The multiple faces of papillomavirus

The 23rd T. B. Teoh Foundation Lecture
Annual General Meeting, Hong Kong College of Pathology

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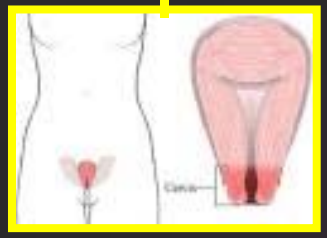
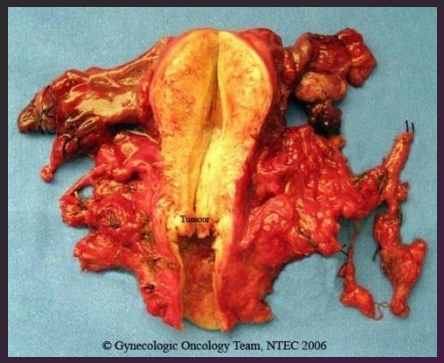
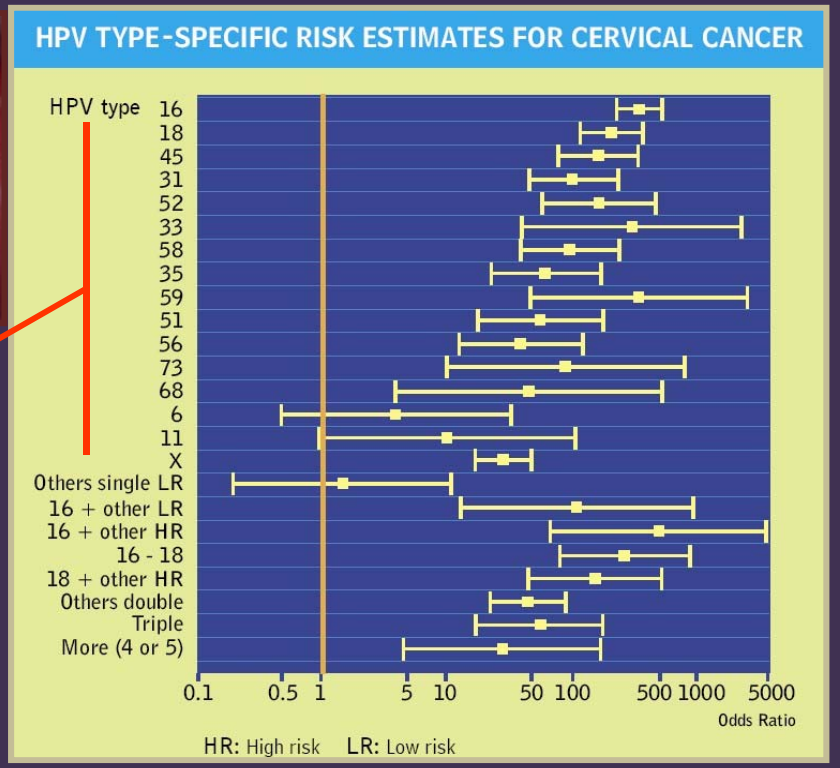
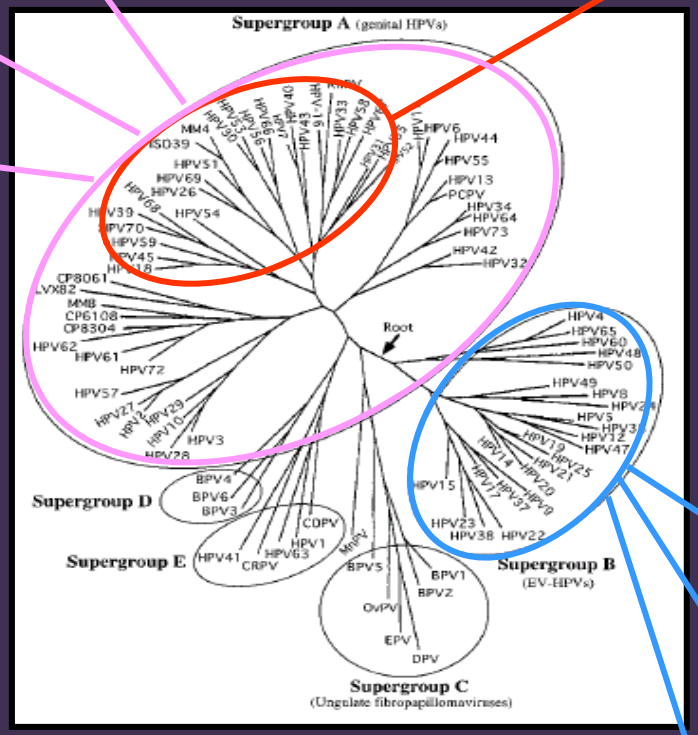
Cervical HPV

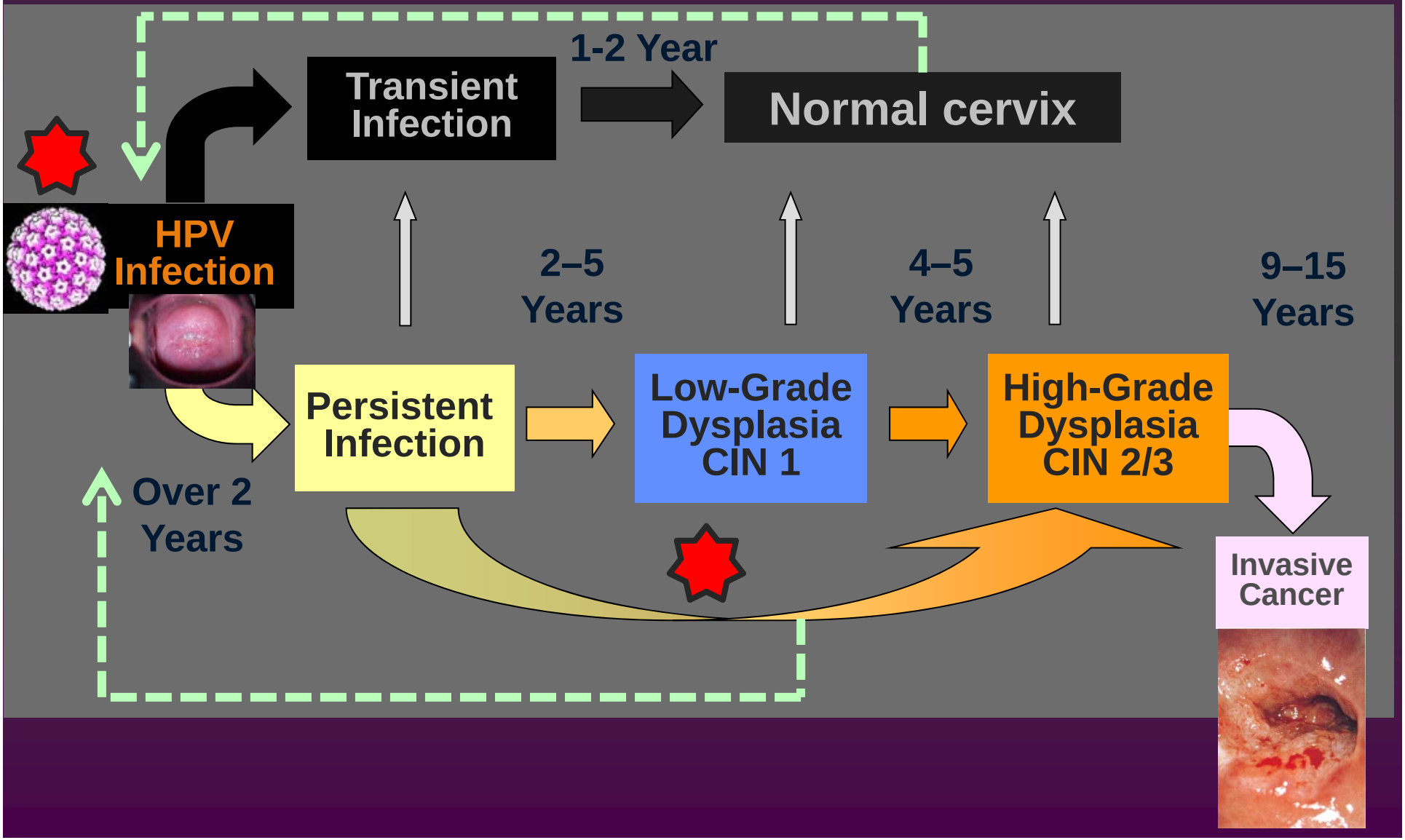


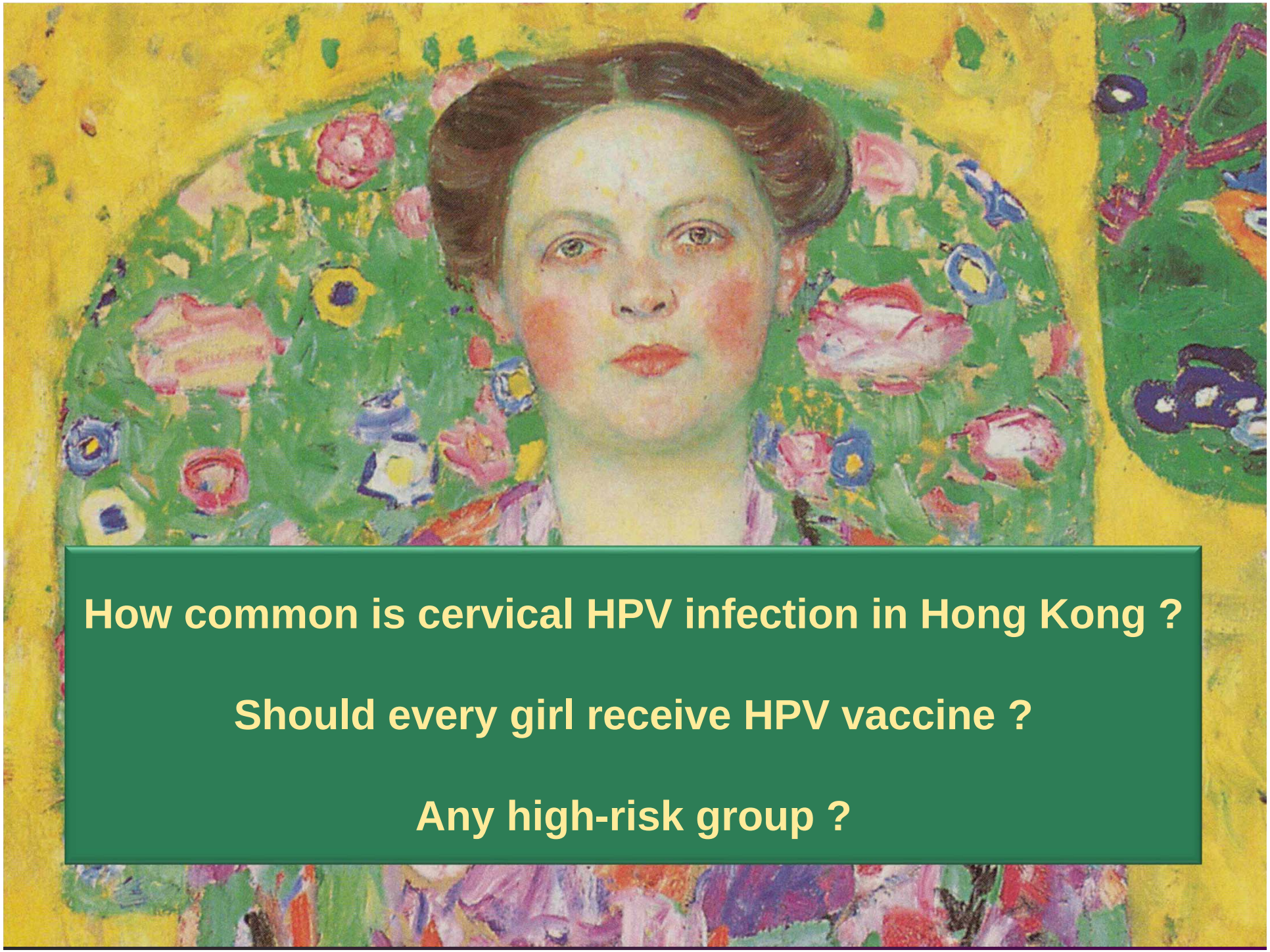



HPV TYPE-SPECIFIC RISK ESTIMATES FOR CERVICAL CANCER
HPV type
16
18
45
31
52
33
58
35
59
51
56
73
68
6
11
X
Others single LR
16 + other LR
16 + other HR
16 - 18
18 + other HR
Others double
Triple
More (4 or 5)
0.1
0.5
1
5
10
50
100
500
1000
5000
Odds Ratio
HR: High risk
LR: Low risk


Supergroup A (genital HPVs)
Root
Supergroup D
Supergroup E
Supergroup B
(EV-HPVs)
Supergroup C
(Ungulate fibropapillomaviruses)

Natural History of High-Risk HPV Infection





How common is cervical HPV infection in Hong Kong ?

Should every girl receive HPV vaccine ?

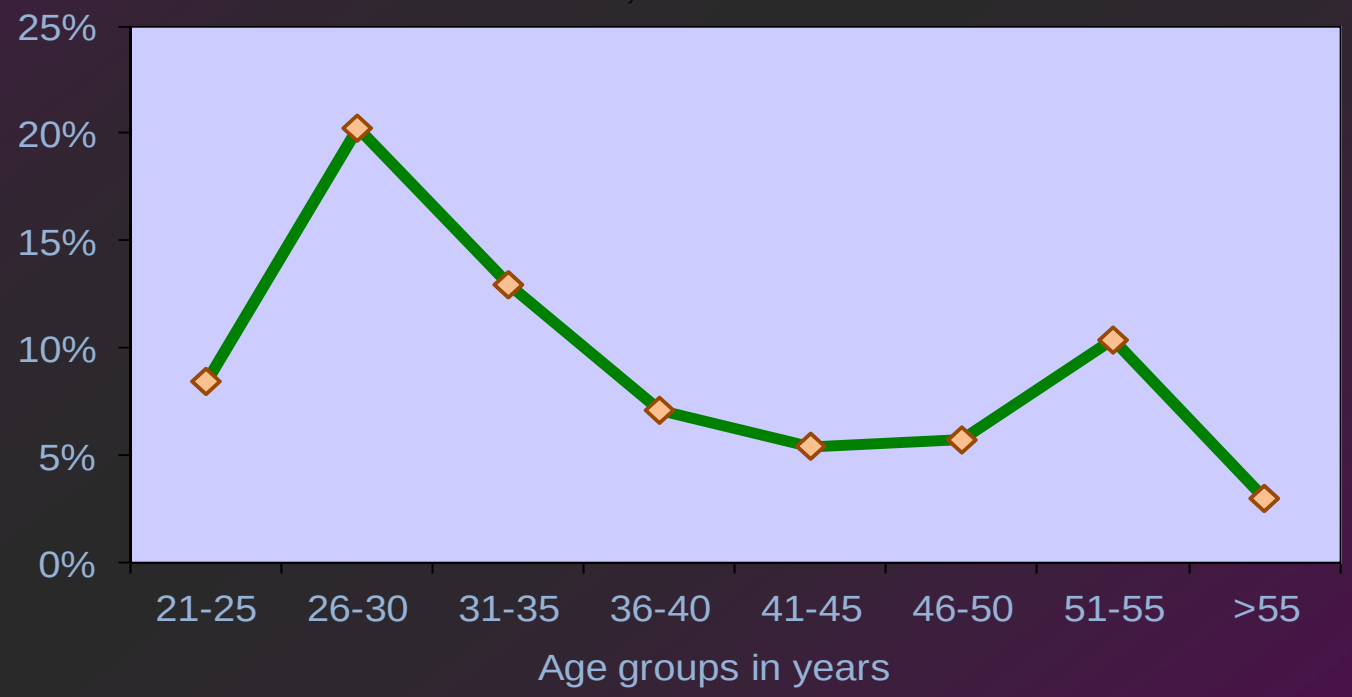
Any high-risk group ?

2080 women enrolled for cervical screening

Hong Kong

Average for 21-45 yr : 10.8%

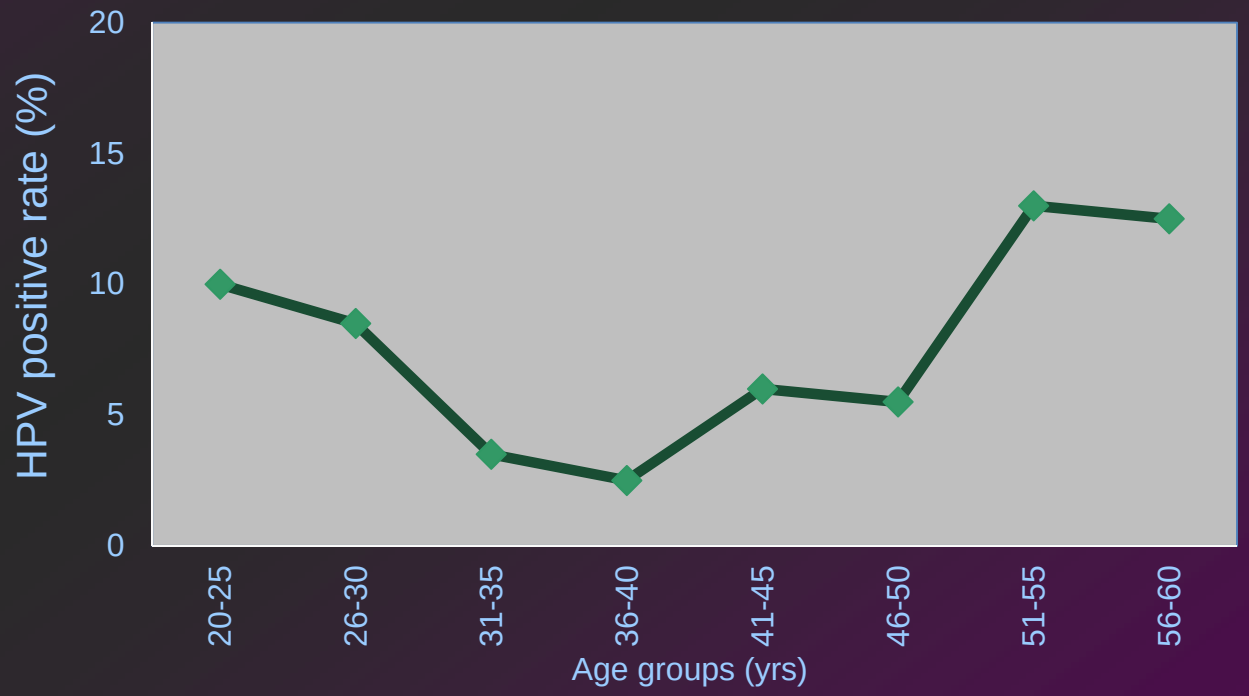
~ 1 / 10



Chan et al. Determinants of cervical human papillomavirus infection: differences between high- and low-oncogenic risk types. ***Journal of Infectious Diseases*** 2002; 185: 28

1600 women enrolled for cytology screening

Macau



Yip & Chan et al. Prevalence and genotype distribution of cervical human papillomavirus infection in Macao. ***Journal of Medical Virology*** 2010;82:1724.

2604 healthy women in Hong Kong:

	HPV	Odds ratio
No. sex partners in life-time		
≤ 1	5.8%	Reference
2-3	10.3%	1.6 (1.1-2.5)
≥4	18.8%	3.2 (1.6-6.2)
Smoking		
No	6.2%	Reference
Yes	19.2%	3.0 (1.7-5.3)

HPV infection is not limited to those with more sex partners & smokers

Chan et al. Epidemiologic risk profile of infection with different groups of human papillomavirus. ***Journal of Medical Virology***. 2009; 81:1635-1644.


Any priority group ?

