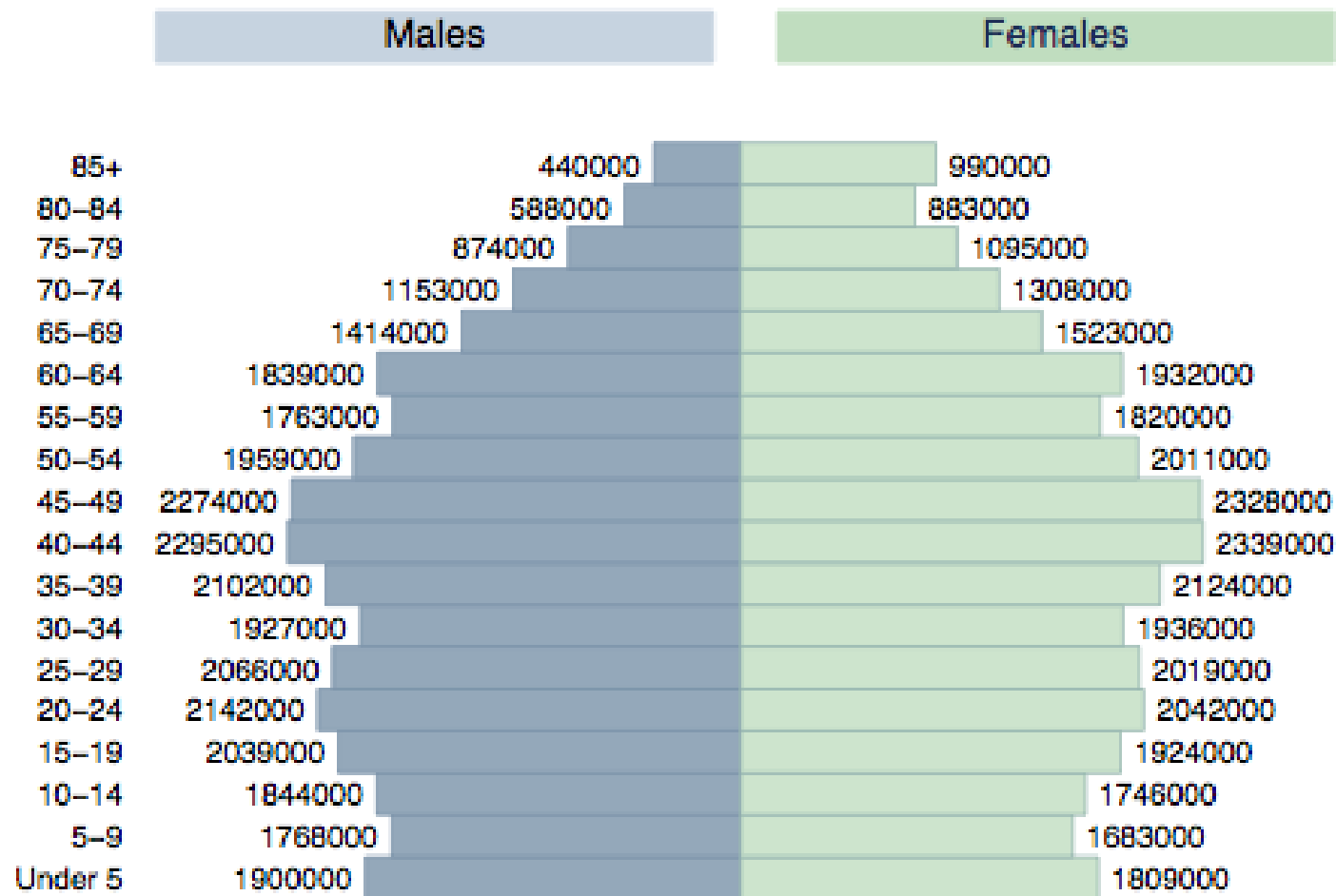


Role of HPV in Cervical Screening

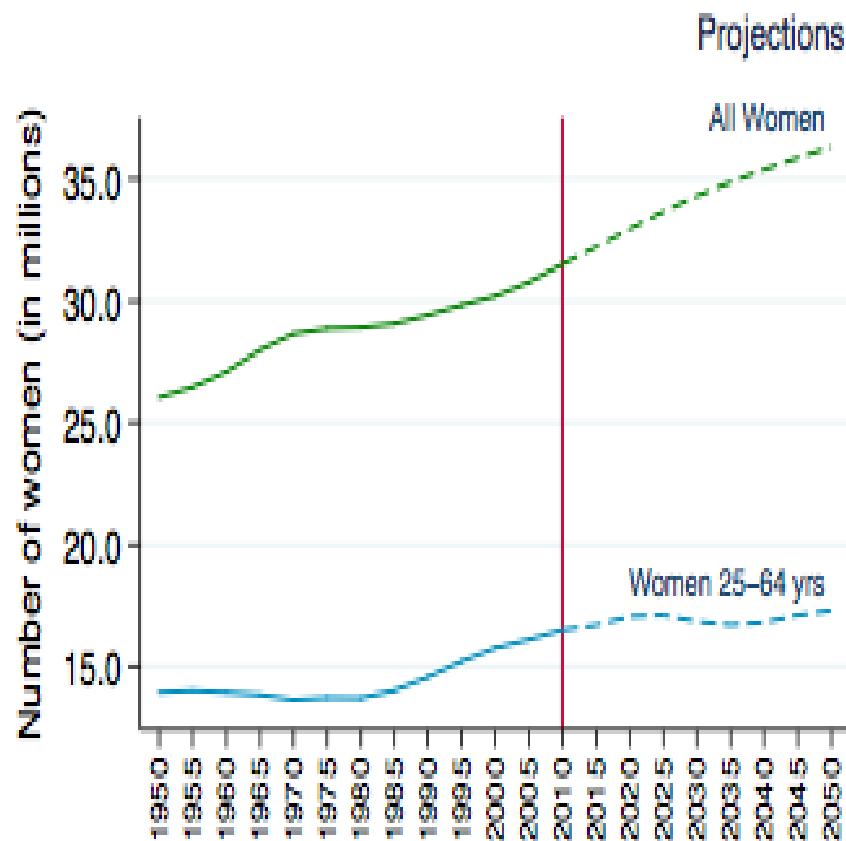
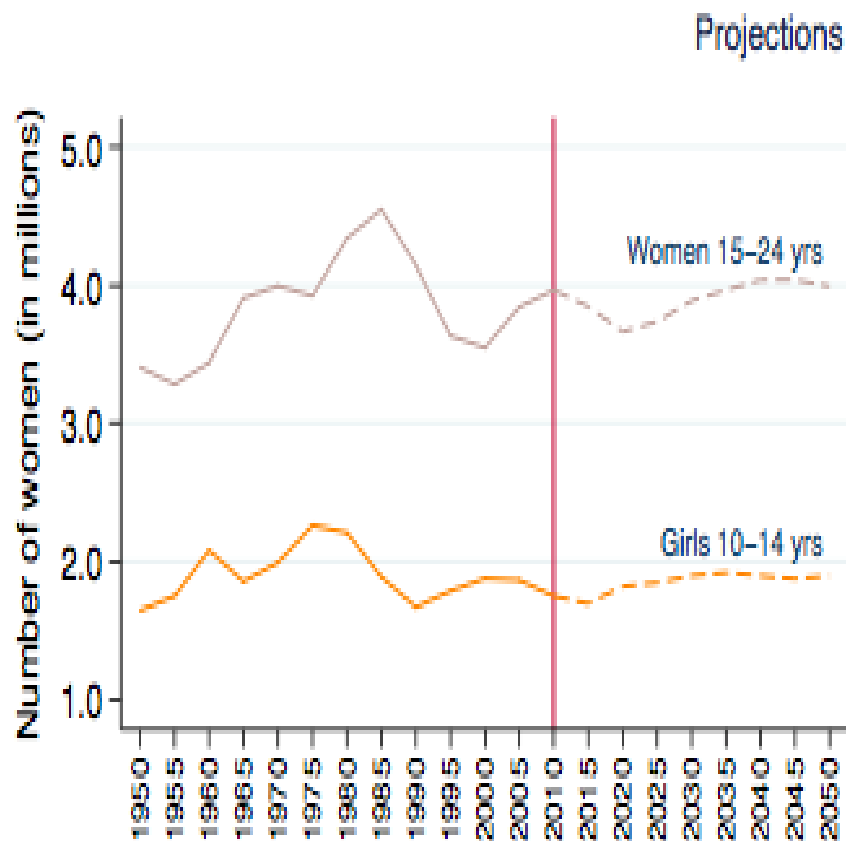
Mr Nick Nicholas MD FRCOG
Lead Colposcopist

