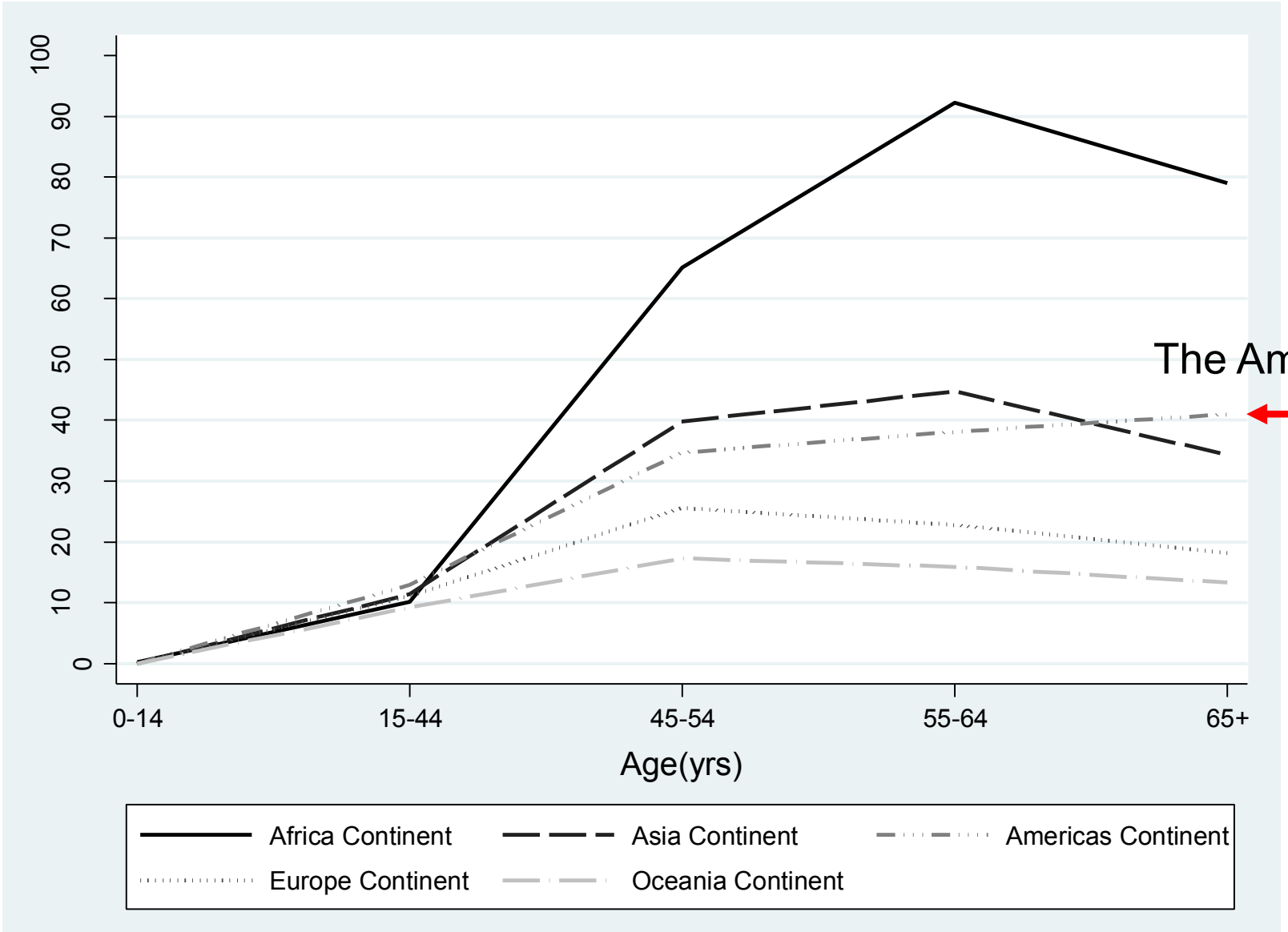
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

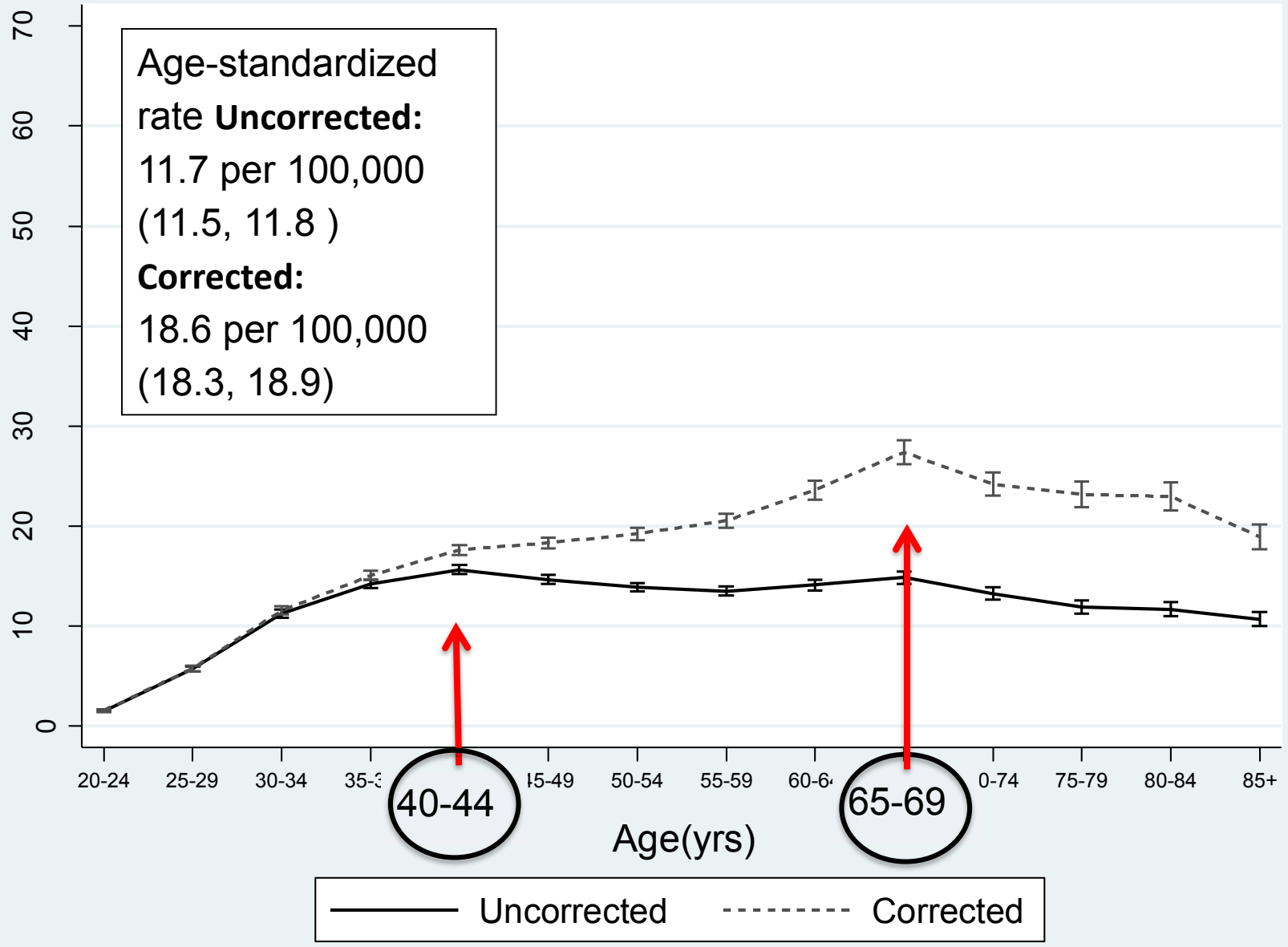
World Health Organization

GLOBOCAN 2012: http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp
SEER cancer report 2017: https://seer.cancer.gov/statfacts/html/cervix.html