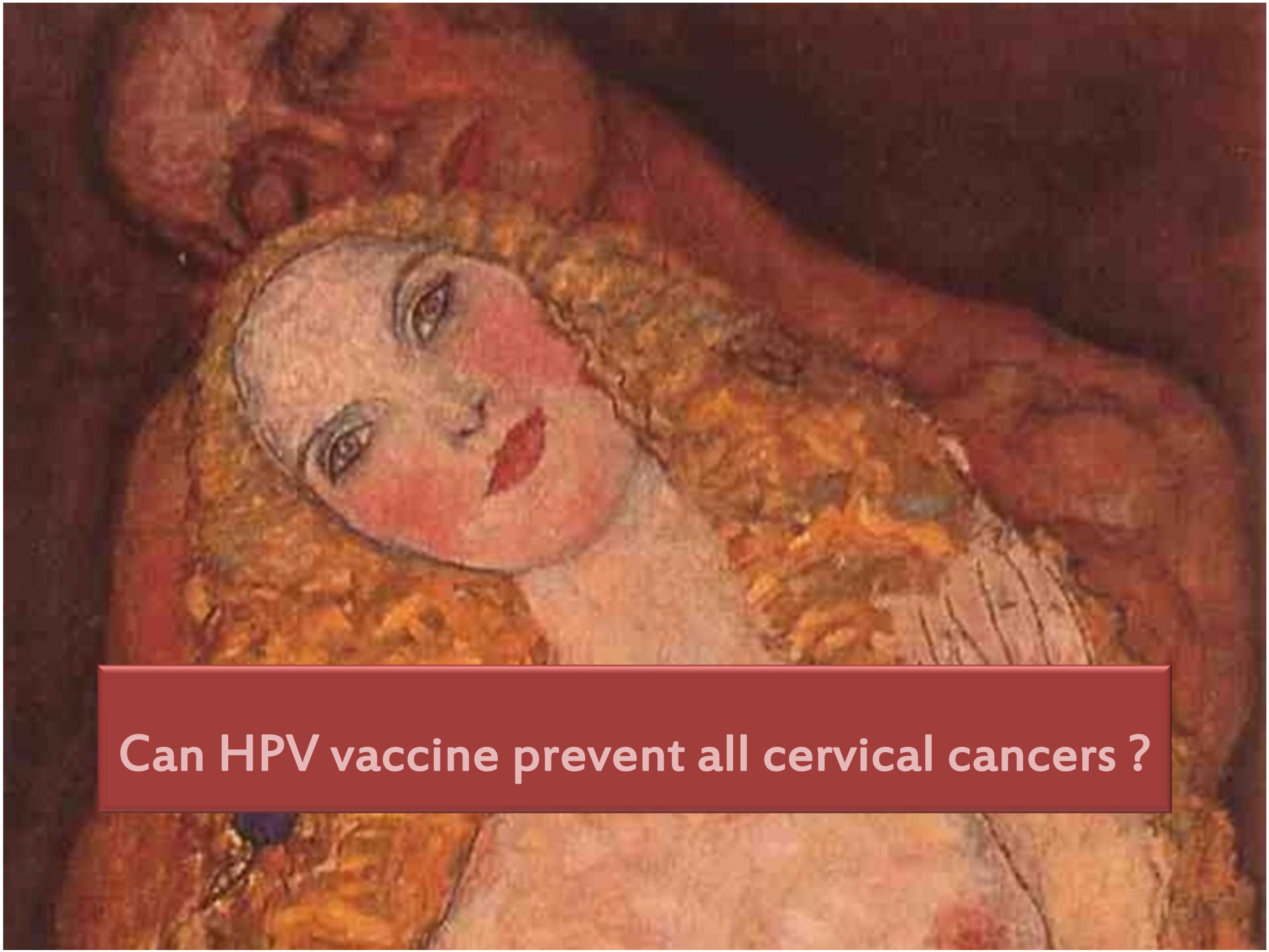
Systemic Lupus Erythematous

	SLE patients N = 85 Mean age = 42 yr	Controls N = 2080 Mean age = 44 yr
Abnormal Pap smear	16.%	5.7%
Squamous intraepithelial lesions	11.8%	2%
HPV (all types)	11.8%	7.3%
HPV (high-risk)	10.6%	4.2%
HPV16	4.7%	1.6%

45.5% of SLE patients with HPV (high-risk) develop SIL within 3 yr

SLE patients have impaired ability to clear high-risk HPV infection

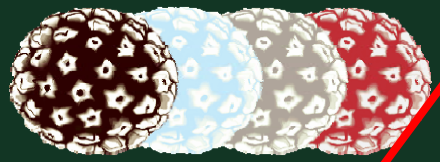
Tam, Chan et al. Increased prevalence of squamous intraepithelial lesions in Systemic Lupus Erythematosus: Association with human papillomavirus infection. ***Arthritis & Rheumatism*** 2004; 50: 3619.
Tam, Chan et al. Risk factors for squamous intraepithelial lesions in Systemic Lupus Erythematosus: a prospective cohort study. ***Arthritis Care & Research*** 2011; 63: 269


Can HPV vaccine prevent all cervical cancers ?

High-risk HPVs

加衛苗

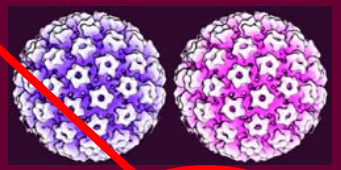
MSD Quadrivalent HPV Vaccine QARDASIL®



HPV 6, 11, 16, 18

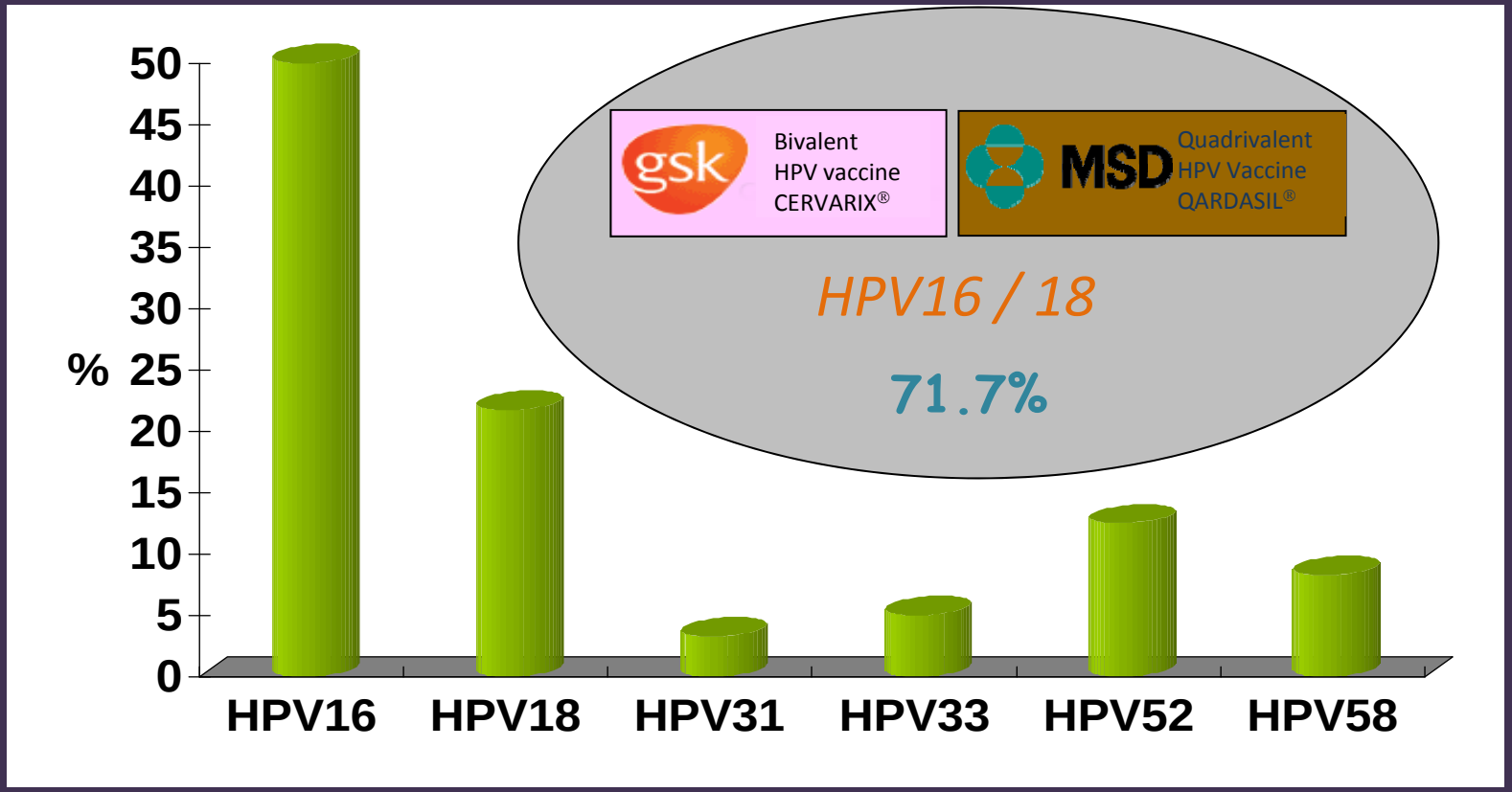
卉妍康

gsk Bivalent HPV vaccine CERVARIX®



HPV 16, 18

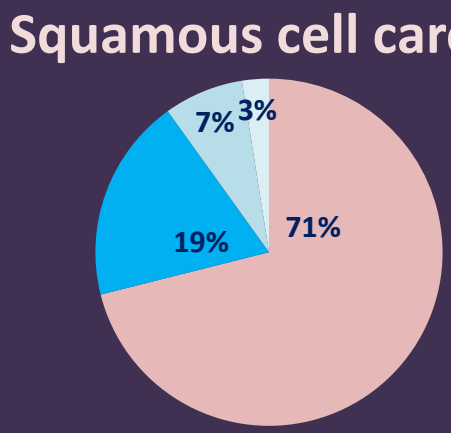
Coverage of current HPV vaccines for cervical cancers in Hong Kong

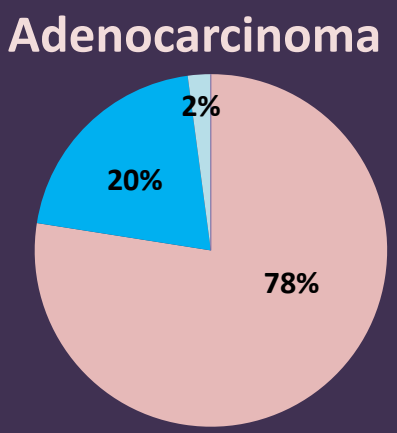


120 cervical cancers, 21% adenocarcinoma

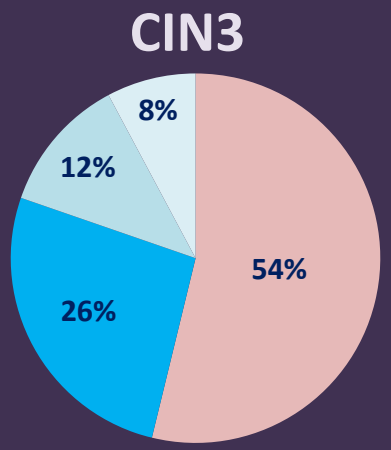
Chan et al. Biases in HPV genotype prevalence assessment associated with commonly used consensus primers. ***International Journal of Cancer*** 2006; 118: 243.

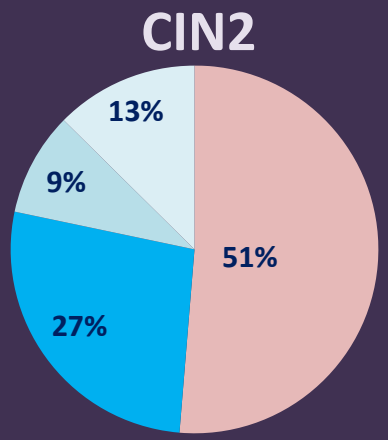
Coinfection with multiple HPV types

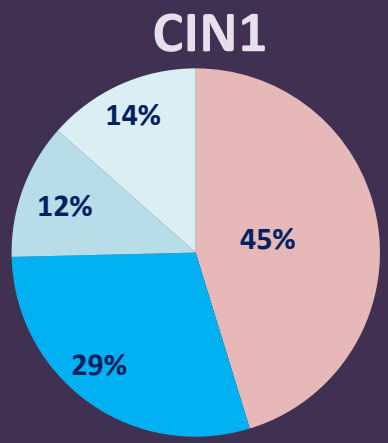




- Single-type
- 2 HPV types
- 3 HPV types
- 4 or more HPV types

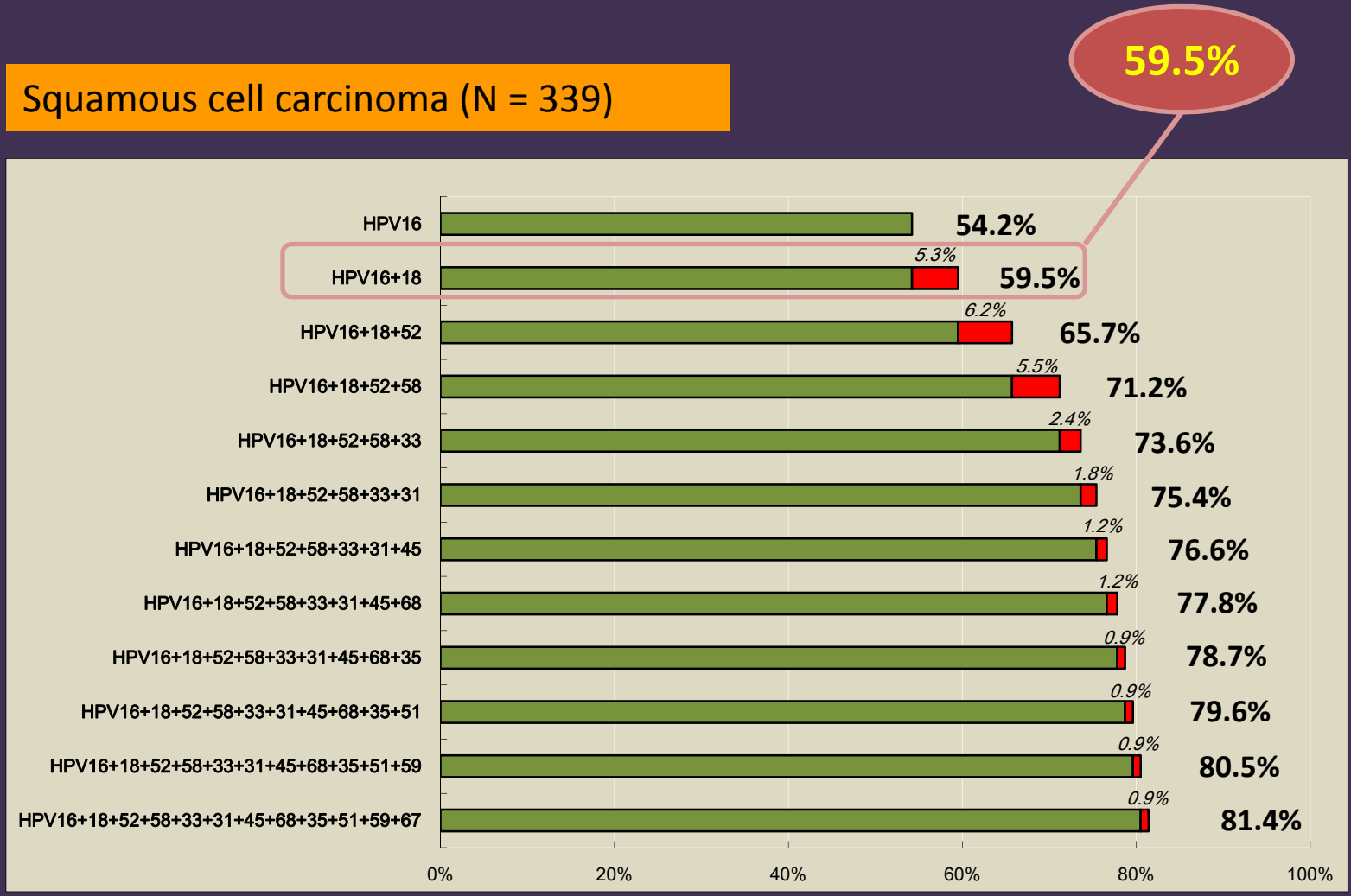






Cumulated Attribution of HPV types to Cervical Cancers in Hong Kong

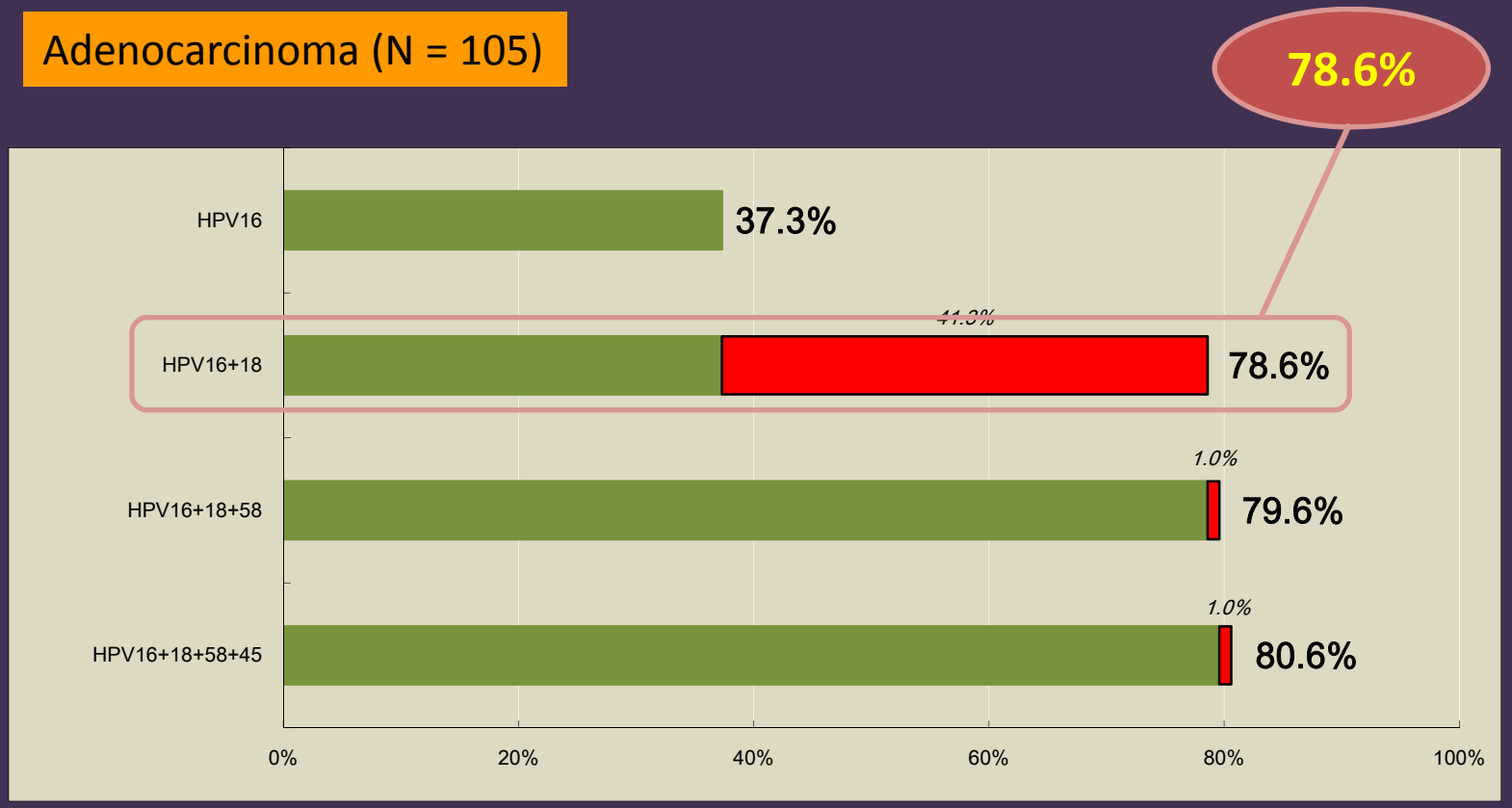
Squamous cell carcinoma (N = 339)



Chan et al. Attribution of HPV types to cervical intraepithelial neoplasia and invasive cancers in Southern China. ***International Journal of Cancer*** 2012;131:692.

