Cervical cancer screening in vaccinated population

Cytology and molecular testing

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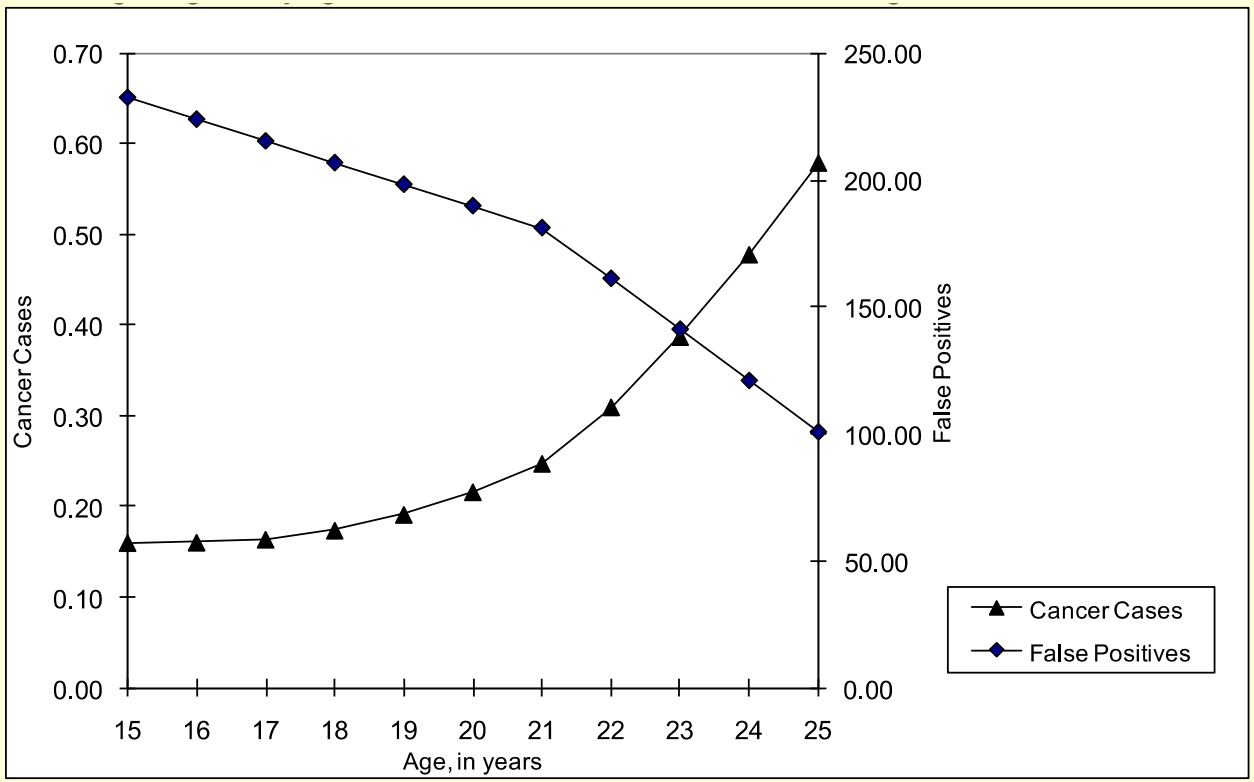
Izmir, November 2017

General principles of cervical screening

When should screening begin?



*Results presented assume an annual screening interval and are calculated per 1,000 women

Only 0.1% of cases of cervical cancer occur before age 20 years which translates to approximately 1–2 cases per year per 1,000,000 females aged 15–19 years

Kulasingam SL, Havrilesky L, Ghebre R, Myers ER. Screening for Cervical Cancer: A Decision Analysis for the U.S. Preventive Services Task Force. AHRQ Publication No. 11-05157-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2011.

In a report of 10,090 Pap test results in females aged 12–18 years, 422 specimens (5.7%) were reported as LSIL and only 55 specimens (0.7%) were HSIL .

Wright JD, Obstet Gynecol 2005;106:115–20.

Cervical cancer screening should begin at age 21 years

regardless of the age of sexual initiation
or the presence of other behavior-related risk factors.

Which tests should be performed for screening?