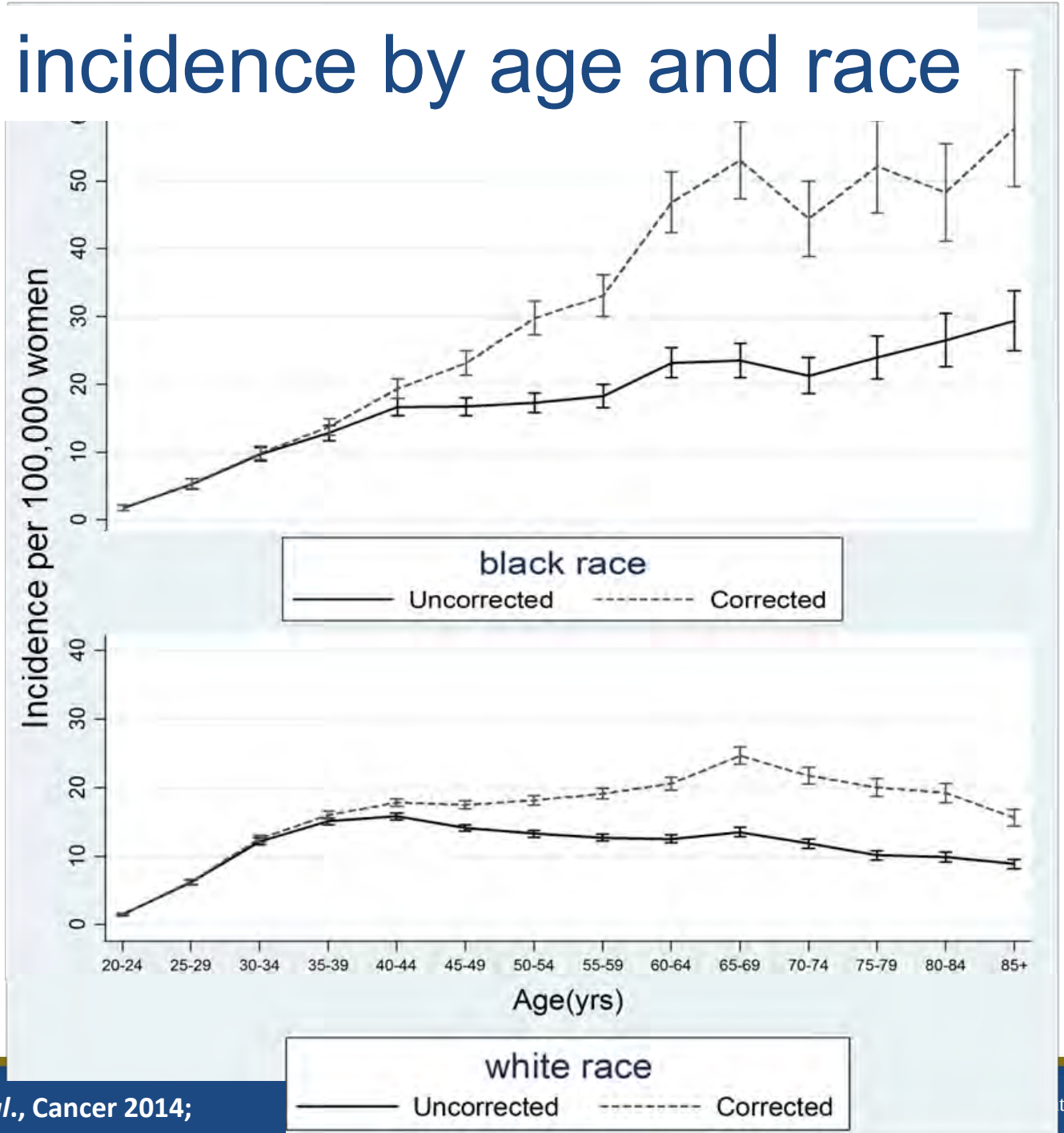
Global age-specific incidence of cervical cancer