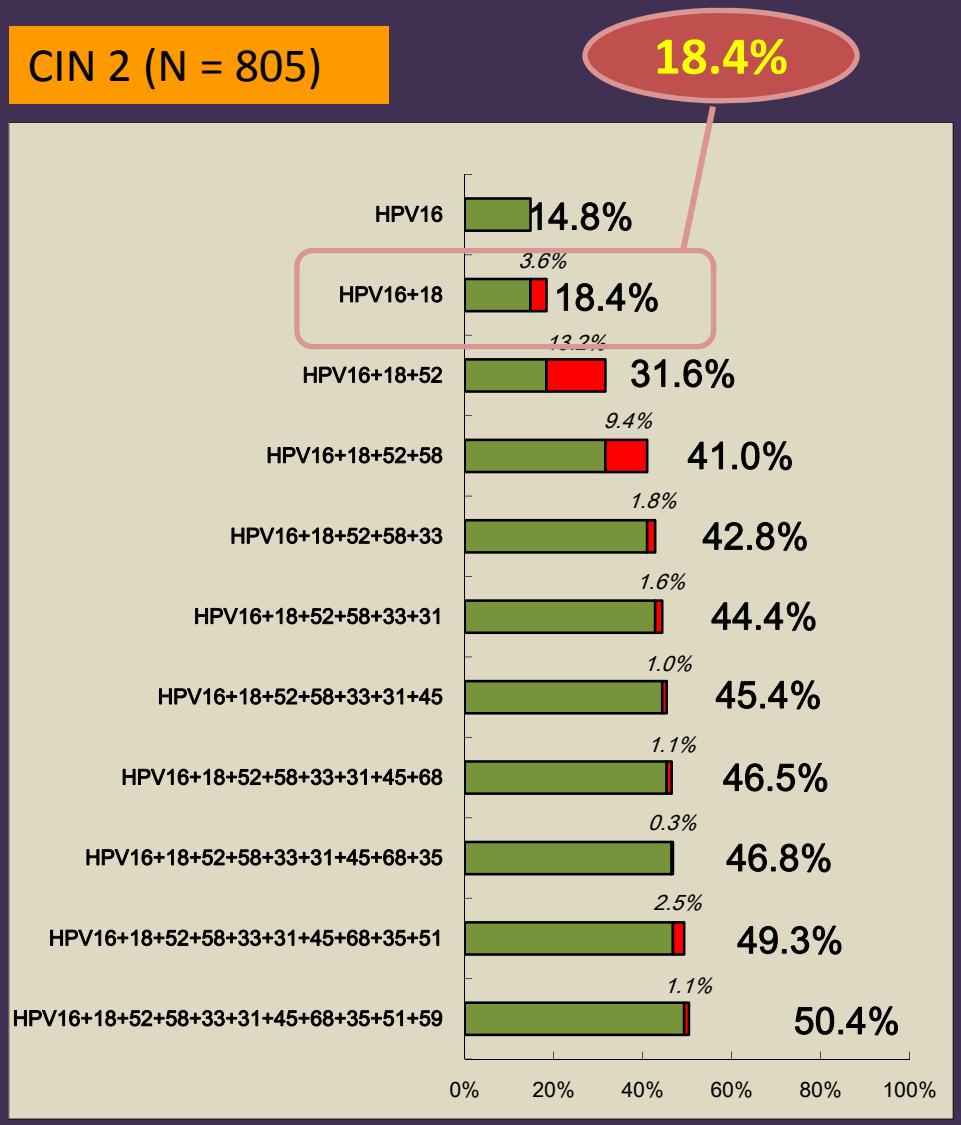
Cumulated Attribution of HPV types to Cervical Cancers in Hong Kong

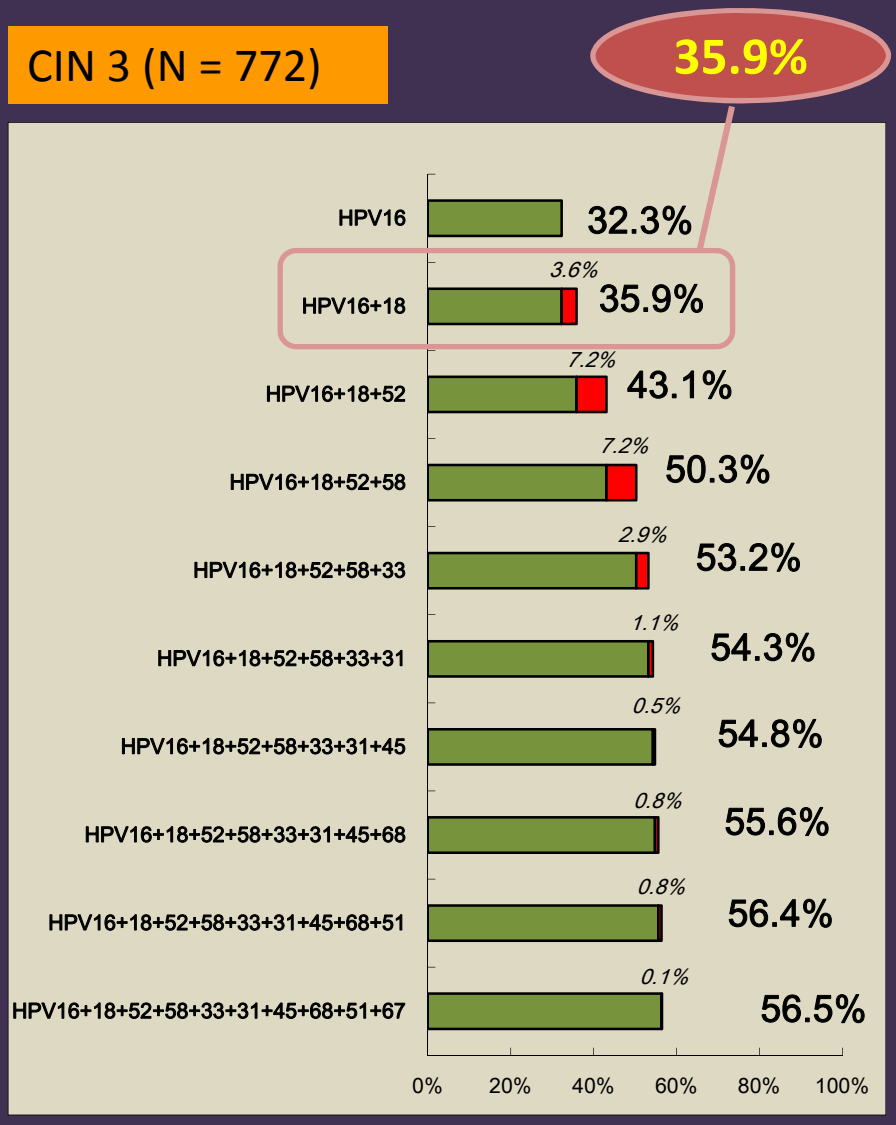
Adenocarcinoma (N = 105)



Chan et al. Attribution of HPV types to cervical intraepithelial neoplasia and invasive cancers in Southern China. ***International Journal of Cancer*** 2012;131:692.

Cumulated Attribution of HPV types to Cervical Intraepithelial Lesions in Hong Kong





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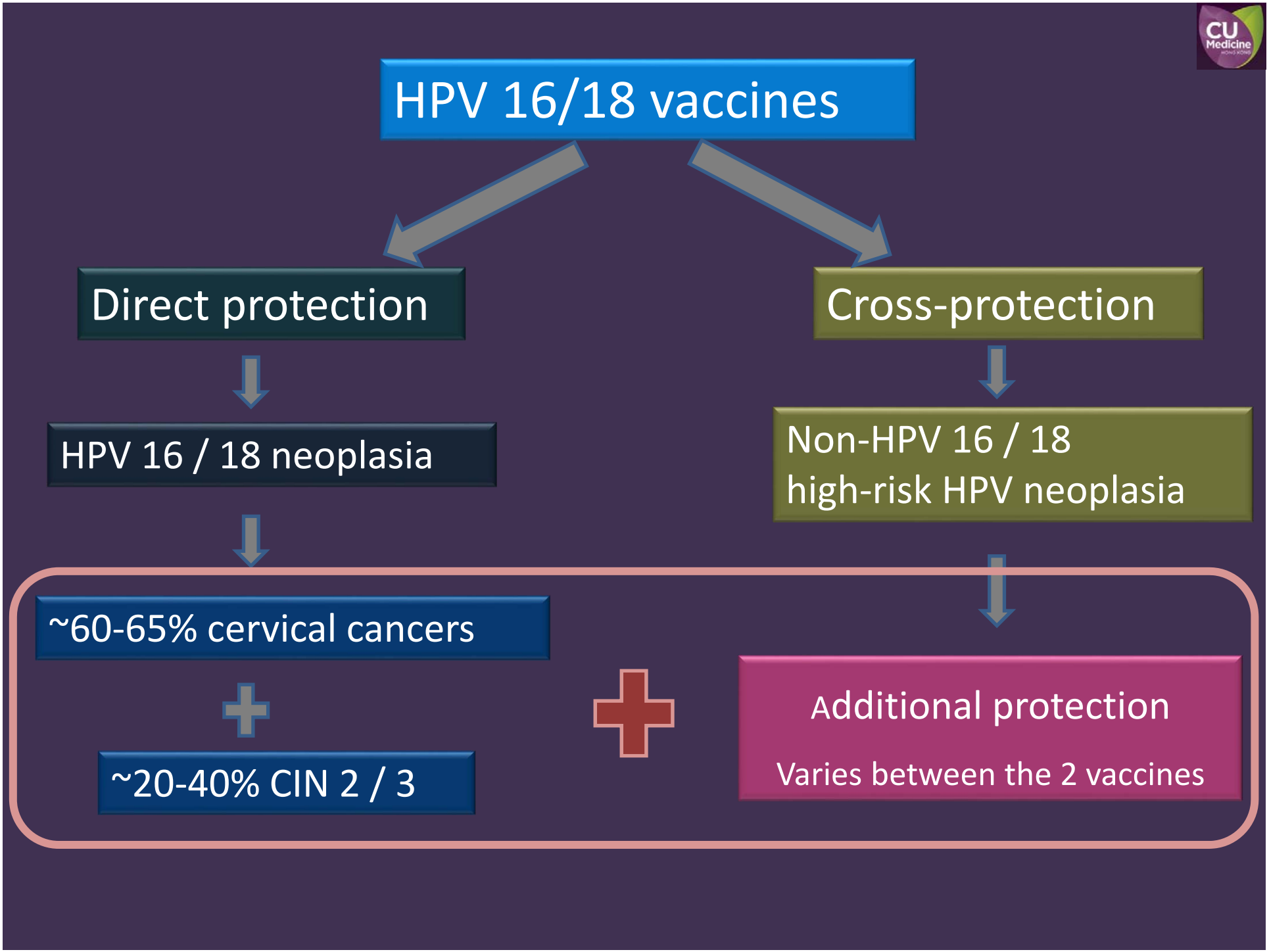
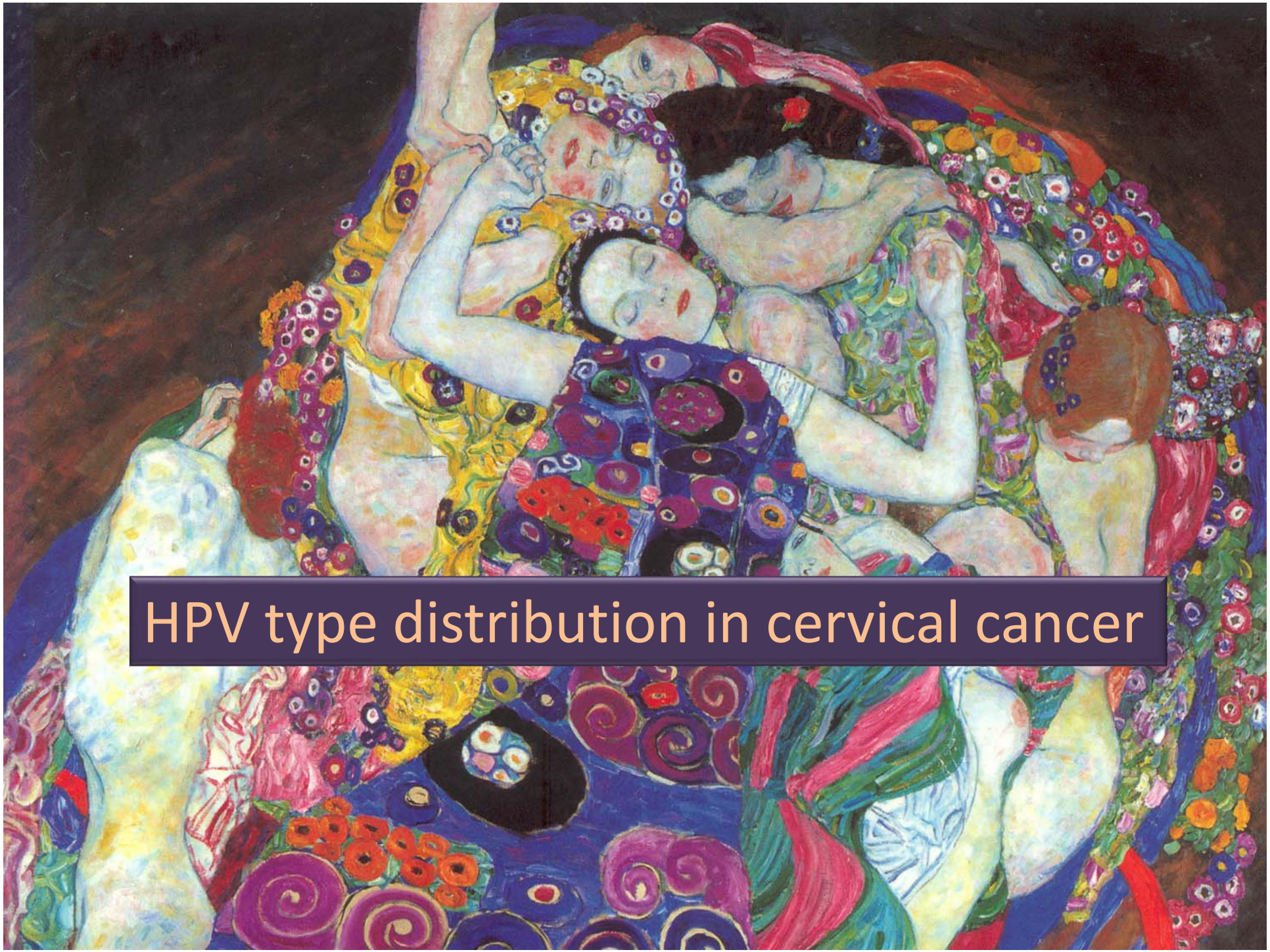

HPV 16/18 vaccines
Direct protection
Cross-protection
HPV 16 / 18 neoplasia
Non-HPV 16 / 18
high-risk HPV neoplasia
~60-65% cervical cancers
~20-40% CIN 2 / 3
Additional protection
Varies between the 2 vaccines

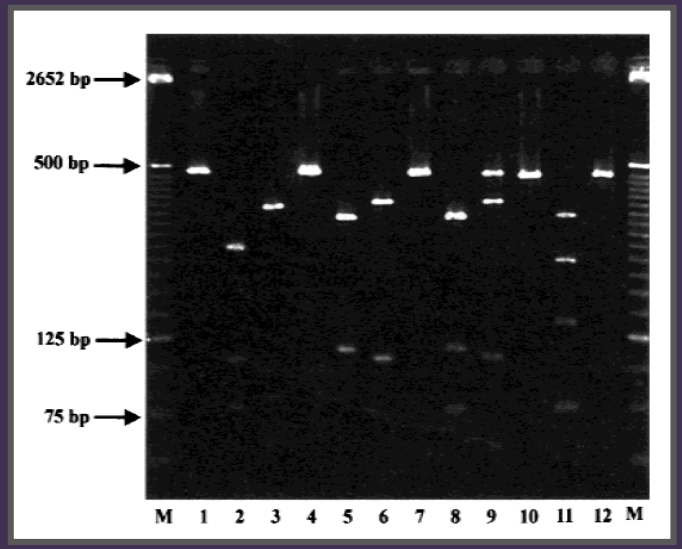

HPV type distribution in cervical cancer

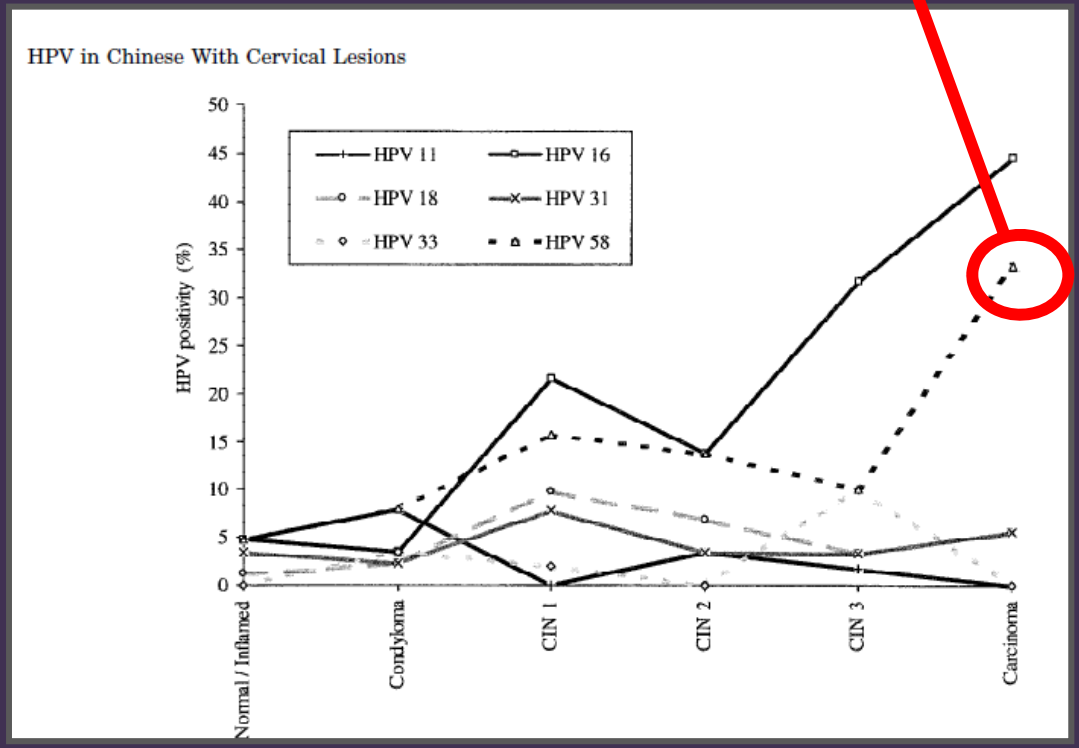
Journal of Medical Virology 59:232–238 (1999)

High Prevalence of Human Papillomavirus Type 58 in Chinese Women With Cervical Cancer and Precancerous Lesions

Paul K.S. Chan,[1]* Wai-Hon Li,[2] May Y.M. Chan,[2] Wei-Ling Ma,[2] Jo L.K. Cheung,[1] and Augustine F. Cheng[1]

[1]Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
[2]Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Kowloon, Hong Kong





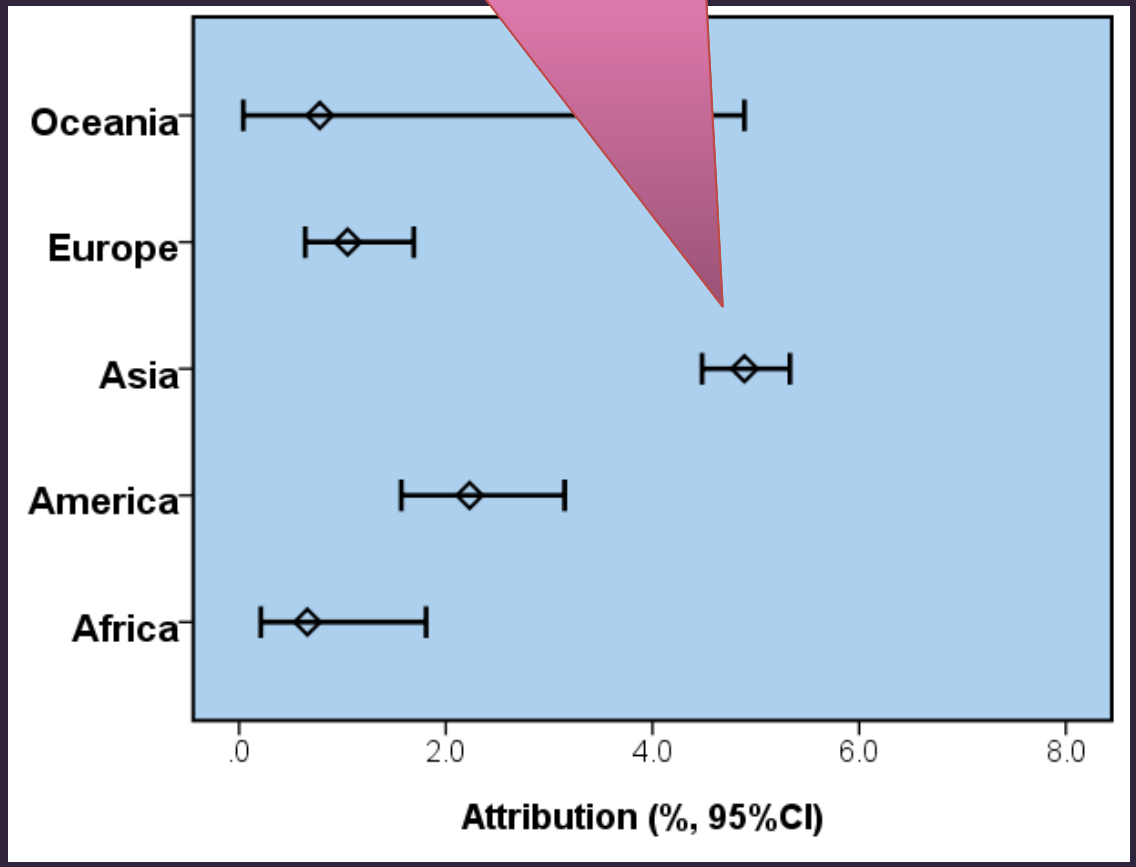
Meta-analysis on attribution of HPV58 in cervical cancers (worldwide)