Cytology alone

Co-testing

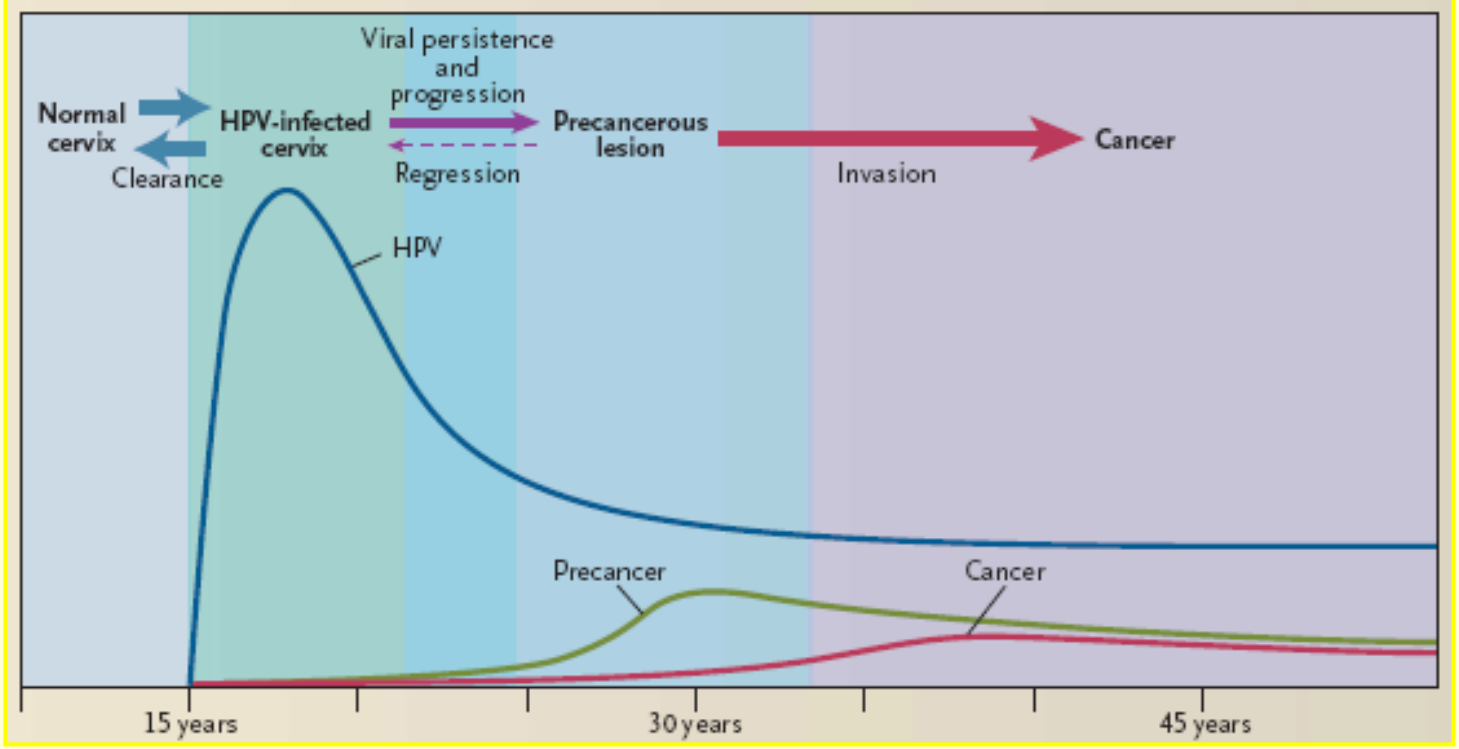
HPV testing alone

Cytology is a cornerstone of cervical screening.

Sensitivity and Specificity of Cytology and HPV Testing for Primary Screening

Screening or Triage Test	Sensitivity of Test for CIN2+	Specificity of Test for <CIN2	Delta of HPV Compared to Cytology in Same Study	
			Sensitivity (CIN2+)	Specificity (CIN2+)
Cytology				
EPC-QRS[35]	0.569	0.945		
Mayrand et al[8]	0.564	0.973		
Koliopoulos et al[36]	0.727	0.919		
Range[8,37,41-43]	0.20-0.772	0.847-0.990		
Triage for ASC-US[44]	0.762	0.638		
Range[45-47]	0.45-0.956	0.475-0.756		
HPV DNA using HC2				
EPC-QRS[35]	0.964	0.906	0.395	-0.039
Mayrand et al[8]	0.974	0.943	0.41	-0.03
Koliopoulos et al[36]	0.948	0.86	0.221	-0.059
Range[8,37,41-43]	0.341-1.00	0.767-0.966		
Triage for ASC-US[44]	0.892	0.641	0.13	0.003
Range[45-47]	0.67-0.976	0.31-0.672		

Kulasingam SL, Havrilesky L, Ghebre R, Myers ER. Screening for Cervical Cancer: A Decision Analysis for the U.S. Preventive Services Task Force. AHRQ Publication No. 11-05157-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2011.



Cytology negatif women

Yaş	Onkojenik HPV Pozitifliği
25-29	%15
> 30	%4

Castellsagué X Gynecologic Oncology 2009

Women aged 21–29 years should be tested with cervical cytology alone

Annual screening leads to a very small increase in cases of cancer prevented at the cost of a very large excess of procedures and treatments and should not be performed.

Compared with screening every 3 years, screening every 2 years was associated with negligible change in risk of cancer

(37 cases per 100,000 women versus 39 cases per 100,000 women)

more colposcopy procedures

(176 procedures per 100,000 women versus 134 procedures per 100,000 women).

http:// www.ncbi.nlm.nih.gov/books/NBK92546/pdf/Bookshelf_NBK92546.pdf. Retrieved September 4, 2015