Hysterectomy-corrected ICC incidence

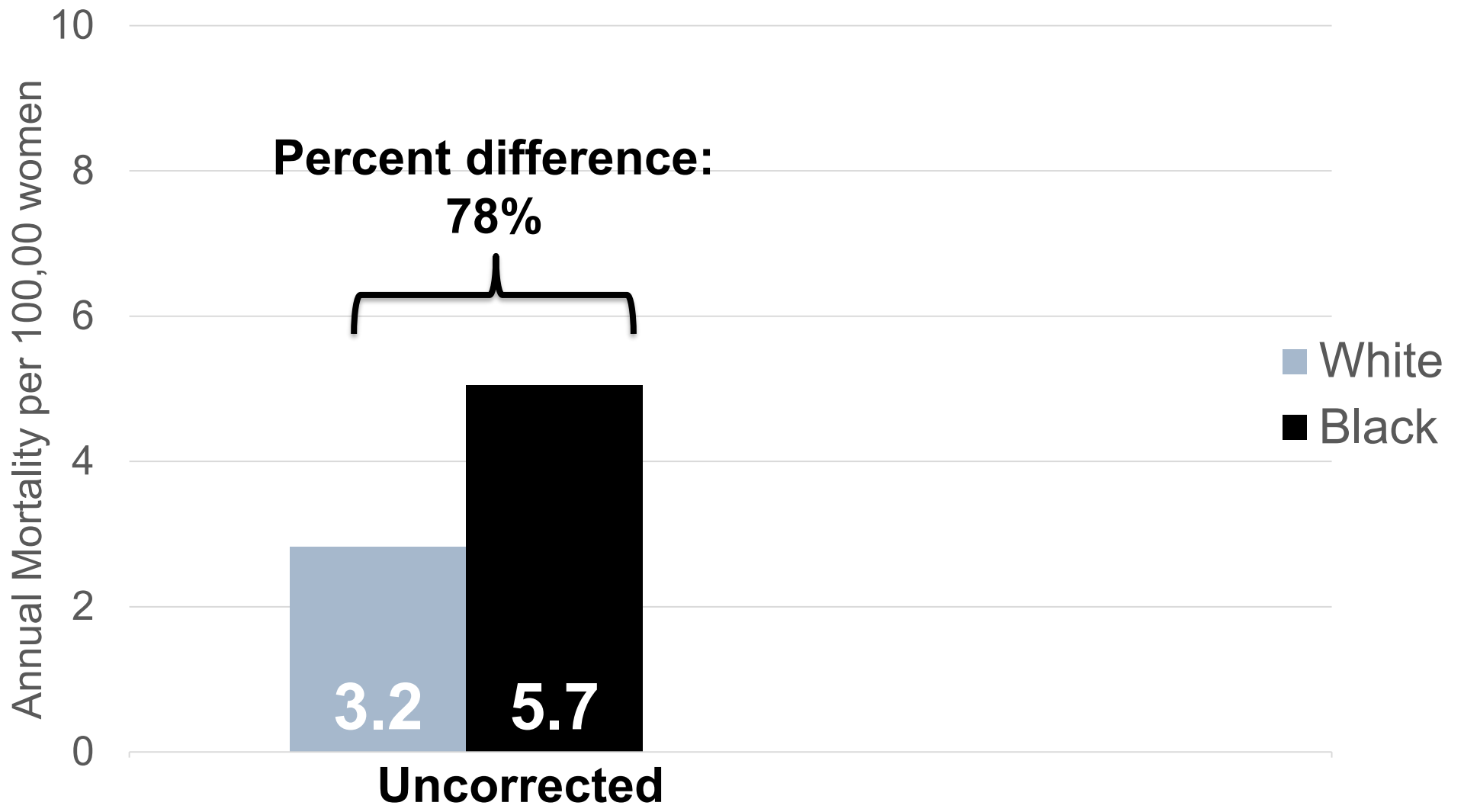


ICC incidence by age and race

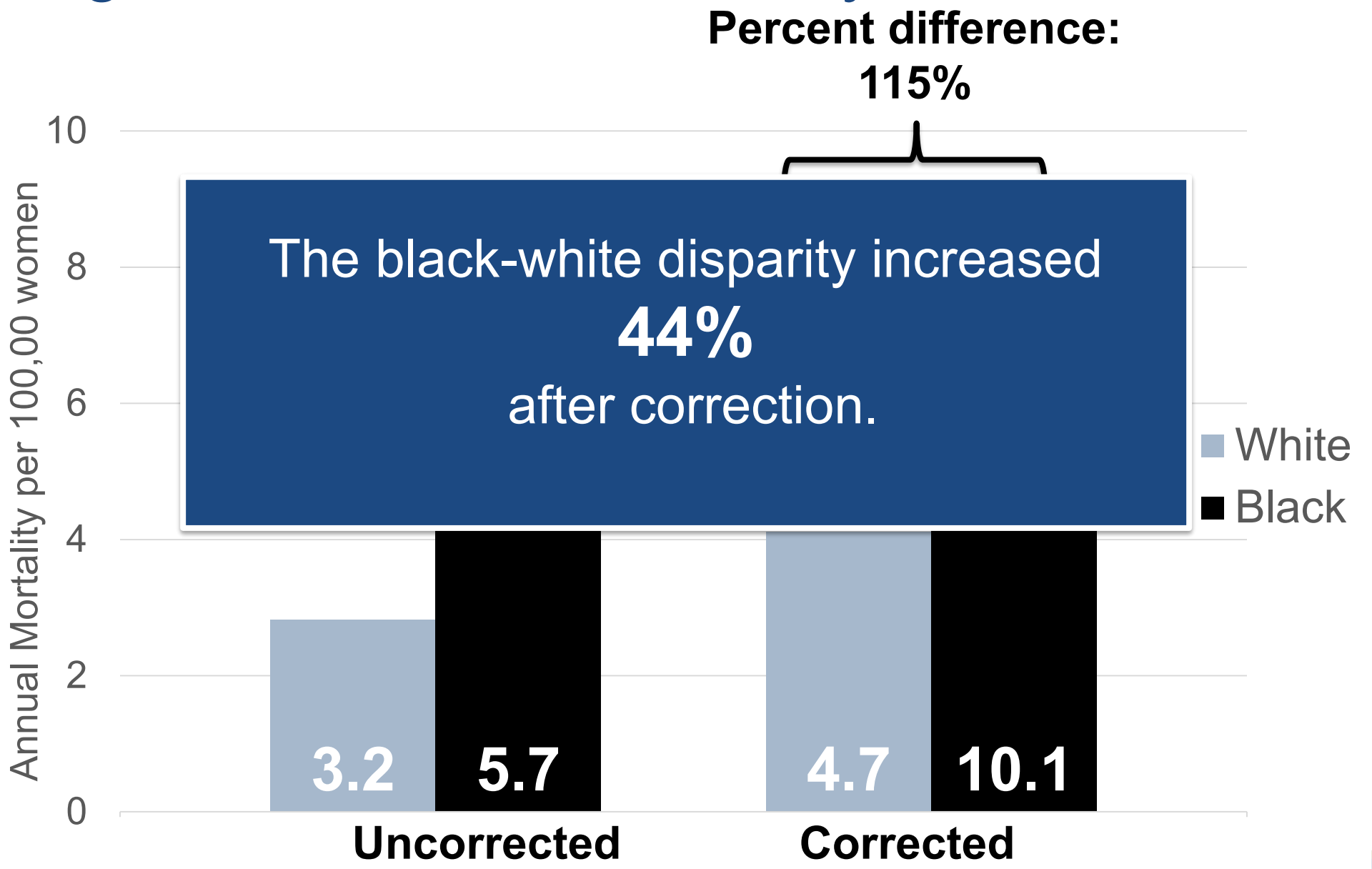


Rositch AF, *et al*., Cancer 2014;