HPV58 in HPV-positive cervical cancers

4.9 (4.5-5.3)% in Asia

Significantly higher than Americas, Europe and Africa , P <0.001

	No. of Studies	No. of Patients
Oceania	2	129
Europe	10	1732
Asia	44	9845
America	10	1498
Africa	5	599
Total	71	13803



Chan et al. Meta-analysis on prevalence and attribution of HPV types 52 and 58 in cervical neoplasia worldwide. ***PLoS ONE*** 2014;9:e107573

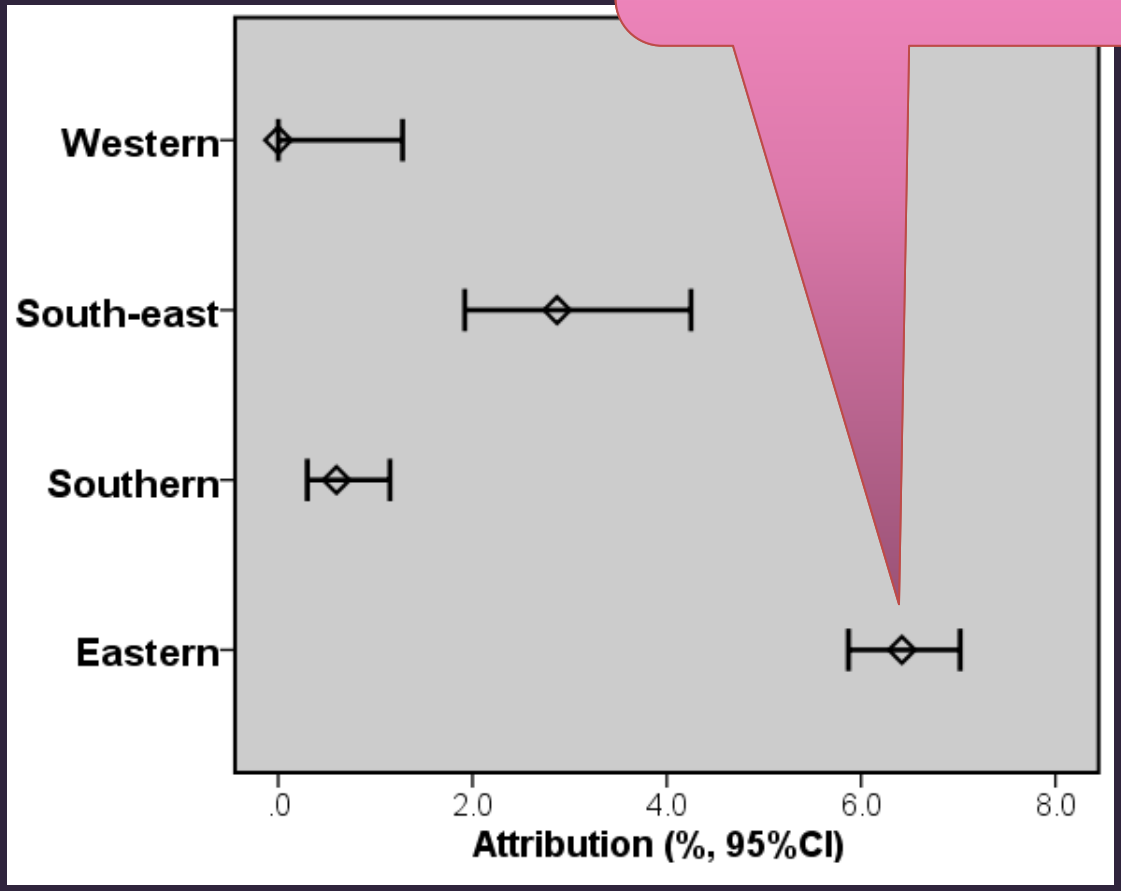
Meta-analysis on attribution of HPV58 in cervical cancer (Asia)

No. of studies	No. of Patients
2	371
5	895
8	1622
29	6957
Total	44	9845

HPV58 in HPV-positive cervical cancers

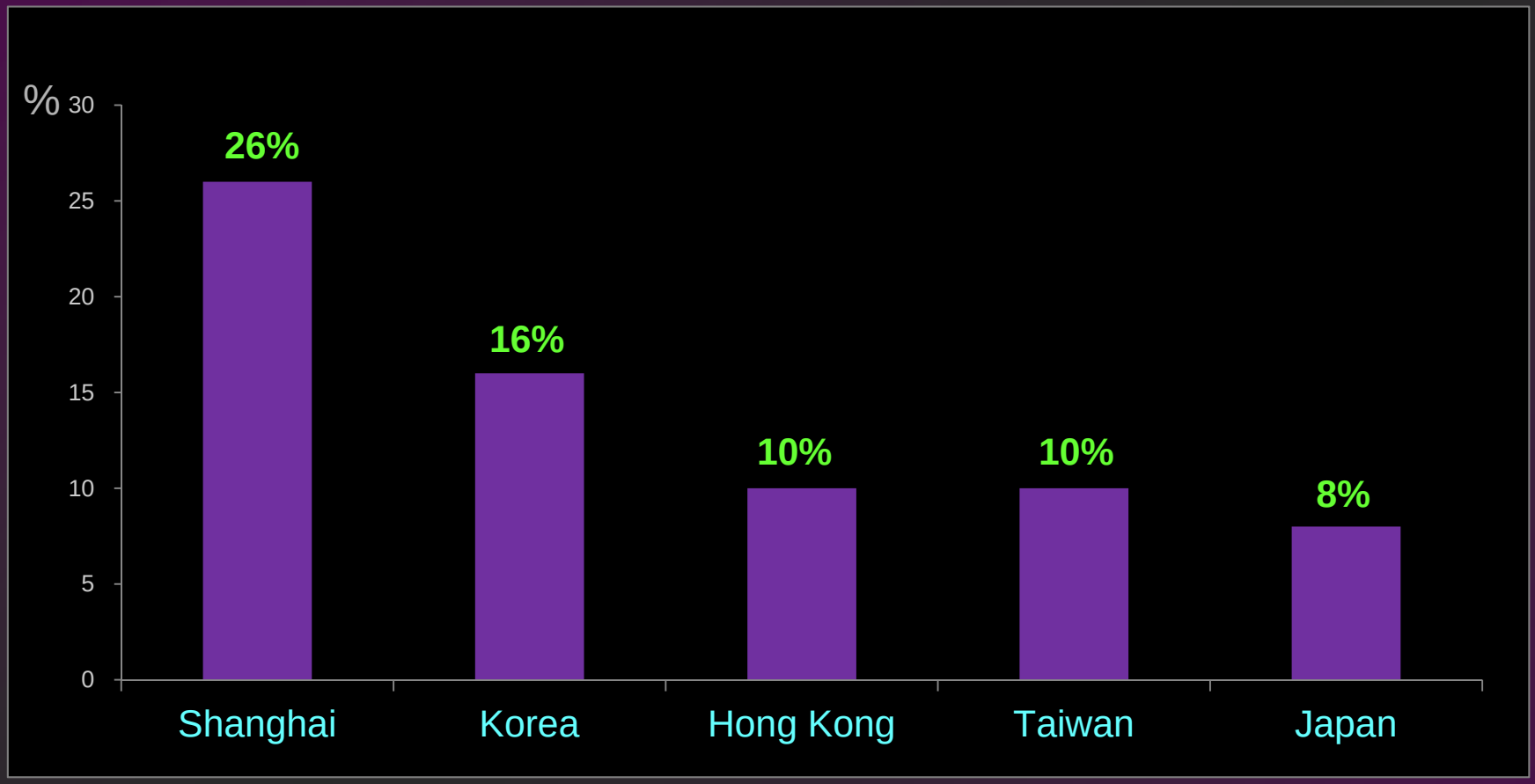
6.4 (5.9-7.0)% in Eastern Asia

Significantly higher than others, P <0.001



Chan et al. Meta-analysis on prevalence and attribution of HPV types 52 and 58 in cervical neoplasia worldwide. ***PLoS ONE*** 2014;9:e107573

Prevalence of HPV58 in SCC in East Asia




Why HPV58-cancer is more common in East Asian women ?

HLA DRB1*06

↑ HPV58 CIN3/ cancer

Odds ratio: 3.68 [1.37-9.92]

Higher oncogenicity ??

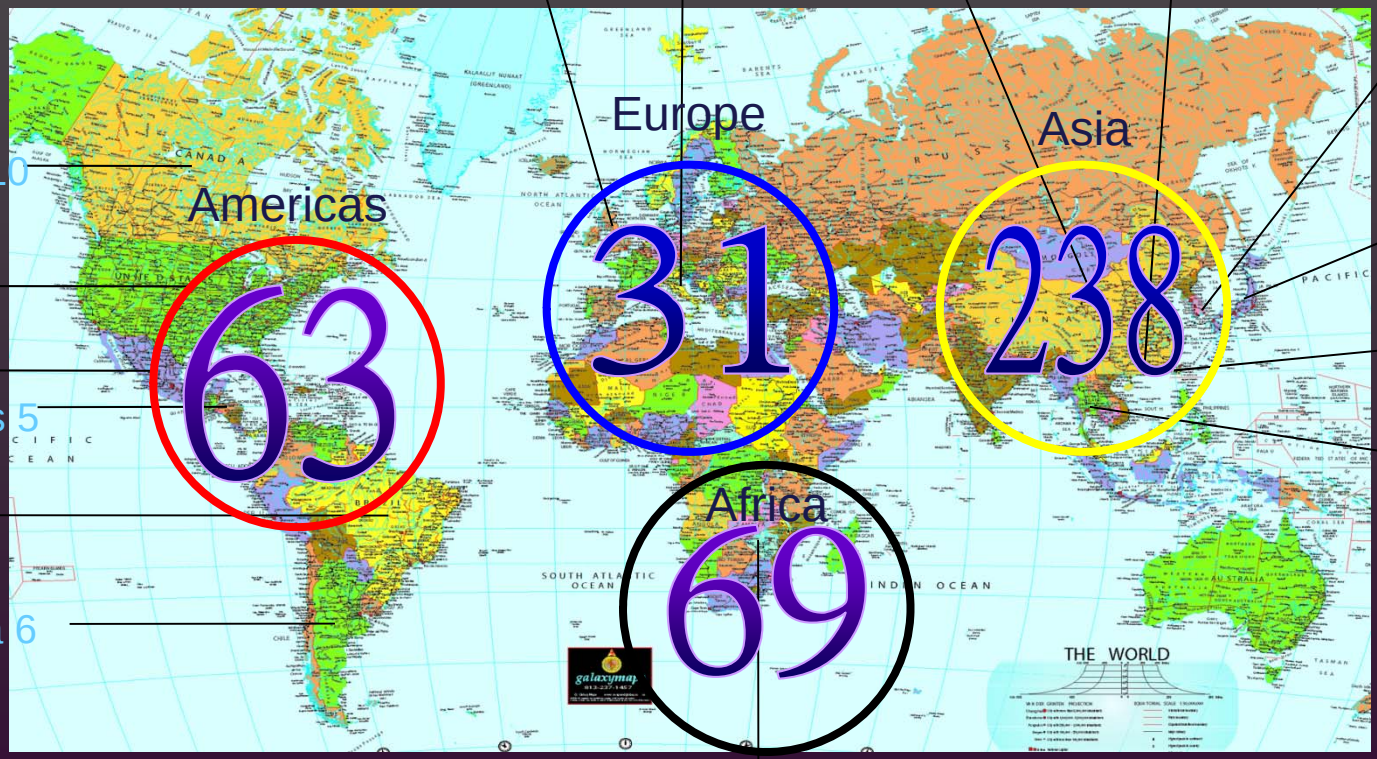
Ethno / geographical distribution ??

Chan et al. Association between HLA-DRB1 polymorphism, high-risk HPV infection and cervical neoplasia in Southern Chinese . ***Journal of Medical Virology*** 2007;79:970.

HPV58 International Study

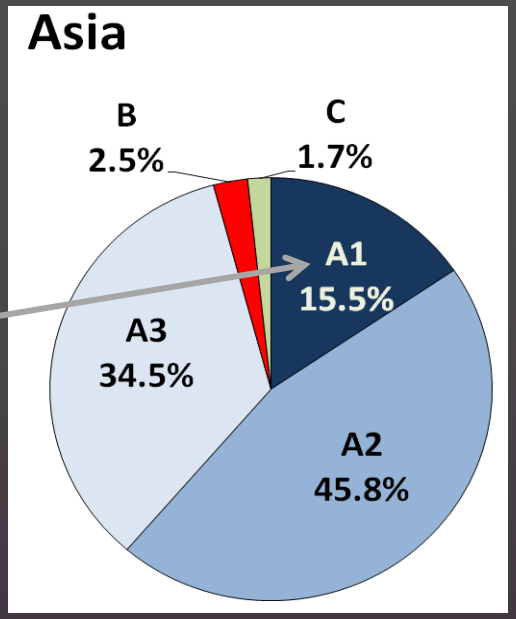
15 sites

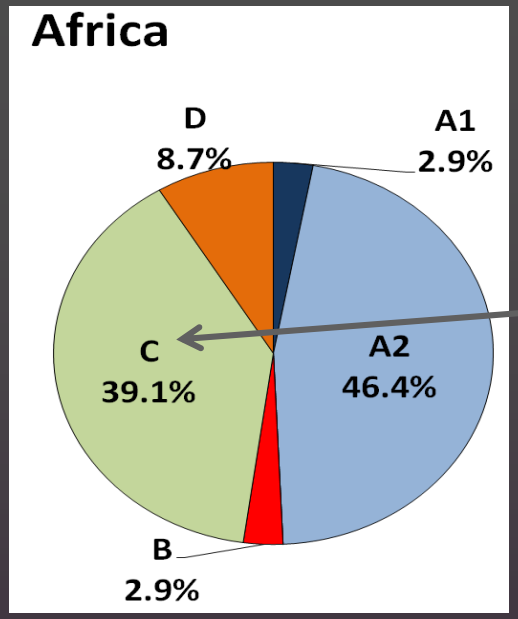
401 HPV58 +ve samples



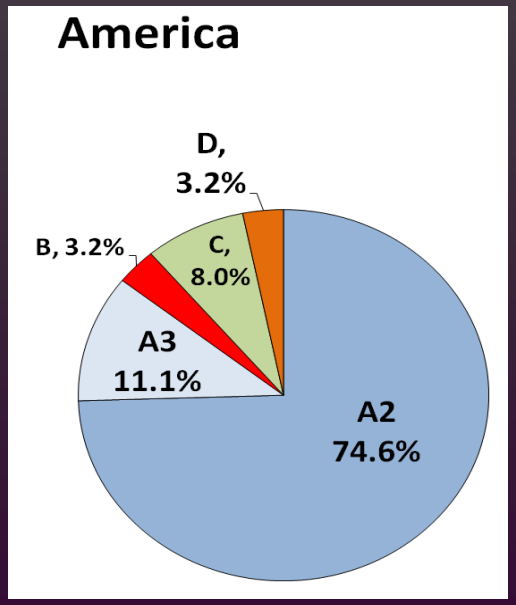
Distribution of HPV58 variants

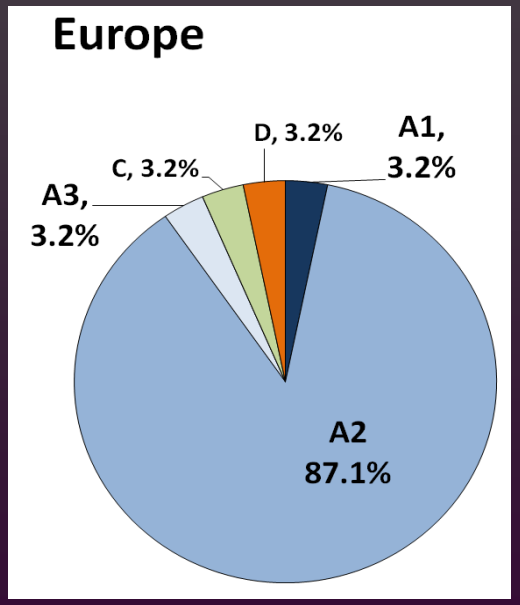
A1 rare worldwide, expect in Asia





Lineage C more common in Africa





Chan et al. Identification of HPV type 58 lineages and the distribution worldwide. ***Journal of Infectious Diseases*** 2011;203:1565

Amino acid substitution	Normal ($N = 79$)	CIN3/ICC ($N = 64$)	p-value[2]	Odds ratio (95% CI)[3]
E7				
R9K	0	2	0.199	–
T20I	15	27	0.004	3.11 (1.38–7.07)
G41R	46	25	0.035	0.46 (0.22–0.95)
T50I	1	0	1.000	–
G63D	47	25	0.024	0.44 (0.21–0.90)
G63H	1	1	1.000	1.24 (0.00–46.34)
G63S	18	27	0.021	2.47 (1.13–5.44)
T74A	7	2	0.188	0.33 (0.05–1.84)
D76E	7	2	0.188	0.33 (0.05–1.84)
V77A	1	6	0.045	8.07 (0.92–182.76)

HPV58 T20I G63S

Higher oncogenic risk

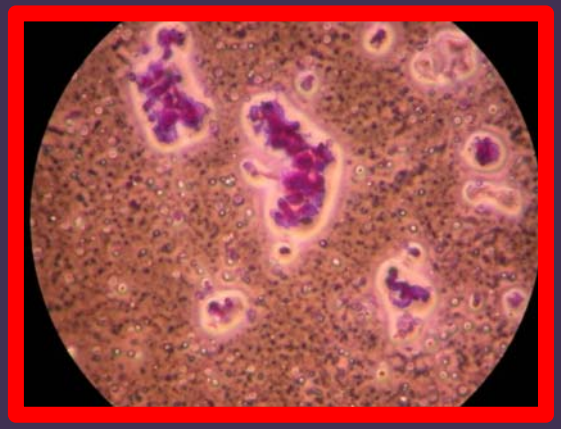
Asia – 33%
America – 10%
Europe – 3%
Africa – 0%

HK-2 (26%)
7 – fold ↑ cancer risk

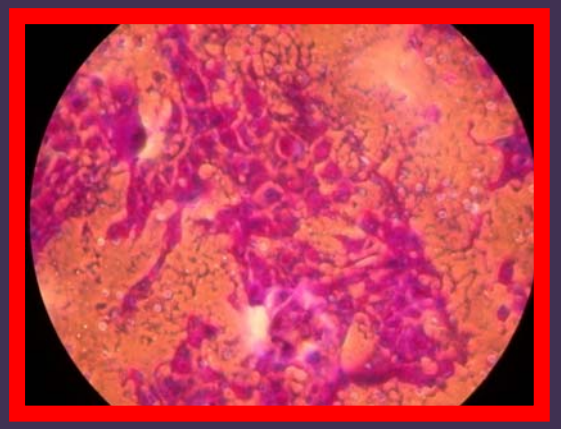
Chan et al. Association of HPV type 58 variant with the risk of cervical cancer. ***Journal of National Cancer Institute*** 2002; 94:1249.
Chan et al. Geographical distribution and oncogenic risk association of HPV type 58 E6 and E7 sequence variations ***International Journal of Cancer*** 2013;132:2528.

