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Virology Research Center

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Primary HPV testing for the prevention of cervical cancer

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Tehran, IRAN

19 March, 2019

Tehran- Iran

Cervical cancer incidence in Iran

KEY STATS.

About **947 new cervical cancer cases** are diagnosed **annually** in **Iran** (estimations for 2012).

Cervical cancer **ranks as the 12th cause** of female cancer in **Iran**.

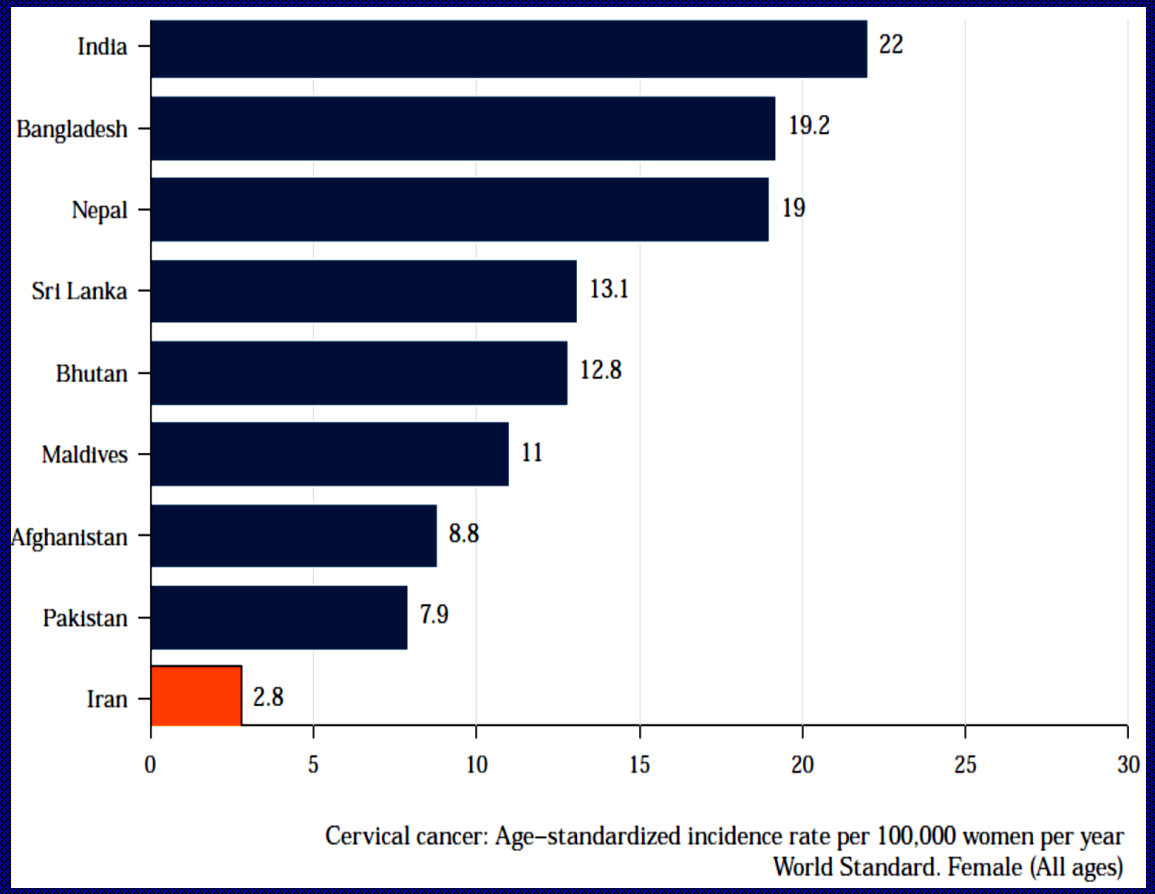
Cervical cancer is the **9th most common** female cancer in **women aged 15 to 44 years in Iran**.

Indicator	Iran	Southern Asia	World
Annual number of new cancer cases	947	145,946	527,624
Crude incidence rate[a]	2.5	17.1	15.1
Age-standardized incidence rate[a]	2.8	19.3	14.0
Cumulative risk (%) at 75 years old[b]	0.3	2.1	1.4

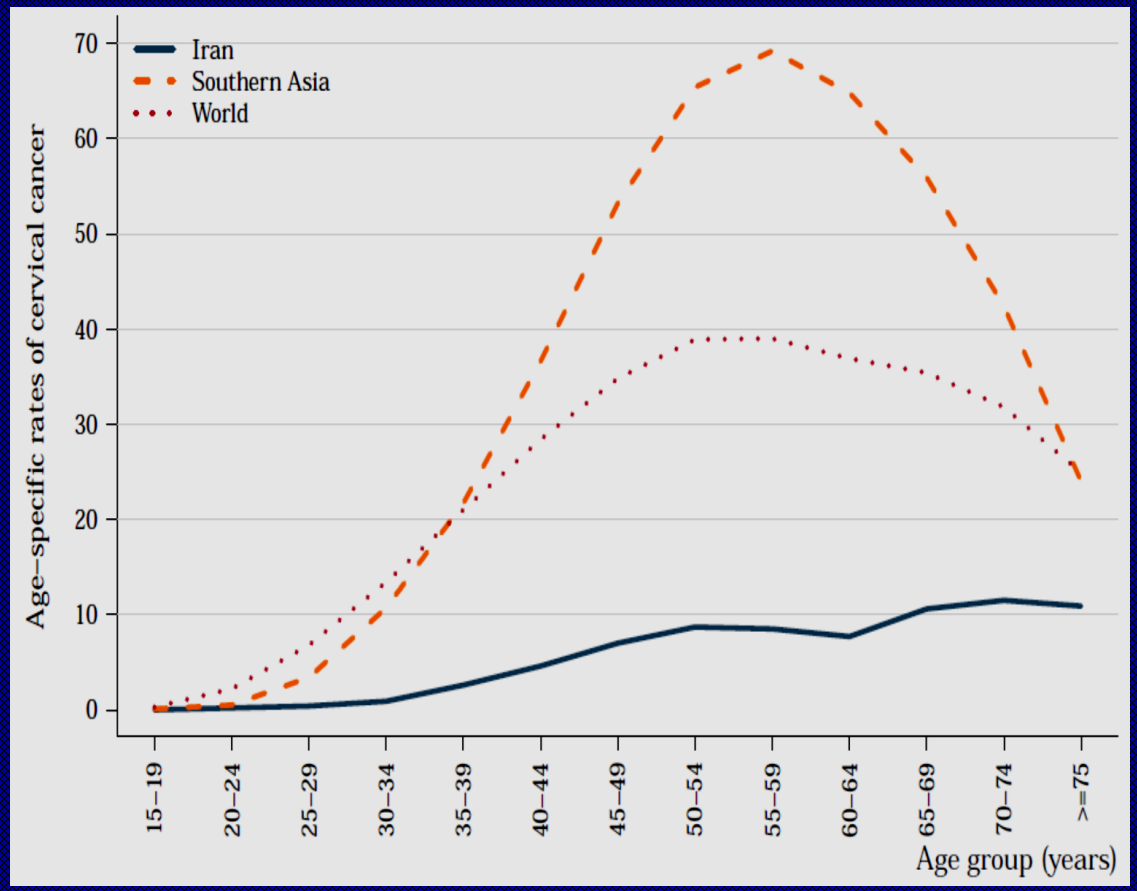
Data accessed on 15 Nov 2015.

Data accessed on 15 Nov 2015.
Incidence data is available from high quality regional (coverage lower than 10%). Data is included in Cancer incidence in Five Continents (CI5) volume IX and/or X. Incidence rates were estimated as the weighted average of the local rates. For more detailed methods of estimation please refer to http://globocan.iarc.fr/old/method/method.asp?country=364
aRates per 100,000 women per year.
b Cumulative risk (incidence) is the probability or risk of individuals getting from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to develop from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.
Data sources:
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr.

Age-standardized incidence rates of cervical cancer of Iran (estimations for 2012)



Age-specific incidence rates of cervical cancer in Iran compared to its region and the world