Figure 2: Population pyramid of United Kingdom



Population of United Kingdom by sex and age group

Figure 3: Population trends of four selected age groups in United Kingdom

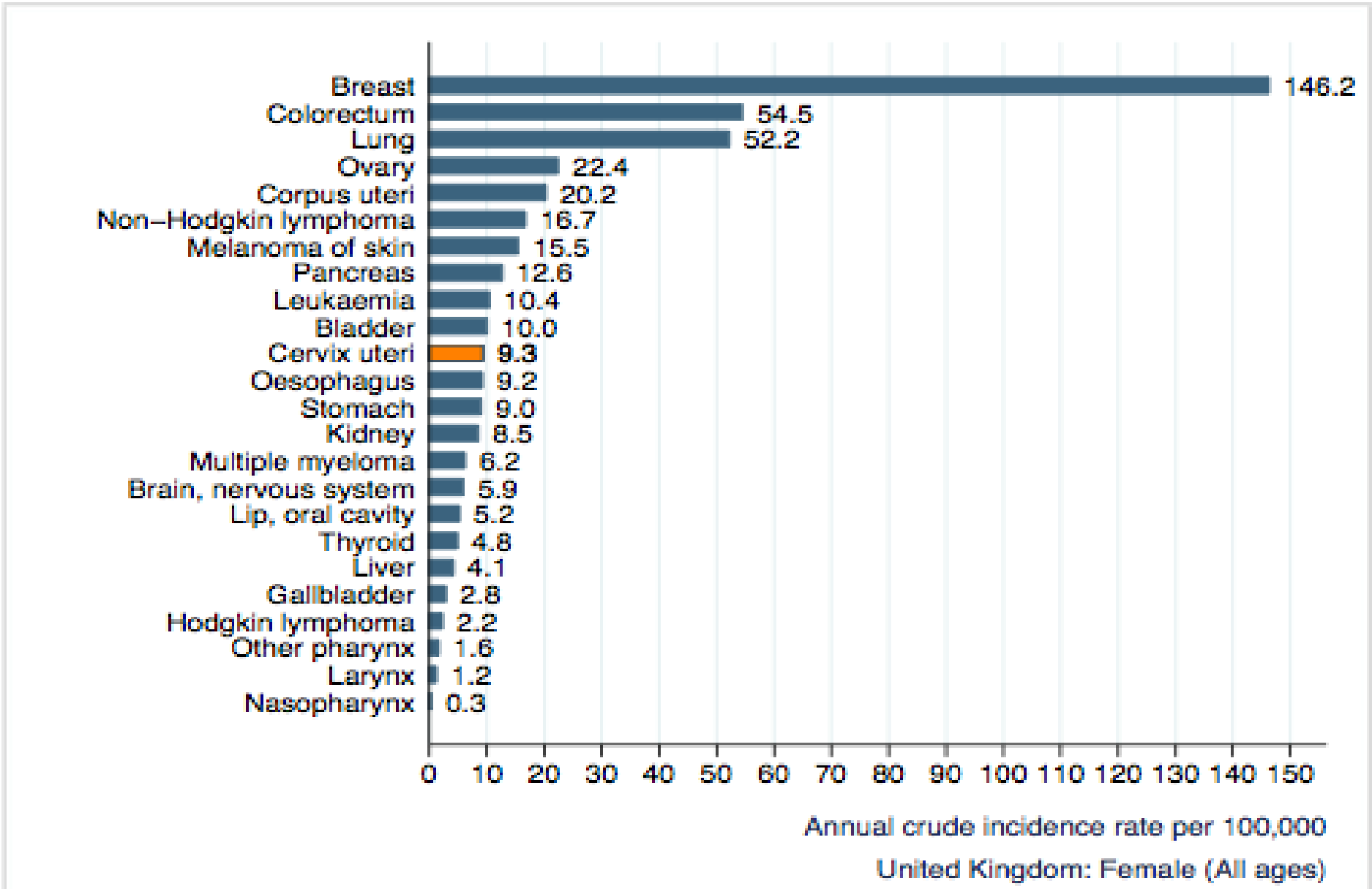


Female population trends in United Kingdom
Number of women by year and age group

Population in thousands. Data sources:

World population prospects: the 2008 revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2009.

Figure 4: Incidence of cervical cancer compared to other cancers in women of all ages in United Kingdom



How often should you take a smear?

<u>Age group(years)</u>	<u>Frequency of screening</u>
25	First invitation
25–49	Three yearly
50–64	Five yearly
65+	Only screen those who have not been screened since age 50 or who have had recent abnormal tests

Risk Factors for Cervical Cancer

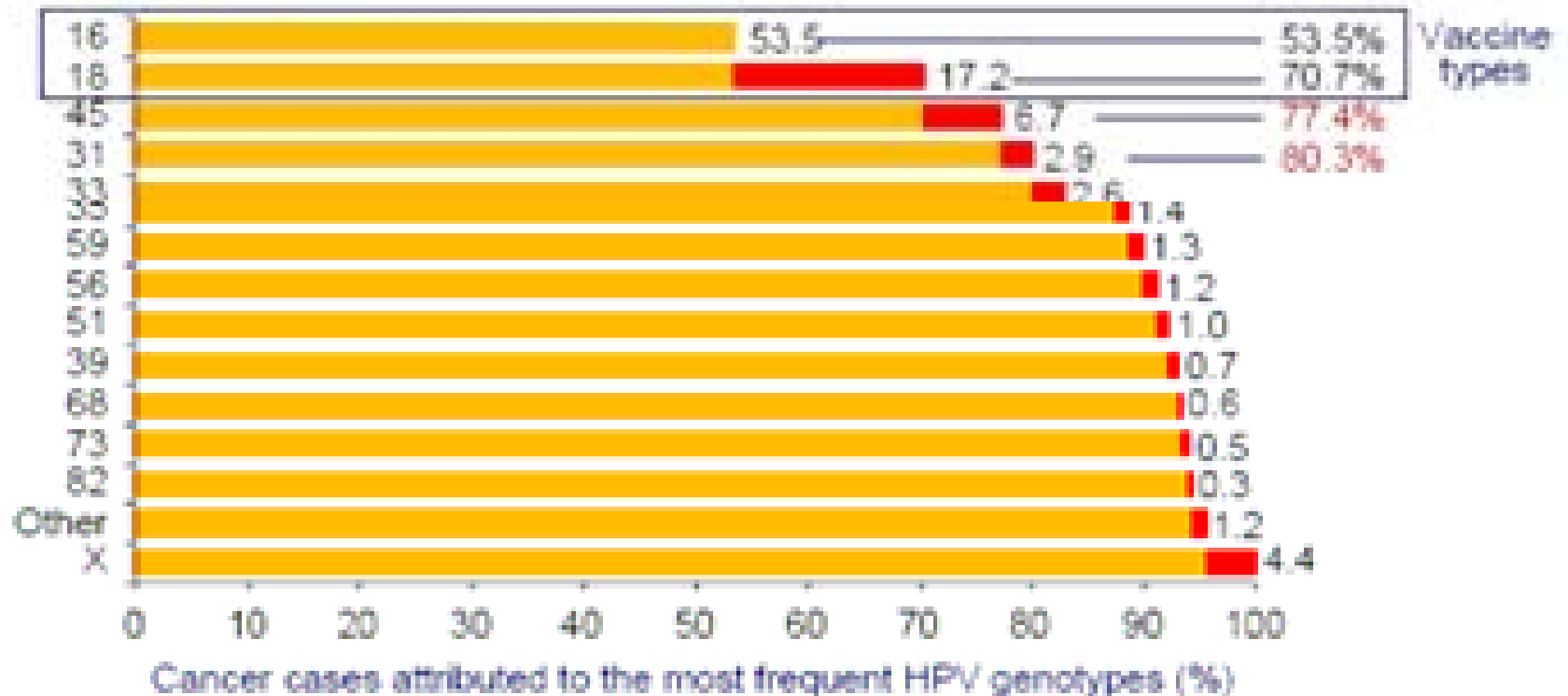
- HPV infection
 - Recent infection, persistent infection
 - # of sexual partners
 - Age of onset of sexual activity
- Smoking
- Dietary factors
- Lack of physician contact
 - >50% women who develop cervical cancer have never had pap smears or no pap in > 5 years
- Race and ethnicity
- Socioeconomic status
- Immunocompromised state
 - Promotes persistent HPV infectious state

Human Papilloma Virus (HPV)

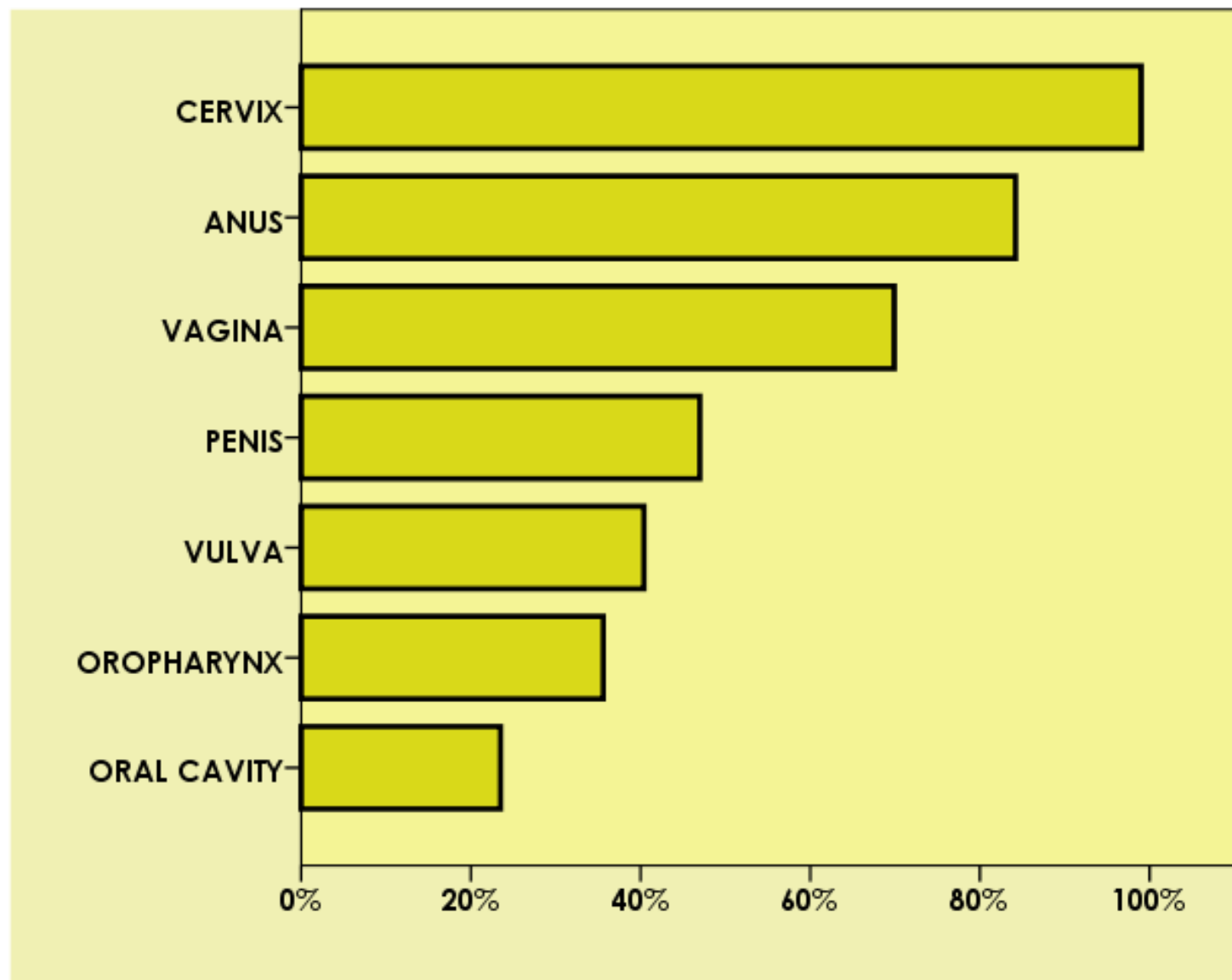
- There are over 100 subtypes of HPV. Most do not cause significant disease.
- The high risk HPV subtypes are 16, 18, 31 & 33 – types 16 & 18 are found in 70% of cervical cancers. Non oncogenic types are 6 & 11, which cause visible genital warts.
- Transient HPV is common especially in women under 35 years.
- It persists in 20-30% of women putting them at increased risk of developing cervical cancer.
- Women or their partners may have had HPV for many years without knowing it.
- There is no reliable treatment to clear the virus.