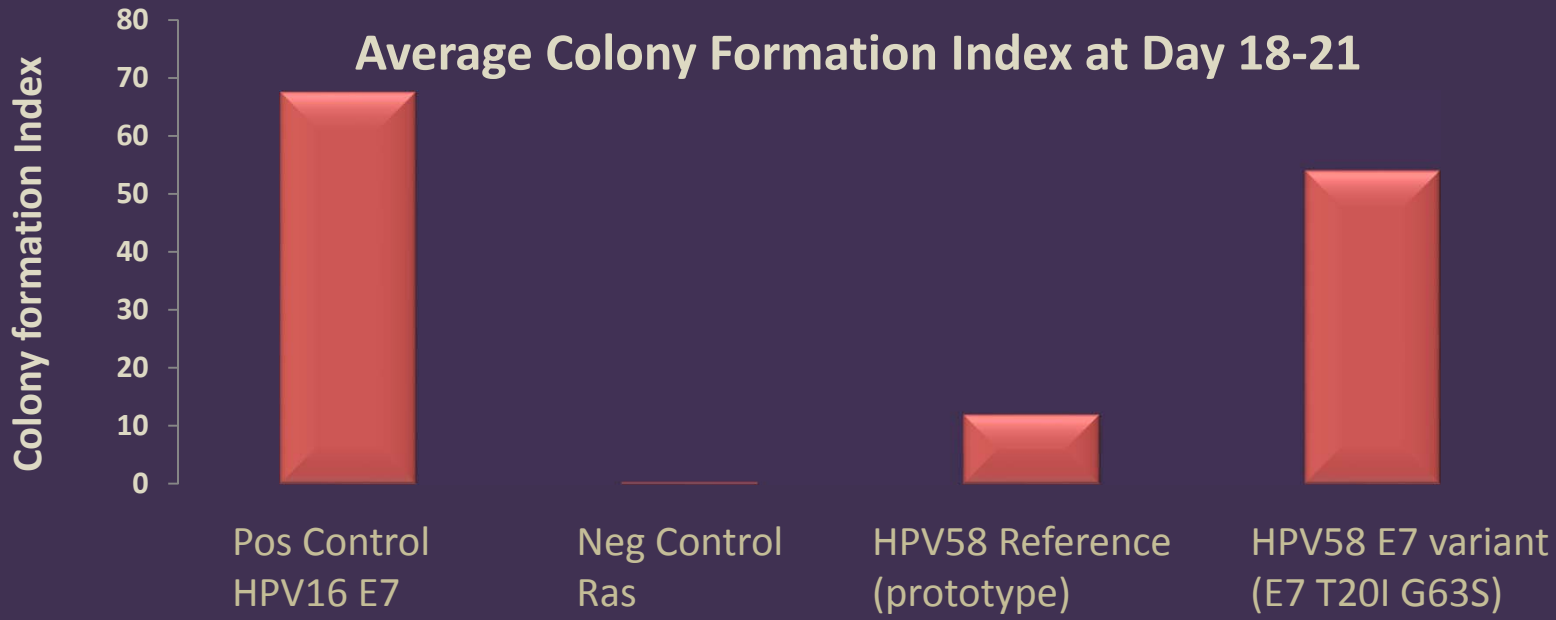
Transformation of primary baby rat kidney cells with E7 protein

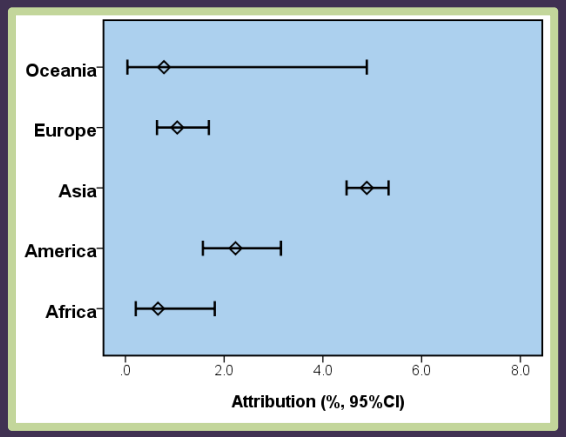
HPV58 Prototype E7



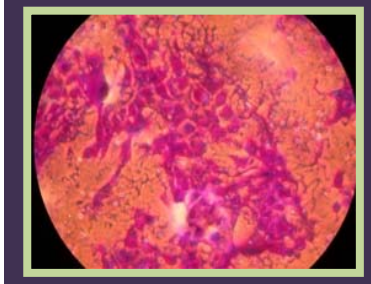
HPV58 E7 Variant: E7 T20I G63S





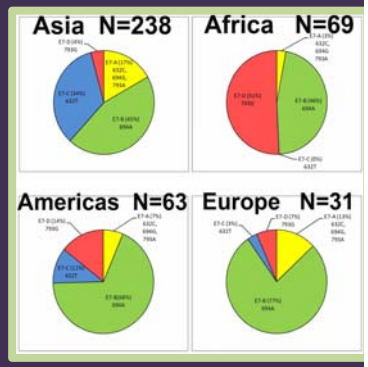


HPV58 disease burden

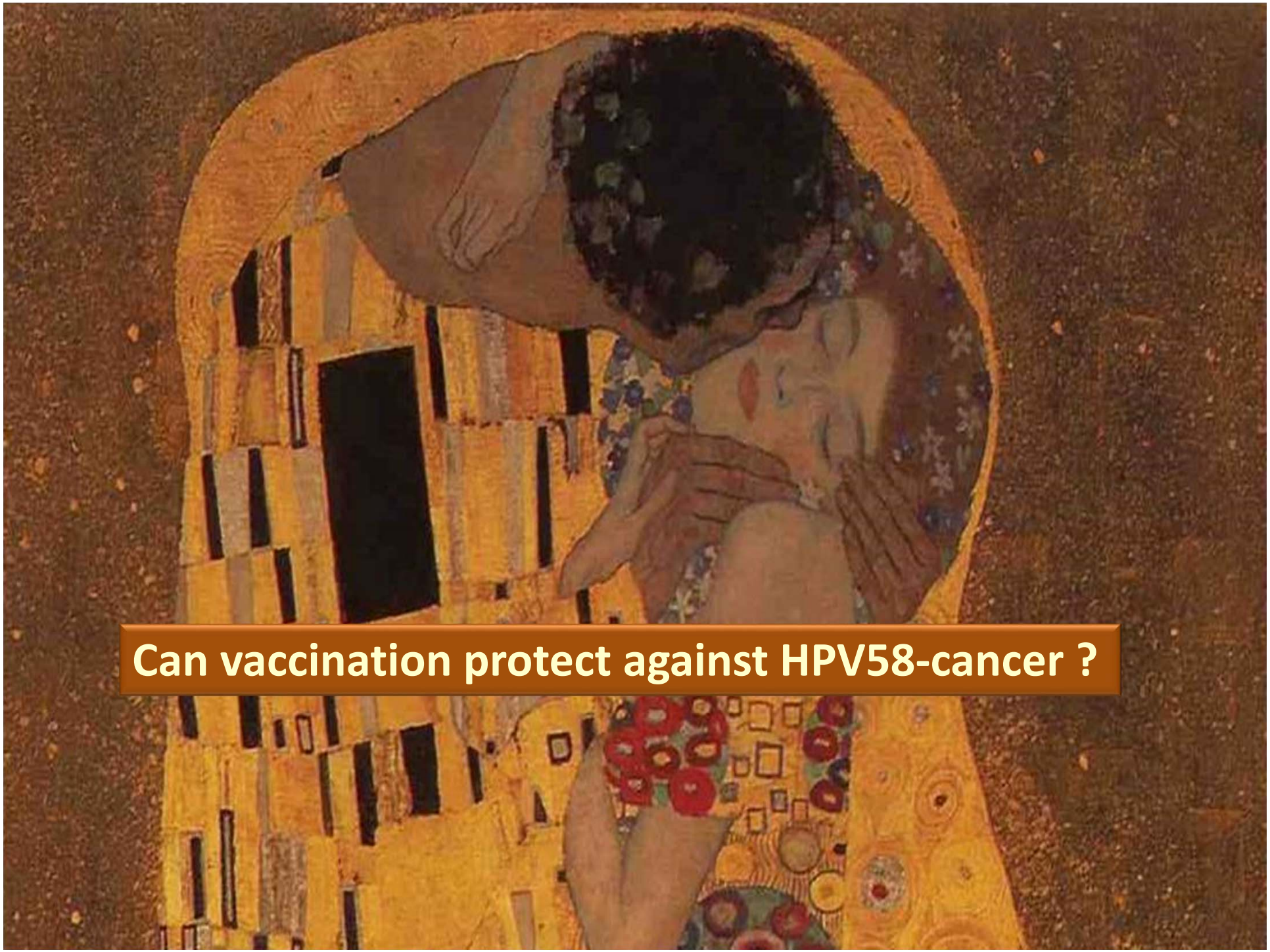


variant oncogenicity

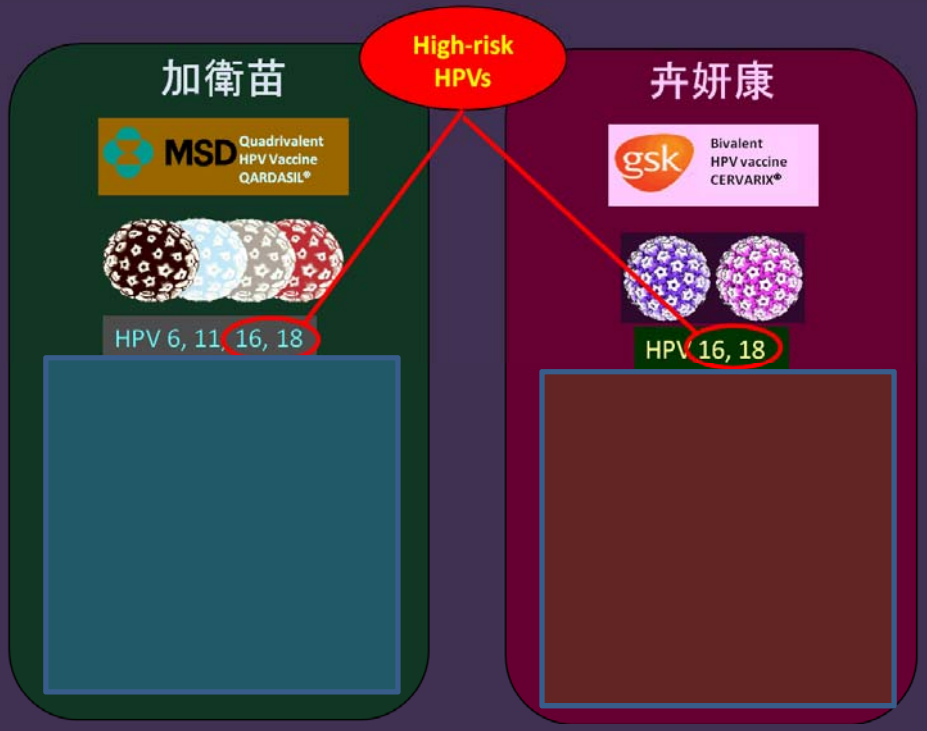
geographical distribution



East Asian host genetic susceptibility


Can vaccination protect against HPV58-cancer ?

1st generation vaccines



Relies on cross-protection

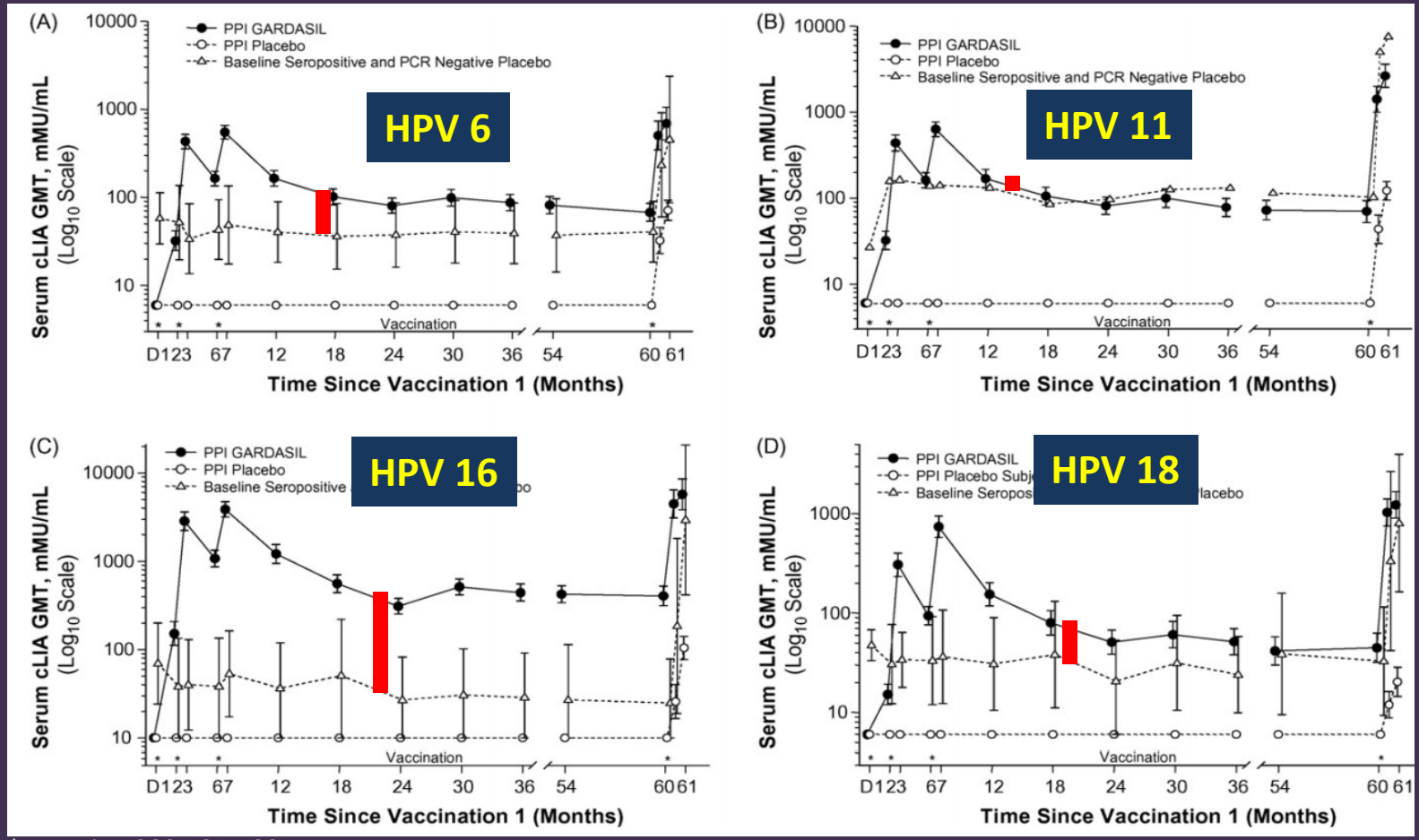
Bi-valent vaccine is better

2nd generation vaccine

Nonavalent HPV vaccine

16 18 31 33 45 52 58 6 11

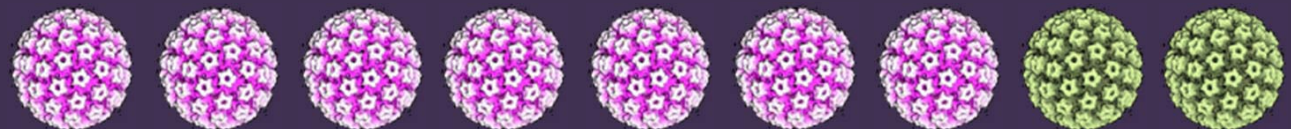
Antibody response to quadrivalent vaccine (1st generation)



Olsson et al., Vaccine 2007;25:4931

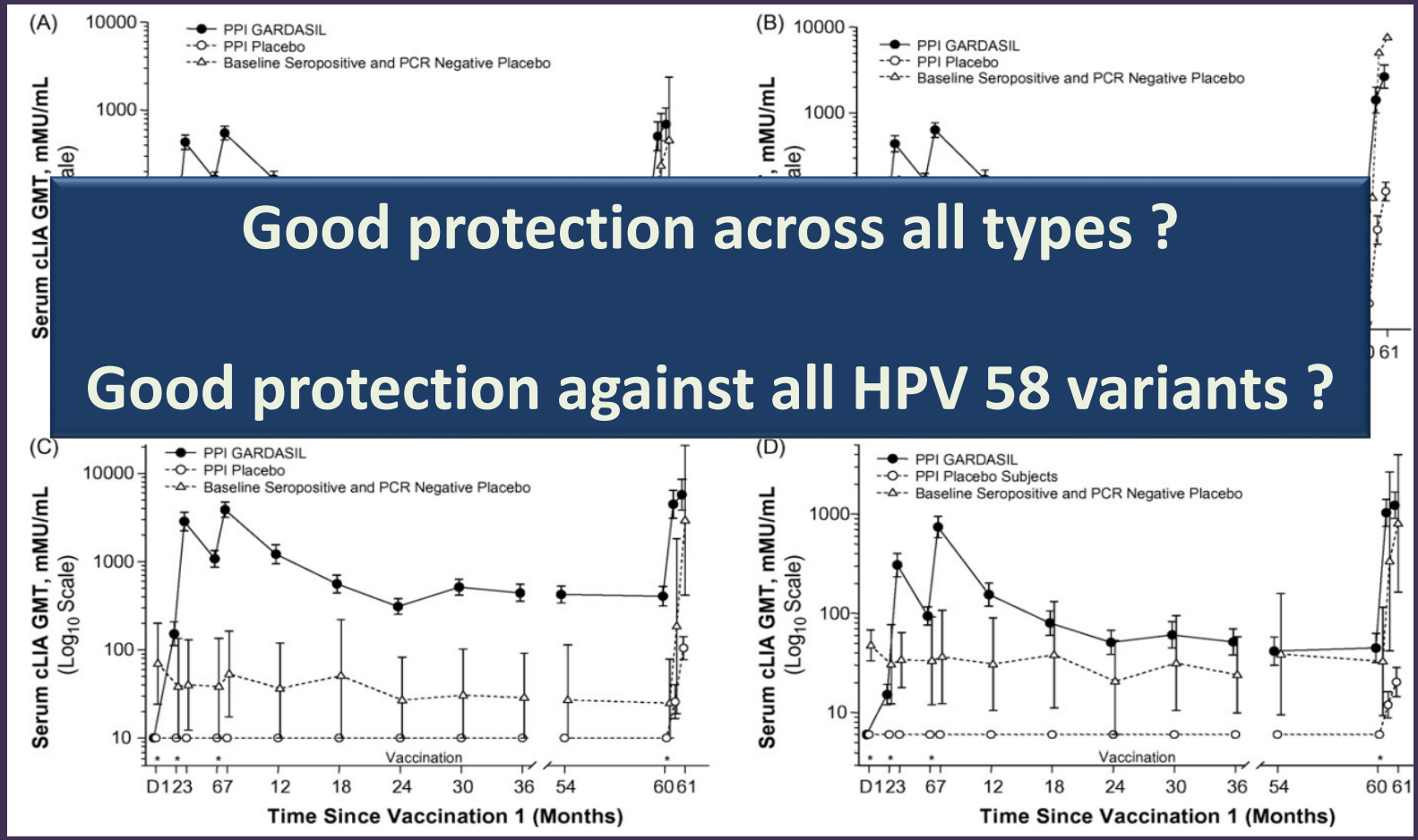
2nd generation vaccine

Nonavalent HPV vaccine



Good protection across all types ?

Good protection against all HPV 58 variants ?