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Rates per 100,000 women per year.
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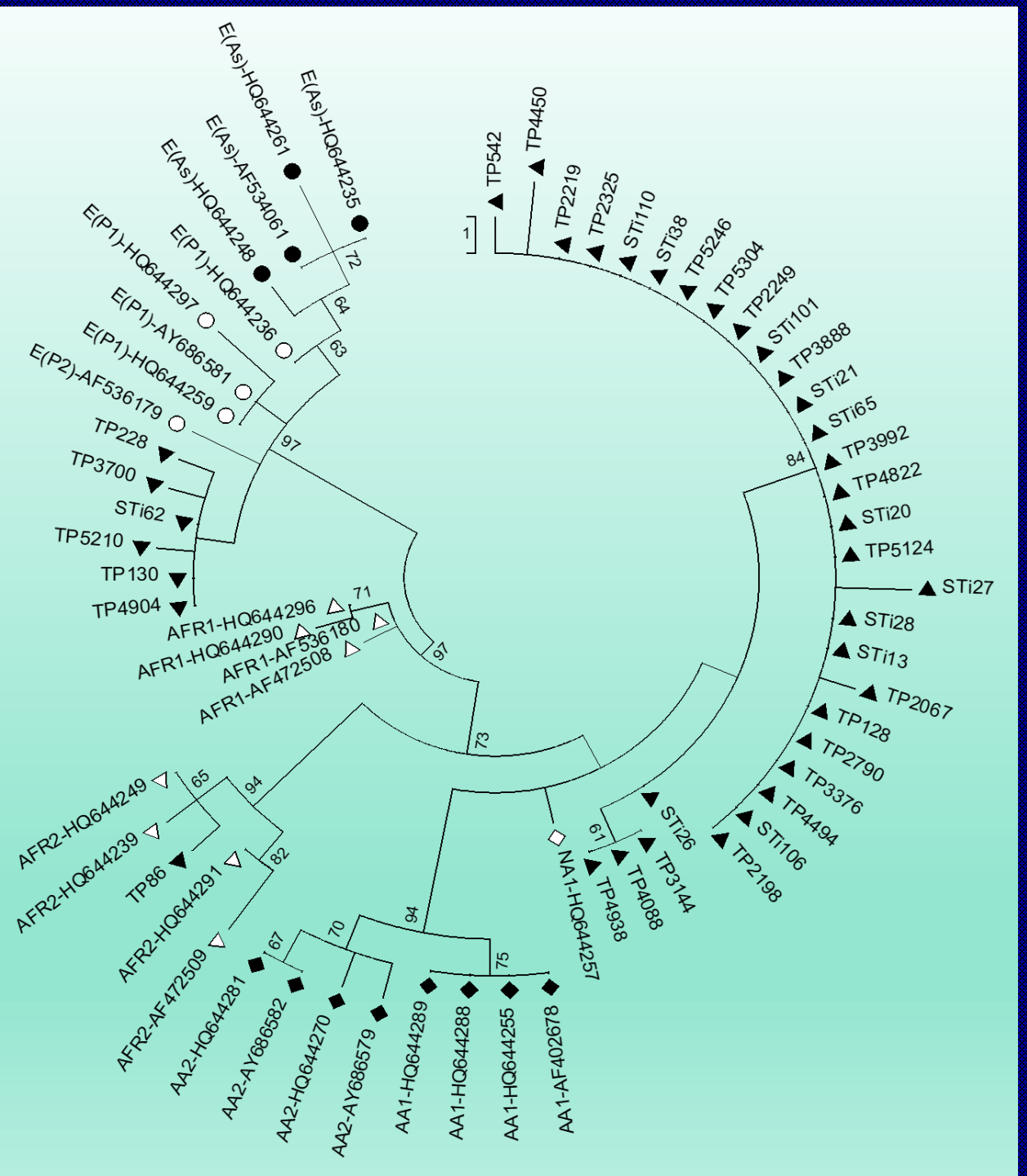
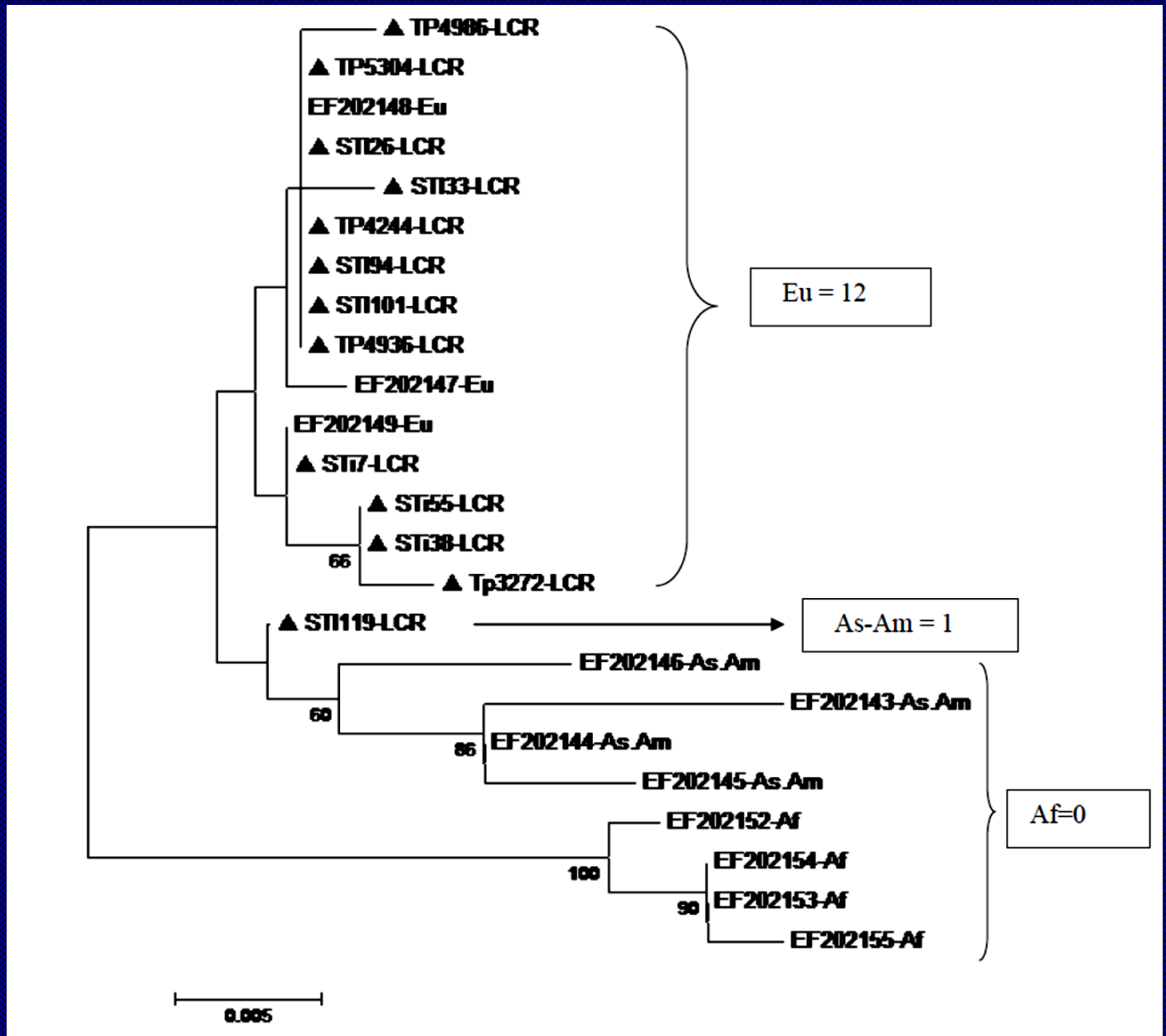


Molecular Phylogenetic analysis of HPV-16 Lineages by Maximum Likelihood method

Samples with small black triangle ▲ were under studied

Phylogenetic tree of HPV-18 variants

Samples with small black triangle ▲ were under studied



Ranking of the 7 most common HPV types

Rank	Cervix	Vulva	Vagina	Penis	Anus
1	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16
2	HPV 18	HPV 33	HPV 31	*HPV 6*	HPV 18
3	HPV 45	HPV 18	HPV 18	HPV 33	HPV 33
4	HPV 33	HPV 45	HPV 33	HPV 45,35	HPV 31
5	HPV 31	HPV 52	HPV 45,58	HPV 59	HPV 58,*6*
6	HPV 52	HPV 56	HPV 52	HPV 18,52,*11*	HPV 35
7	HPV 58	HPV 31,58,74	HPV 51	HPV 58	*HPV 11*

- **Type distribution for nearly 30’000 HPV related cancers from 38 countries participants in ICO surveys 2005 - 2014**

Burden of HPV related Cancers

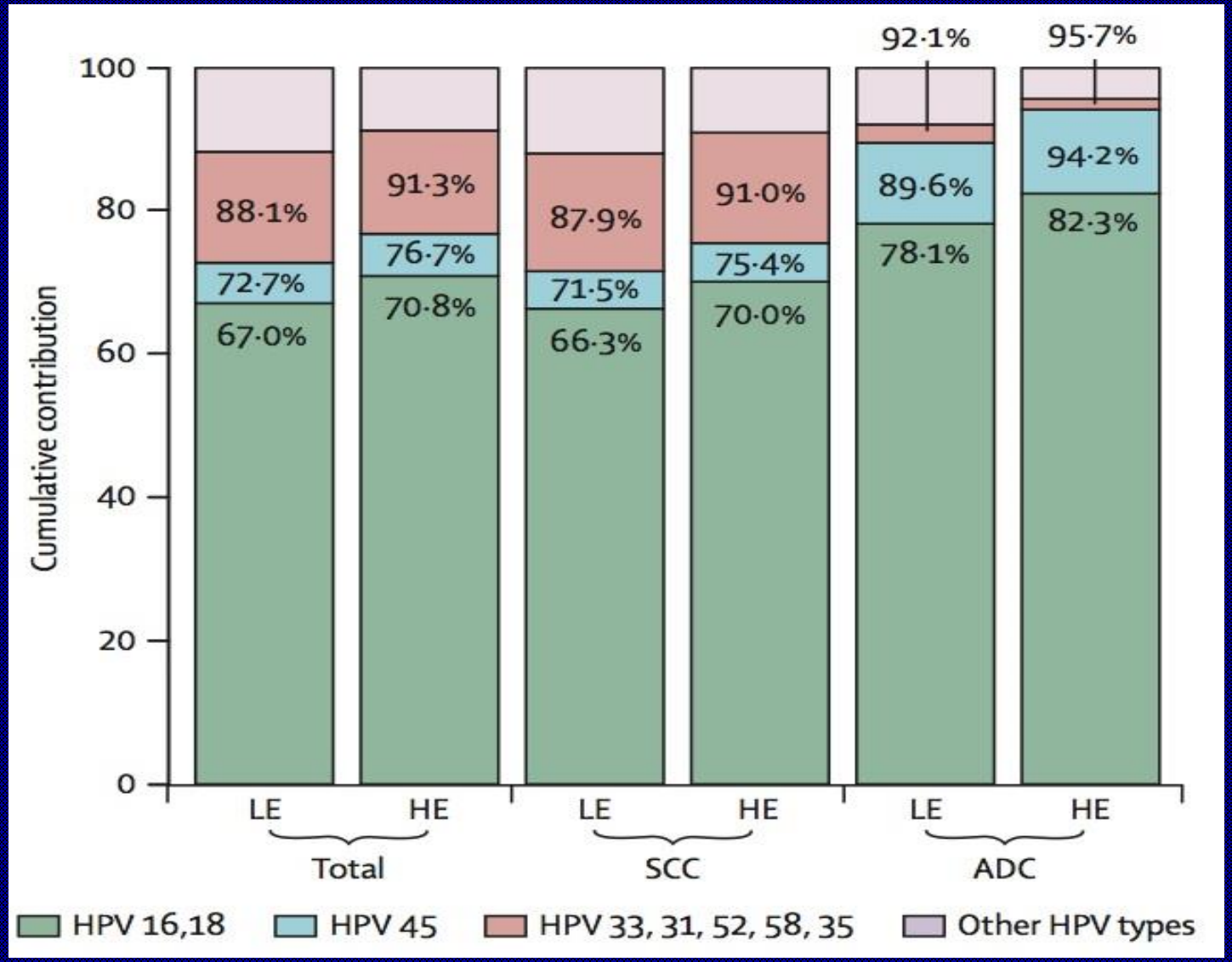
	CERVIX	VULVA	VAGINA	PENIS	ANUS
Incidence [1,2]	14.0%	0- 4.6%	0.5- 1.7%	14.0%	1.0%
Annual number of cancers [3]	530,000	27,000	13,000	22,000	27,000
Cancers attributable to HPV [3]	530,000	12,000	9,000	11,000	24,000
HPV prevalence [3]	100%	43%	70%	50%	88%
Worldwide population attributable fraction **4.8%** [3]					

1) Age–standardized incidence rate per 100,000 women per year
2) de Martel C et al. Lancet Oncol 2012;13(6):607-15
3) Forman et al. *Vaccine*. 2012;30S:F12–F23

Estimation of HPV attributable fractions (AF) from cancer case series

HPV-related cancer site		Region	AF (%)
Cervix uteri	PCR	World	100
Anus	PCR	World	88
Penis	PCR	World	51
Vagina	PCR	World	78
Vulva	PCR	Age 15–54 years	48
		Age 55–64 years	28
		Age 65+	15
Oropharynx (including tonsils and base of Tongue)	PCR + E6/E7 mRNA	North America	51
		North-West Europe	42
		East Europe	50
		South Europe	24
		China	23
		Japan	46
		India	22
		Rep. Korea	60
		Australia	41
		Elsewhere	13
Oral cavity/Larynx	E6/E7 mRNA	World	4