HPV Types in Cervical Cancer Worldwide

HPV genotype



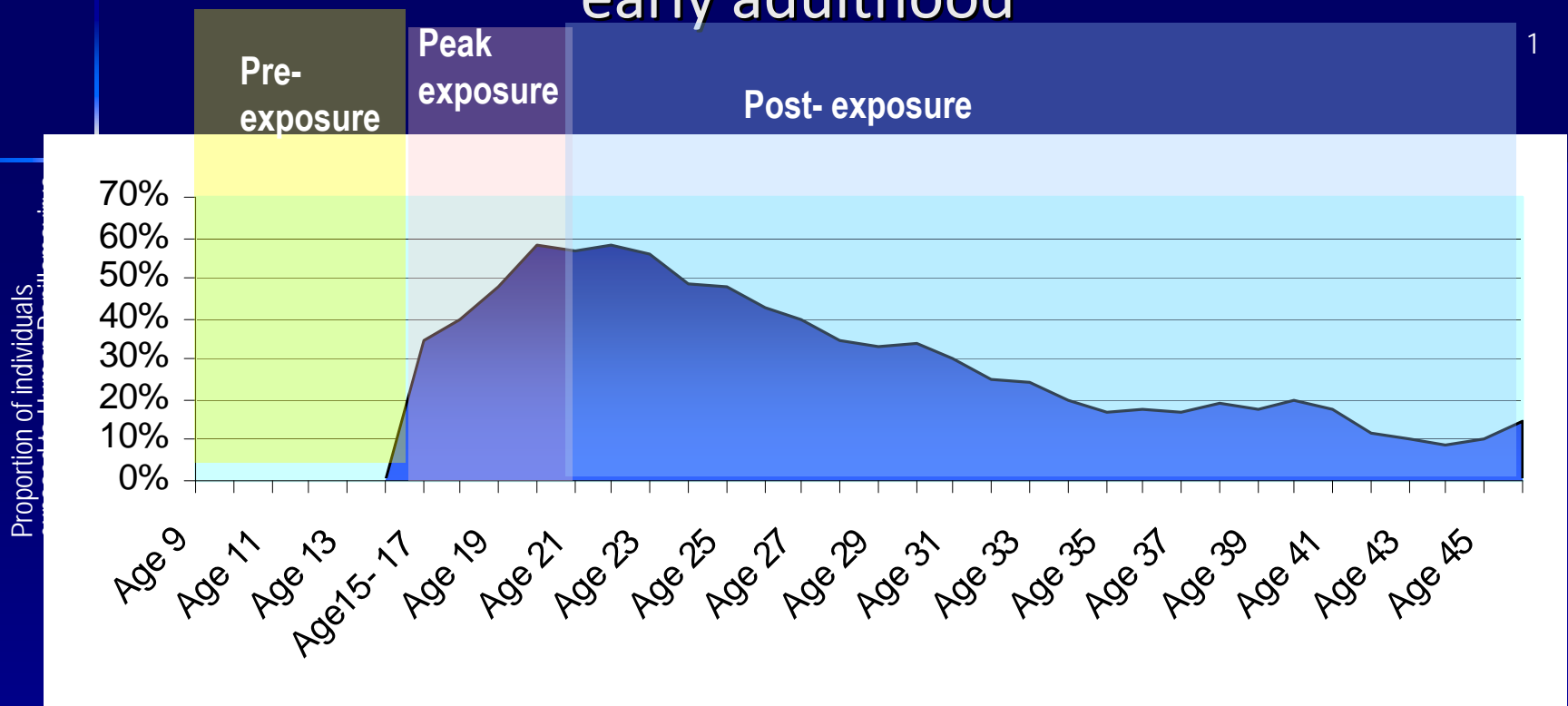
HPV and Cancer



HPV Infection

- 75 - 80% of sexually active adults will acquire a genital tract HPV infection before the age of 50
- Can be detected in 99.7% of all cervical cancers
- 15 genotypes are considered oncogenic
- 2 most common: 16, 18 are found in >70% of all cervical cancers
- Increases risk of HG disease by 250x
- Causative factor in squamous cell cancers of multiple sites:
 - cervical, anal, vulvar, penile, oropharyngeal
- HPV 6 and 11 responsible for ~80% of genital warts

HPV - a common virus encountered in adolescence and early adulthood



- An estimated 70% of sexually active people will be exposed to the virus at some point during their life^{2,3,4}
- Infection is very common^{2,3,4}
- The majority of Human Papillomavirus infections occurs early in adolescence or adulthood^{2,3,4}

[1] Sanofi Pasteur MSD, data on file.

[2] Koutsky LA. Am J Med 1997

[3] Koutsky LA et al. Epidemiology Rev 1988

[4] Syrjänen K et al. Sex Transm Dis 1990

Natural History of CIN

	Regress	Persist	Progress To CIN3	Progress to Invasion
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	56%		>12%

THE GOOD NEWS

- Vast majority clear the virus or suppress it to levels not associated with CIN 2/3+, and for most women this occurs promptly
- The duration of HPV positivity is shorter and the likelihood of clearance is higher in younger women
- Only 1 in 10 to 1 in 30 HPV infections are associated with abnormal cervical cytology

MORE GOOD NEWS

- Only 15% of women with negative cytology reports and positive HPV will have abnormal cytology within 5 years
- The risk of cervical cancer in women who do not harbour oncogenic HPV is extremely low
- The time course from CIN 3 to invasive cancer averages between ***8.1 and 12.6 years***

Natural History

- Currently no “cure” for genital HPV infection, most cases are transient and clear themselves without medical intervention.
- Approximately 80% of all HPV infections in women between the ages of 15 and 25 years are transient.
- Repeated HPV DNA testing showed that 70 percent of the women cleared their HPV infections within one year through the natural immune process, and only 9% were still infected after 2 years.
- Another study conducted in Sweden supported these findings, with a five-year clearance rate of 92 percent (Elfgren, et al., 2000).

HPV Infection

- Duration of incubation period unclear
- Immunologic clearance of HPV infection
 - 50% of patients at 15 months*
 - 80% at 2 years*
- **Persistence** of infection is the greatest risk of progression to cancer.
 - Older cross-sectional studies showed progression rate at 5-15 years
- Recent longitudinal studies suggest 7-20% of new infection showing progression to CIN 2 or 3 over 36 months.

TYPE OF TESTING

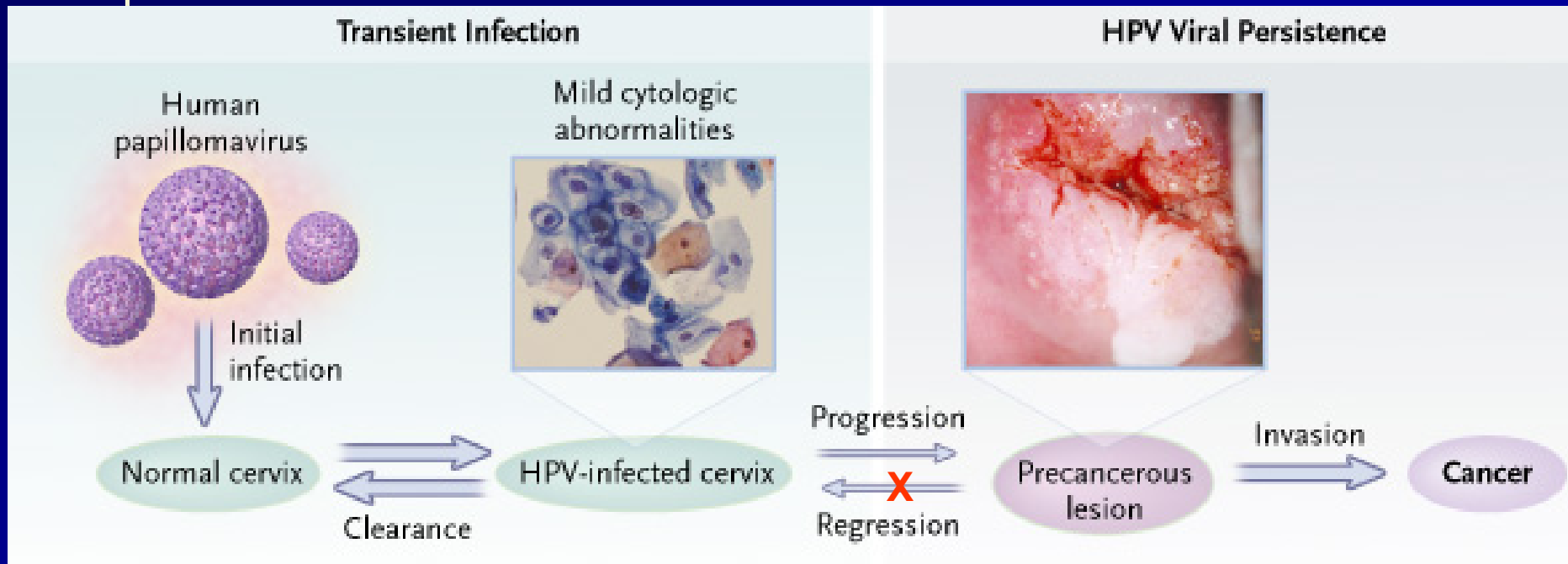
- Cytology vs. Cytology + HPV testing
 - Cytology alone low sensitivity
 - Cytology + HPV testing much higher sensitivity
 - HPV testing especially helpful in patients > 30 years old