Annual vaccination campaign since 2008

>1500 students / yr received

Voluntary, self-paid at a discount

香港中文大學
健康教育及促進健康中心

香港中文大學醫學院

The Hong Kong Institute of Family Education
香港家庭教育學院

香港醫學會沙田醫生網絡
HKMA – Sha Tin Doctors Network

Started 2011

1st dose free at school

2nd & 3rd dose at doctor's clinic at market price

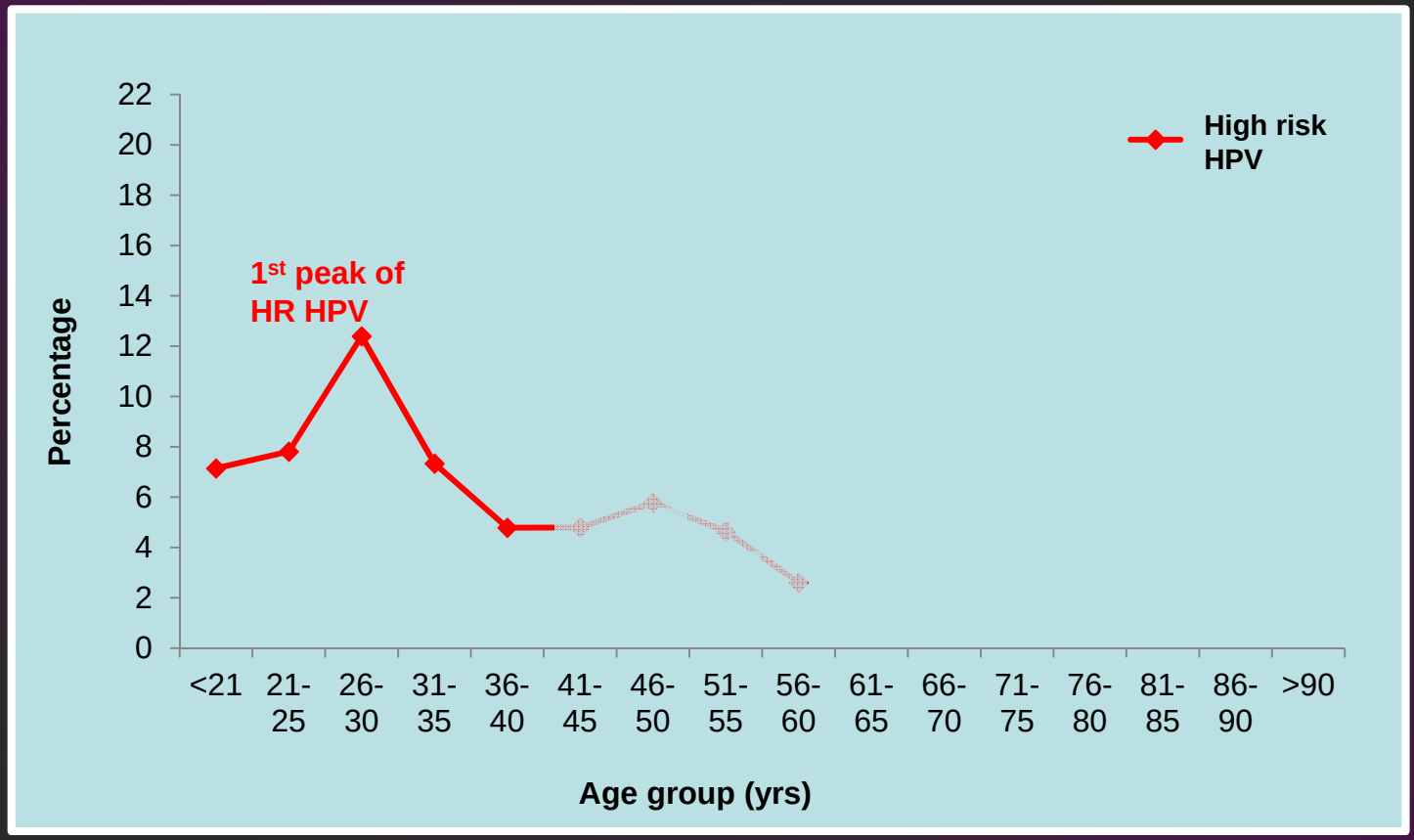
>3000 students received

How to improve cervical cancer screening in Hong Kong ?

Age-specific prevalence of high-risk HPV infection in HK

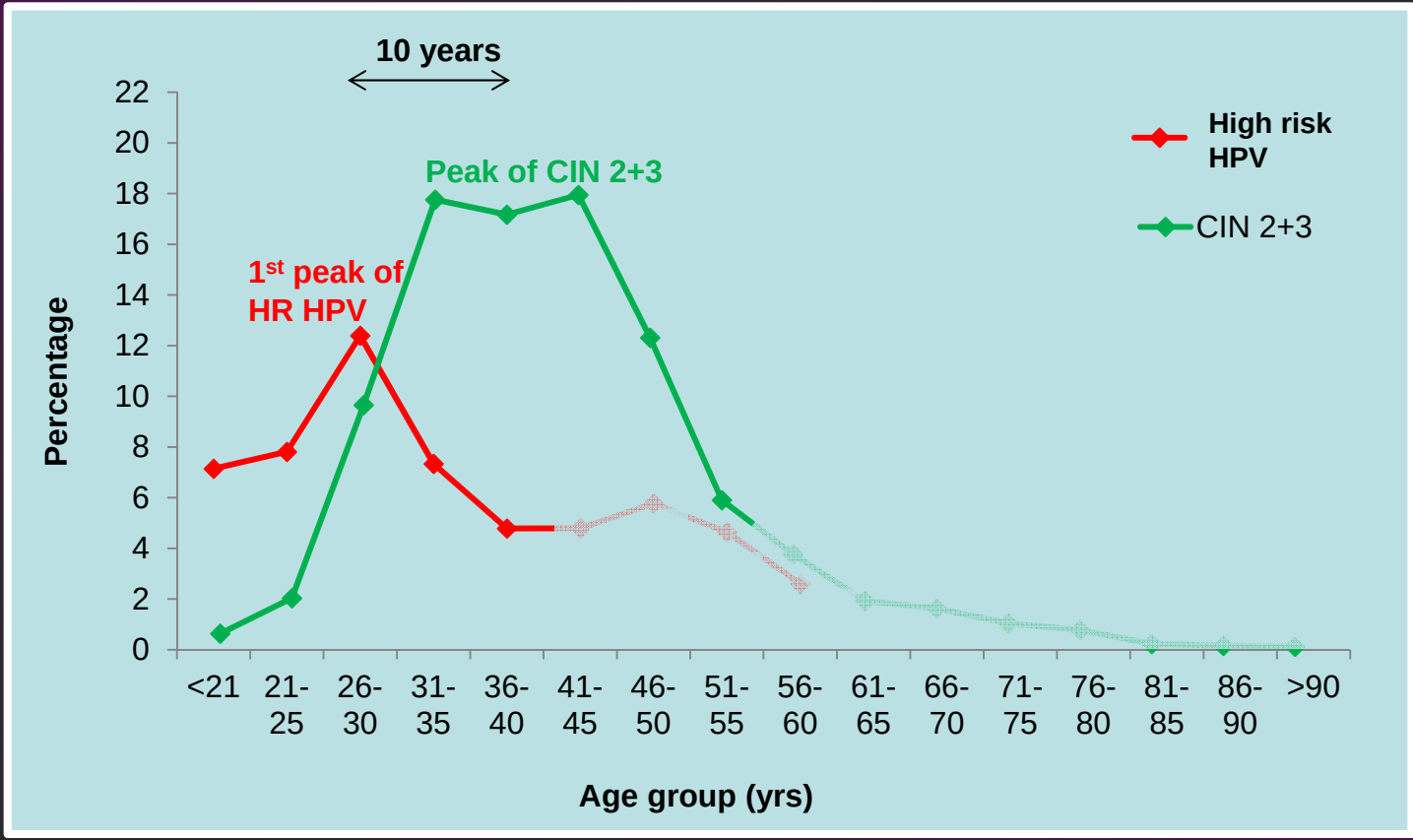
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

1st high-risk HPV infection peak in Hong Kong



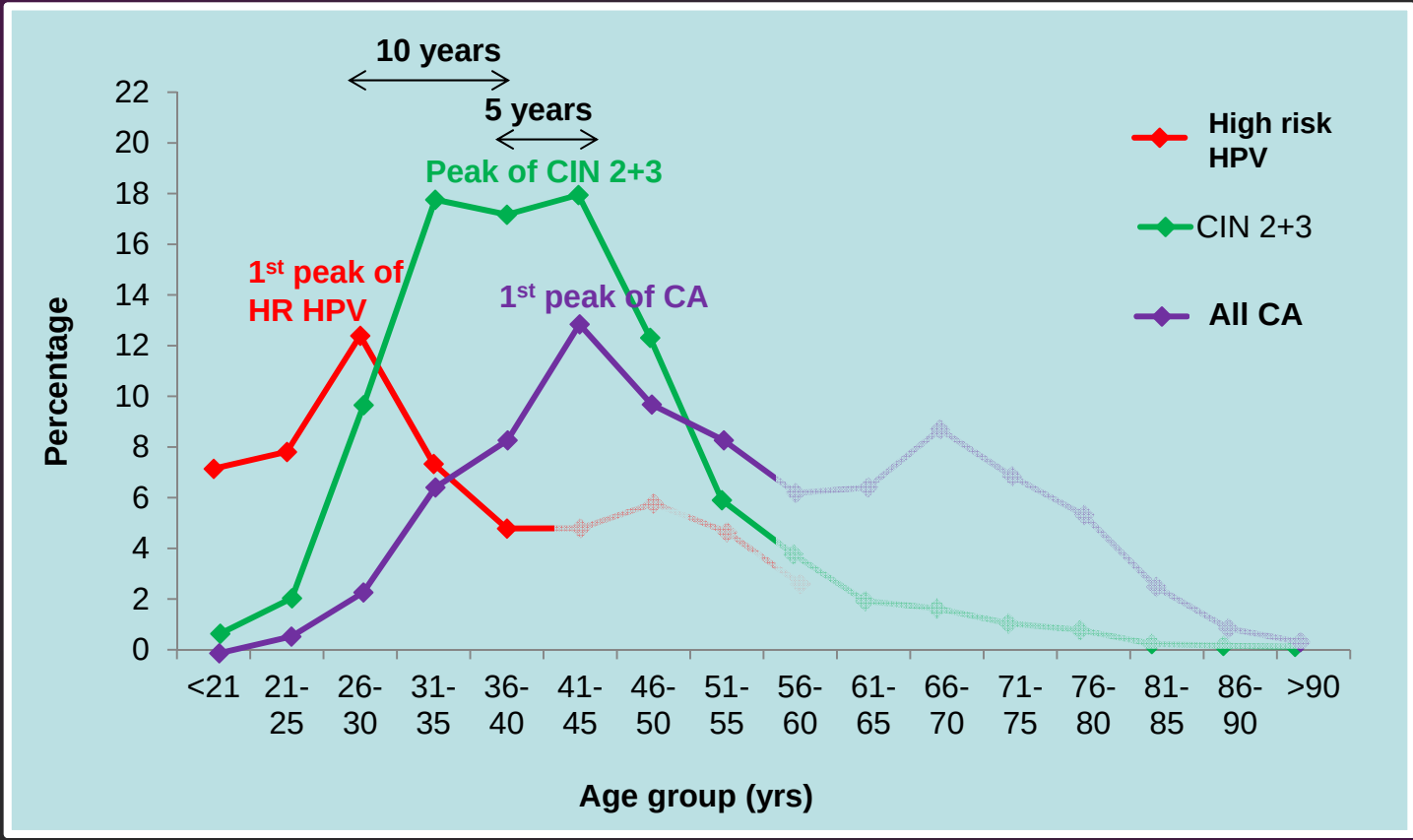
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

Age distribution of CIN 2 / 3 following 1st infection peak



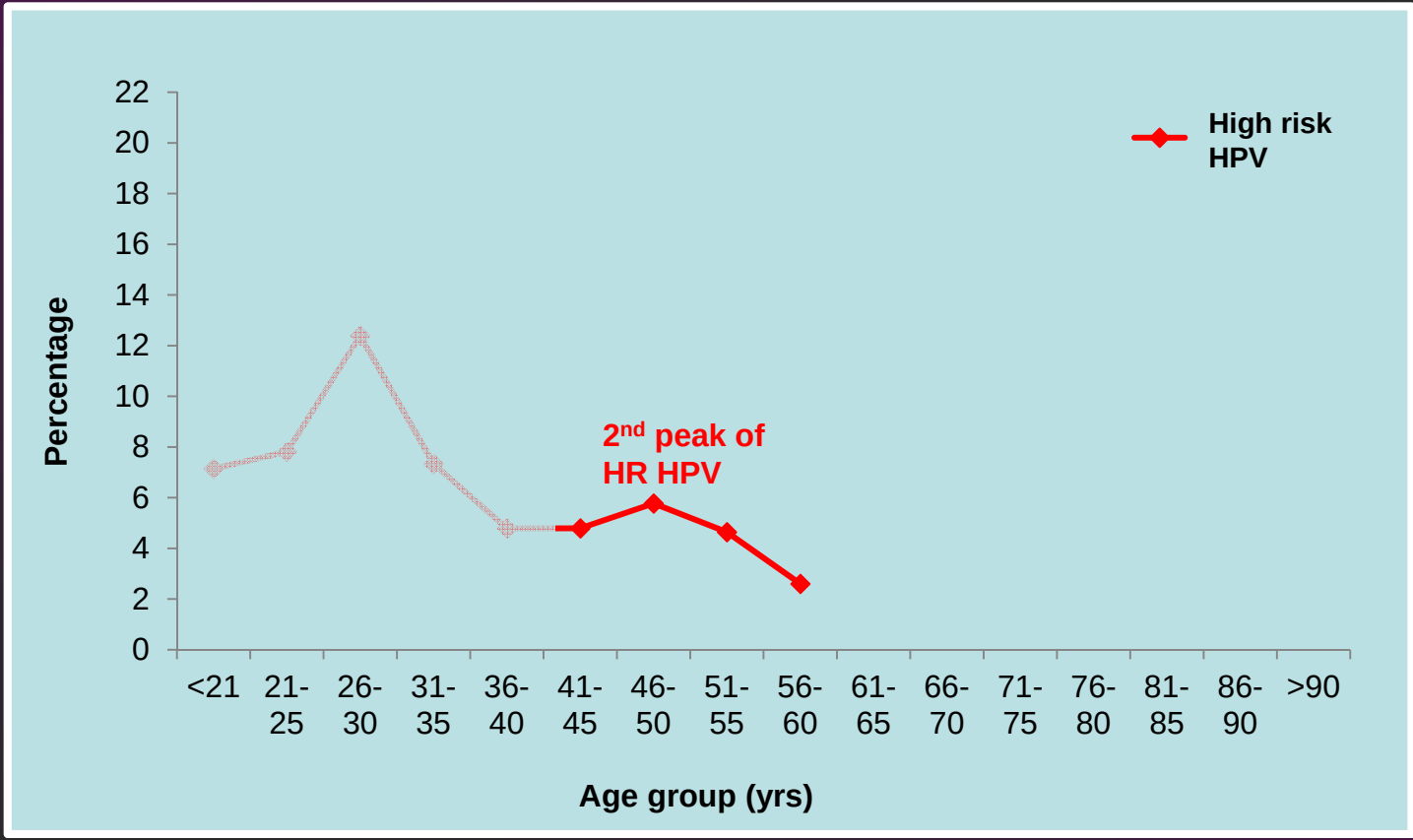
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

Age distribution of CIN 2 / 3, cervical cancer following 1st infection peak



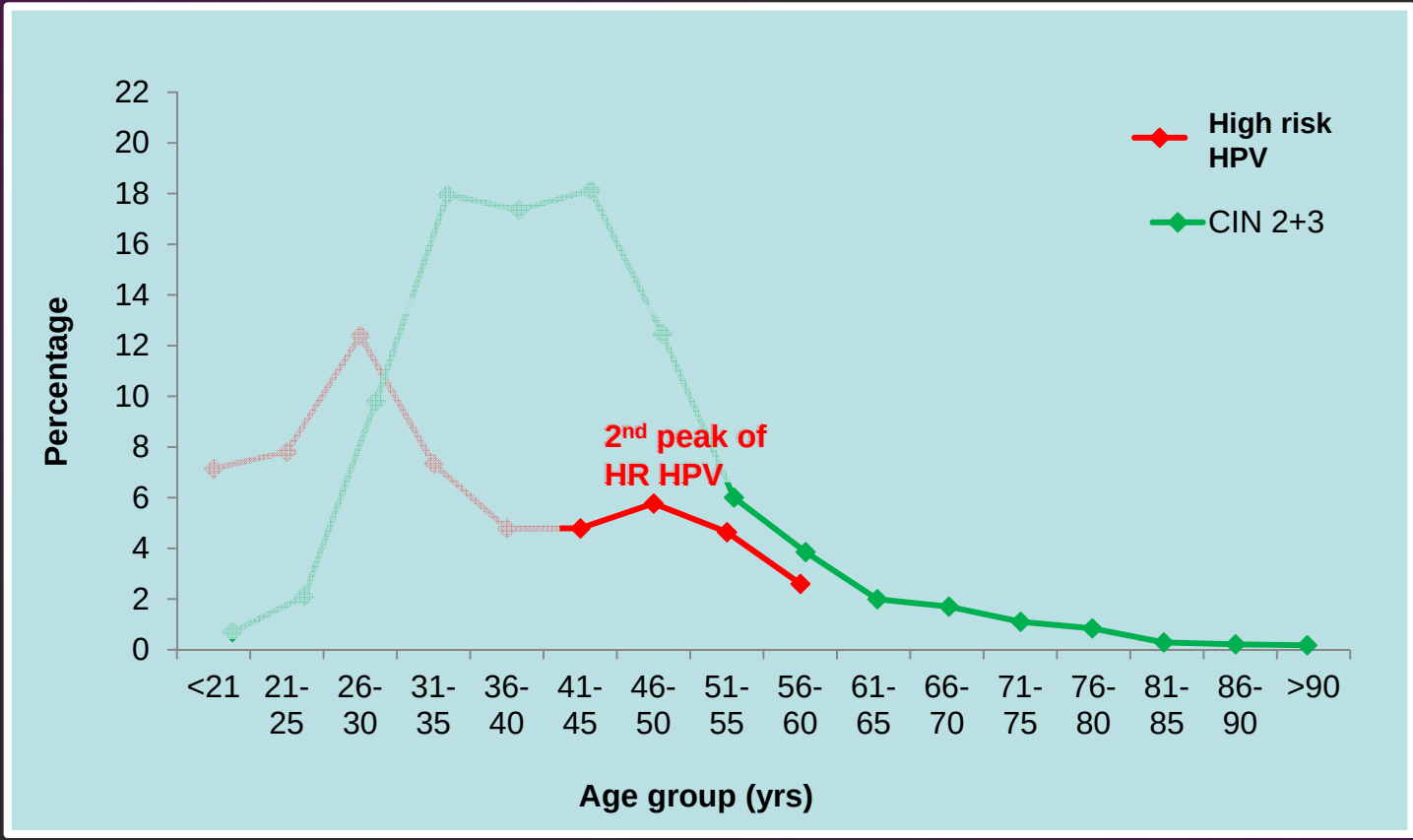
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

2nd high-risk HPV infection peak in Hong Kong



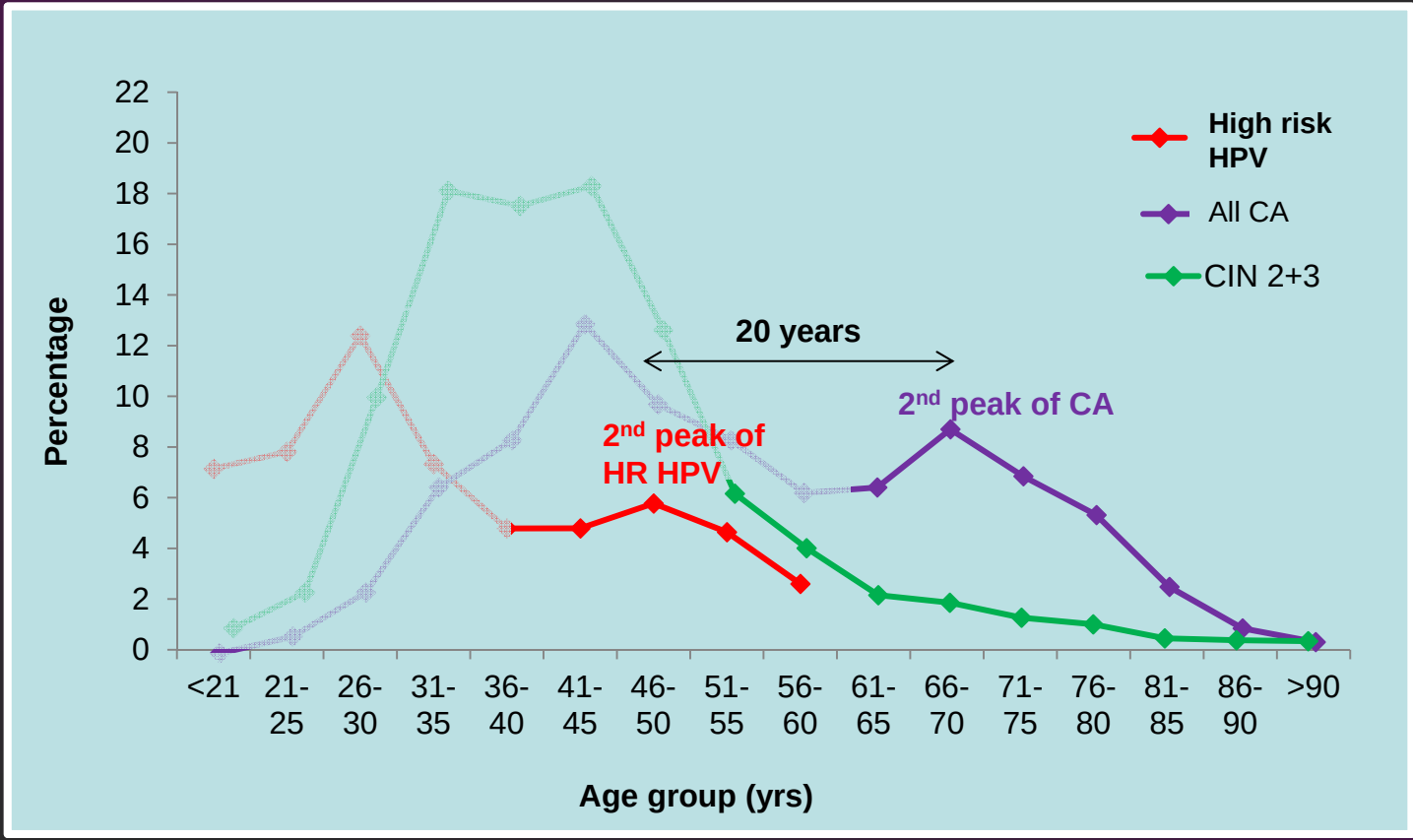
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