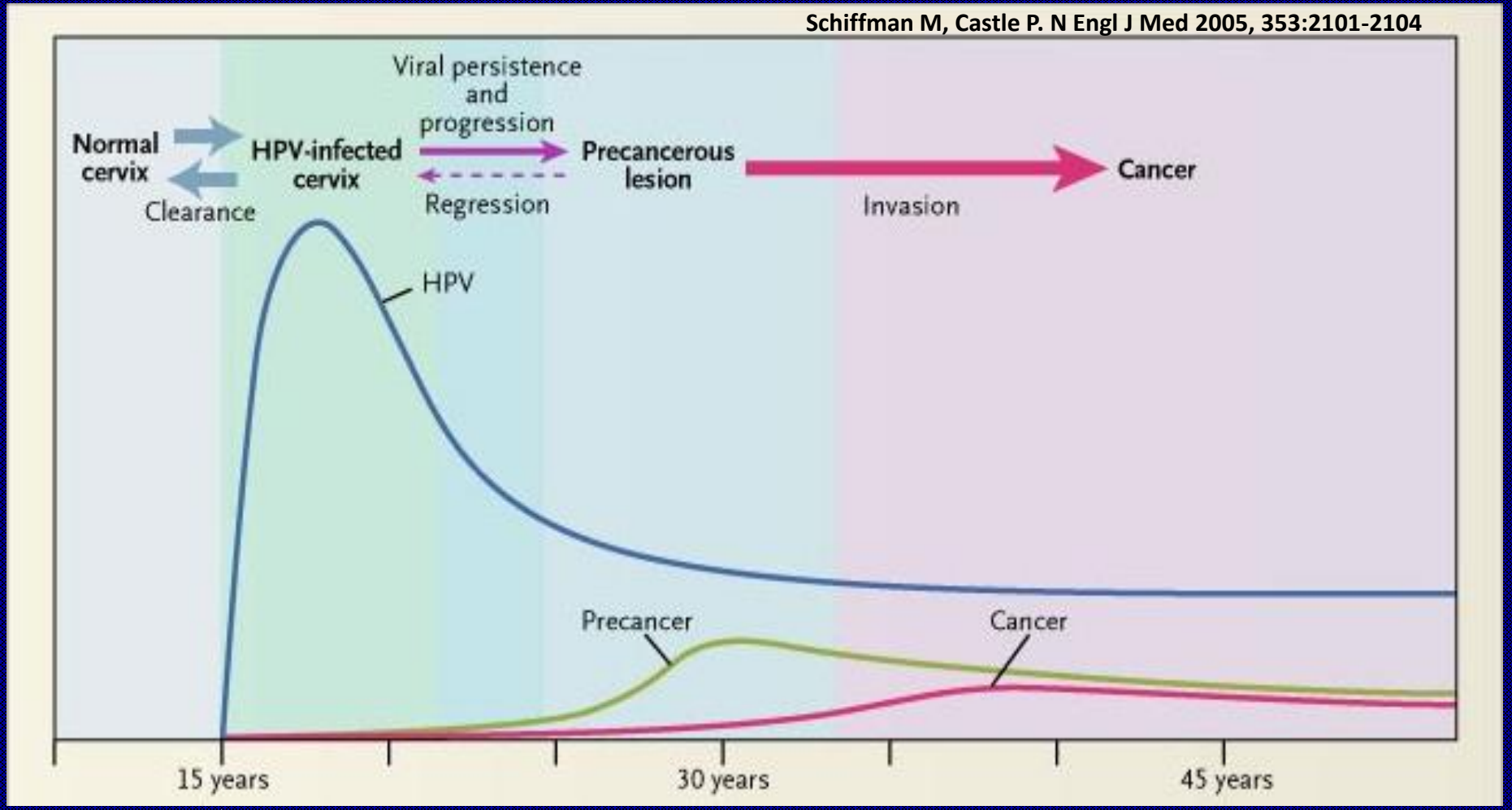
Cumulative relative contributions of **8 most common HPV types** by histologic category (38 countries) in women with Cancer.



de Sanjose S et al. Lancet Oncol 2010;11:1048-56

Natural history of HPV infection and Cervical cancer

Schiffman M, Castle P. N Engl J Med 2005, 353:2101-2104



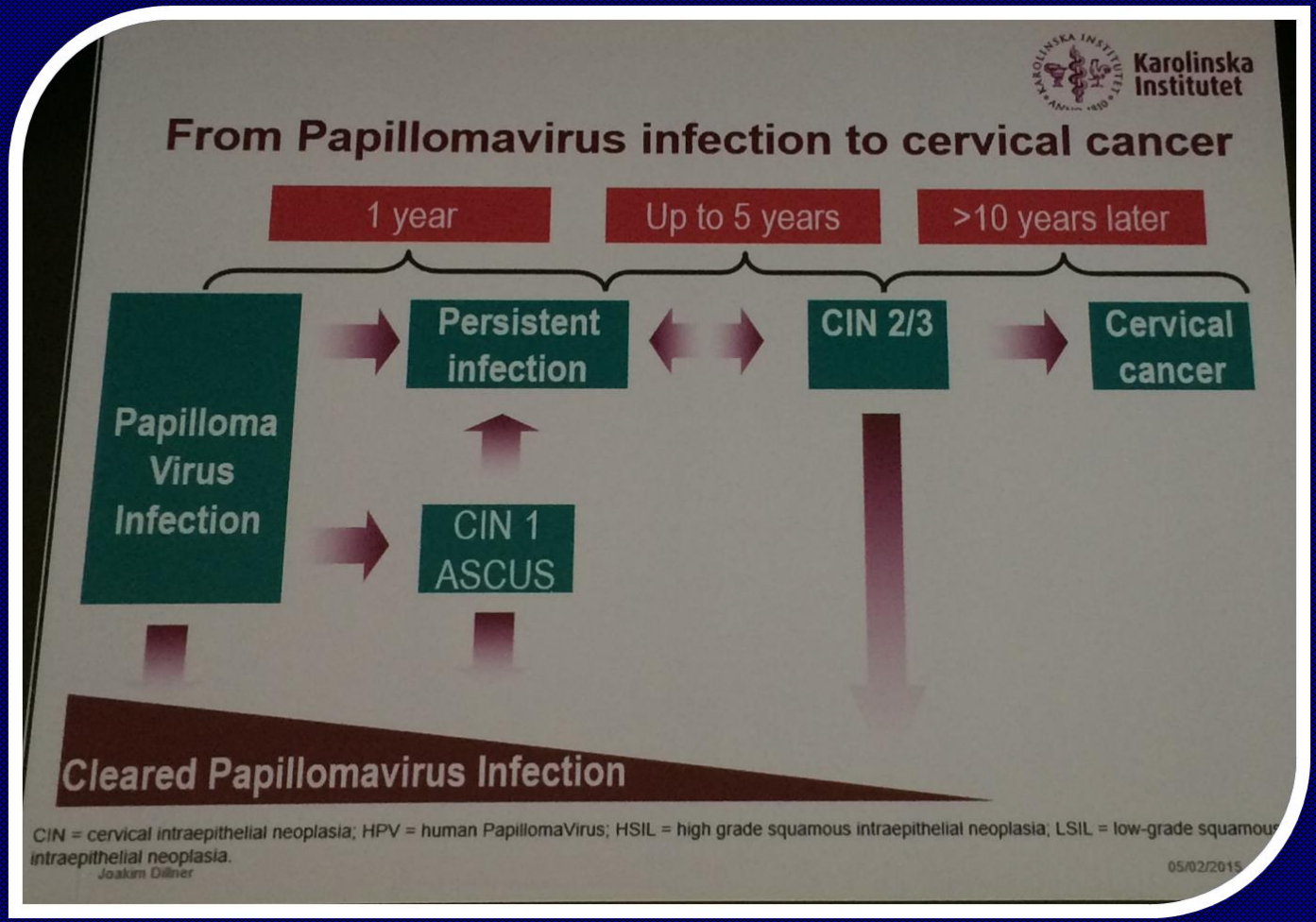
HPV vaccination

Pap tests

HPV test

Natural hx of HPV infections

- Most are transient and do not increase a woman's risk for cervical cancer.
- *If oncogenic HPV is persistent, the risk of cervical cancer is increased substantially*.
  - Longer persistence = greater the risk.
- The early natural history of HPV infections does not predict the outcomes.

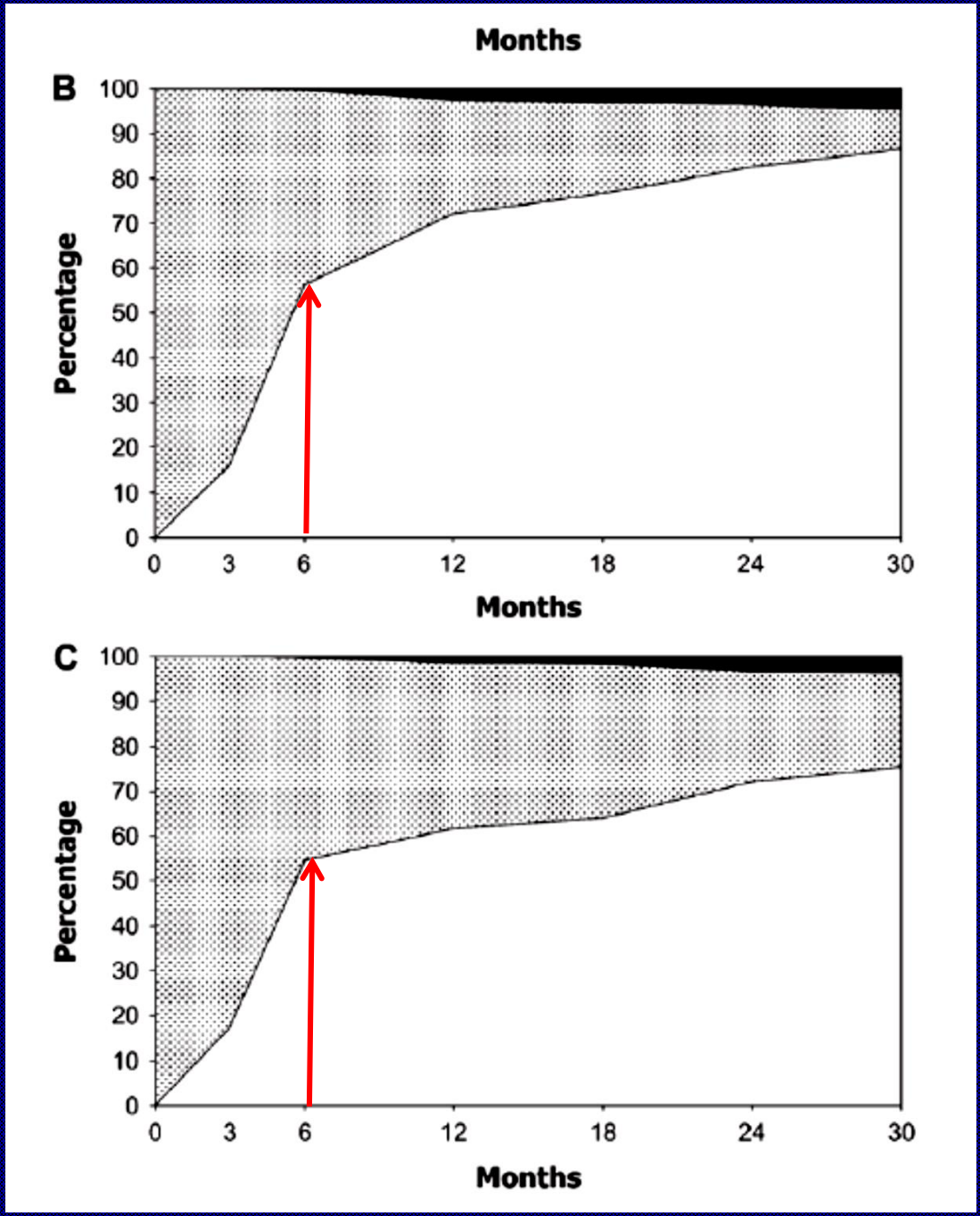


Clearance of carcinogenic HPV infections

Women >age 30

Behavior of carcinogenic HPV during 30 months of follow-up (800 infections)