Age-standardized mortality rates, 2002-2012

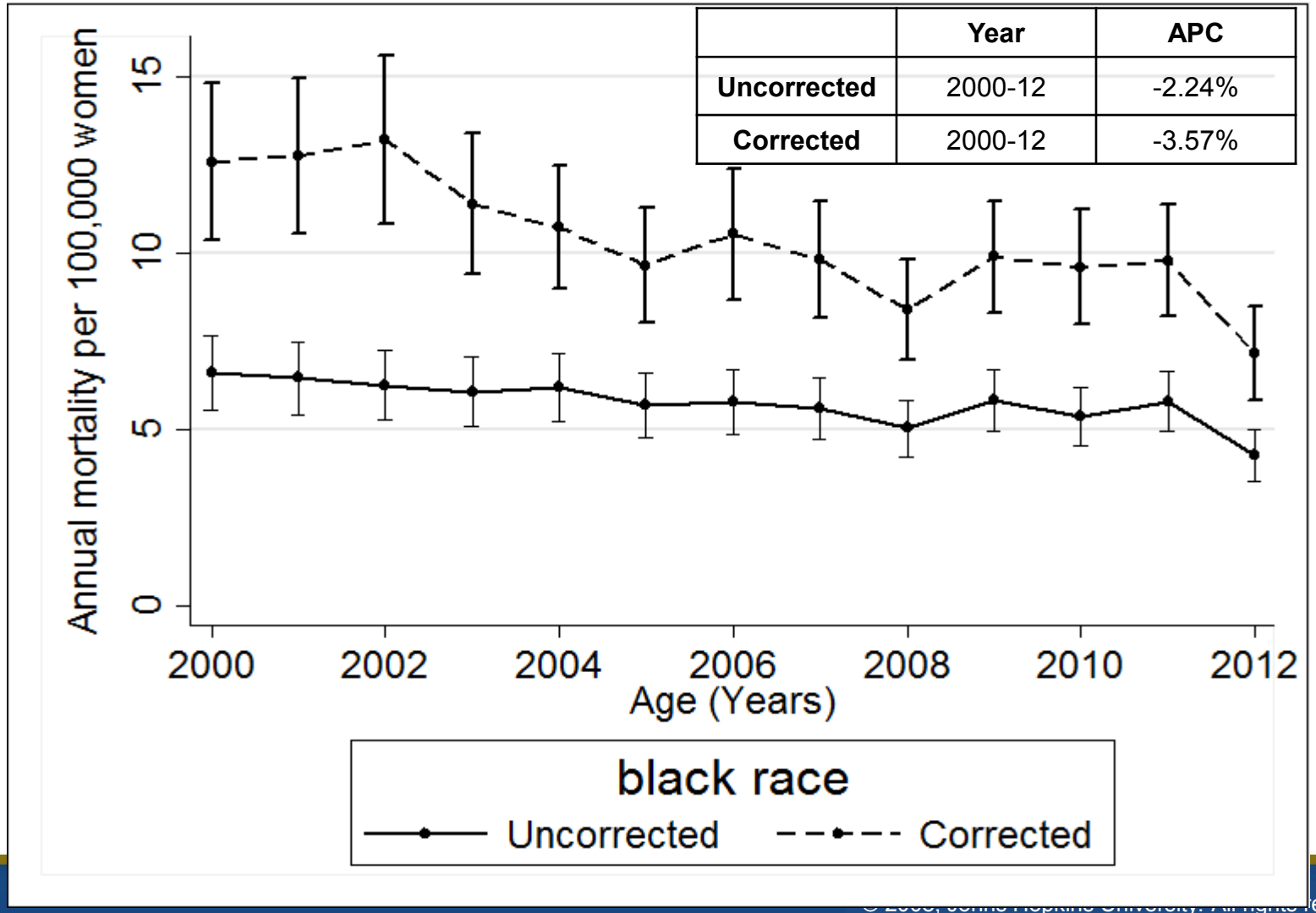


Age-standardized mortality rates



Beavis and Rositch, Cancer 2017

Results: Trends in Mortality Rates

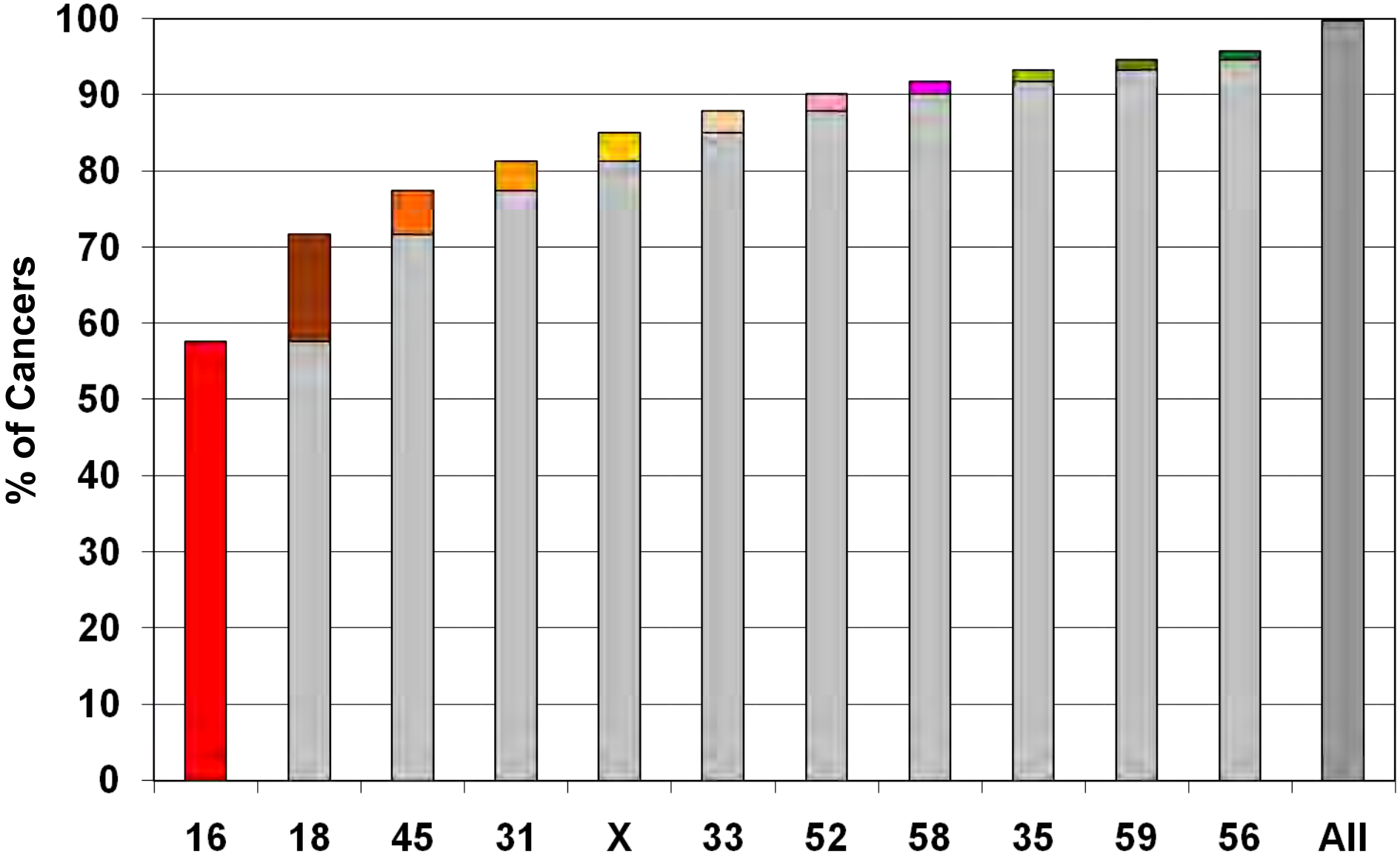


	Year	APC
Uncorrected	2000-12	-2.24%
Corrected	2000-12	-3.57%

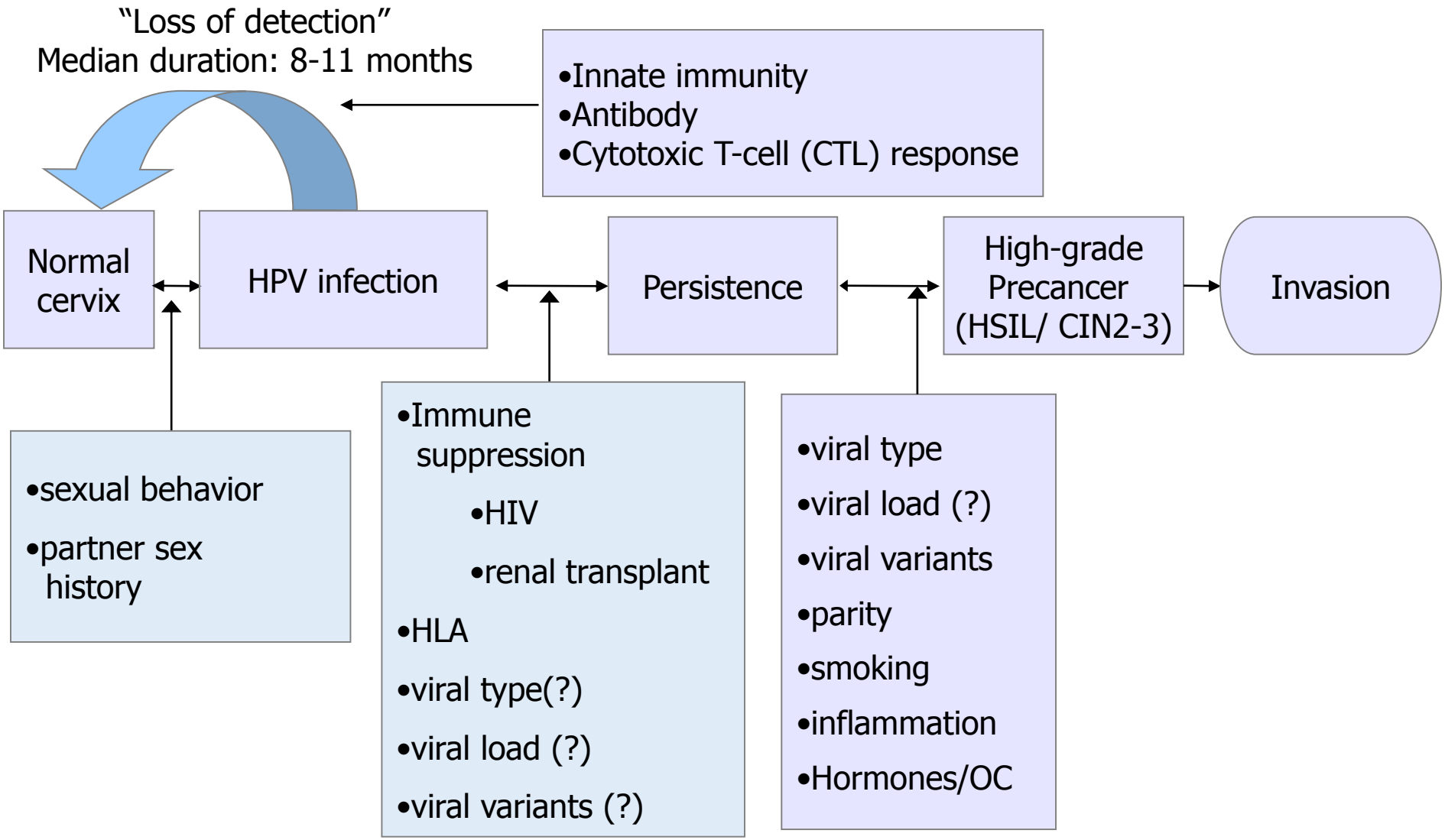
HPV infections and cervical cancer

- High risk HPV infection is necessary, but not sufficient for development of invasive cervical cancer
- More than 100 genotypes identified which infect human epithelium, ~50 which specifically infect the anogenital tract
- Approximately 14-18 are high risk (HR-HPV) or oncogenic.
  - HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82
- Remaining HPV types are not associated with cancer (low risk or non-oncogenic), but can cause low grade cervical abnormalities or benign proliferative warts (esp HPV 6 and 11)

Incremental Contributions of HPV Types to cervical cancer



Working Model of Cervical Carcinogenesis



Most HPV infections are “transient”