HPV Persistence

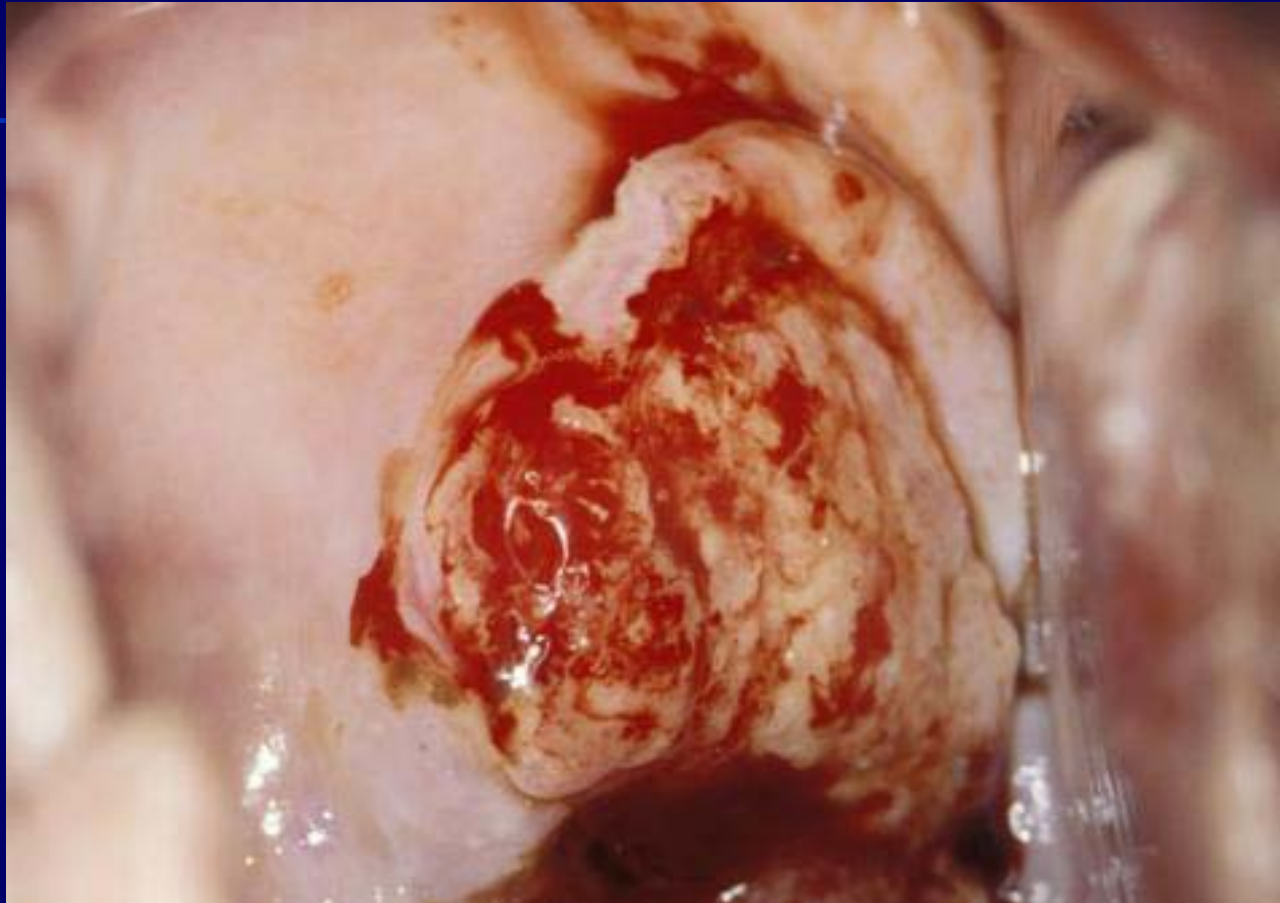
- Persistence of HR types of HPV is crucial for development of cervical precancer and cancer.
- Other associated factors:
 - Age * (≥ 30 years)
 - Infection with multiple HPV types
 - Immune suppression
- Currently, no antivirals available to treat the underlying HPV infection

1. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr.* 2003;31:14–19. 2. Hildesheim A, Schiffman MH, Gravitt PE, et al. *J Infect Dis.* 1994;169:235–240. 3. Ho GYF, Burk RD, Klein S, et al. *J Natl Cancer Inst.* 1995;87:1365–1371. 4. Kobayashi A, Greenblatt RM, Anastos K, et al. *Cancer Res.* 2004;64:6766–6774. 5. Stanley M. *J Natl Cancer Inst Monogr.* 2003;31:117–124.

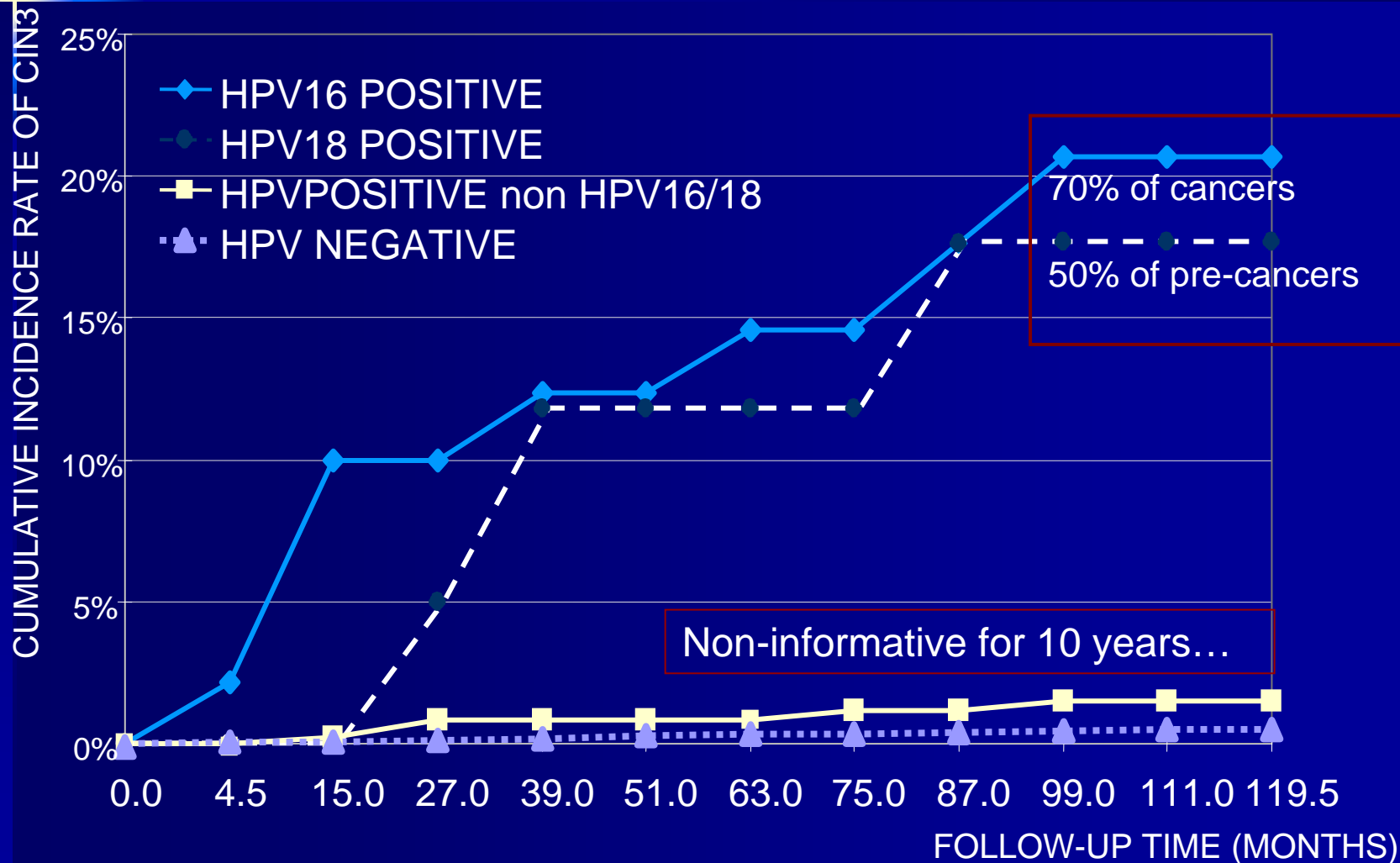
Molecular Pathology Model of Cervical Cancer



HPV-Associated Malignant Disease 5% of ALL cancers

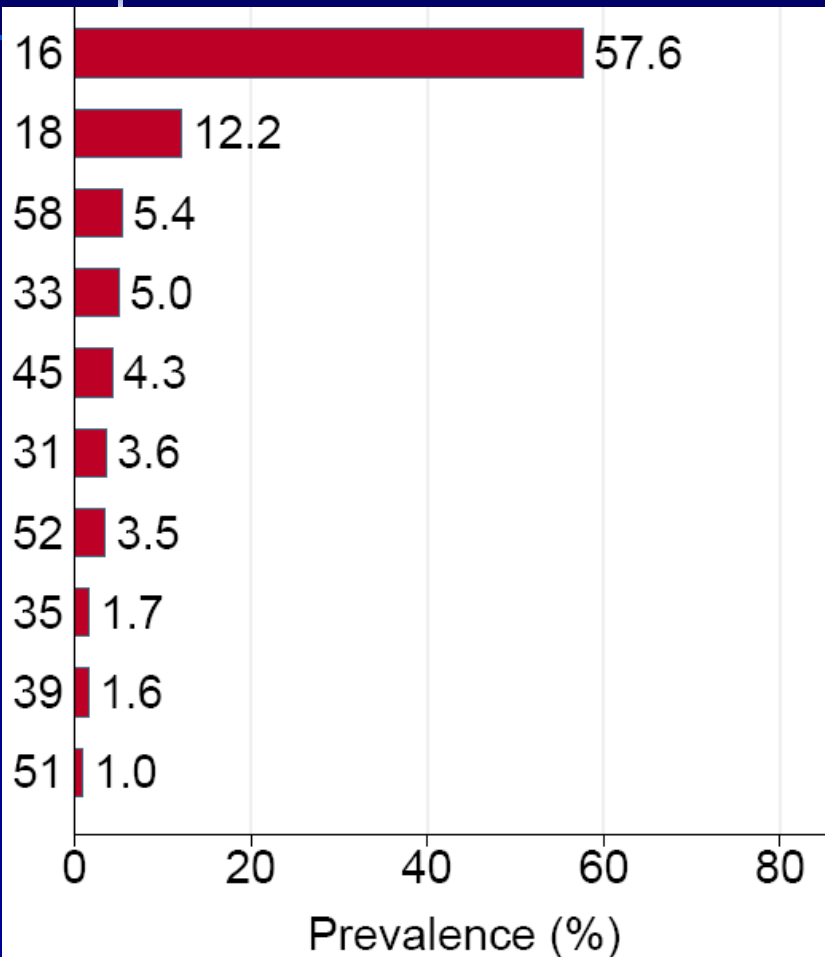


The cumulative incidence of cin3+ in 13,229 women over a ten year period by single HPV test result at enrolment