Women ≤ age 30



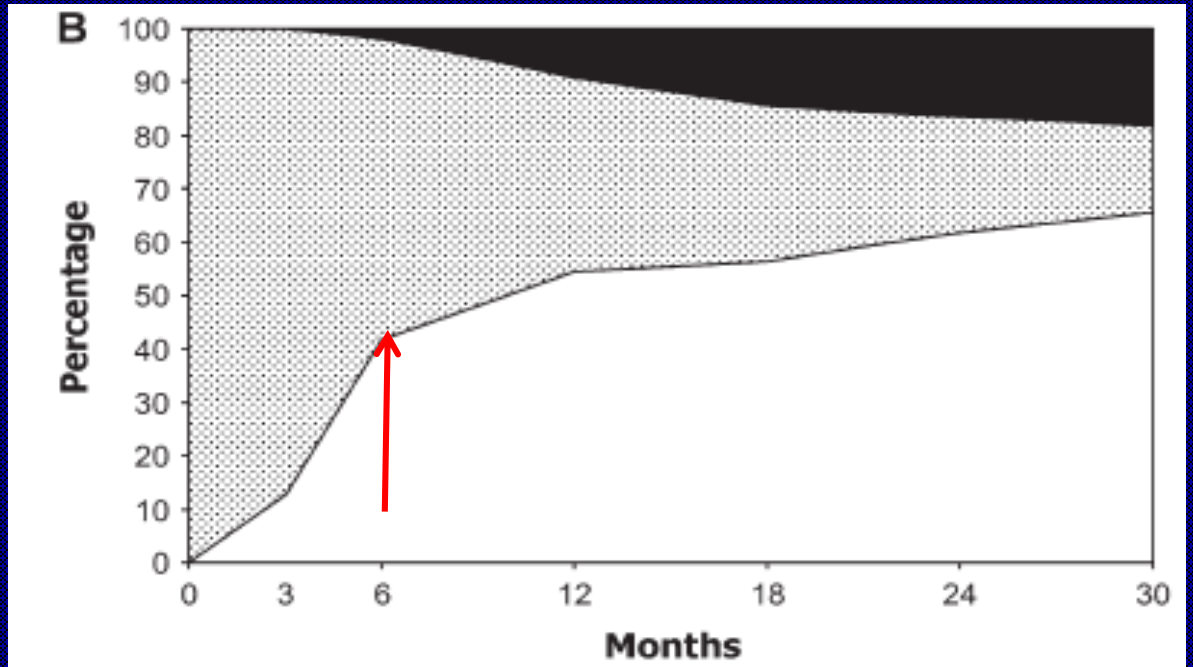
Rodriquez AC et al. J Natl Cancer Inst 2008;100:513-517

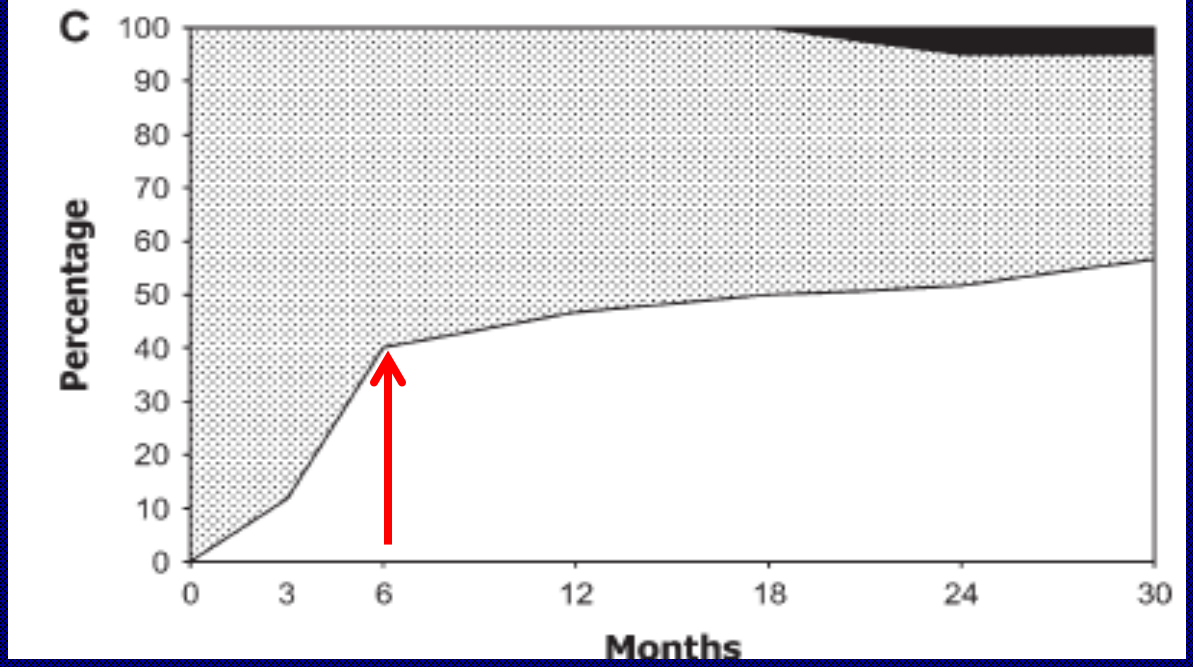
Clearance of HPV type 16 infections

Women >age 30

Behavior of HPV 16 during 30 months of follow-up (800 infections)

women ≤ age 30





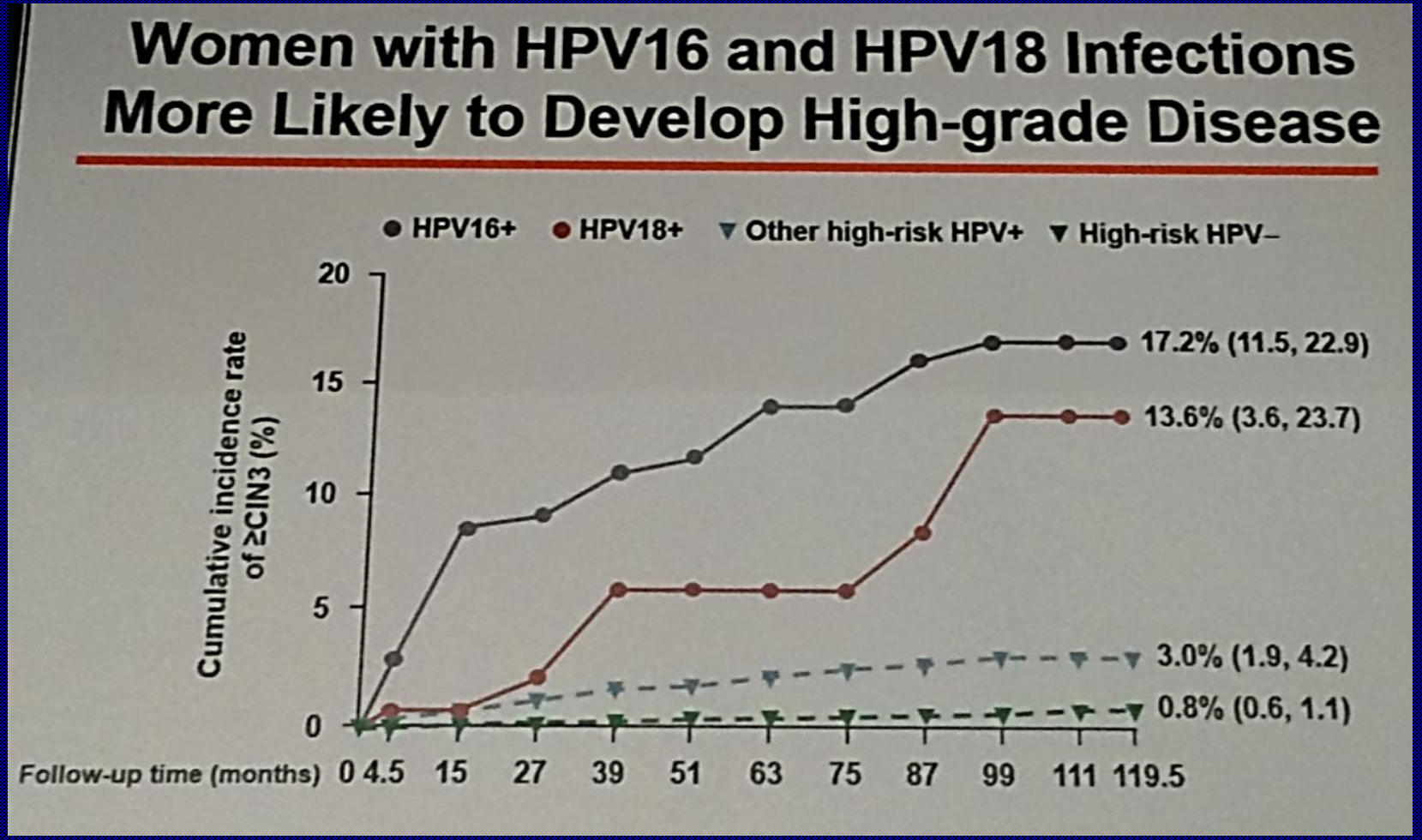
Rodriquez AC et al. J Natl Cancer Inst 2008;100:513-517

RCTs of HPV Testing in Screening

- POBASCAN study: the Netherlands (Mej\ijer et al., Int J Cancer 2004; Bulkmans et al., Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial(Elfgren et al., AJOG 2005; Naucler et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al., Br J Cancer 2012)
- Athena Trial: United States (Wright, et al., GynOnc 2015)

Risk of Cervical Precancer and cancer in Women With Human Papillomavirus

HPV screening that distinguishes HPV16 and HPV18 from other oncogenic HPV types may identify women at the greatest risk of ≥ CIN3 and may permit less aggressive management of other women with oncogenic HPV infections.