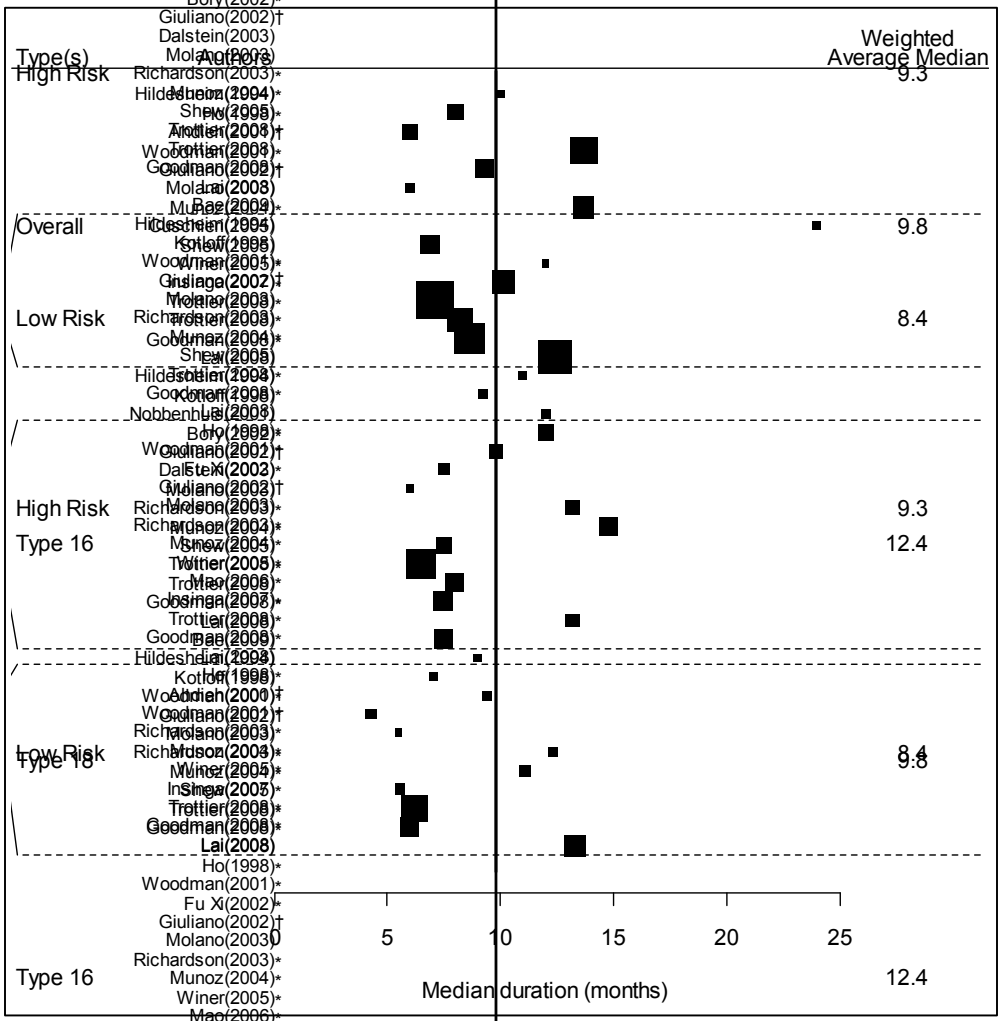
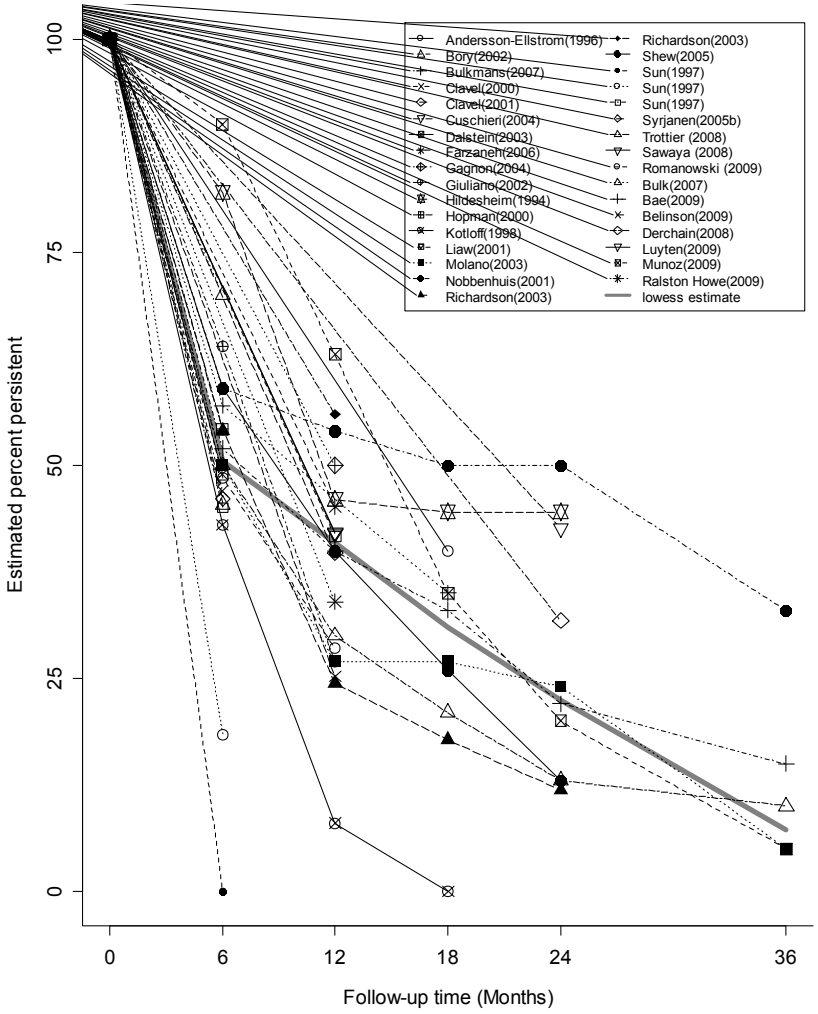
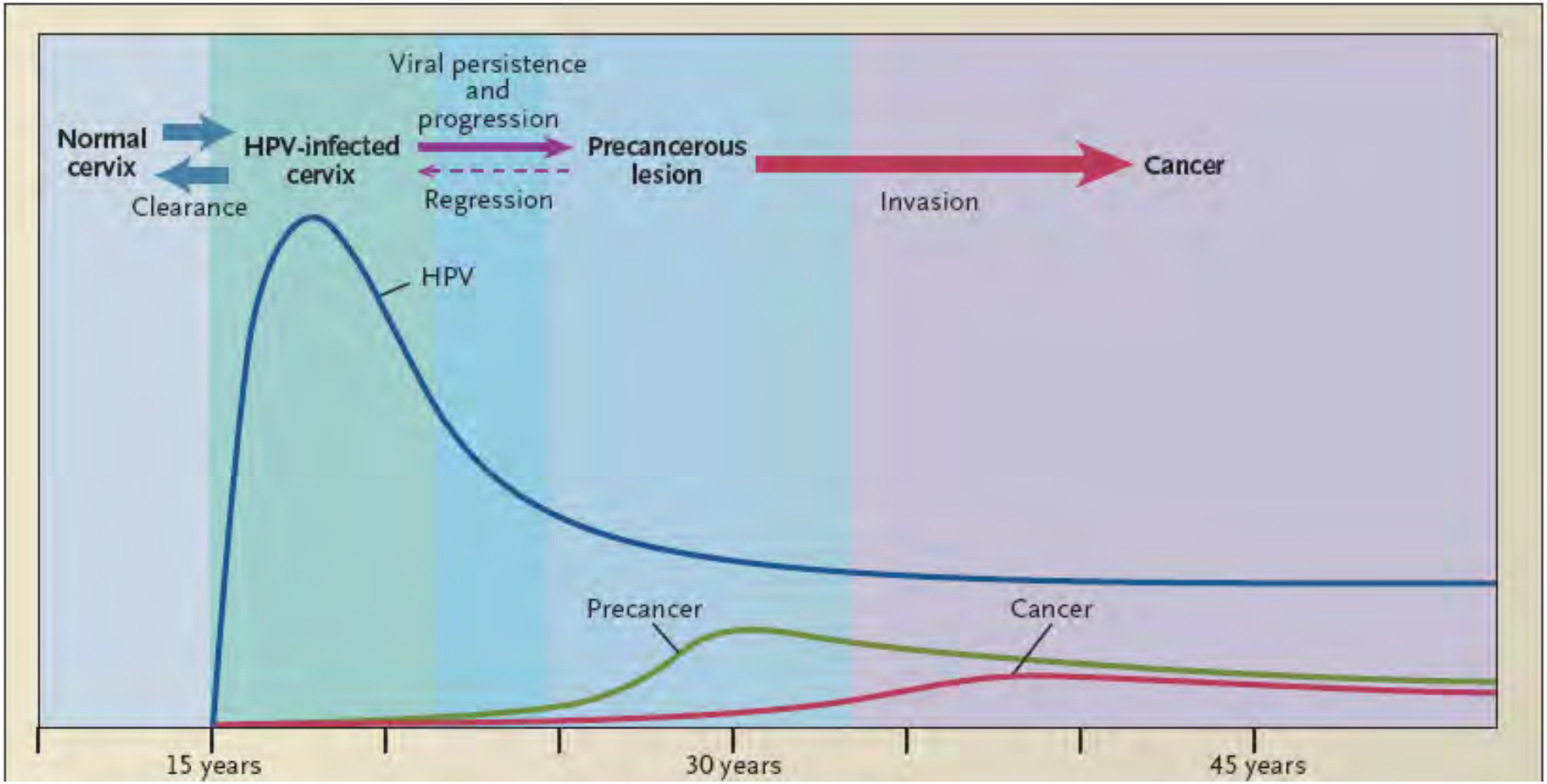


Figure 2B. High Risk



Rositch et al, Int J Cancer. 2013; 133(6): 1271–1285.

Natural History of HPV and Cervical Cancer



Schiffman & Castle, NEJM, 2005

Evolving Screening Guidelines

- Historical: annual screening with Pap smear and cytology
- 2003: American Cancer Society Guidelines begin recommending less than annual screening depending on type of test
  - Conventional cytology annual, LBC every 2 years; over 30 and 3 normal results every 2-3 years
- 2009: American Congress of Obstetricians & Gynecologists Guidelines recommend every 2-3 year screening
  - Pap every 2 years; over 30 and 3 normal results every 3 years; Co-testing every 3 years
- 2012: Guidelines from three major professional organizations: consensus on screening no more than every 3 years
  - Pap every 3 years; Co-testing every 5 years

New draft screening guidelines

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Women ages 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years. The USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years. See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women age 30 years or older.	A
Women older than age 65 years	The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for a discussion of adequate prior screening and risk factors that support screening after age 65 years.	D
Women younger than age 21 years	The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