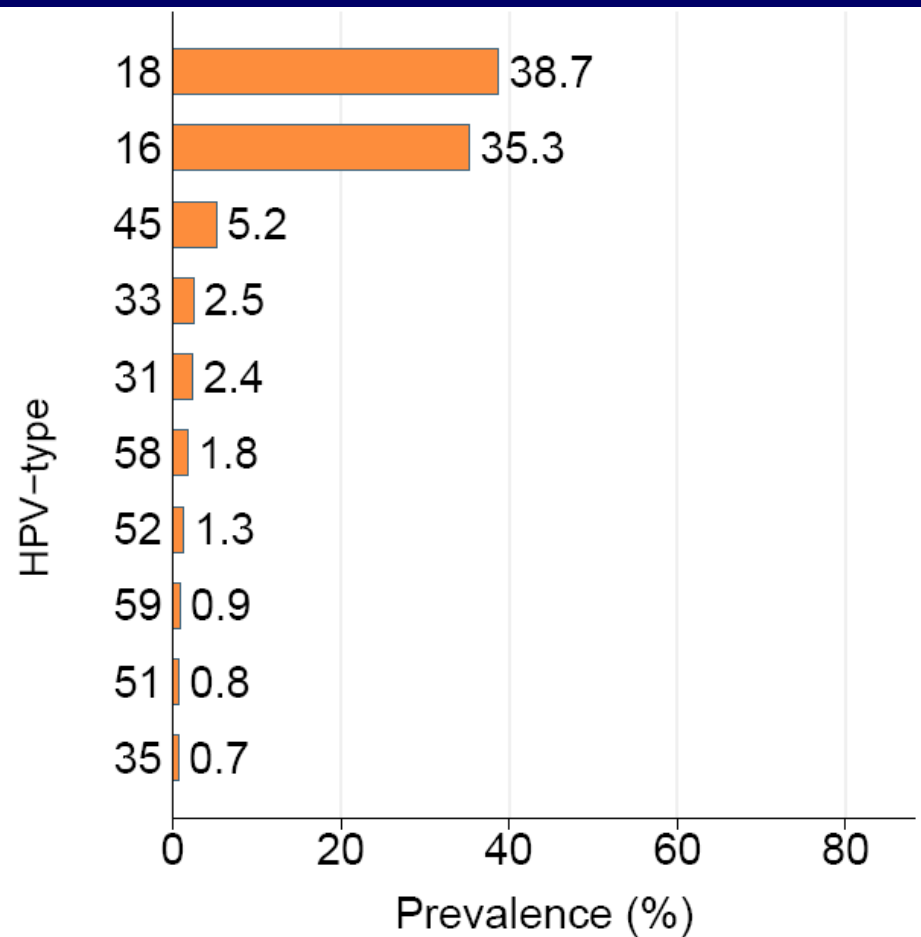


TEN MOST FREQUENT HPV TYPES AMONG CERVICAL CANCER CASES WORLDWIDE BY HISTOLOGY

SQUAMOUS CELL CARCINOMA



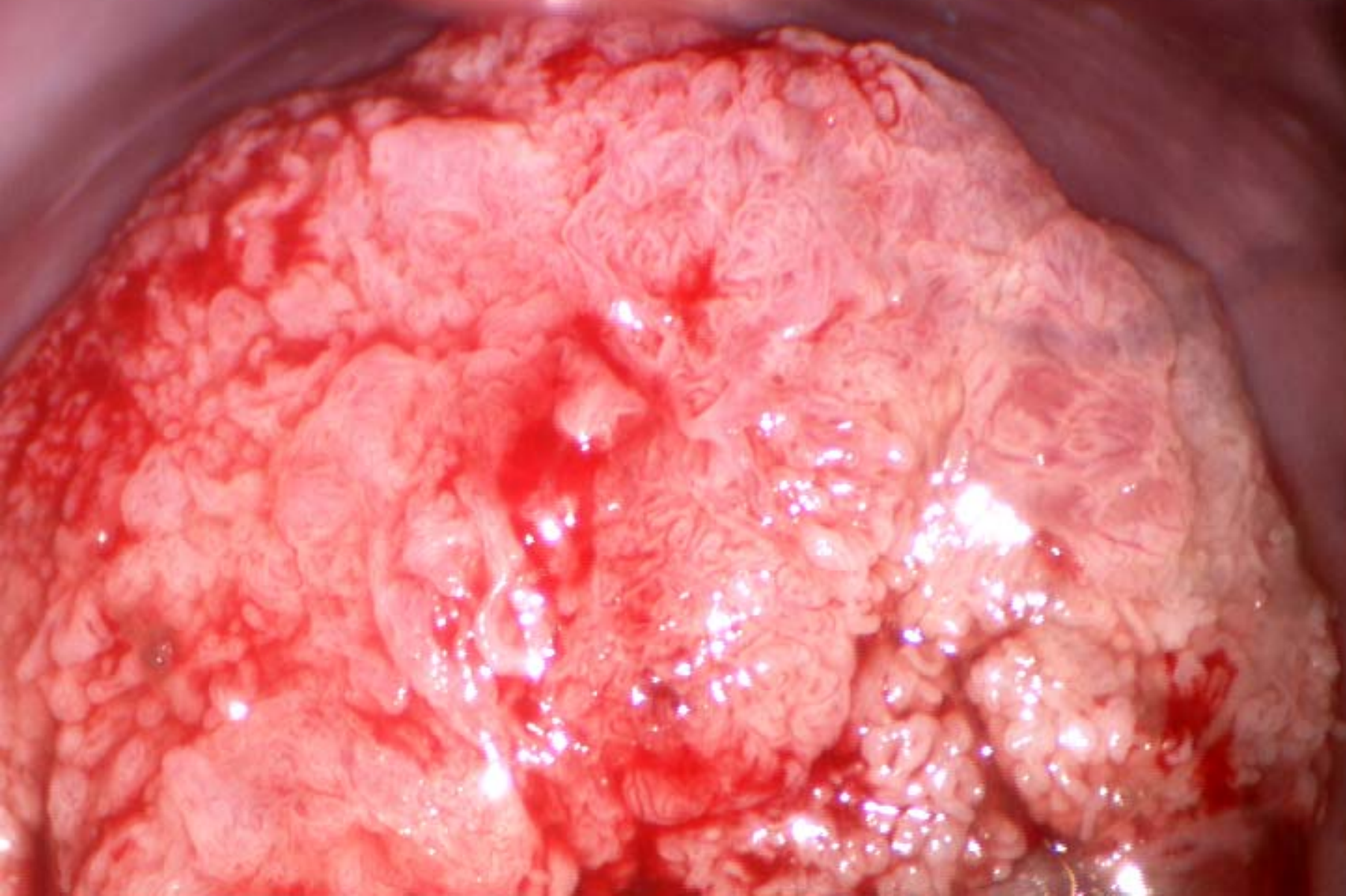
ADENOCARCINOMA



C8101205
AC-LOWER



D9051005
AC-UPPER



Biopsy in Diagnosing Women with CIN 2 or Worse

• Colpo biopsy	208/364 (57.1%)
• Colpo biopsy + 2 o'clock	256/364 (70.3%)
• Colpo biopsy + 2, 4 o'clock	297/364 (81.6%)
• Colpo biopsy + 2, 4, 8 o'clock	329/364 (90.4%)
• Colpo biopsy + 2, 4, 8, 10 o'clock	344/364 (94.5%)
• Colpo biopsy + 2, 4, 8, 10 + ECC 3	64/364 (100%)

57.1% vs. 70.3% vs. 81.6% vs. 90.9% vs. 94.5% vs. 100%,
Chi-Square = 326, df=5, P<.001

Pretorius et al, Int J Cancer, 2007

Conclusion of study

Regardless of colposcopic skill, performing 4 random biopsies plus Endo Cervical Curettage (ECC) increases the yield of CIN3+ per colposcopy !!!

Putting risk into perspective:

- Risk of cervical cancer if HPV 16 (+) positive compared to HPV 16 (-) is 434
- Risk of lung cancer in U.S. white male smoker compared to non-smoker is only 8
- *Risk of breast cancer with HRT in Women's Health Initiative only 1.3*

HPV-DNA Testing?

1. **Primary screening** for cervical neoplasia
2. In **triage** of minimally abnormal and inconclusive smears ie **ASCUS / Borderline (5-7%)**
3. As a **test of cure**

1. Use of HPV DNA test

As a primary screening

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 18, 2007

VOL. 357 NO. 16

Human Papillomavirus DNA versus Papanicolaou
Screening Tests for Cervical Cancer

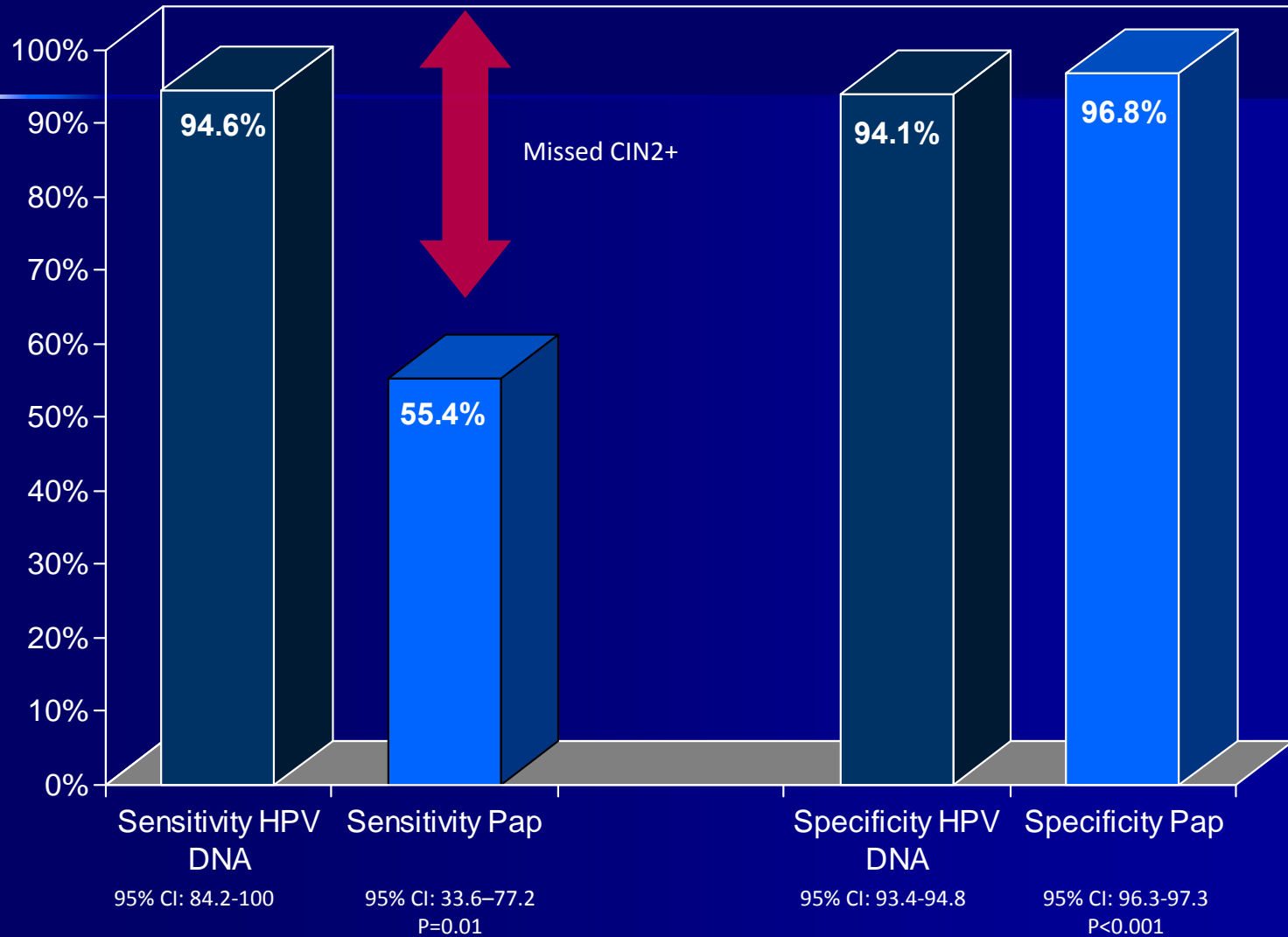
Marie-Hélène Mayrand, M.D., Eliane Duarte-Franco, M.D., Isabel Rodrigues, M.D., Stephen D. Walter, Ph.D.,
James Hanley, Ph.D., Alex Ferenczy, M.D., Sam Ratnam, Ph.D., François Coutlée, M.D.,
and Eduardo L. Franco, Dr.P.H., for the Canadian Cervical Cancer Screening Trial Study Group*