Age distribution of CIN 2 / 3, cervical cancer following 2nd infection peak



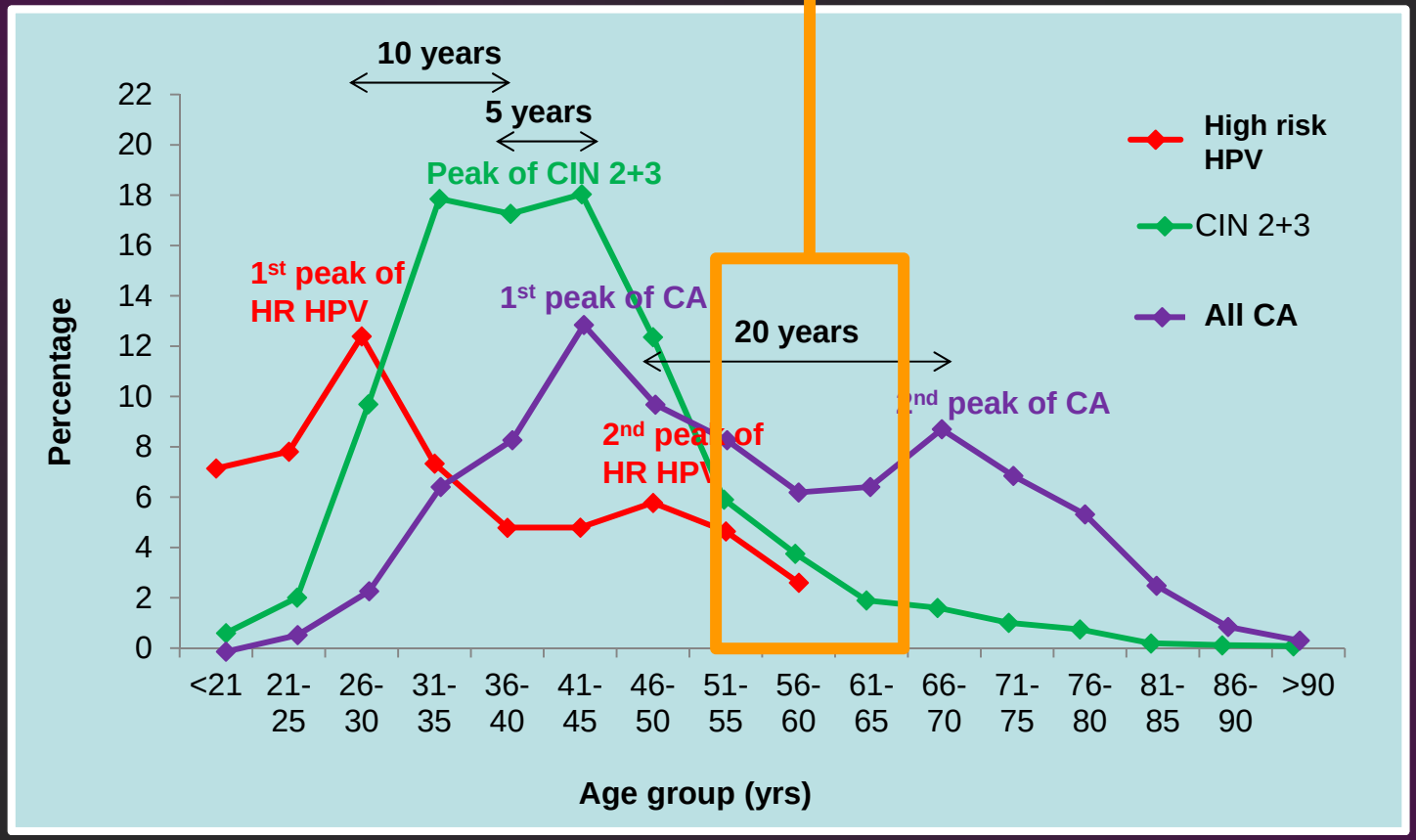
Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

Age distribution of CIN 2 / 3, cervical cancer following 2nd infection peak



Chan et al. Age distribution of HPV infection and cervical neoplasia reflects caveats of cervical screening policies. ***International Journal Cancer*** 2010; 126: 297

2nd CIN 2/3 peak expected at 51-65 yr NOT observed
Poor screening rate ?
Poor screening sensitivity ?



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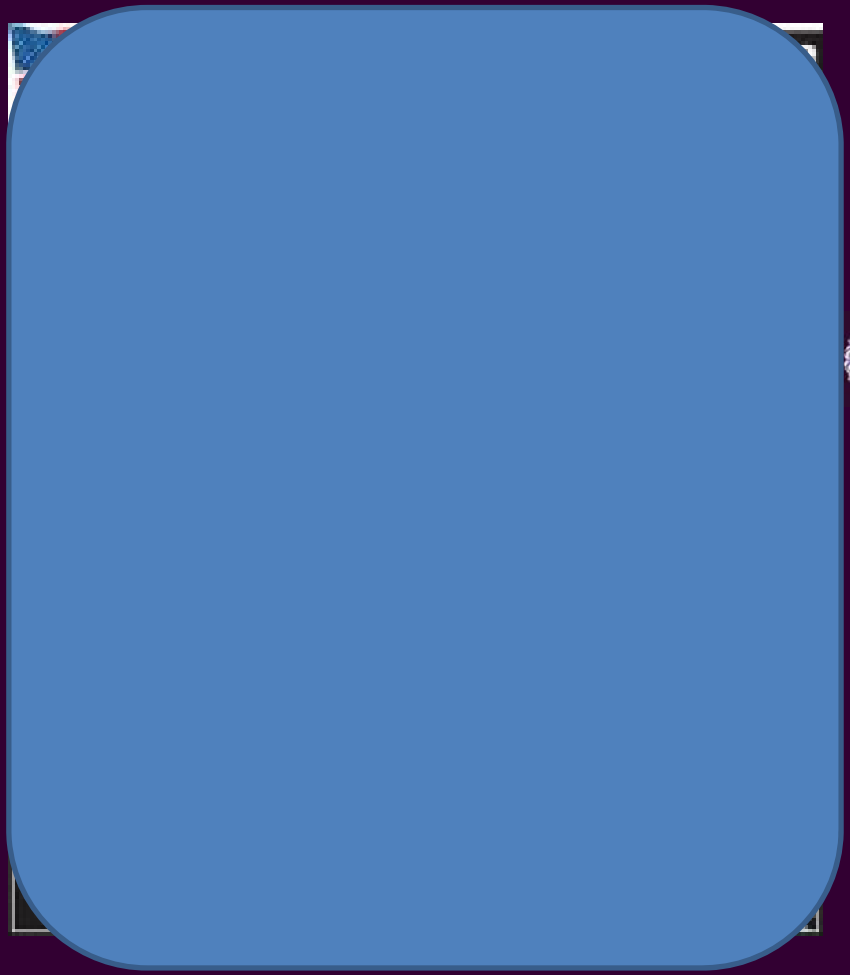
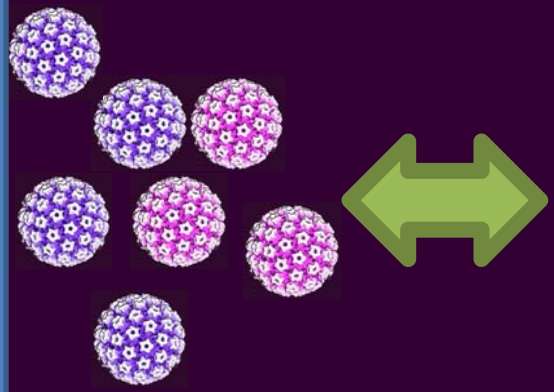
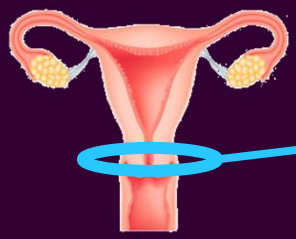
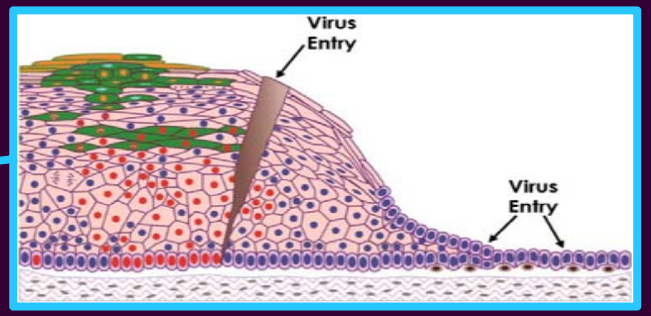






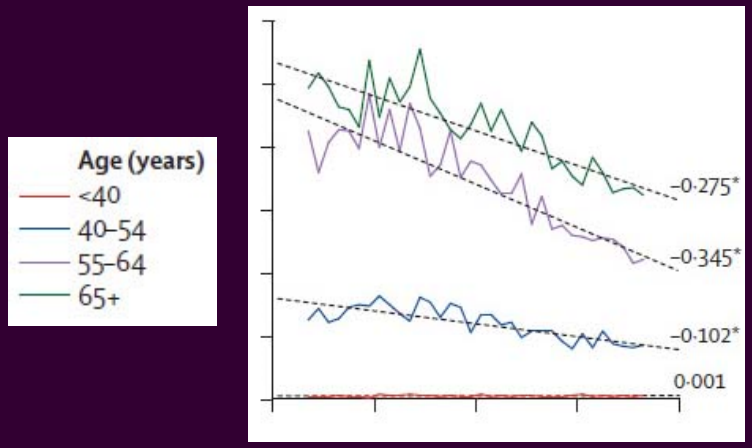


Transformation zone

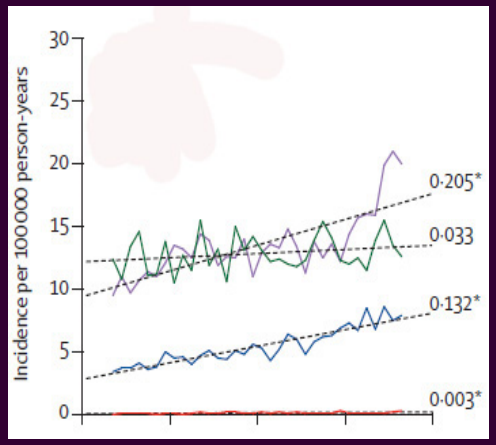
Palatine & lingual tonsils

Changes in incidence of head & neck cancers 1973-2006, USA

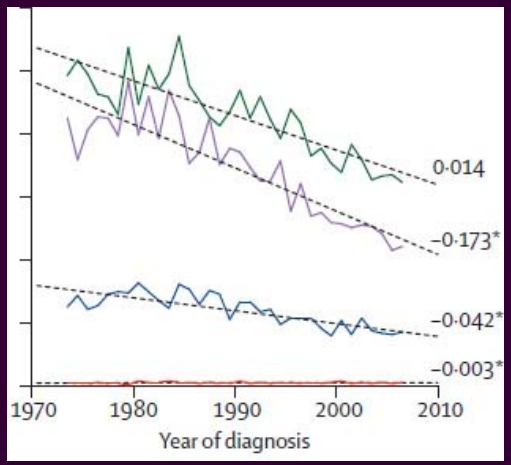
NOT HPV-related sites, men



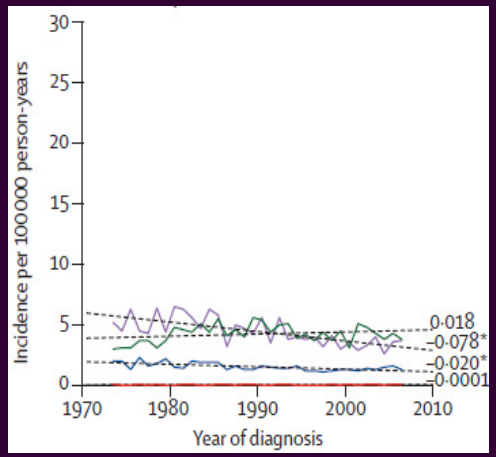
HPV-related sites, Men



NOT HPV-related sites, women

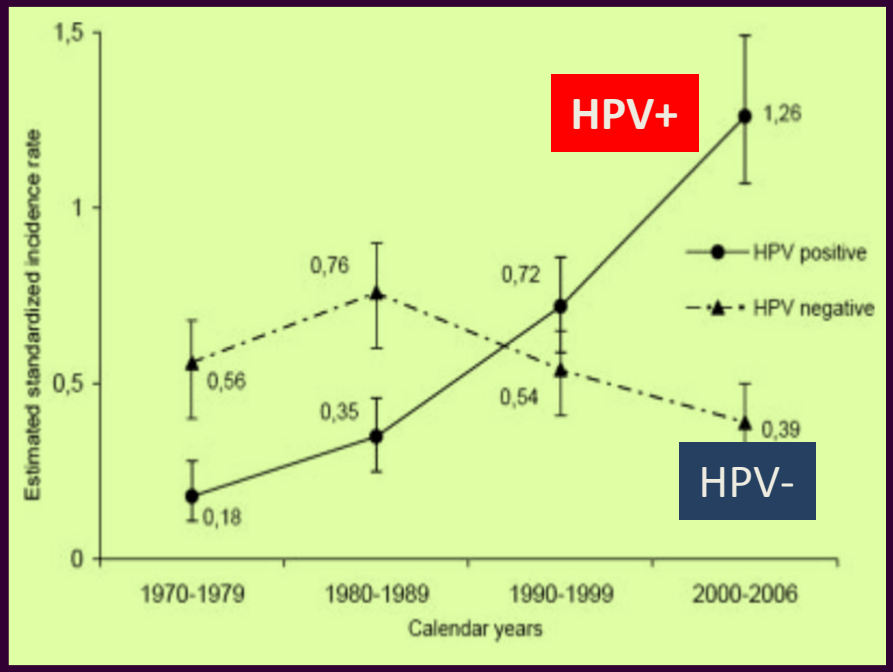


HPV-related sites, Women

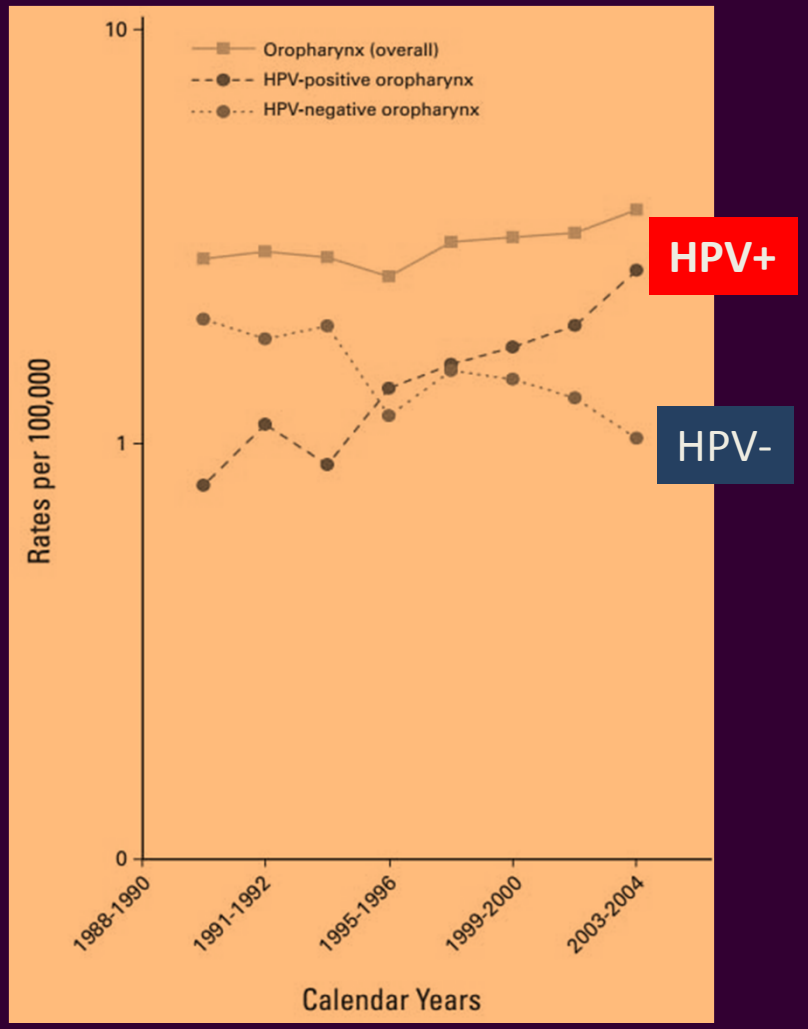


Lancet Oncology 2010; 11: 781

Tonsillar SCC Stockholm 1970-2006,

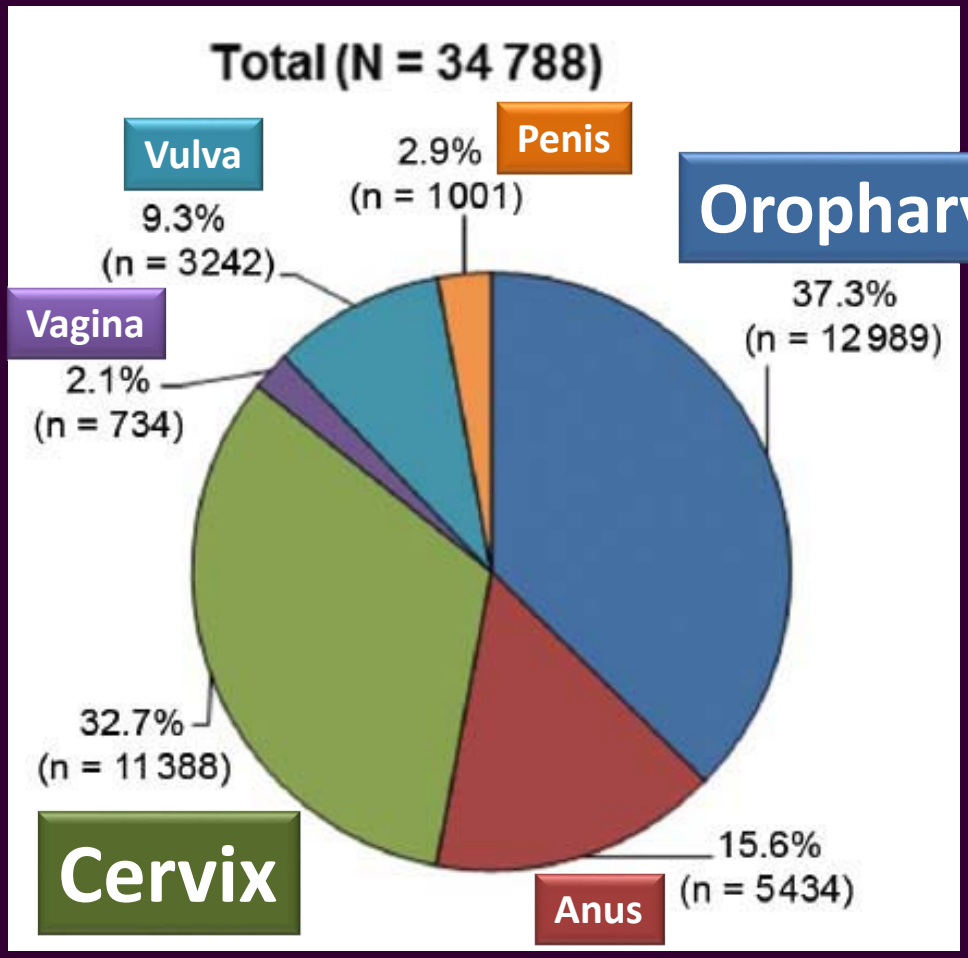


Oropharyngeal SCC Hawaii, Iowa, Los Angeles 1988-2004



Int J Cancer 2009; 125: 362
J Clin Oncol 2011; 32: 4294

No. of new cancers at anatomical sites and cellular types
in which HPV is frequently found
USA, 2009