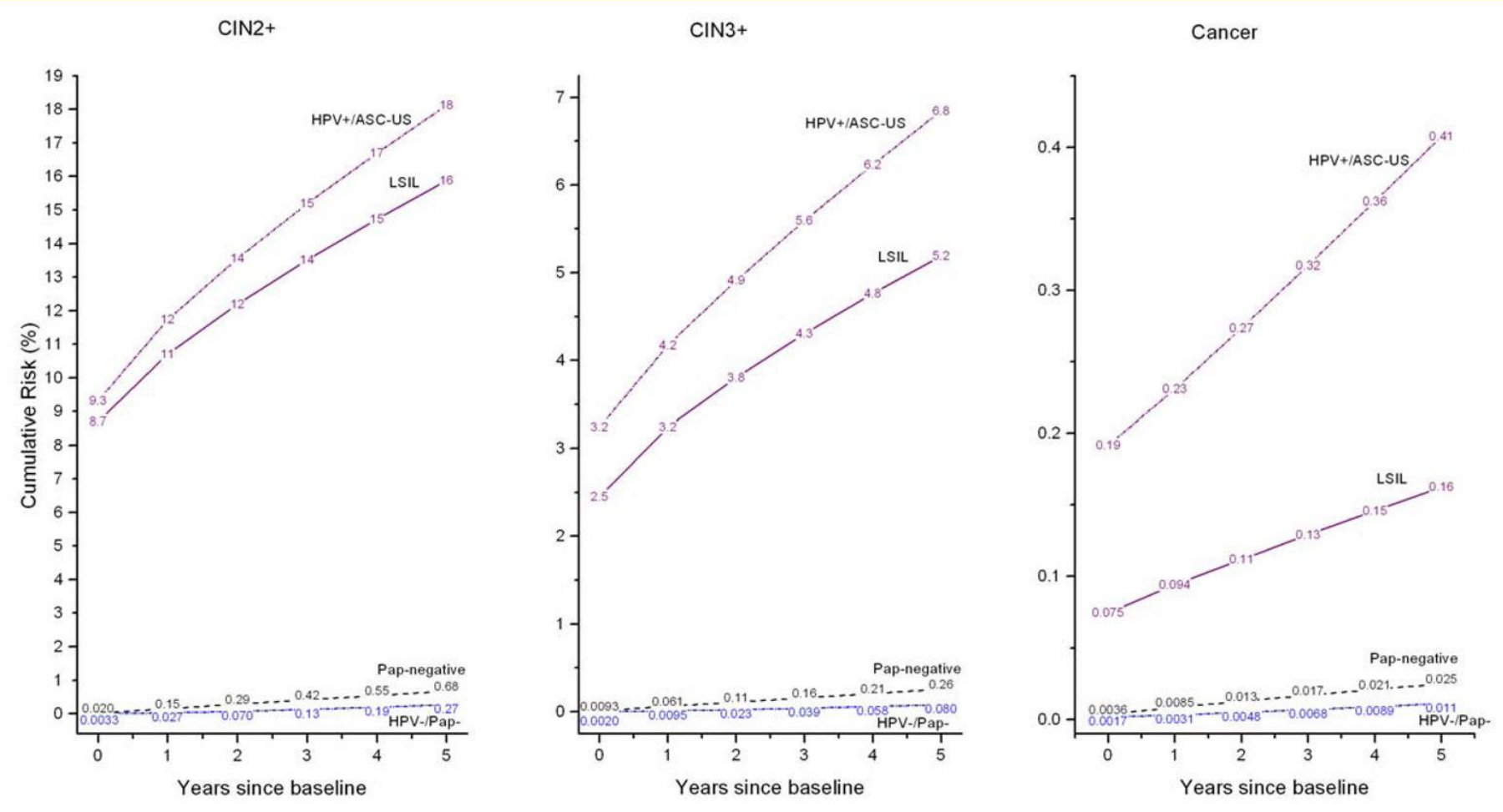
screening should be performed every 3 years for this group of patient.

for > 30 aged women

Cytology alone

Co-testing

According to Pap test and Cotest results the rate of CIN and cancer in 5 years



Katki HA,. J Low Genit Tract Dis 2013

	Cotesting ev. 5 yrs	VS	Cytology alone ev. 3 yrs
per 1,000 women over a lifetime cancer	6.23-7.39		5.98-8.97
death	1.10-1.35		0.95-1.55
number of colposcopy	626-907		416-1090

Screening Method	Result	Management
Cytology screening alone	Cytology negative	Screen again in 3 years
	ASC-US cytology and reflex HPV negative	Cotest in 3 years
	All others	Refer to ASCCP guidelines*
Cotesting	Cytology negative, HPV negative	Screen again in 5 years
	ASC-US cytology, HPV negative	Screen again in 3 years
	Cytology negative, HPV positive	Option 1: 12-month follow-up with cotesting Option 2: Test for HPV-16 or HPV-18 genotypes • If positive results from test for HPV-16 or HPV-18, referral for colposcopy • If negative results from test for HPV-16 and HPV-18, 12-month follow-up with cotesting
	All others	Refer to ASCCP guidelines*

Abbreviations: ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

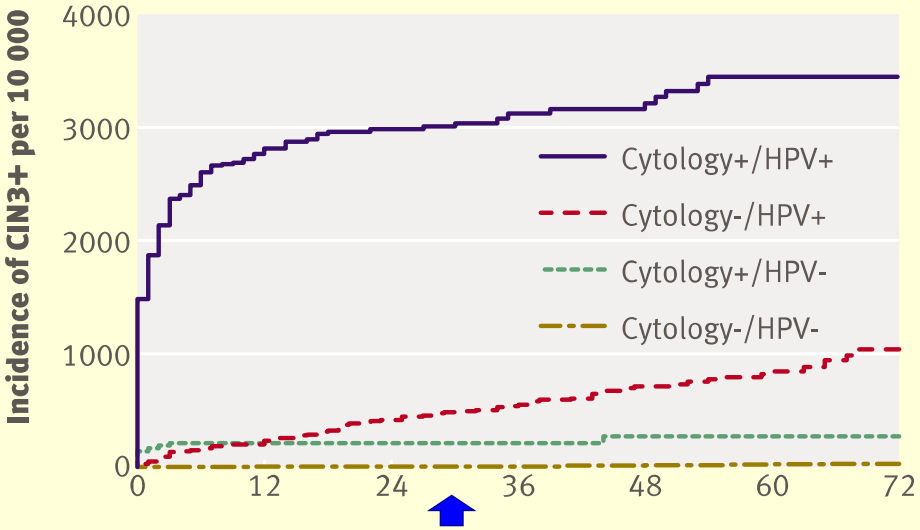
*Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

Modified from Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. CA Cancer J Clin 2012;62:147–72, with additional modifications based on Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

What is the role for cervical cancer screening with HPV testing alone?