*Canadian Cervical
Cancer Screening
Trial (CCCaST)*

- 10,456 women 30-69 yrs of age seeking screening in Montreal or St. Johns
- *Had BOTH digene HPV Test & conventional cytology*
- Women positive on either test had colposcopy

Comparison of HPV DNA to Pap

N Eng J Med, 2007: Canadian Cervical Cancer Screening Trial (CCCaST)

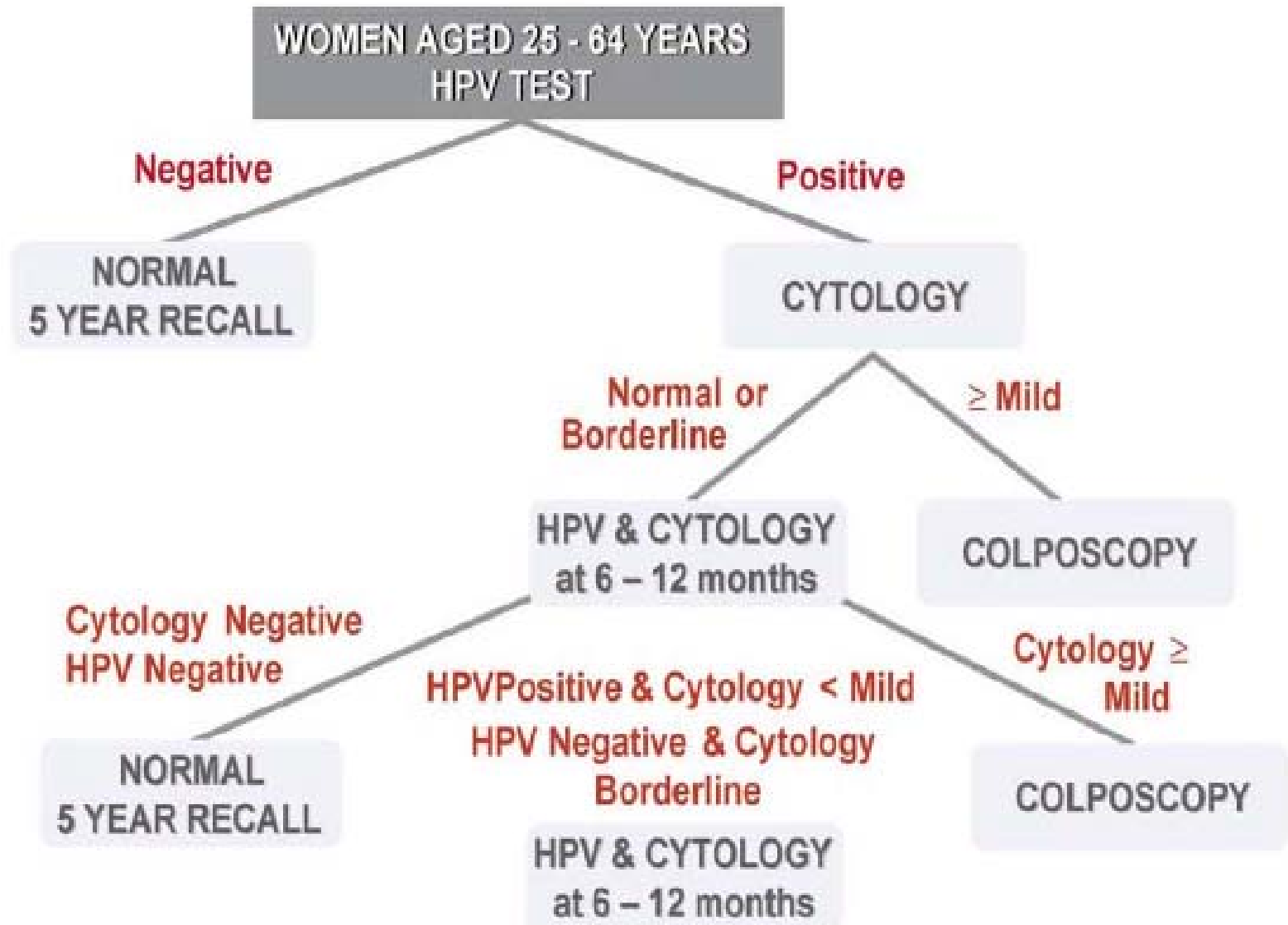


ARTISTIC TRIAL: A Randomised Trial of HPV Testing in Primary Cervical Screening

Kitchener et al HTA 2009 Vol 13:no 51

- The trial reported:
 - No significant psychosocial impact of adding HPV testing to cervical cytology
 - No clear evidence of effectiveness of HPV as a stand-alone test
 - HPV of value as a triage with LBC

POSSIBLE ALGORITHM FOR THE USE OF HPV TESTING AS THE SOLE PRIMARY SCREENING MODALITY FOR WOMEN AGES 25-64, FOLLOWED BY PAP TRIAGE OF HPV POSITIVE WOMEN



2. Use of HPV DNA test

Triage of
Borderline/ASCUS smears

ASCUS-LSIL Triage Study (ALTS)

- The trial compared 3 management strategies for ASCUS Pap smears:
- reflex HPV-DNA testing (the initial Pap sample is tested for HPV only if the results are ASCUS),
- immediate referral for colposcopy,
- and repeat Pap smears

ASCUS-LSIL Triage Study (ALTS)

- *Reflex HPV testing -sensitivity of 96% for detecting HSIL and a negative predictive value of 98%.*
- The 44% of women with ASCUS who tested negative for high-risk HPV were able to avoid colposcopy.
- A single repeat Pap smear within 4 to 6 months, with referral for colposcopy if abnormal, had a sensitivity of 85% and a similar colposcopy referral rate

ASCUS-LSIL Triage Study (ALTS)

- The colposcopy results showed that about 5 percent to 10 percent of women with ASCUS had precancer or cancer and that, of these women, 96.3 percent had a positive HPV test.
- As a corollary, 99.5 percent of women with a negative HPV test **did not** have precancer or cancer.

LSIL(CIN 1): ALTS summary points

- CIN 3 is found in about 15%
- CIN 2 is found in about 10%
- CIN 2 may regress
- Colposcopy sensitivity for detection of CIN 3 is only 50-70%
- 83% tested positive for high-risk HPV
- The majority had repeat abnormal Pap

HPV & LSIL (CIN1)