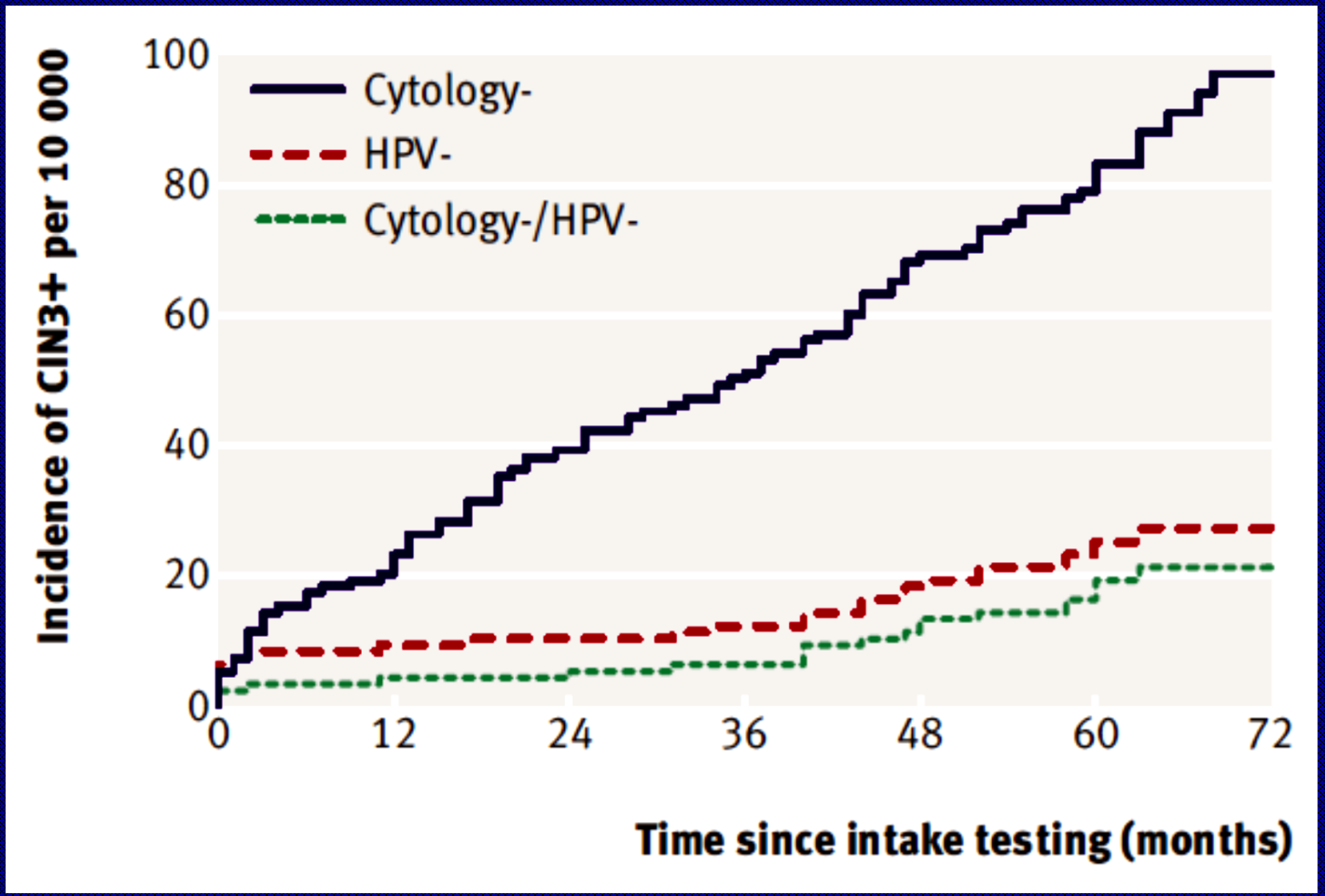


[J Natl Cancer Inst 2005;97:1072 – 9]

Long term predictive values of cytology and HPV testing in cervical cancer screening

- Cervical screening with HPV testing is more sensitive for detection of CIN3 or cervical cancer (CIN3+)
- A joint analysis of seven different studies in six European countries consistently found a low six year cumulative incidence rate of CIN3+ among women negative for HPV
- Cervical screening strategies with HPV testing every six years is safe and effective

Cumulative incidence rate for CIN3+ according to baseline test results in European Site



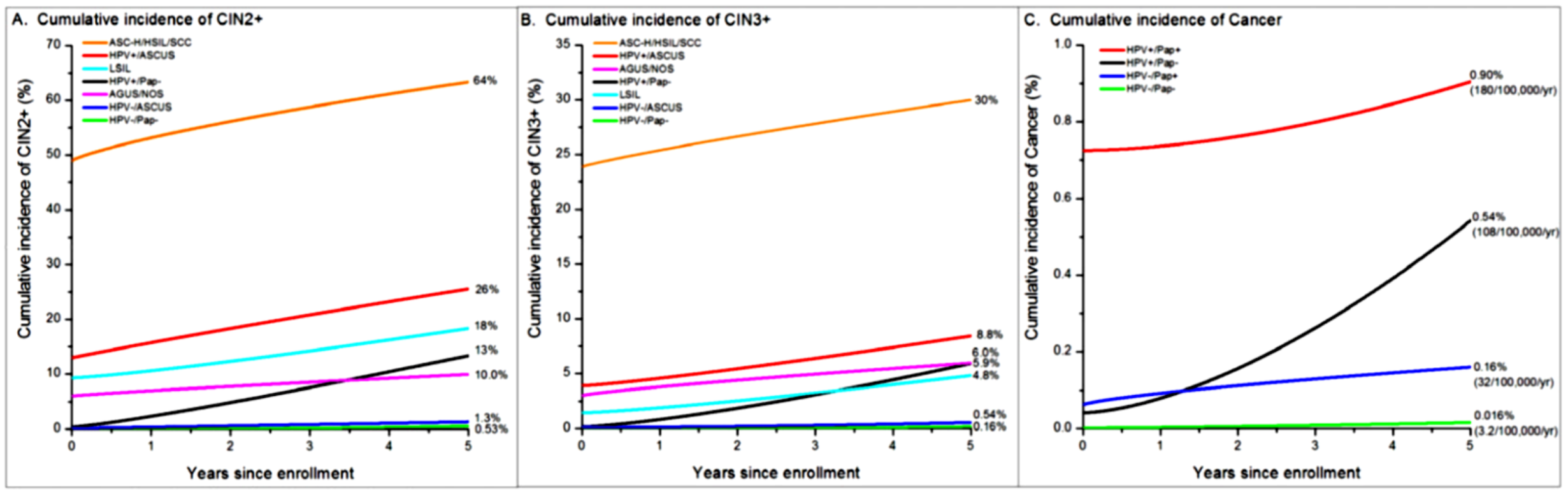
BMJ 2008;377:a1754

HPV Testing Finds More Women at High 5- year Risk of Cancer or Precancer

Test Result	5-year Risk	Excess Risk
HPV+	7.6%	7.4%
HPV-	0.2%	
Cytol+	4.7%	4.3%
Cytol-	0.4%	

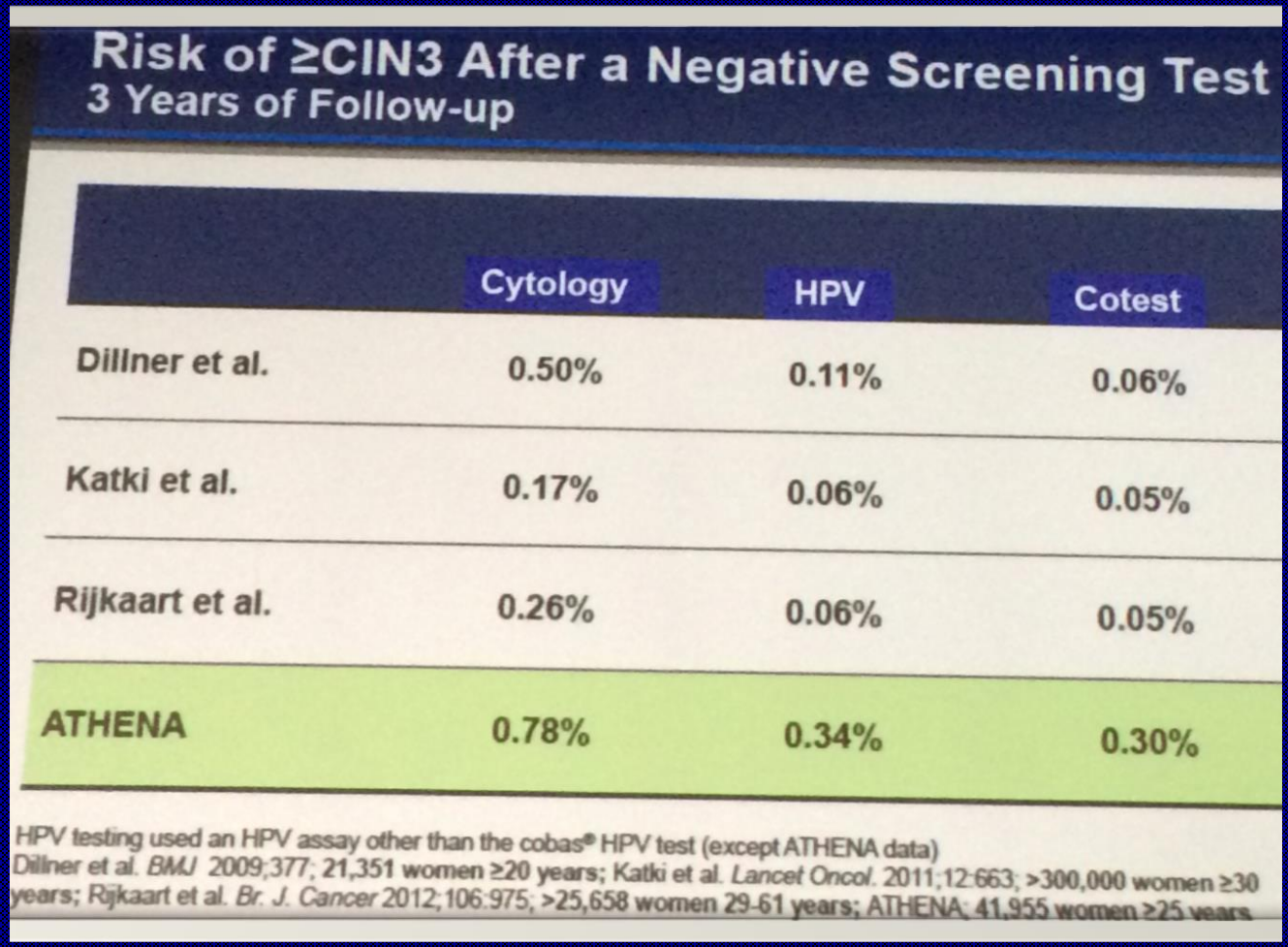
HPV Test	Cytol. Test	5-year Risk	Excess Risk
HPV+	Cytol+	12%	6%
HPV+	Cytol-	6%	
HPV-	Cytol+	0.9%	0.7%
HPV-	Cytol-	0.2%	