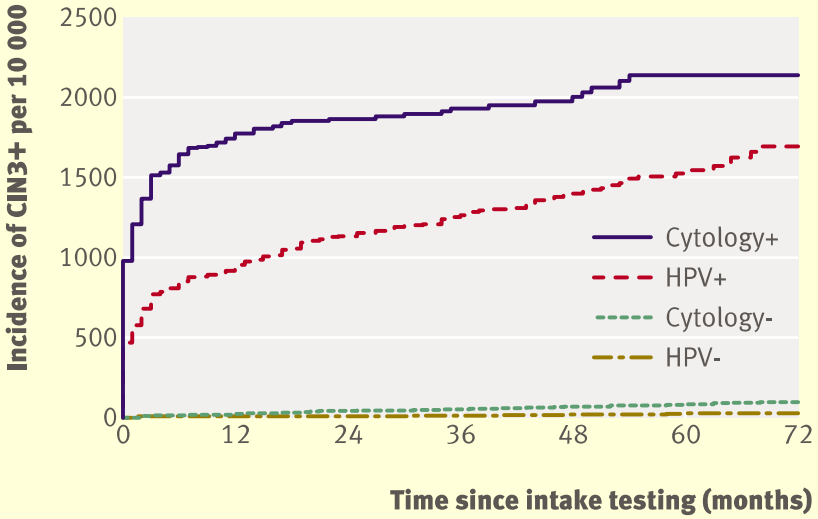
Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study

Joakim Dillner, professor,[1] Matejka Rebolj, researcher,[2] Philippe Birembaut, professor and head of department,[3] Karl-Ulrich Petry, professor,[4] Anne Szarewski, clinical consultant and honorary senior lecturer,[5] Christian Munk, researcher ,[6] Silvia de Sanjose, researcher,[7,9] Pontus Naucler, research fellow,[1] Belen Lloveras, researcher,[7] Susanne Kjaer, professor,[6,8] Jack Cuzick, professor and head of department,[5] Marjolein van Ballegooijen, professor,[2] Christine Clavel, professor,[3] Thomas Iftner, professor and head of section[10]



The cumulative incidence rate among women with negative cytology results who were positive for HPV increased continuously over time, reaching 10% at six years, whereas the rate among women with positive cytology results who were negative for HPV remained below 3%.

The cumulative incidence rate of CIN3+ after six years was 0.27%(CI 0.12%-0.45%) among women with negative for HPV at baseline but among women with negative results on cytology was 0.97%,(CI 0.53% to 1.34%)



BMJ 2008;377:a1754

Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test☆

Thomas C. Wright [a,*], Mark H. Stoler [b], Catherine M. Behrens [c], Abha Sharma [c], Guili Zhang [c], Teresa L. Wright [d]

Methods. 42,209 women ≥25 years were enrolled and had cytology and hrHPV testing. Women with abnormal cytology (≥atypical squamous cells of undetermined significance) and those HPV positive were referred to colposcopy. Women not reaching the study endpoint of CIN2+ entered the 3-year follow-up phase.

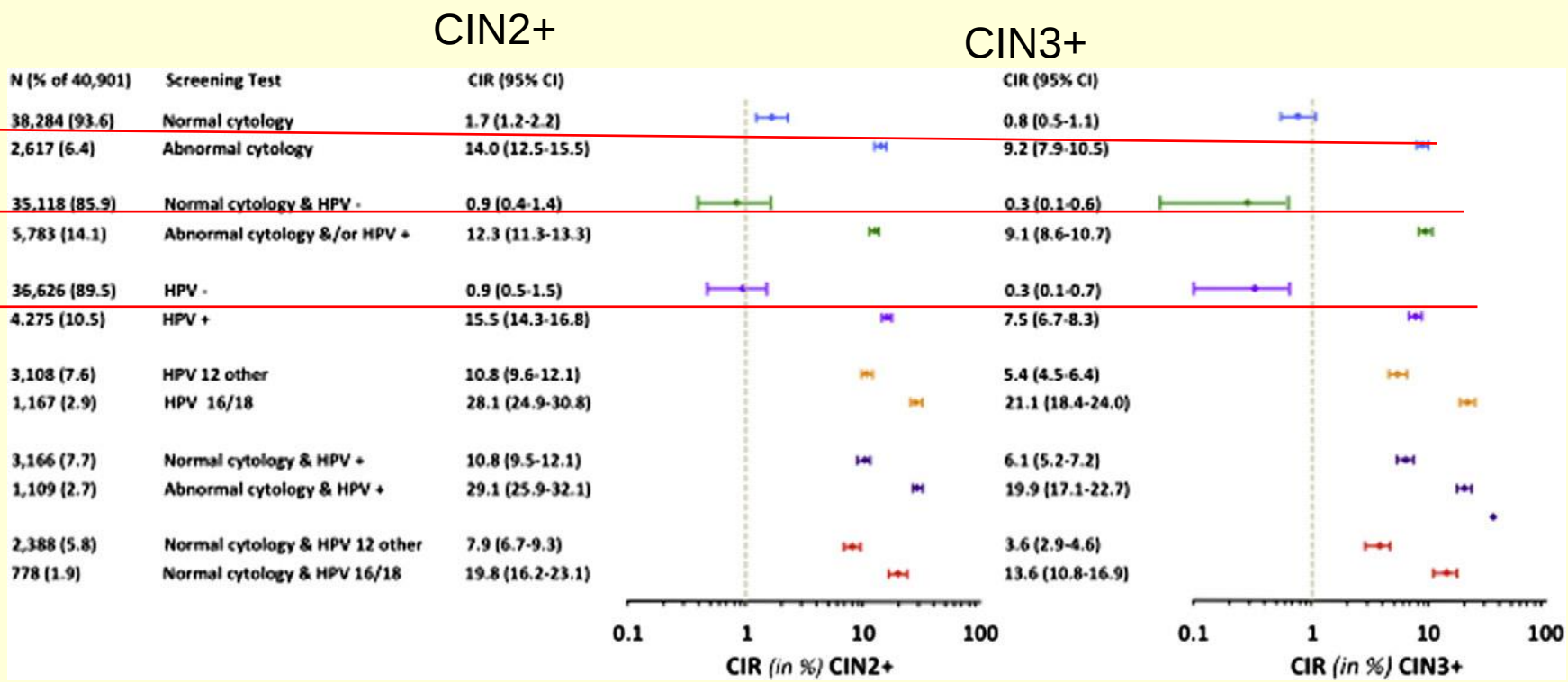


Fig. 3. Verification bias-adjusted (VBA) 3-year cumulative incidence rates of consensus pathology cervical intraepithelial neoplasia 2+ (CIN2+) and CIN3+ stratified by differe combinations of baseline cervical cytology and HPV results. Note the x-axis is logarithmic.