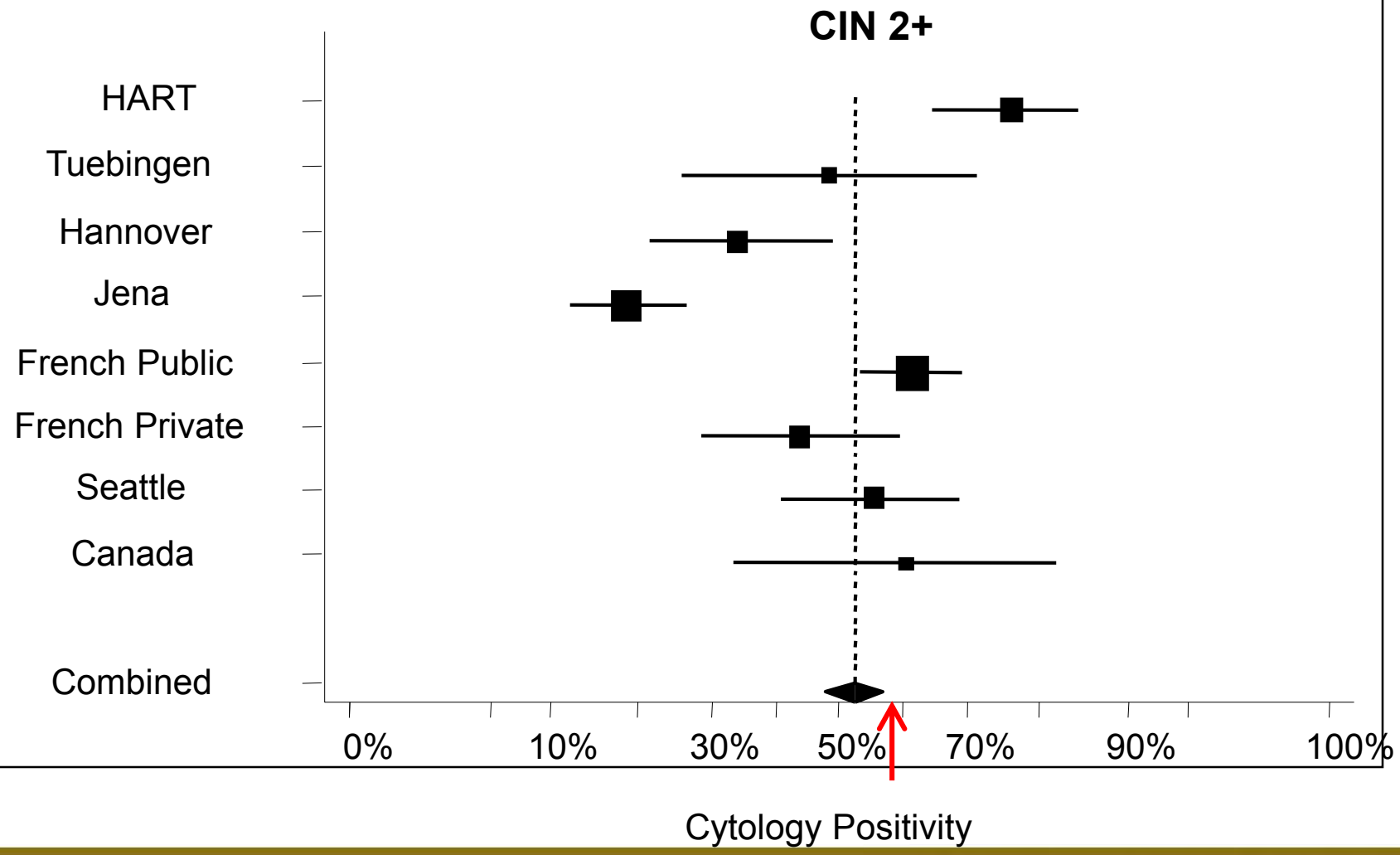
Note: The first three recommendations apply to women who have a cervix, regardless of their sexual history or HPV vaccination status. None of these recommendations apply to women who have been diagnosed with a

https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2

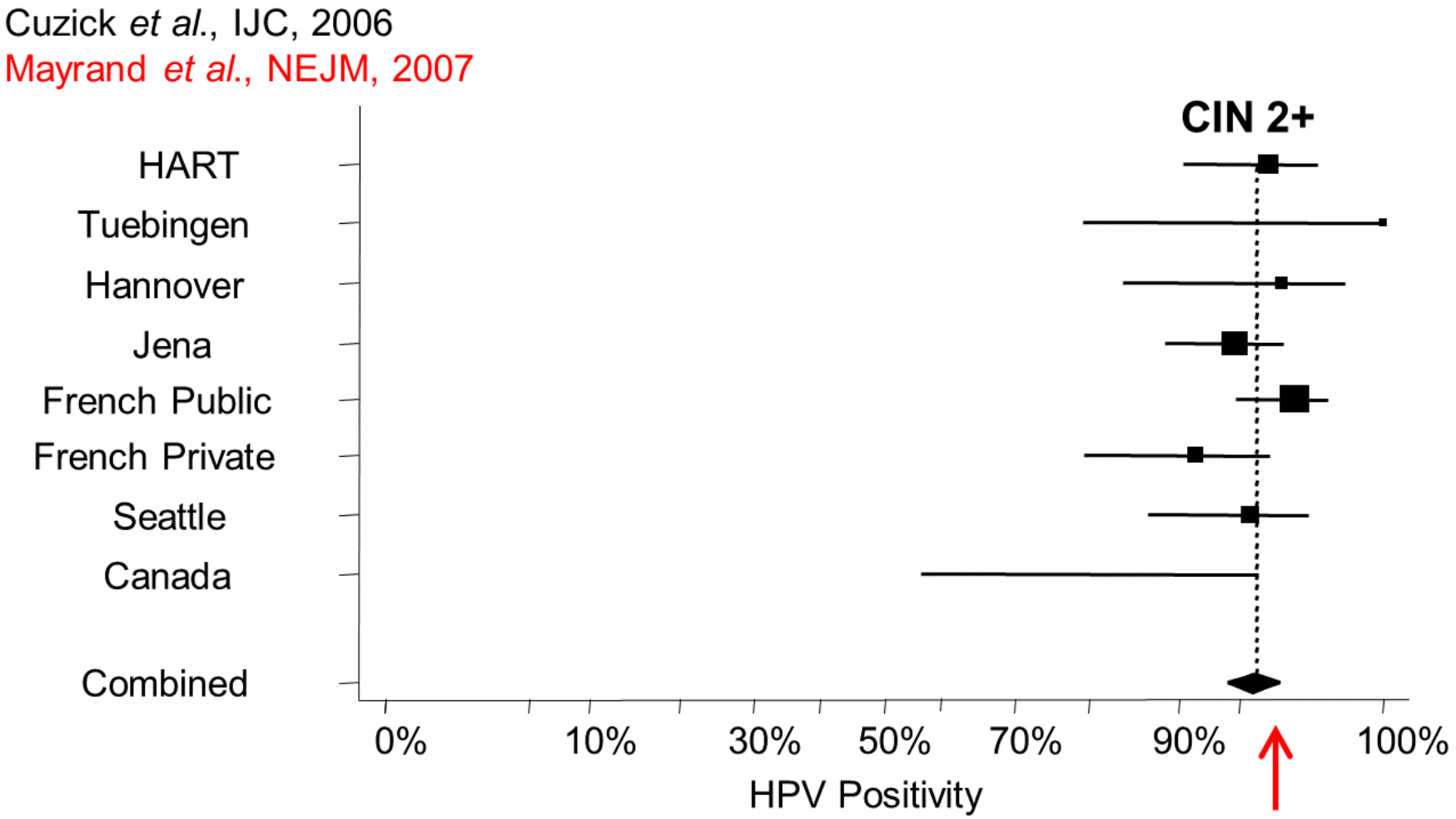
Single cytology not very sensitive or reproducible