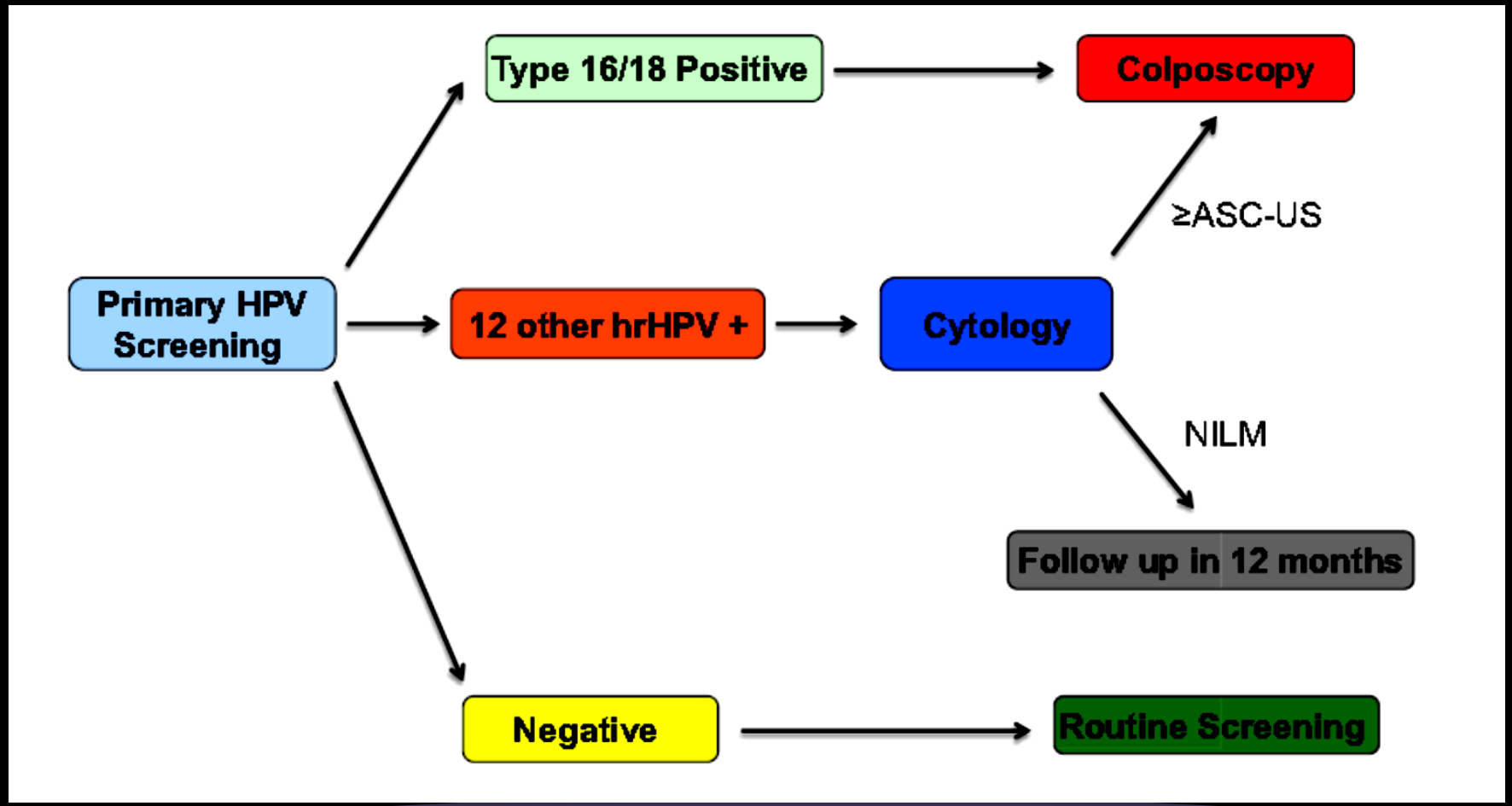
Katki et al, Lancet Oncology, 2011



Why 1st HPV DNA Testing for Cervical Cancer Screening?

- More sensitive and reproducible than cytology
- More "upstream" in carcinogenic process, thus enabling a longer safety margin for screening intervals
- Assesses future risk (and not just the presence of current disease)
- Can be automated, centralized, and quality- checked for large specimen throughput
- May be more cost- effective than cytology if deployed for high volume testing, such as primary screening
- A more logic choice for screening women vaccinated against HPV infection.





HPV As an Initial Screening Test

Proposed Primary Screening Algorithm

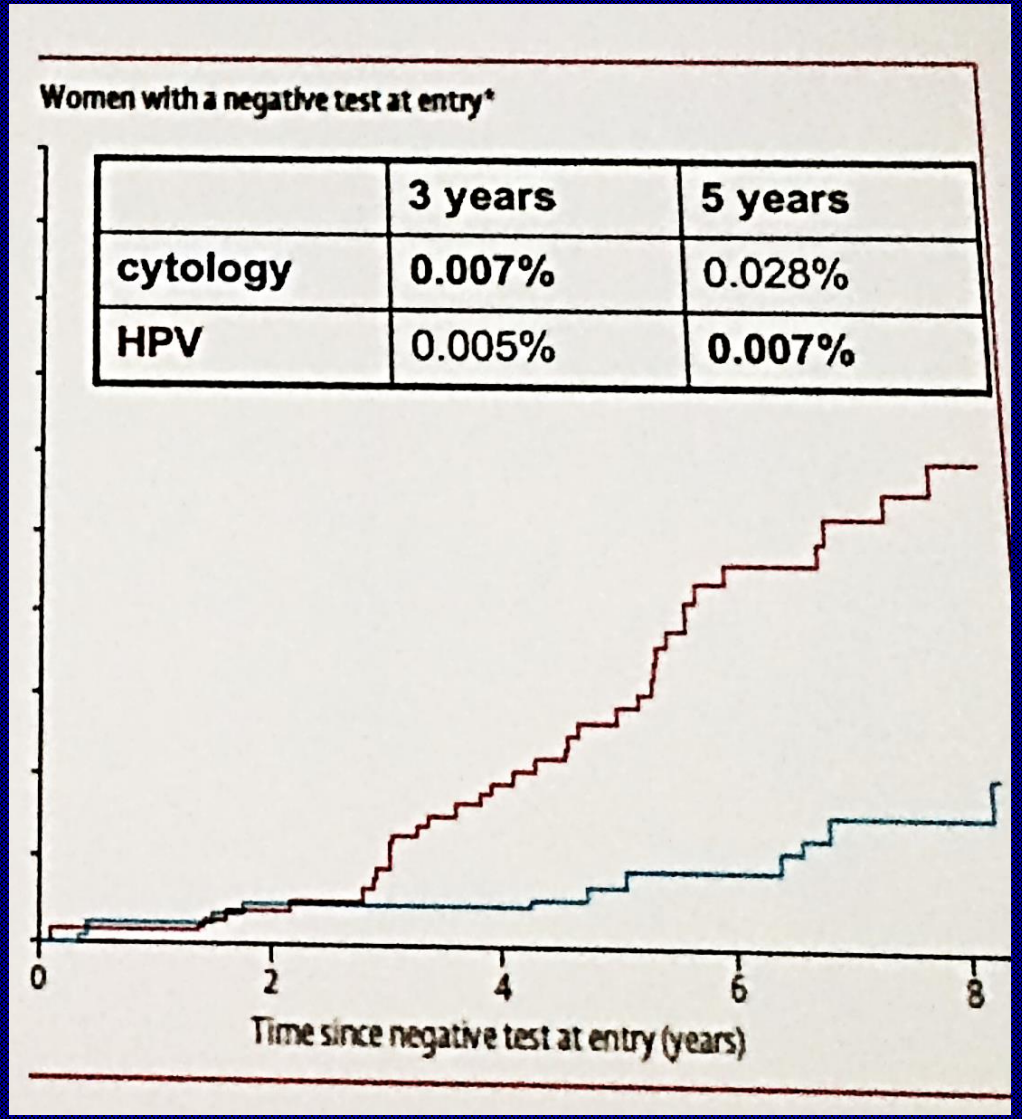
HPV with 16/18 genotyping and reflex cytology

From 3/12/2014 FDA panel Materials

What to do if HPV-? Interval of screening

- ***3 yearly wth Cytology***
- ***5 yearly wth HPV***

- **Screening interval for HPV – women is more political than scientific question.**
  - **Balancing health gain, resource, side effect, and convenience**
  - **From 3 to 10 years interval in different EU countries**

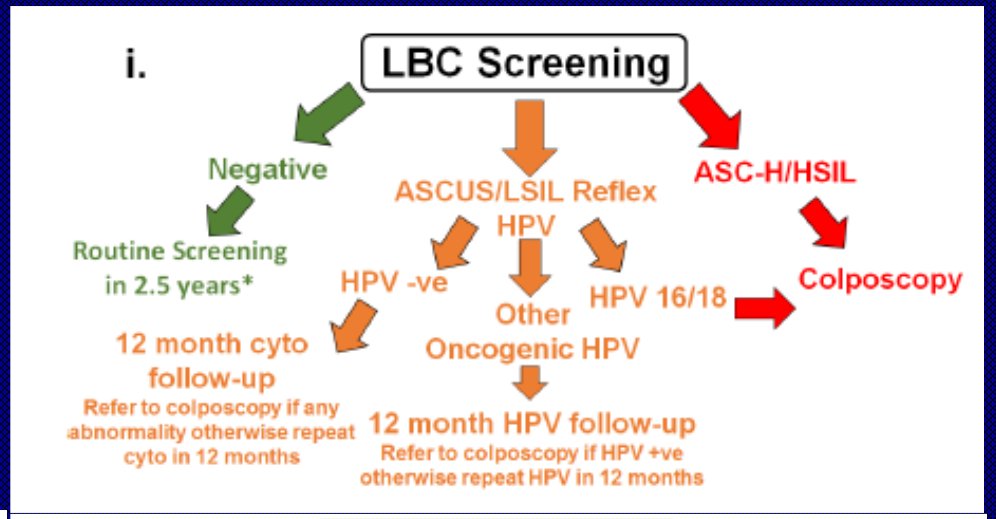


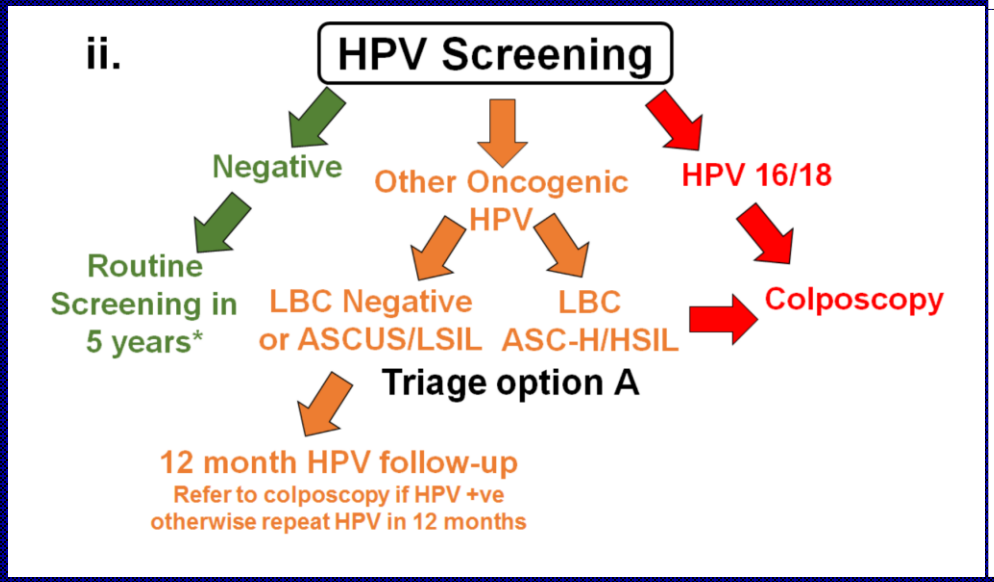
Elfsfrom, 2014, bmj

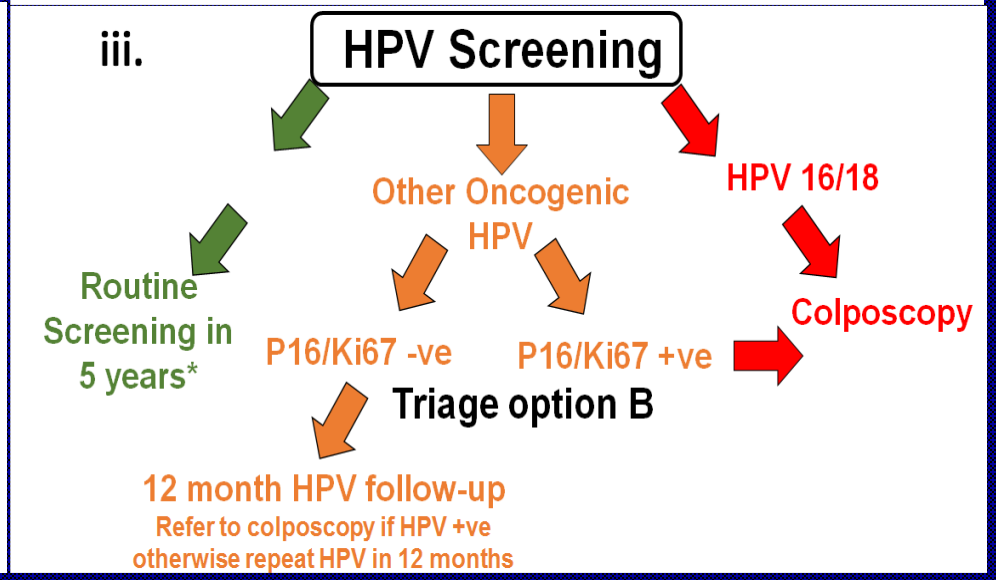
Cervical screening conducted in an extensively HPV-vaccinated population

higher detection rate for CIN2+ in the first screening round is observed in HPV-screened women even in a vaccinated population suggests that HPV screening will also provide increased long-term protection against cervical cancer in this context.