After 5 years of follow-up, the cumulative probability of CIN3+ was

0.17% in HPV-negative women and 0.16% in women

with negative results for both cytology and HPV in

Kaiser Permanente, Northern California.

Katki HA,. J Low Genit Tract Dis 2013

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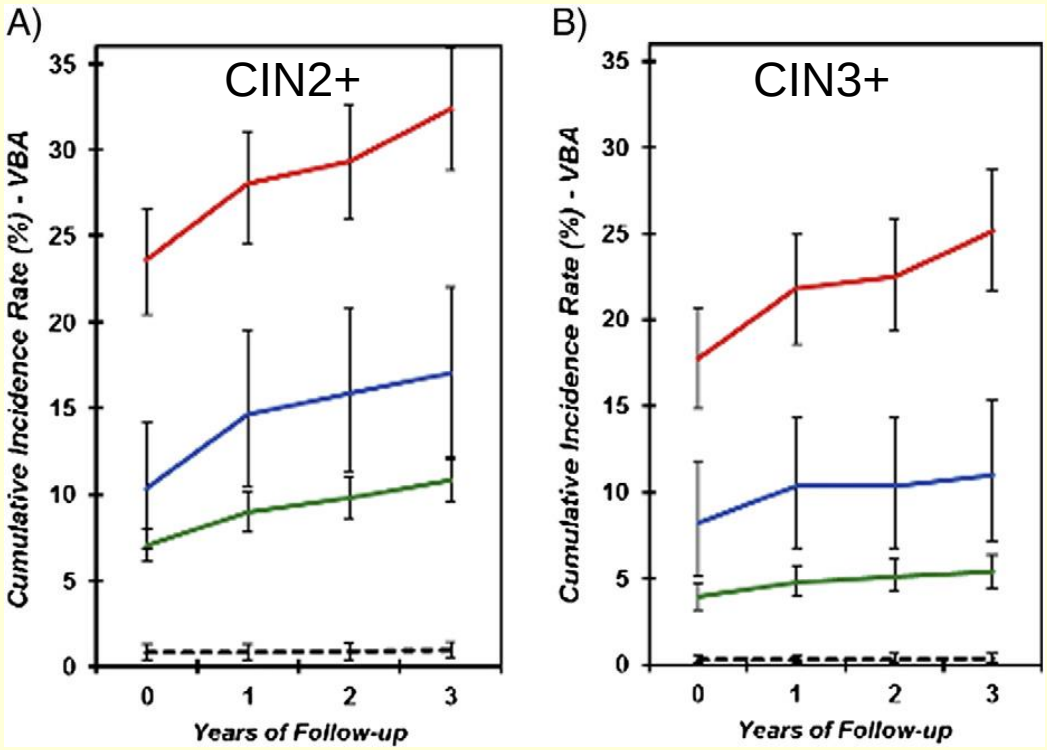


Fig. 2. Verification bias-adjusted (VBA) cumulative incidence of consensus pathology cervical intraepithelial neoplasia 2+ (CIN2+) (A) and CIN3+ (B) during 3 years of follow-up stratified by baseline human papillomavirus (HPV) status. Red solid line, HPV-16 positive; blue solid line, HPV-18 positive; green solid line, 12 other HPV genotypes positive; black dotted line, HPV-negative.

HPV testing alone

HPV-negative women

re-invited in 3-5 years

HPV-positive women

reflex cytology

to colposcopy if it is ASC-US or more

(X)

if cytology is normal women are re-invited for newHPV testing after 12 months and referred to colposcopy if still positive.

If the newHPV test is negative a new screening in 3- 5 years.

(X)
HPV type 16/18 positive, Cytology normal
Refered to colposcopy

Should administration of the HPV vaccine change how cervical cancer screening is performed?

BMJ Open

The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark

2015;5:e007921

Mie Sara Hestbech,[1] Elsebeth Lynge,[2] Jakob Kragstrup,[1] Volkert Siersma,[1] Miguel Vazquez-Prada Baillet,[2] John Brodersen[1]

Table 1 Efficacy of HPV vaccination on all-type cervical abnormalities in HPV-naïve women reported in the literature

Study	Study design	Setting/year	Study population (stratum of study population included)	Outcome measure reported	Reported vaccine efficacy, % reduction (95% CI)			
					ASCUS+	Any cervical biopsy	CIN2+	CIN3+
Munoz *et al*[27]	Randomised controlled trial	Multinational 2001–2006	16–26 years+several other criteria*	Rate ratio	17.1 (10 to 23)	22 (16 to 30)	42.7 (23.7 to 57.3)	43† (13.0 to 63.2)
Crowe *et al*[28]	Nested case–control study	Queensland, Australia 2007–2011	15–18 years in 2007, presenting for first smear, received all 3 doses of vaccine	OR	NA	NA	60 (44 to 70)‡	NA
Gertig *et al*[25]	Data linkage study	Victoria, Australia 2007–2011	≤17 years in 2007, had started cervical screening, received all 3 doses of vaccine	HR	NA	NA	39 (22 to 52)	47 (23 to 64)
Baldur-Felskov *et al*[36]	Cohort study	Denmark 2006–2012	14–15 years in 2008 (1993–1994 cohort), had a history of cervical cytology	HR	§	NA	67 (17 to 87)	75* 10 to 93)
Mahmud *et al*[37]	Cohort study	Manitoba, Canada 2006–2011	14–17 years in 2006–2010, had ≥1 Pap smear	HR	45 (32 to 56)	NA	NA	NA
Pooled estimate					32	22	49	47

*(1) Participants had 0–4 sex partners during their lifetime; (2) no history of abnormal Pap smear test; (3) no history of genital warts; (4) no genital wart detected at enrolment; (5) received at least one vaccination; (6) were seronegative; HPV 6, 11, 16 and 18 negative, and negative for 10 other HPV types at enrolment; (7) had a negative day 1 Pap smear test and (8) had any follow-up visit.