- 80% - 85% of LSIL (CIN 1) is HPV pos
- 10% - 15% is non-oncogenic HPV pos

Of the approximately 10% of LSIL HPV Negative

- 5% due to False Negative HPV test
- 5% due to a False Positive LSIL

ASCUS



Immediate HR HPV



pos

neg



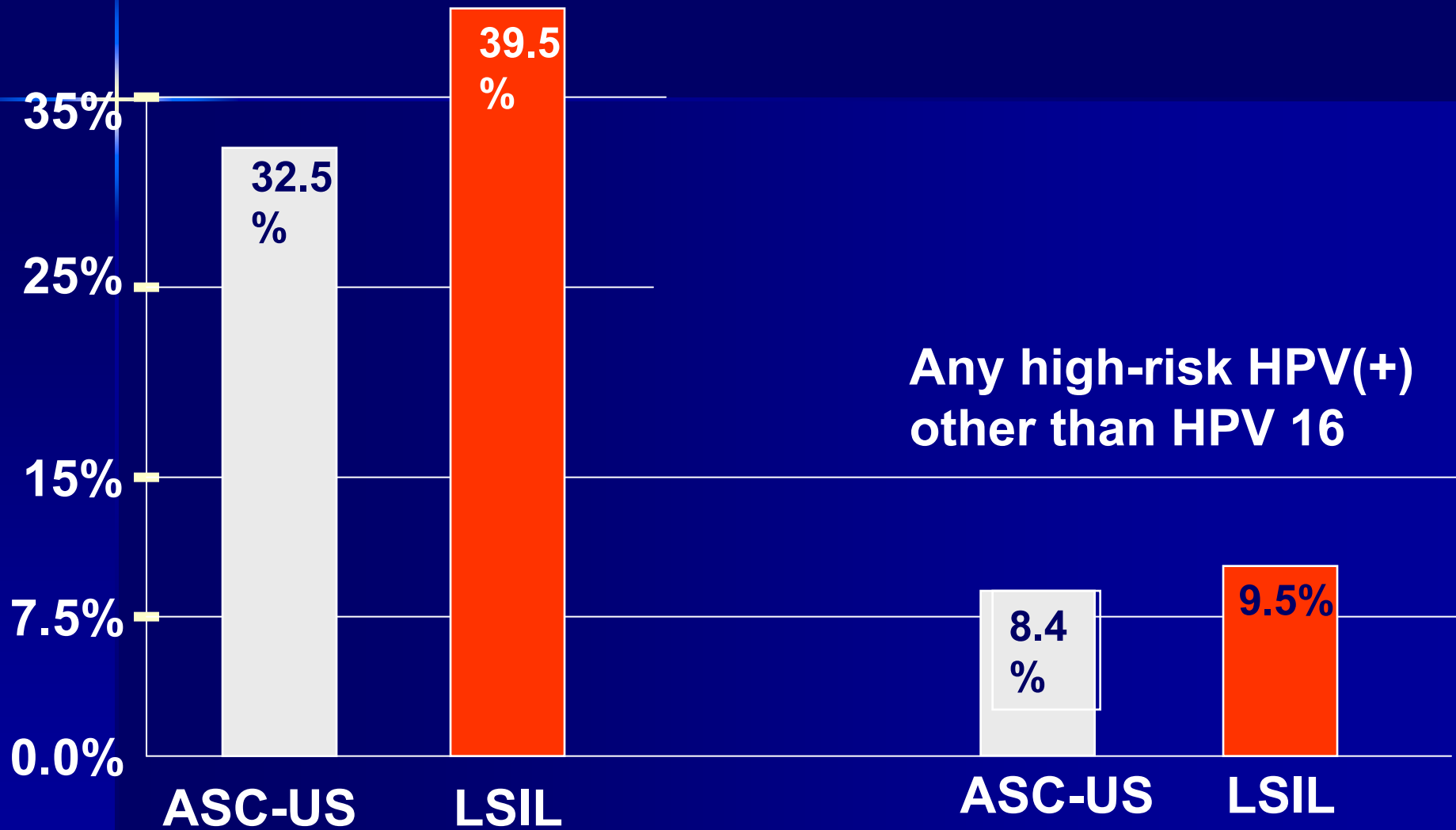
Colposcopy

Loss to follow up 10%

Screening Pap Cycle

Risk for CIN 3+

HPV 16 positive



HPV testing the pros and cons

- HPV testing is more reproducible and sensitive than cytology but only slightly less specific.
 - sensitivity 96% vs 53%; specificity 90% vs 96%
- BUT
- Detection of limited value in HPV positive women with transient infections and no or regressing lesions
- Need to prevent over-referral and colposcopy

Use of HPV DNA test

**3. TEST OF CURE AFTER
TREATMENT OF CERVICAL
PRECANCER**

Risk of Invasive Cervical Cancer after treatment

Soutter WP, de Barros Lopes, Fletcher, Monaghan, Duncan, Paraskevaidis E, Kitchener HC. Lancet, 1997

Kalliala I, Anttila A, Pukkala E, Nieminen P. BMJ, 2005

Soutter WP, Sasieni P, Panoskaltsis T. Int J Cancer, 2006

- Risk x 4-5 times > general population
- Long-term Risk for 20 years
- Incidence of Cx Ca: SIMILAR between treatment methods

HPV testing as an adjunct to cytology in the follow up of women treated for CIN

- 917 women recruited at 6 months of follow up,
- 778 (85%) and 707 (77.1%) being recruited at 12 and 24 months, respectively.
- At recruitment:
 - 700 women had had high-grade CIN (grades 2 or 3) and 217 had CIN1.
- **At 6 months:**
 - **14.6% were HPV positive and 10.7% had non-negative cytology.**
- Of those with negative cytology, 9% were HPV positive.

(HPV) testing in combination with cytology in the follow up of treated women

- Of the 744 women who were cytology negative/HPV negative at baseline:
 - **Only 6** developed further abnormal smears
- 9 of 10 cases of CIN3 were in the HPV-positive women
- At 23 months, 1 cancer in woman with CGIN with clear resection margins, who had been cytology negative/HPV negative at both 6 and 12 months.
- ***Women who are cytology negative and HPV negative at 6 months after treatment for CIN can safely be returned to 3-year recall.***

Test of Cure Protocol (Follow up of treated CIN)

- HPV testing following treatment for CIN.
- Women who are cytology negative and HPV negative proceed to a three year recall period – avoiding the need for 10 years of annual tests.
- Untreated CIN1 followed up at colposcopists discretion.
- Women who are cytology +ve or HPV +ve at 6 months post treatment are colposcoped.

Guidance on Explaining HPV Triage to Women

- We cannot know when an individual woman became infected.
- We cannot know from whom this infection was transmitted.
- High risk HPV does not cause genital warts and wart associated types do not cause CIN.
- HPV infection cannot be treated, only CIN.
- HPV vaccination will help prevent HPV infection/CIN in the future.

Explaining HPV

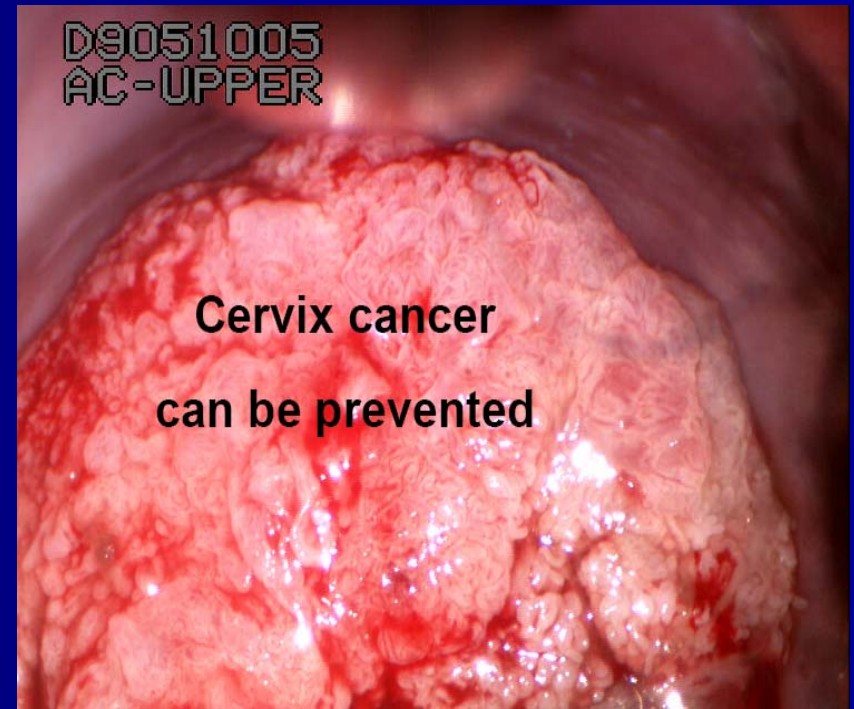
- A positive HPV test does not mean their current partner has been unfaithful
- HPV is very common. Many women will acquire it when they become sexually active.
- Most women will clear an HPV infection, approx 90%

Explaining HPV

- HPV is usually cleared by the immune system.
- Having HPV is not a marker for sexual behaviors, infidelity or timing of infection.

Explaining HPV

Cervical cancer should be considered a very rare complication of a very common virus.

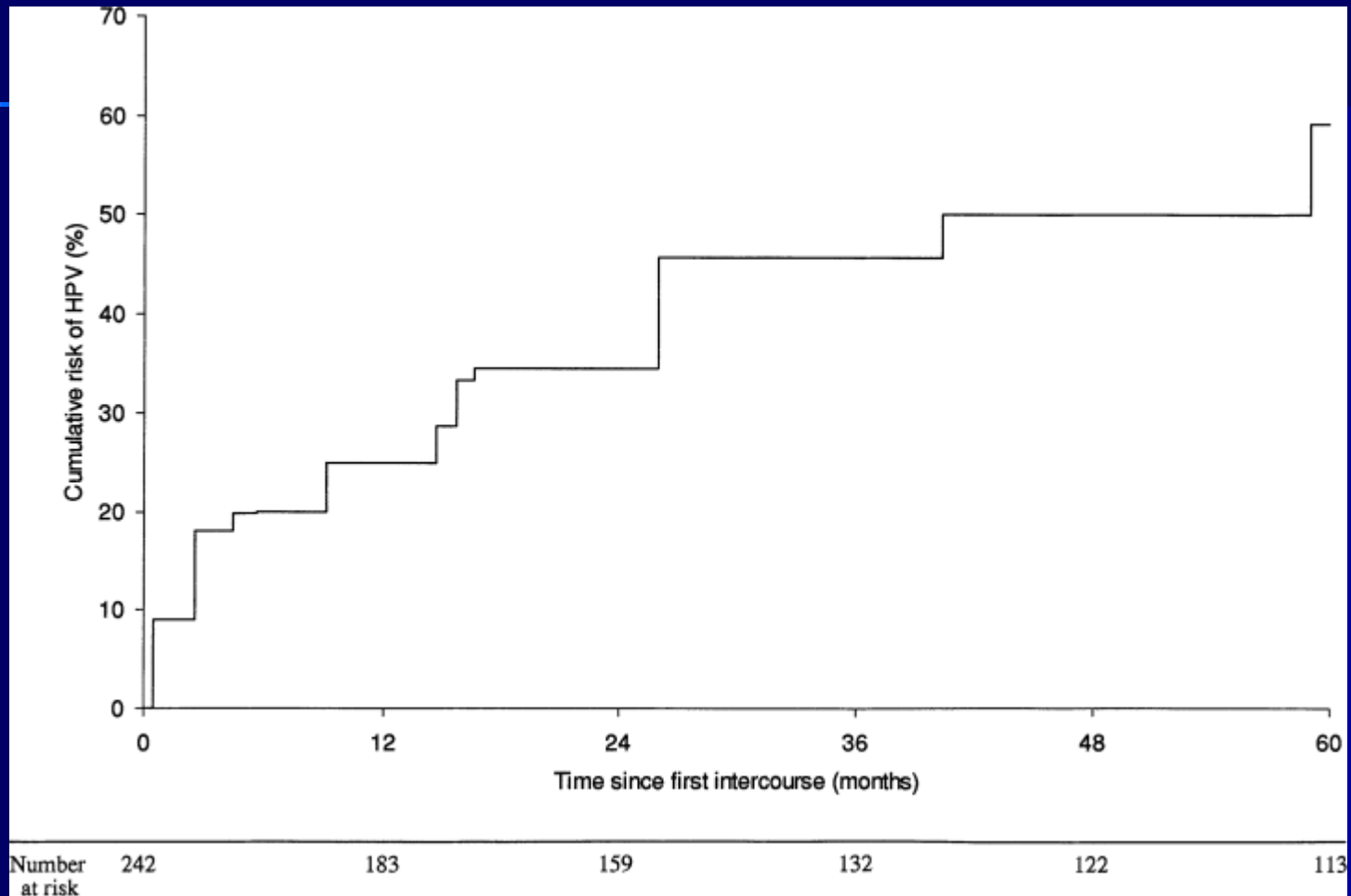


Vaccines

Misconception:
My daughter doesn't
need this vaccine now because she isn't
sexually active.....