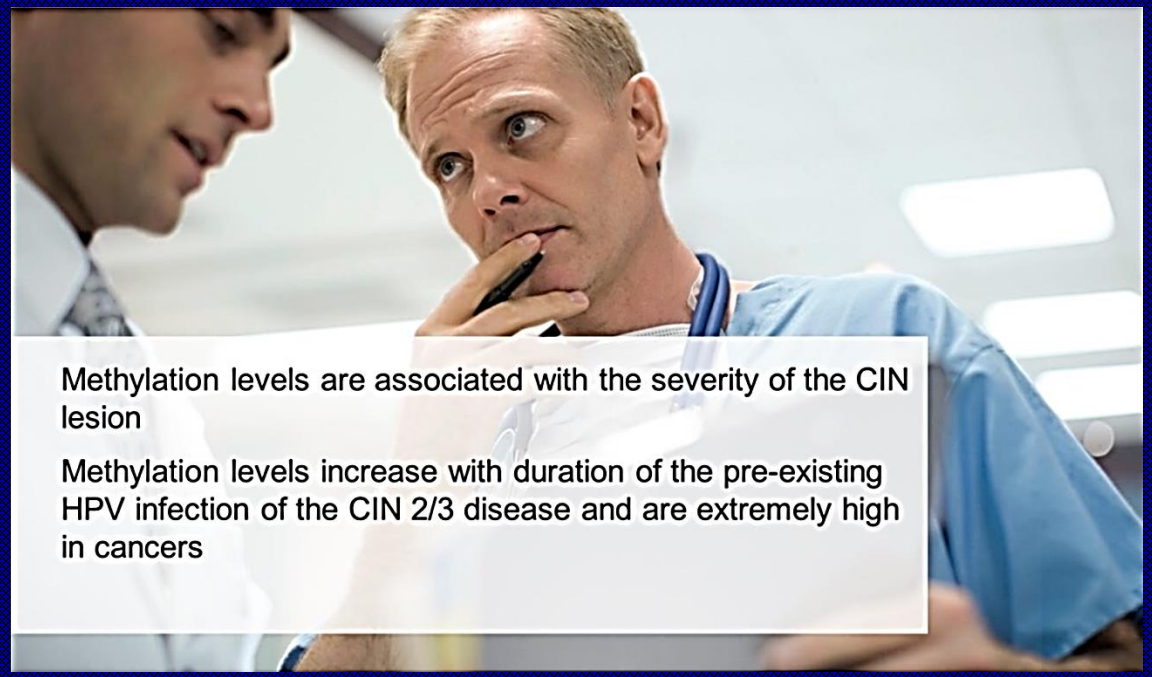
These findings for the relative benefits of HPV versus cytology screening are consistent with those from earlier trials conducted in unvaccinated populations.







Methylation Markers in Cervical Carcinogenesis

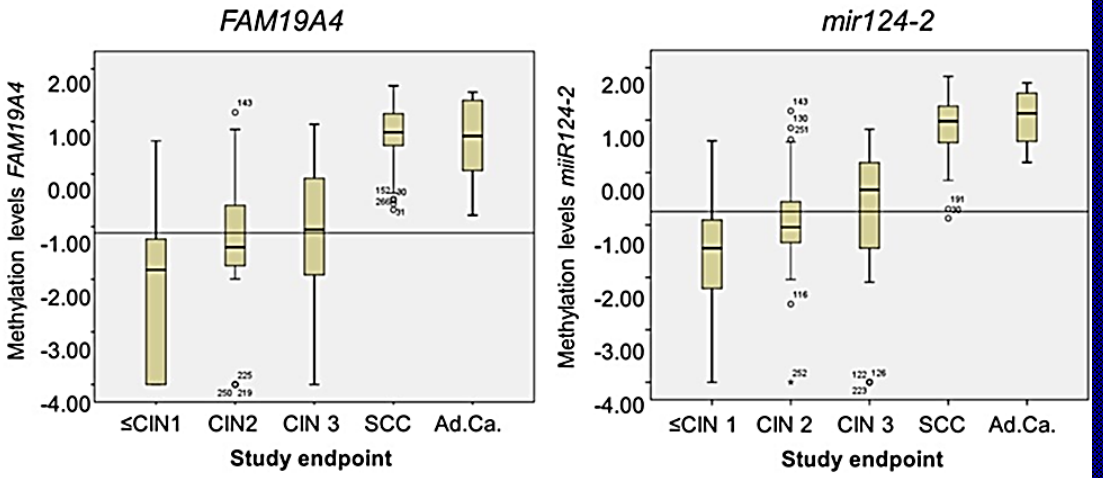


Methylation levels are associated with the severity of the CIN lesion

Methylation levels increase with duration of the pre-existing HPV infection of the CIN 2/3 disease and are extremely high in cancers

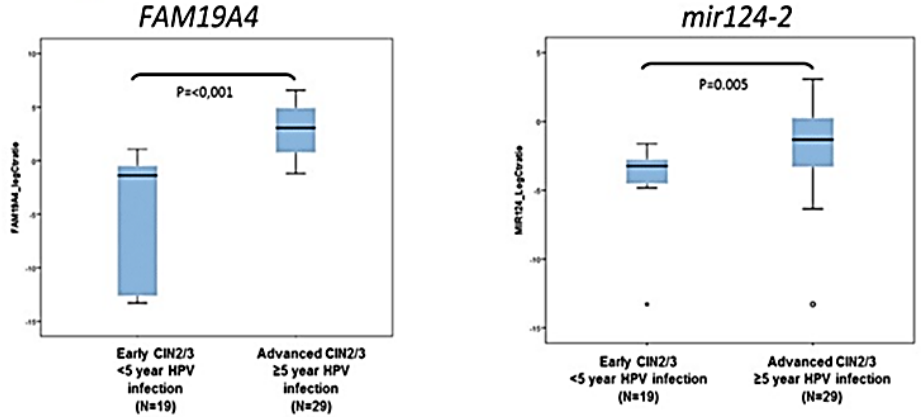
- ***FAM19A4* family** with sequence similarity 19 (chemokine (C-C motif)-like) memberA4
  - Identified by methylation-specific digital karyotyping of HPV16 E6/E7 immortalized human keratinocytes
- **mir124-2** encodes microRNA
  - Identified by candidate gene approach

Increased methylation levels in cervical scrapes proportional to severity of cervical disease



Similiar data for self samples

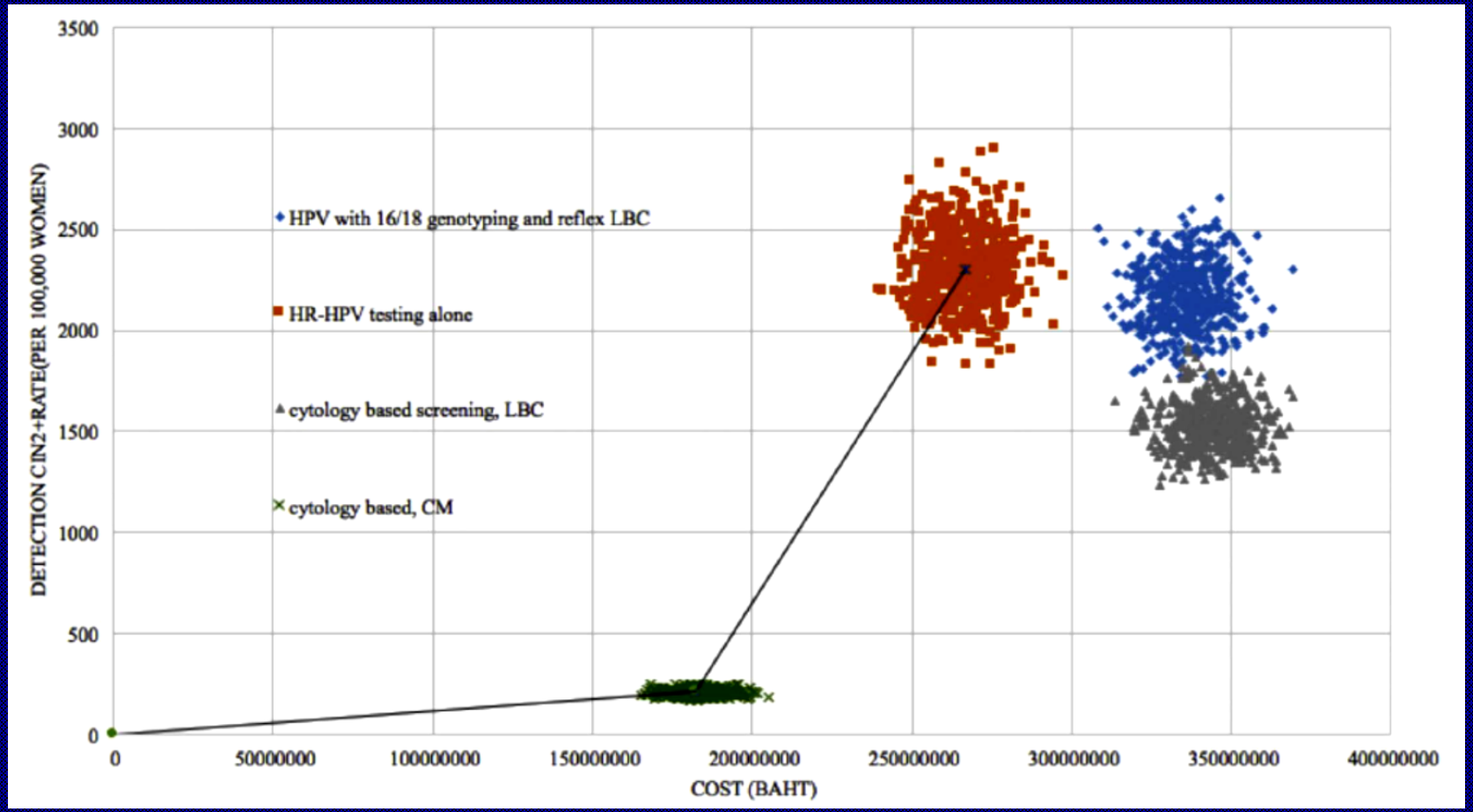
Increased methylation levels in cervical scrapes of women with CIN 2/3 with longer duration of pre-existing HPV infection



- Hypermethylation particularly associated with advanced disease; all advanced CIN 2/3 lesions (100%; 29/29; 95%CI: 88–100) scored methylation–positive for *FAM19A4* and/or *mir124-2*, compared with 47% (9/19; 95%CI: 27–69) of early CIN 2/3 lesions