†The reported vaccine effect is on CIN3, not CIN3+. No cases of higher grade of severity are reported.

‡Relative risk calculated from reported data.

§Vaccine efficacy on 'atypia or worse' of 53% is not included in our pooled estimate, because this classification includes reactive changes.

ASCUS, Atypical Squamous Cells of Undetermined Significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NA, not applicable.

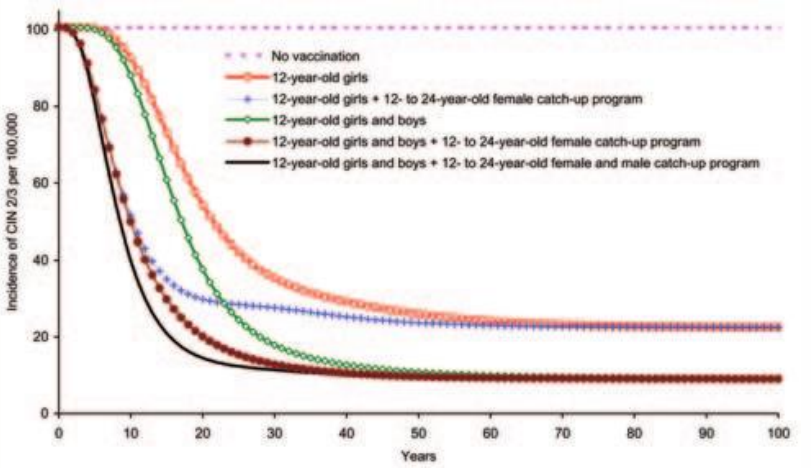


Figure 3. Incidence of cervical intraepithelial neoplasia (CIN) 2/3 due to human papillomavirus 6/11/16/18 infection among girls and women ≥12 years of age, by vaccination strategy.

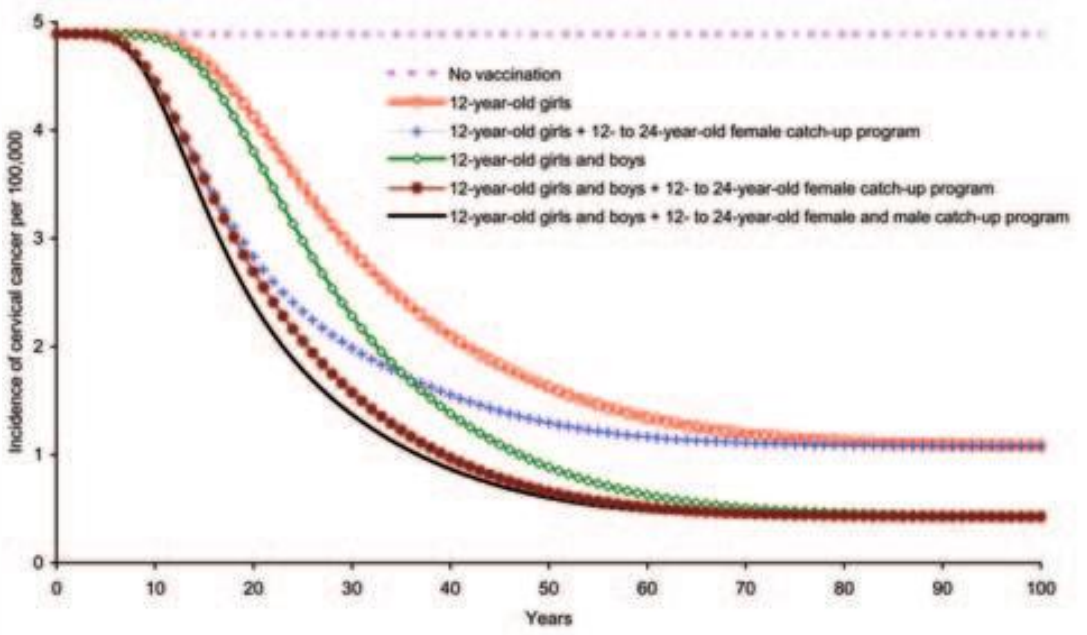


Figure 4. Incidence of cervical cancer due to human papillomavirus 16/18 infection among girls and women ≥12 years of age, by vaccination strategy.