Cuzick *et al*., IJC, 2006

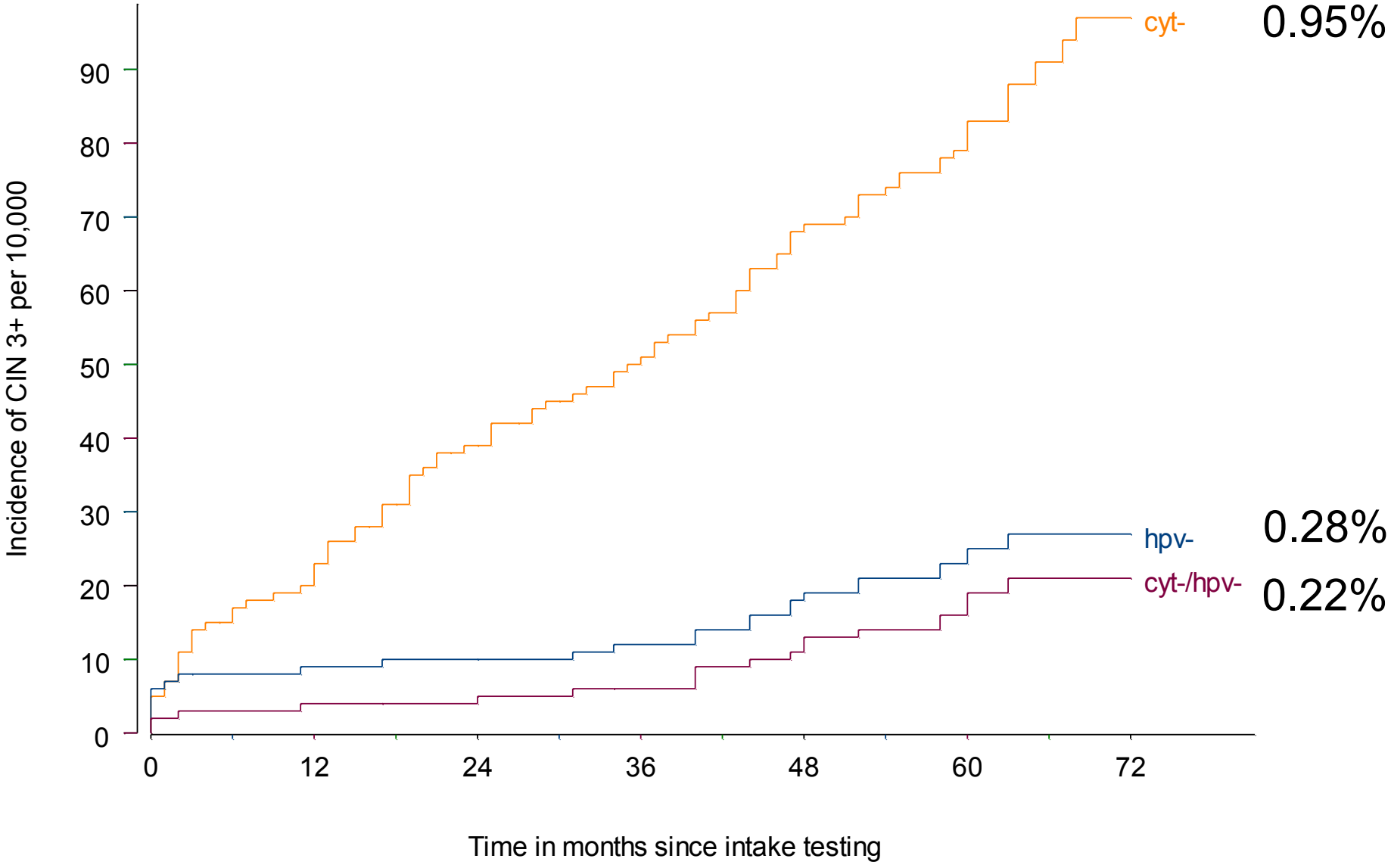
Mayrand *et al*., NEJM, 2007



HPV DNA testing more reproducible and sensitive



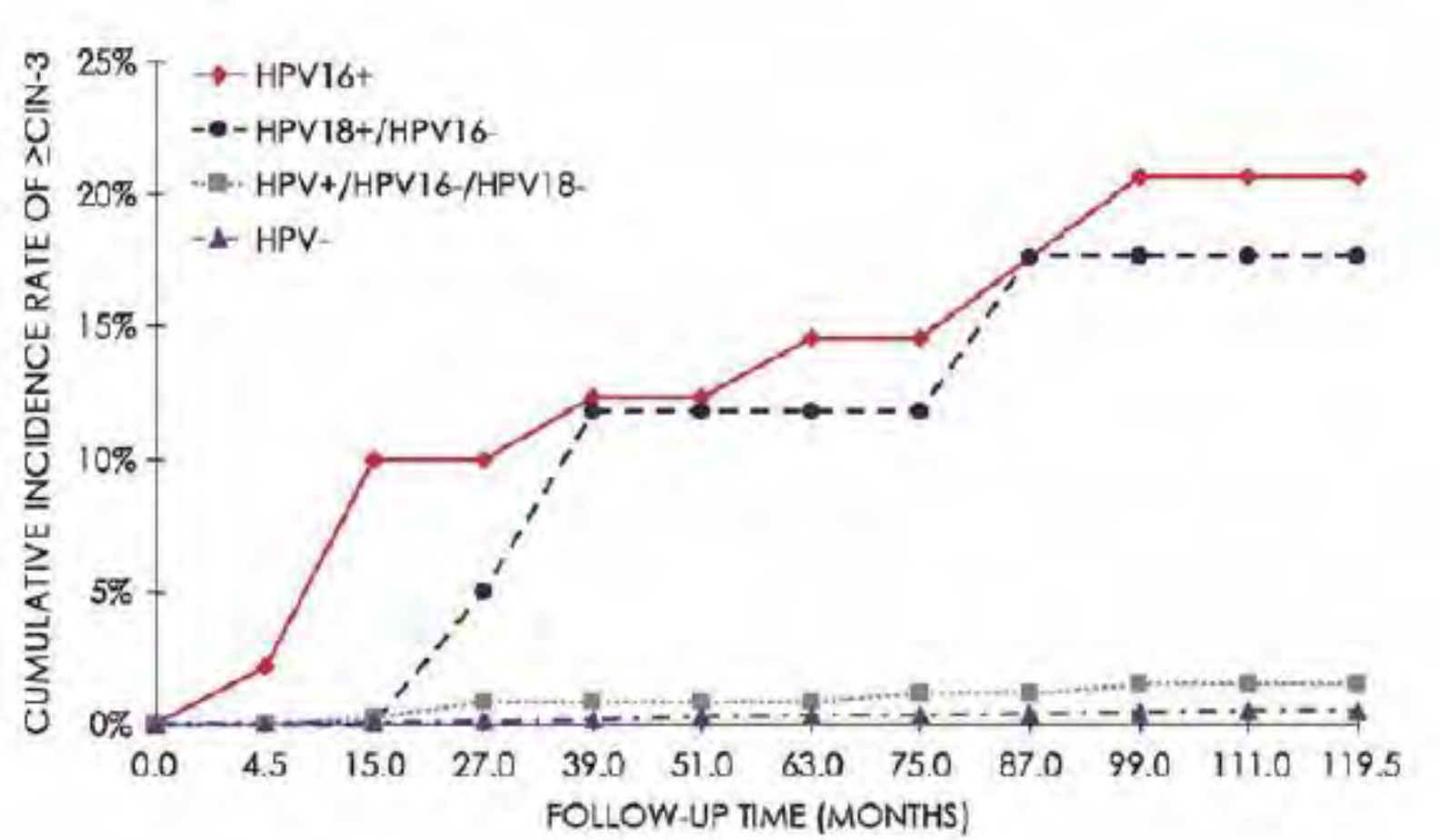
High NPV allows safe increase in screening interval