- *FAM19A4/mir124-2* methylation analysis specifically detects "advanced" CIN lesions, which harbor a cancer-like methylation profile and have an expected high short-term risk of progression to cancer

cost-effectiveness analysis support the full scale implementation of HPV testing as a primary cervical cancer screening



Gynecologic Oncology Reports 22 (2017) 58–63

1st HPV TESTING enables self-collection of specimens for Cervical Cancer Screening

SCIENTIFIC REPORTS

OPEN

A prospective pilot evaluation of vaginal and urine self-sampling for the Roche cobas 4800 HPV test for cervical cancer screening

Received: 17 January 2018
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Sang-Hyun Hwang[1], Hye Young Shin[2,3], Dong Ock Lee[4], Na Young Sung[2], Bomyee Lee[2,5], Do-Hoon Lee[6] & Jae Kwan Jun[2]

This pilot study sought to evaluate the feasibility of utilizing vaginal self-swabs and urine samples for HPV-based cervical cancer screening in 700 women who had undergone conventional Pap smear screening via the national cervical cancer program in Korea. The cobas 4800 HPV test was utilized to detect HPV in the self-samples. Pap smear results revealed three cases of atypical squamous cells of undetermined significance, 649 cases of negative for an intraepithelial lesion or malignancy, and 48 non-specific inflammatory findings. High-risk HPV was detected in 6.7% of urine samples and 9.6% of vaginal self-swab samples. The overall agreement for HPV 16/18 between urine and vaginal self-swab samples was 99.1% (95%CI 98.1% to 99.6%). Colposcopic biopsy revealed one cervical intraepithelial neoplasia (CIN) 3 lesion, 12 CIN1 lesions, and 23 normal or chronic cervicitis lesions. In conclusion, urine and vaginal self-swab sampling was feasible and deemed a potential alternative for HPV detection in women who hesitate to participate in cervical cancer screening programs. Meanwhile, due to overall lower rates of abnormal cytology and sexual risk behaviors in Korea, a larger sample size than expected is needed to assess the sensitivity of CIN2+ detection via self-samples.

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Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens

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The World Health Organization has recommended that testing for high-risk human papillomavirus (HPV) (hrHPV) infection be incorporated into cervical screening programs in all settings worldwide. In many high-burden, low-income countries, it will not be feasible to achieve high cervical screening coverage using hrHPV assays that require clinician-collected samples. We conducted the first evaluation of self-collected vaginal specimens compared with clinician-collected cervical specimens for the detection of hrHPV infection using the Xpert HPV test. Women aged 30 to 54 years attending two well-woman clinics in Papua New Guinea were invited to participate and provided self-collected vaginal and clinician-collected cervical cytobrush specimens. Both specimen types were tested at the point of care by using the Xpert HPV test. Women were given their cervical test result the same day. Those with a positive hrHPV test and positive examination upon visual inspection of the cervix with acetic acid were offered same-day cervical cryotherapy. A total of 1,005 women were enrolled, with 124 (12.3%; 95% confidence interval [CI], 10.3%, 14.4%) being positive for any hrHPV infection. There was a 99.4% overall percent agreement (OPA) between vaginal and cervical tests for HPV-16 (95% CI, 98.9%, 99.9%), a 98.5% OPA for HPV-18/45 (95% CI, 97.7%, 99.3%), a 94.4% OPA for other hrHPV infections (95% CI, 92.9%, 95.9%), and a 93.4% OPA for all hrHPV types combined (95% CI, 91.8%, 95.0%). Self-collected vaginal specimens had excellent agreement with clinician-collected cervical specimens for the detection of hrHPV infection using the Xpert HPV test. This approach provides for the first time an opportunity to incorporate point-of-care hrHPV testing into clinical cervical screening algorithms in high-burden, low-income settings.

HPV Tests Used for Cervical Cancer Screening

HPV tests vary and use different methods to detect the HPV: some HPV tests will detect the DNA and other HPV tests will detect E6/E7 mRNA.

- **Tests that are commercially available at this time, and being used in some countries for cervical cancer screening include:**
  - **Hybrid Capture 2 (Qiagen), CareHPV (Qiagen), Cobas HPV Test (Roche), Cervista (Hologic), Aptima HPV Assay (Hologic), BD HPV Assay (BD) and Xpert HPV (Cepheid).**
- **In choosing which HPV test will be used in the screening program, consideration needs to be given to results of clinical trials, clinical validation of the test, and other operational and logistical aspects of the test and its requirements.**

TEST	TECHNIQUE	NAME
DNA	Direct: Genome detection	Hybrid Capture 2
		CareHPV test
	Amplification	GP5+/GP6+ bio PCR-EIA
		Cervista HPV HR
	Amplification and genotyping of HPV-16 and HPV-18	Cervista HPV 16/18
		Cobas HPV test
		Xpert HPV
		Abbott RealTime High Risk (HR) HPV assay
		PapilloCheck
RNA	Amplification of E6/E7 proteins	Aptima HPV Assay
		PreTect HPV-Proofer HV
	Monoclonal antibodies	AVantage HPV E6 Test

TEST	SENSITIVITY (%)	SPECIFICITY (%)
Hybrid Capture 2	97.5	84.3
CareHPV	90.0	84.2
Cervista HPV	100	
Cobas HPV Test	97.3	84.5
Abbott RealTime High Risk (HR) HPV assay	95.0	87.2
Aptima HPV Assay	97.6	90.2
Xpert HPV	100	81.5

Cuzick J et al. 2013.

cobas® HPV

cobas® HPV product summary

Sample type

- PreservCyt® Solution, SurePath™ Preservative Fluid and Roche Cell Collection Medium

Minimum amount of sample required (µL)

- 1,000

Specimen processing volume (µL)

- 400

Internal cellular control

- ß-globin

Simultaneous 16/18 genotyping

- Yes; HPV 16, HPV 18 and 12 hrHPV

Genotypes

- 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

12 pooled hrHPV

31 33 35 39 45 51

52 56 58 59 66 68

HPV16 HPV 18

CE-IVD (**cobas**® 4800 System)

US-IVD (**cobas**® 4800 System)

Canada-IVD (**cobas**® 4800 System)

CE-IVD (**cobas**® 6800/8800 Systems)

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Clinical Performance of Roche Cobas 4800 HPV Test

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Evaluation of the Cobas 4800 test demonstrated that Cobas had a low rate of cross-reactivity with low-risk human papillomavirus (lrHPV), a 3.74% disconcordance rate between prealiquots and postaliquots, and failure rates of 4.57% and 1.16%, respectively, after vortexing and swirling. This study demonstrated that the Cobas test has good sensitivity, accuracy, and reproducibility for detecting 14 high-risk HPV (hrHPV) genotypes.

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Clinical Validation of the cobas 4800 HPV Test for Cervical Screening Purposes[▽]‖

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This study shows that the clinical performance and reproducibility of the cobas 4800 HPV test for high-risk human papillomavirus (HPV) detection fulfill the criteria as formulated in international guidelines of HPV test requirements for cervical screening purposes. Accordingly, the cobas 4800 HPV test can be considered clinically validated for cervical screening.

Xpert® HPV

- 14 HPV Genotypes
- 1mL
- 1 Hour
- Easy to use
- Scale-up
- Can be integrated in any set-up

Xpert® HPV Assay Concept

The Xpert HPV assay utilizes six fluorescent channels.

Channel	Analyte Targets
1	HPV 16
2	HPV 18,45
3	HPV 31, 33, 35, 52, 58
4	HPV 51, 59
5	HPV 39, 56, 66, 68
6	HMBS (Specimen Adequacy Control)

Pooled Result

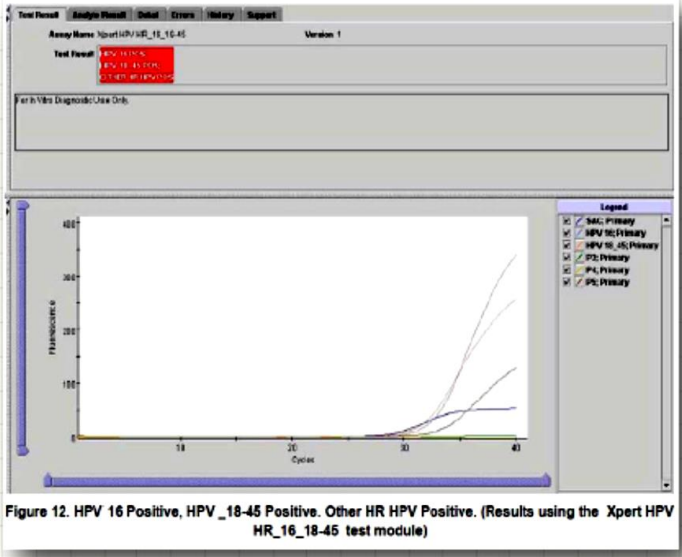

Figure 12. HPV 16 Positive, HPV _18-45 Positive. Other HR HPV Positive. (Results using the Xpert HPV HR_16_18-45 test module)

Simple Workflow

1. Obtain one appropriately collected and labeled cervical specimen*.
2. Transfer 1 mL of cervical specimen to the cartridge.
3. Insert cartridge and start assay. Results in less than 60 minutes.

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Clinical Evaluation of the Cartridge-Based GeneXpert Human Papillomavirus Assay in Women Referred for Colposcopy

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High-risk human papillomavirus (hrHPV) testing is now being introduced as a potential primary screening test for improved detection of cervical precancer and cancer. Current U.S. Food and Drug Administration-approved tests are batch tests that take several hours to complete. A rapid, non-batch test might permit point-of-care (POC) testing, which can facilitate same-day screen and management strategies. For a non-batch, random-access platform (GeneXpert; Cepheid, Sunnyvale, CA), a prototype hrHPV assay (Xpert) has been developed where testing for 14 hrHPV types can be completed in 1 h. In the first clinical evaluation, Xpert was compared to two validated hrHPV tests, the cobas HPV test (cobas, Roche Molecular Systems) and Hybrid Capture 2 (hc2, Qiagen), and to histologic outcomes using specimens from colposcopy referral populations at 7 clinical sites in the United States ($n = 697$). The sensitivity of Xpert for cervical intraepithelial neoplasia grade 2 or more severe diagnoses (CIN2+) ($n = 141$) was equal to that of cobas (90.8% versus 90.8%, $P = 1$) and greater than that of hc2 (90.8% versus 81.6%, $P = 0.004$). Xpert was more specific than cobas (42.6% versus 39.6%, $P = 0.02$) and less specific than hc2 (42.6% versus 47.7%, $P < 0.001$). Similar results were observed for cervical intraepithelial neoplasia grade 3 or higher (CIN3+) ($n = 91$). HPV16 detection by Xpert identified 41.8% of the CIN2+ specimens with a positive predictive value (PPV) of 54.6%. By comparison, HPV16 detection by cobas identified 42.6% of the CIN2+ specimens with a PPV of 55.0%. hrHPV detection by the Xpert demonstrated excellent clinical performance for identifying women with CIN2+ and CIN3+ that was comparable to that of currently available clinically validated tests.

Comparison	n	Kappa	% total agreement	% positive agreement	p
Xpert vs cobas	697	0.84	92.7	96.2	0.02
Xpert vs HC2	697	0.73	86.9	85.2	<0.0001
cobas vs HC2	697	0.67	84.5	82.1	<0.0001

Einstein et al ***J Clin Microbiol***. 2014

Thank you for your patience ☺