- **Significant number of girls are sexually active by age 16 but not as many at age 12**
- **HPV is acquired soon after sexual debut**
- **This is a preventative vaccine and needs to be administered BEFORE possible acquisition of disease**

Risk of Acquiring HPV After First Intercourse in Female Adolescents



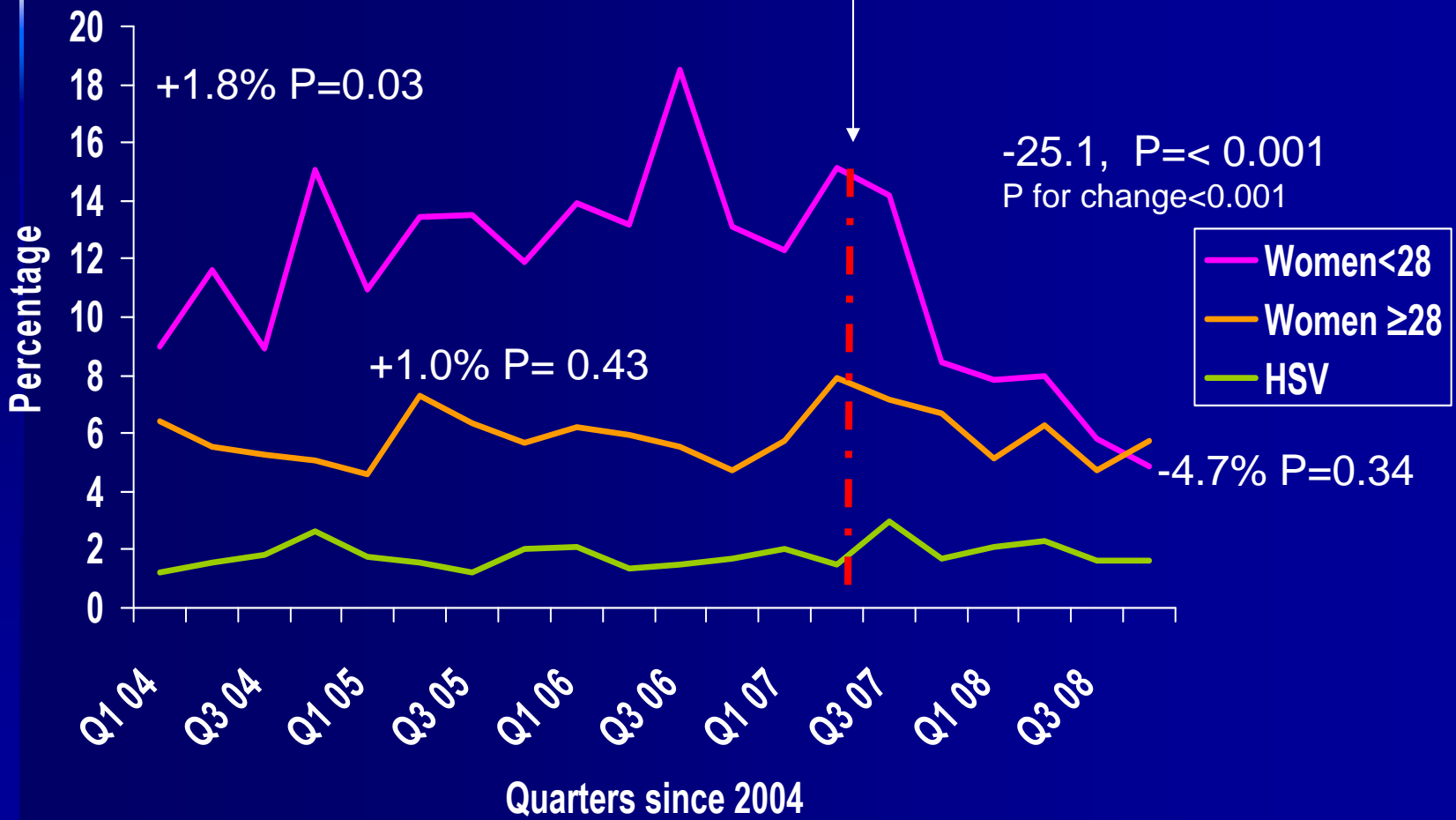
From Collins S, Mazloomzadeh S, Winter H, et al. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. *Br J Obstet Gynaecol.* 2002;109:96–98.

The Australian Experience: Study Results



Proportion of new cases with Warts per quarter

Vaccination program started July 2007



Thank You

What is HPV Triage?

- All cervical samples with first BNC or mild dyskaryosis test result will be tested for HPV to distinguish between women who need referral to colposcopy and women who can be safely returned to routine recall.
- Women who test positive for HPV will be referred to colposcopy. Women who are HPV negative will be returned to routine recall.

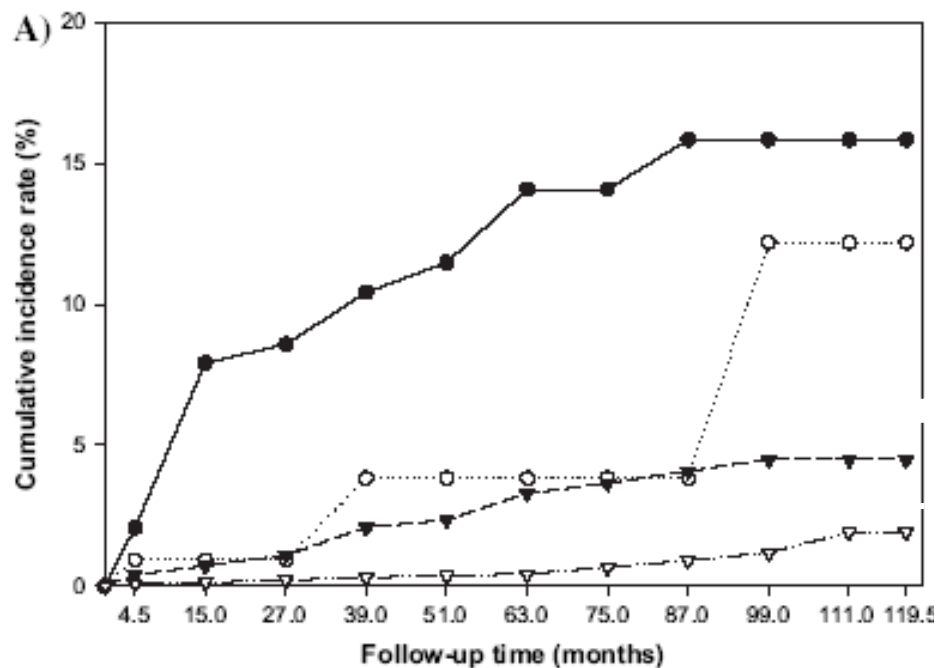
Test of Cure Protocol (Follow up of treated CIN)

- HPV testing will be used following treatment for CIN.
- Women who are cytology negative and HPV negative will proceed to a three year recall period – avoiding the need for 10 years of annual tests.
- Untreated CIN1 will be followed up at colposcopists discretion.
- Women who are cytology +ve or HPV +ve at 6 months post treatment will be colposcoped.

Sentinel Site Study

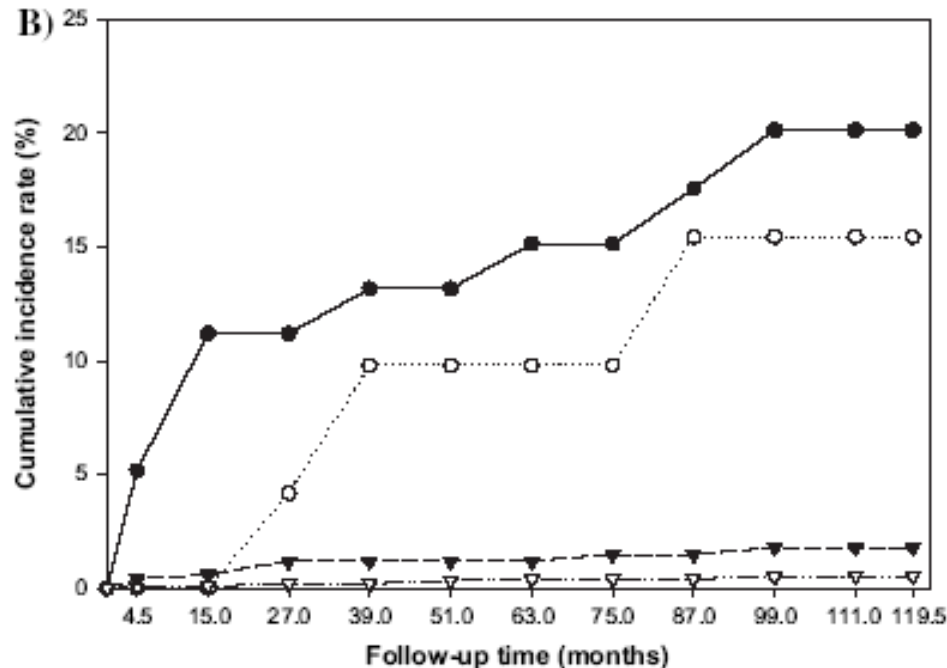
Cytology result (1st Occurrence)	Current Management	HPV Triage Management	
		HPV -ve	HPV +ve
Borderline	Repeat in 6 months	Routine recall	Colposcopy referral
Mild dyskaryosis	Colposcopy referral	Routine recall	Colposcopy referral

Cumulative risk of progression from HPV 16/18 infection to CIN3+ by age group



No. of women seen during follow-up interval

HPV16+	339	184	140	99	84	68	61	49	57	21	1
HPV18+	110	62	50	34	26	26	26	21	23	13	1
HC2+	1249	663	514	407	352	312	261	228	229	112	7
HC2-	5498	2896	2349	1957	1695	1493	1285	1214	1083	543	23



No. of women seen during follow-up interval

HPV16+	116	63	50	45	41	44	33	35	32	14	2
HPV18+	44	23	24	17	17	15	10	16	12	3	0
HC2+	962	545	502	455	403	389	339	300	318	144	10
HC2-	11893	6863	6323	5856	5441	4986	4675	4337	4195	2078	133

HPV in management of low grade abnormalities

- HPV +ve and ASCUS=LSIL biologically
- HPV -ve and ASCUS is relatively safe

histology	ASCUS HPV-	ASCUS HPV+	LSIL all
CIN2&3	3.1	27	28
CIN3	1.7	15	16