Dillner et al., BMJ, 2008

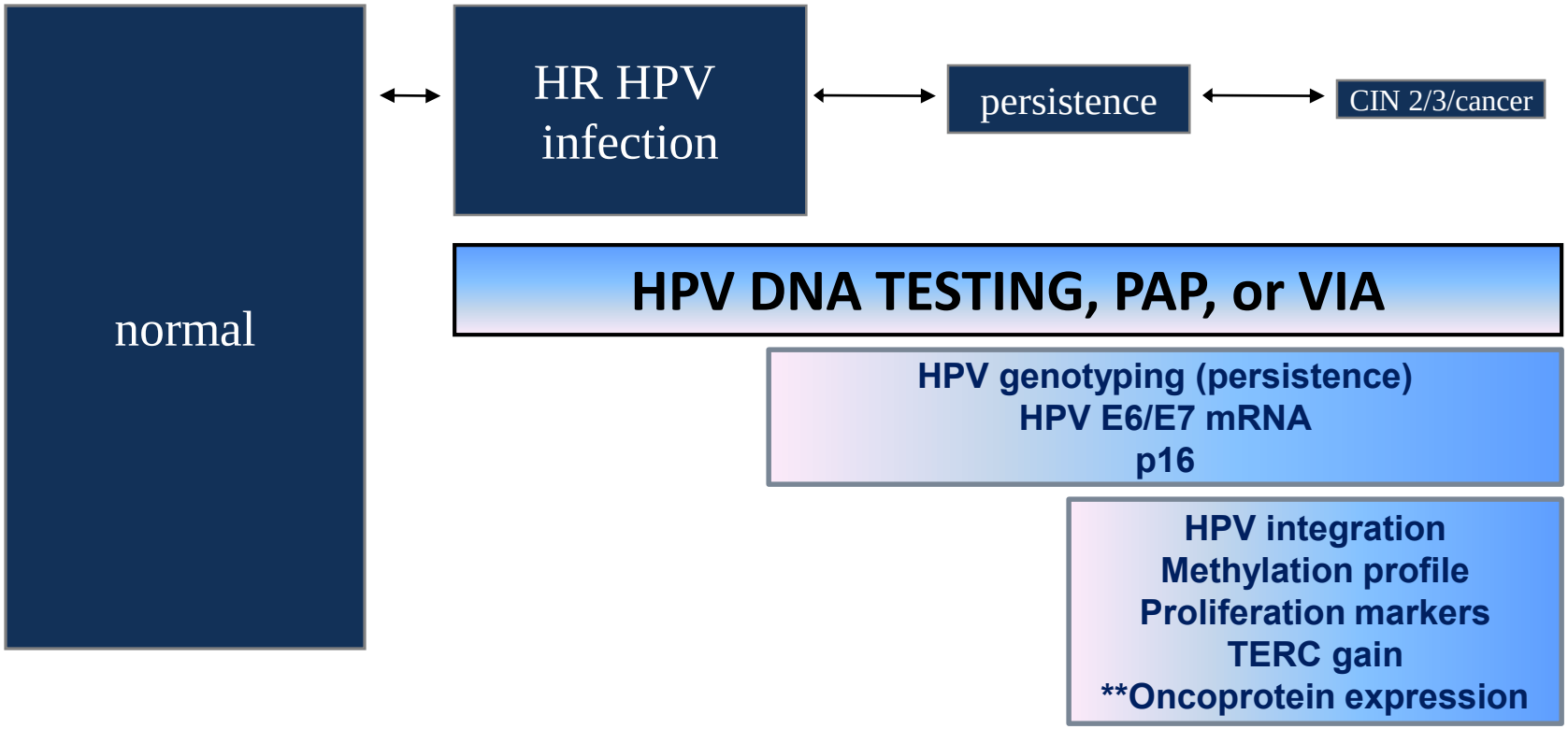
HPV genotyping

The cumulative incidence of CIN3 or greater over a 10-year period in women ages 30 and older as a function of a single HPV result at enrollment.



Khan M et al. JNCI 2005;97:1072.

Ultimate goal – maintain sensitivity with substantial increase in specificity



Challenges—cost, clinical feasibility/translation, sample types and buffers, objective vs. subjective output

1st generation HPV vaccines

- **Gardasil®, Merck Research Laboratories (MRL)**
  - FDA approved June 2006
  - Targets HPV types 16 & 18 ~70% of cervical cancer and 6 & 11 ~90% of anogenital warts
- **Cervarix™, GlaxoSmithKline (GSK)**
  - FDA approved October 2009
  - Targets HPV types 16 & 18 ~70% of cervical cancer
  - Some cross-protection for HPV-31 and HPV-45

Both are safe – no risk of infection, adverse events minor--site injection pain, fainting

Neither impact pre-existing HPV16/18 (6/11) infection

- Uncertain impact in women with prior exposure (seropositive) but not currently 'infected' (DNA negative)—new post-tx studies are promising

Nonavalent vaccine- current approval

In December, 2014 the FDA approved Gardasil 9

- Nonavalent HPV vaccine: types 6, 11, 16, 18, 31, 33, 45, 52, 58
- Estimated 90% reduction of cervical cancer and similar percentage of other HPV-associated cancers

TABLE 2. Summary of HPV Vaccine Clinical Trials Performed in Cervical Cancer Populations

Trial	Cohort	Vaccine	Control	Follow-Up	Persistent Viral Infection Efficacy (≥6 Months)	Disease Efficacy (CIN2+)
FUTURE I/II	Women aged 15–26 y	Gardasil (quadrivalent) (Merck) N = 7864	Placebo N = 7865	4 y	Not evaluated	98.2%
PATRICIA	Women aged 15–25 y	Cervarix (bivalent) (GlaxoSmithKline) N = 7338	Hepatitis A vaccine N = 7305	4 y	91.4%-94.3%	92.9%
CVT	Women aged 18–25 y	Cervarix N = 2643	Hepatitis A vaccine N = 2697	4 y	90.2%-93.1%	89.5%
9-Valent Trial	Women aged 16–26 y	Gardasil-9 (9-valent) N = 5948	Gardasil (quadrivalent) N = 5943	4 y	Risk reduction: 96.0%[a]	Risk reduction: 96.3%-96.7%[a]

Abbreviations: CIN2+, cervical intraepithelial neoplasia, grade 2 or higher; CVT, Costa Rica HPV Vaccine Trial; HPV, human papillomavirus; PATRICIA, PApilloma TRIal against Cancer In young Adults.

Vaccine efficacy is summarized for the prevention of persistent infection and disease (CIN2+) for each study. Efficacy data shown are limited to participants who received all 3 scheduled doses and demonstrated no evidence of HPV exposure prior to vaccination.

[a] For the 9-Valent Trial, risk reduction for disease or infection associated with HPV type-specifc infections 31, 33, 45, 52, and 58 (types added to the 9-valent vaccine) is shown rather than absolute efficacy.[45-47]

Source: Guo T et al. Cancer. 2016.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm

2-dose vaccine recommendations

Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices

Weekly / December 16, 2016 / 65(49);1405–1408

Routine and catch-up age groups

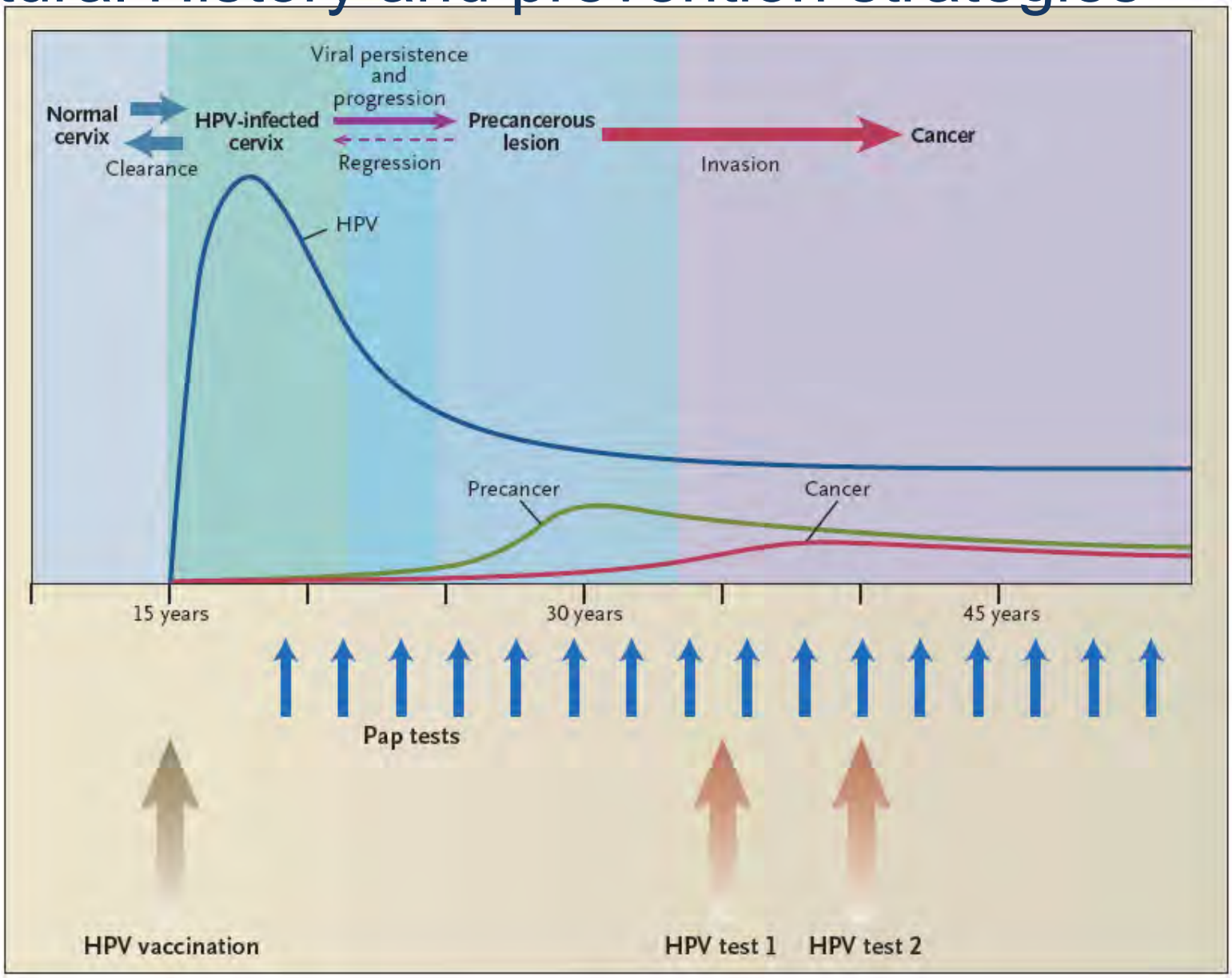
- routine HPV vaccination at age 11 or 12 years but can start at age 9 years.
  - females through age 26
  - males through age 21 (aged 22 through 26 may be vaccinated)

Dosing schedules

- If initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine
- Else 3 doses of HPV vaccine is recommended

**One dose trials are ongoing*

Natural History and prevention strategies



Schiffman & Castle, NEJM, 2005

THANK YOU!

Feel free to contact me with questions: arositch@jhu.edu