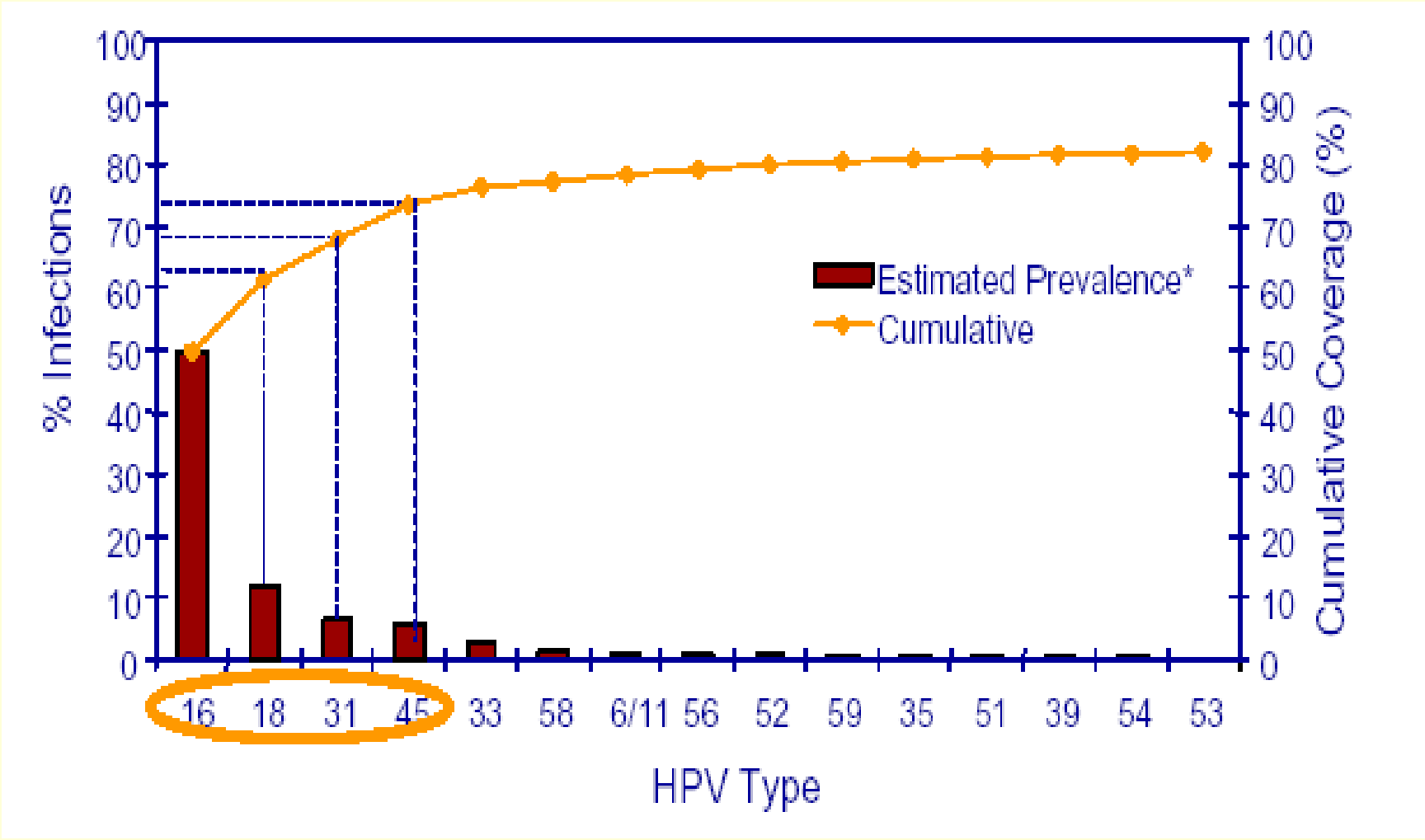
Elbasha EH,.Emerg Infect Dis 2007

1. Bivalent vaccine, which covers HPV-16 and HPV-18;

2. Quadrivalent vaccine, which in addition to HPV-16 and HPV-18 also covers HPV-6 and HPV-11

3. 9-valent vaccine

High risk HPV types and related CIN and cervical cancer



Schiffman, J Nat Cancer Inst, 85:958, 1993 and Liaw, J Nat Cancer Inst, 91:954, 1999

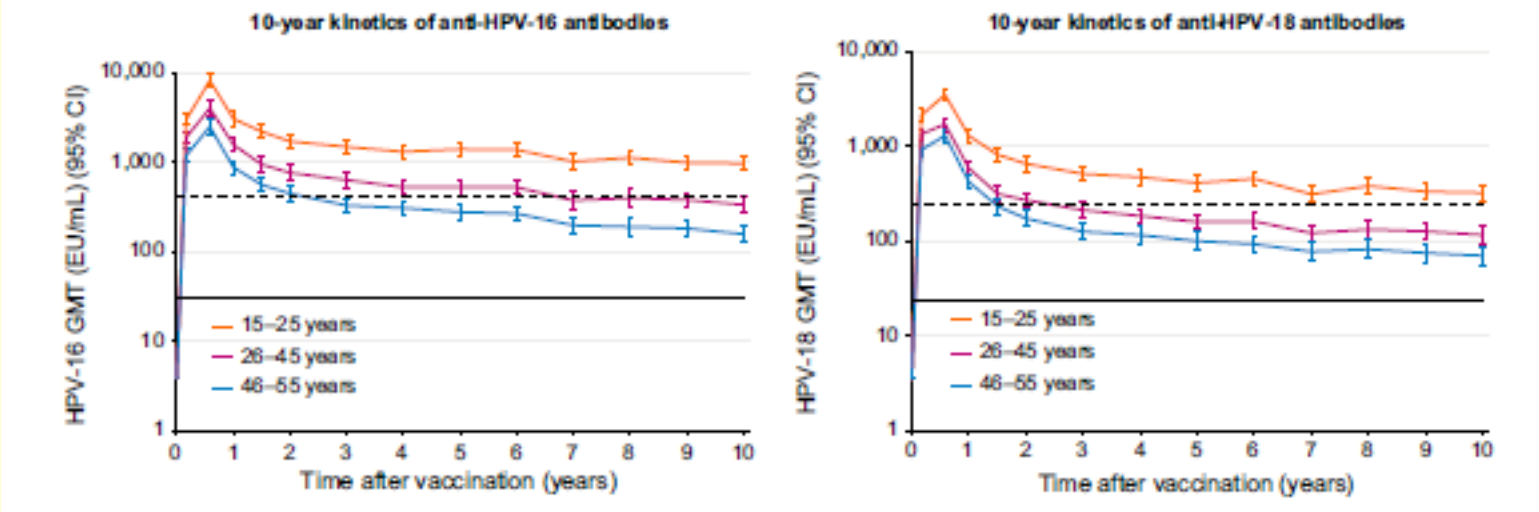
Cancer Medicine

Open Access

ORIGINAL RESEARCH

Ten-year immune persistence and safety of the HPV-16/18 AS04-adjuvanted vaccine in females vaccinated at 15–55 years of age

Tino F. Schwarz[1], Andrzej Galaj[2], Marek Spaczynski[3], Jacek Wysocki[4], Andreas M. Kaufmann[5], Sylviane Poncelet[6], Pemmaraju V. Suryakiran[7], Nicolas Folschweiller[8], Florence Thomas[8], Lan Lin[8] & Frank Struyf[8]



Cancer Medicine 2017; 6(11):2723–2731

Aditional issues

The rate of vaccine administration is far from 100%,

It often is difficult to ascertain who has been vaccinated or who has received all three doses of the vaccine

Long-term efficacy of the vaccine remains incompletely established.

Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated.

Screening with Cytology

In vaccinated women cytology will have a lower positive predictive value (PPV) for CIN2+ in vaccinated women

..due on on the strong reduction in prevalence of CIN2+ among vaccinated women.

..depending on the lower prevalence of infections by high-risk HPV types and on the lower risk of progression to CIN2+ of infections from non-HPV16/18 genotypes.

..are false positive cytological abnormalities caused by low risk HPV infections

Reduced sensitivity of cytology

Palmer TJ,BJC,2016

BMJ Open

The impact of HPV vaccination on future cervical screening: a simulation ' two birth cohorts in Denmark

2015;5:e007921

ch,[1] Elsebeth Lynge,[2] Jakob Kragstrup,[1] Volkert Siersma,[1]
-Prada Baillet,[2] John Brodersen[1]

ABSTRACT

Objectives: To explore the interplay between primary and secondary prevention of cervical cancer by estimating future screening outcomes in women offered human papillomavirus (HPV) vaccination when they were sexually naïve.

Design: Estimation of outcome of liquid-based cytology screening for a post-HPV vaccination cohort using pre-vaccination screening data combined with HPV vaccination efficacy data reported in the literature.

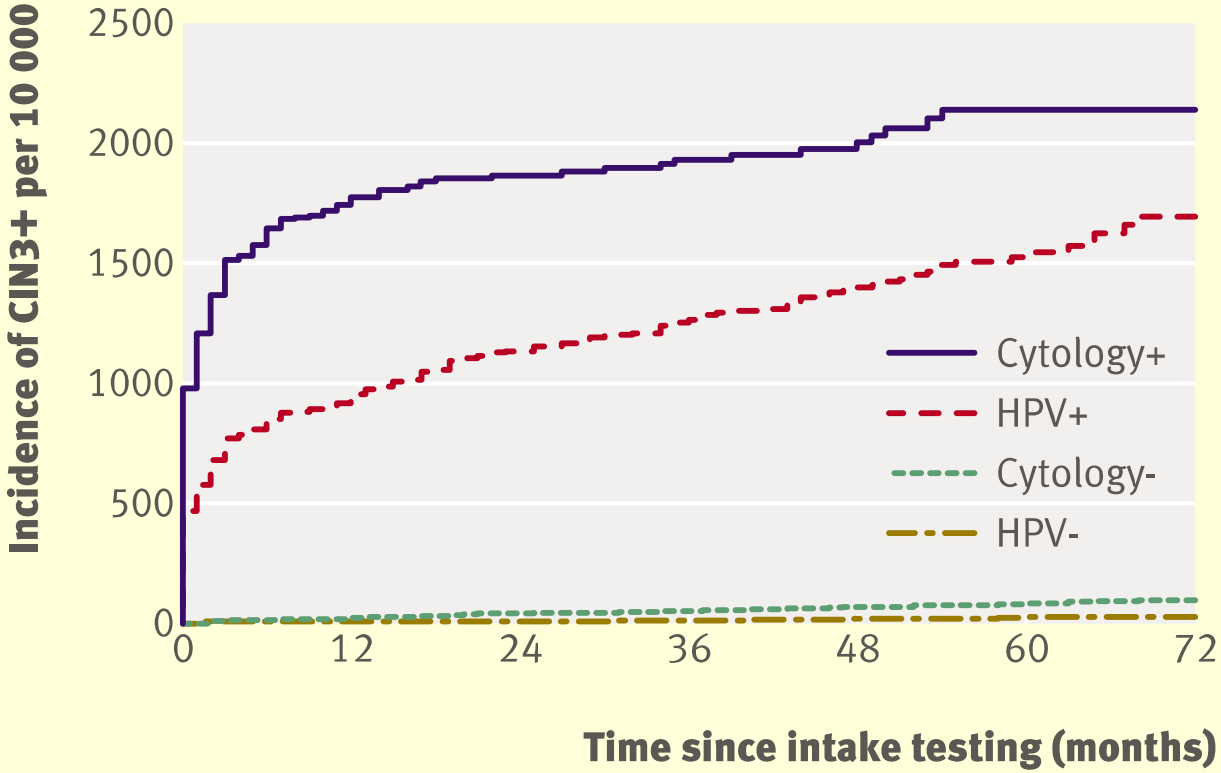
Setting: Denmark.

Data: The number of screening diagnoses at first screen in a pre-vaccination birth cohort was multiplied from 5.5% pre-vaccination to 4.3% post-vaccination,

Results: The proportion of positive screening tests was reduced from 8.7% before vaccination to 6.5% after vaccination, and the proportion of false-positive screening tests using CIN2+ as a cut-off was reduced from 5.5% pre-vaccination to 4.3% post-vaccination, and using CIN3+ as a cut-off from 6.2% to 4.7%. PPVs were reduced from 23% to 19% (cut-off CIN2+), and from 14% to 12% (cut-off CIN3+).

Conclusions: In our calculations, the proportion of positive screening results with liquid-based cytology will be reduced as a consequence of HPV vaccination, but the reduction is small, and the expected decline in PPV is very limited. In this situation, the information general practitioners will have to provide to their patients will be largely unchanged.

For the screening of a vaccinated population, HPV testing alone may be reasonable



BMJ 2008;377:a1754

When and which interval?

> 30 years

Screening intervals longer than the current ones will be safe in vaccinated women

Thank you