Estimated contribution of HPV:

Cervical cancer: ~100%

Anal cancer: 90%

Oropharyngeal cancer: >60%

Vagina, vulva, penile ~40%

THE LANCET Oncology

Volume 11, Issue 8, August 2010, Pages 781–789

HPV-associated head and neck cancer: a virus-related cancer epidemic

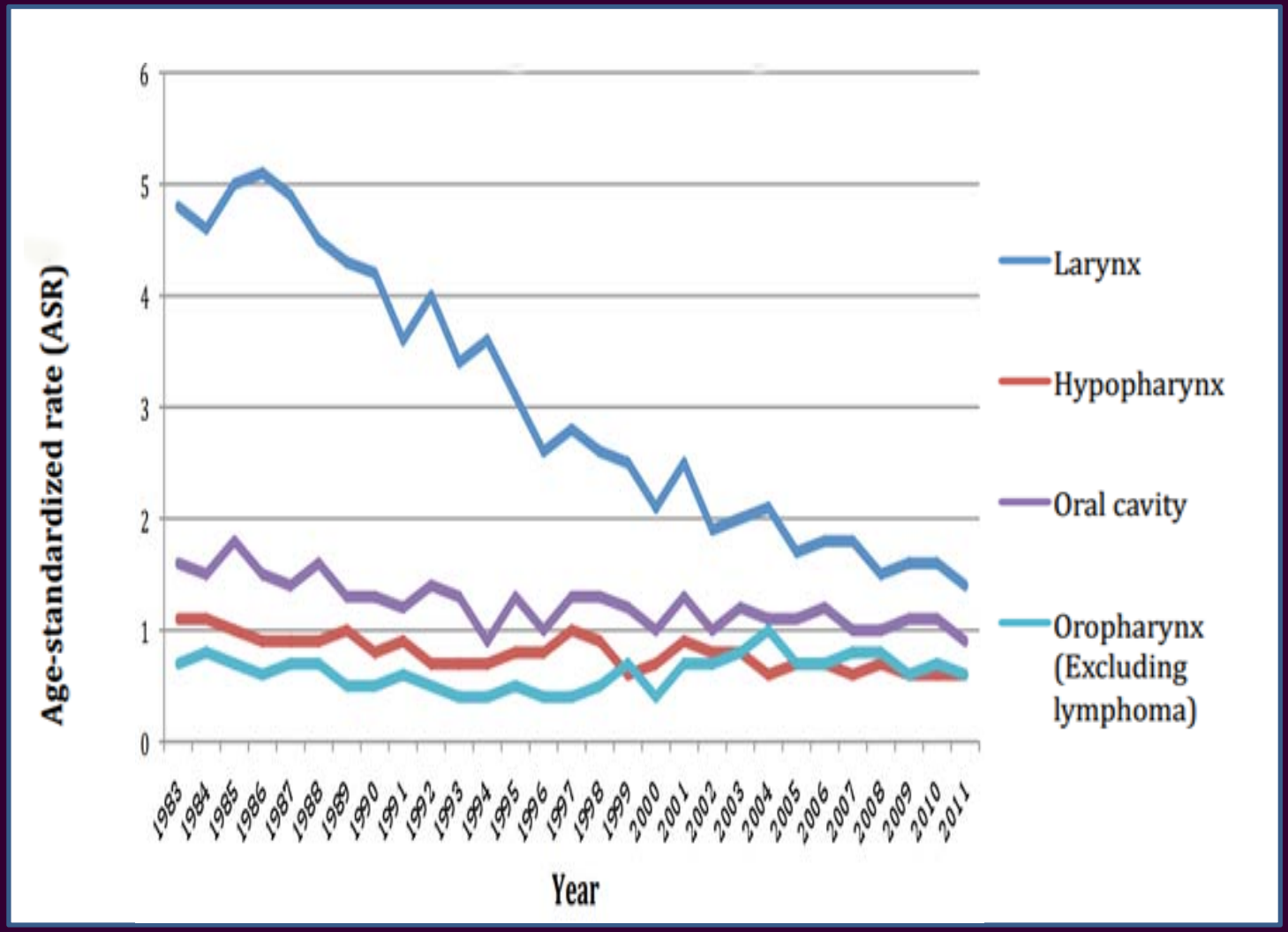
Shanthi Marur, Gypsyamber D'Souza, William H Westra, Arlene A Forastiere

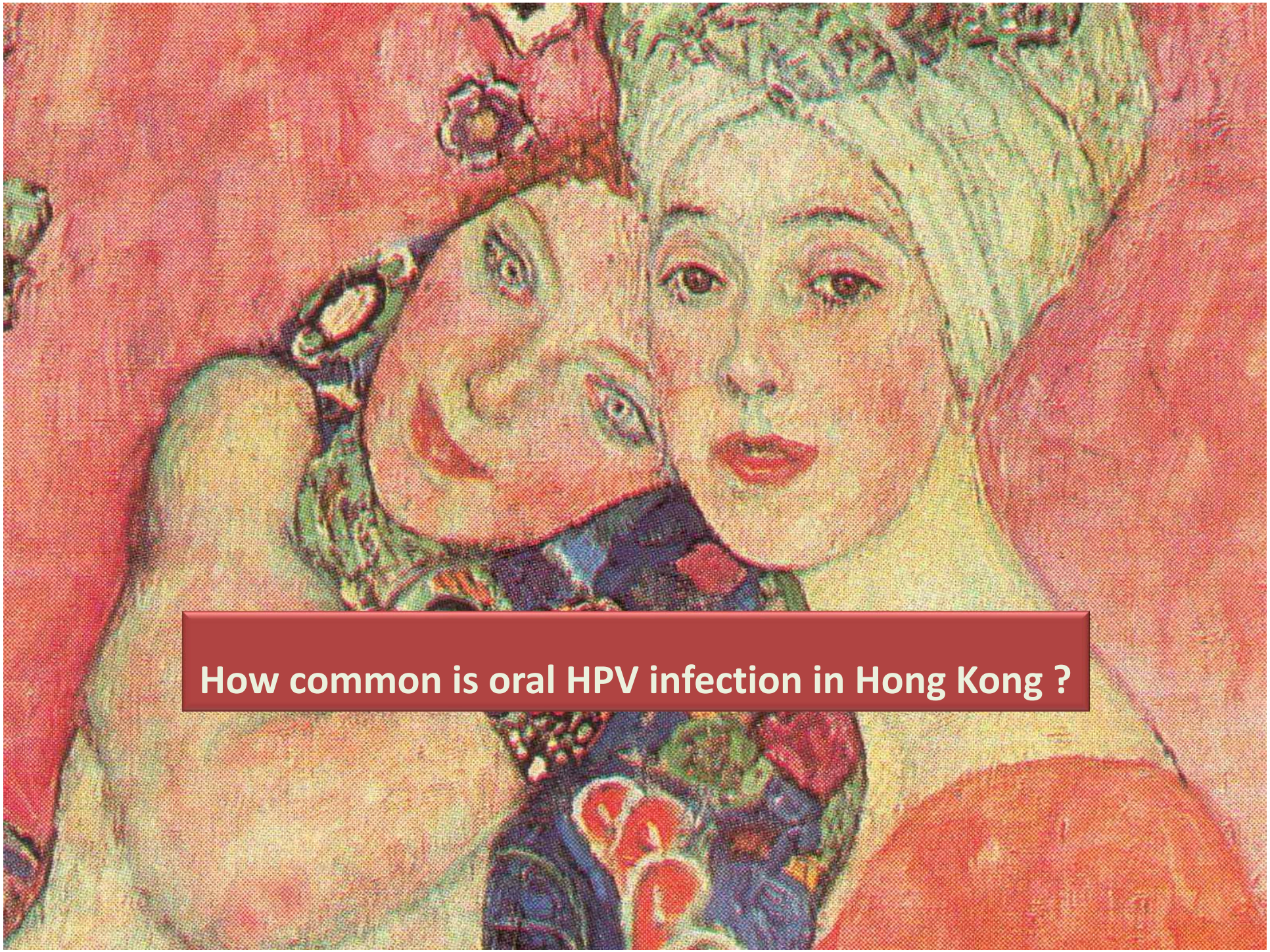
A rise in incidence of oropharyngeal squamous cell cancer—specifically of the lingual and palatine tonsils—in white men younger than age 50 years who have no history of alcohol or tobacco use has been recorded over the past decade. This malignant disease is associated with human papillomavirus (HPV) 16 infection. The biology of HPV-positive oropharyngeal cancer is distinct with P53 degradation, retinoblastoma RB pathway inactivation, and P16 upregulation.

Lancet Oncol 2010; 11: 781–89

Published Online
May 6, 2010
DOI:10.1016/S1470-

Incidence of head & neck cancers in Hong Kong 1983 - 2011




How common is oral HPV infection in Hong Kong ?

	Heterosexual men	Homosexual men	Commercial sex worker	
	N = 201	N = 149	N = 100	
HPV				
Oral	4.5%	5.4%	3.0%	
Peri-anal	8.0%	32.2%		
Penile	17.4%	10.1%	29.0%	cervical

Heterosexual men

N = 201

Homosexual men

N = 149

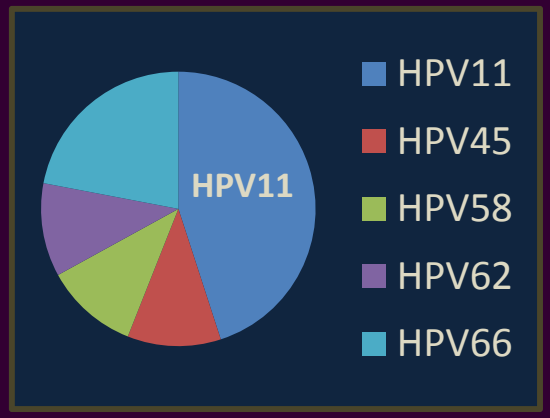
Commercial sex worker

N = 100

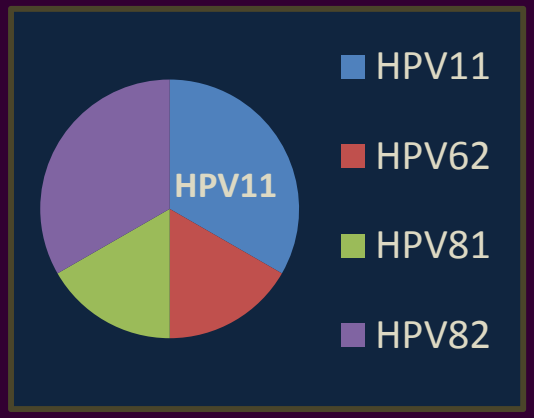
HPV

Oral

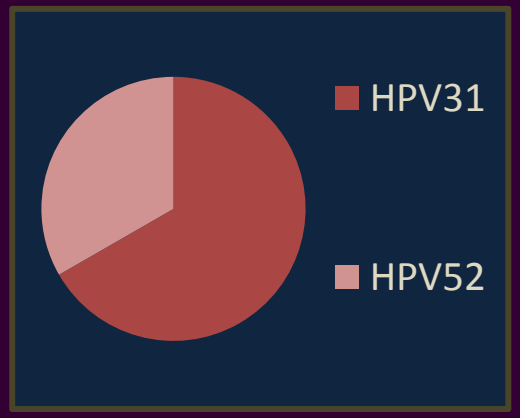
4.5%



5.4%



3.0%



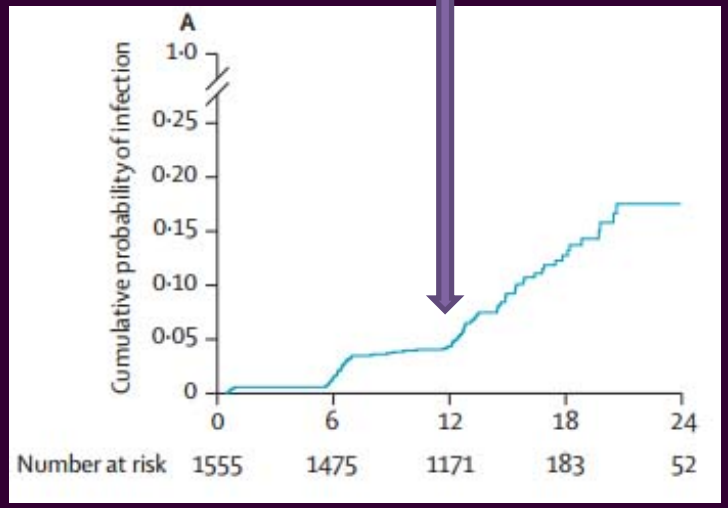
HPV Infection in Men (HIM) study Lancet 2013; 382: 877

Brazil, Mexico, USA

1626 men, age 18-73 yr, healthy, HIV-negative

HPV test every 6 month

4.4% acquired oral HPV (all types) / yr
1.7% acquired oral oncogenic HPV / yr



Acquisition rate of oncogenic HPV / 1000 person-months

Oral: 2.5

Genital : 22.2

Anal : 3.7

HPV Infection in Men (HIM) study Lancet 2013; 382: 877

Brazil, Mexico, USA

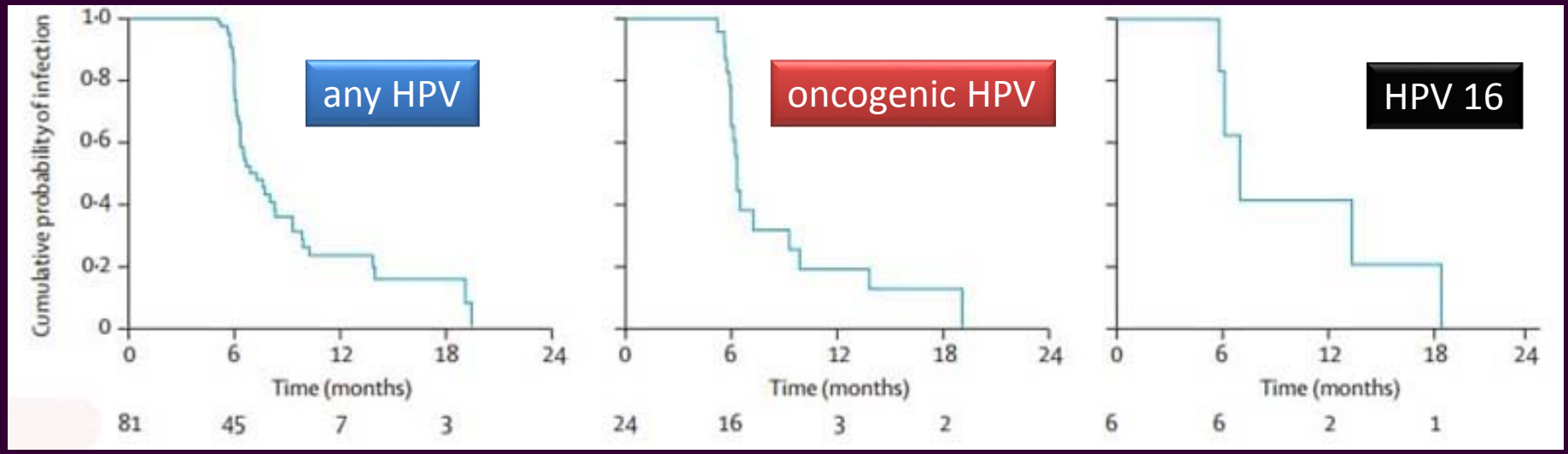
1626 men, age 18-73 yr, healthy, HIV-negative

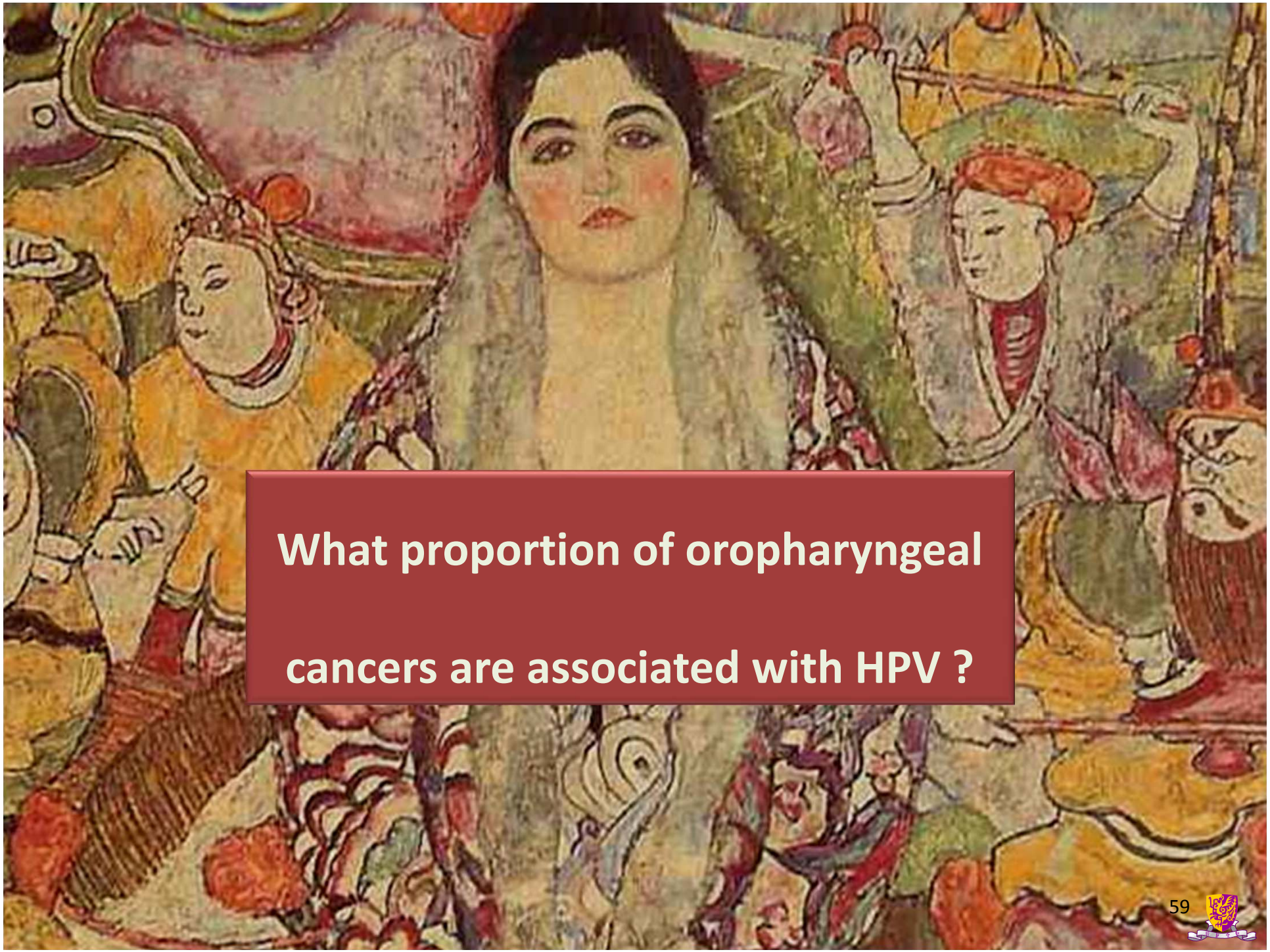
HPV test every 6 month

Clearance :

Most cleared < 1 yr

Similar across HPV groups

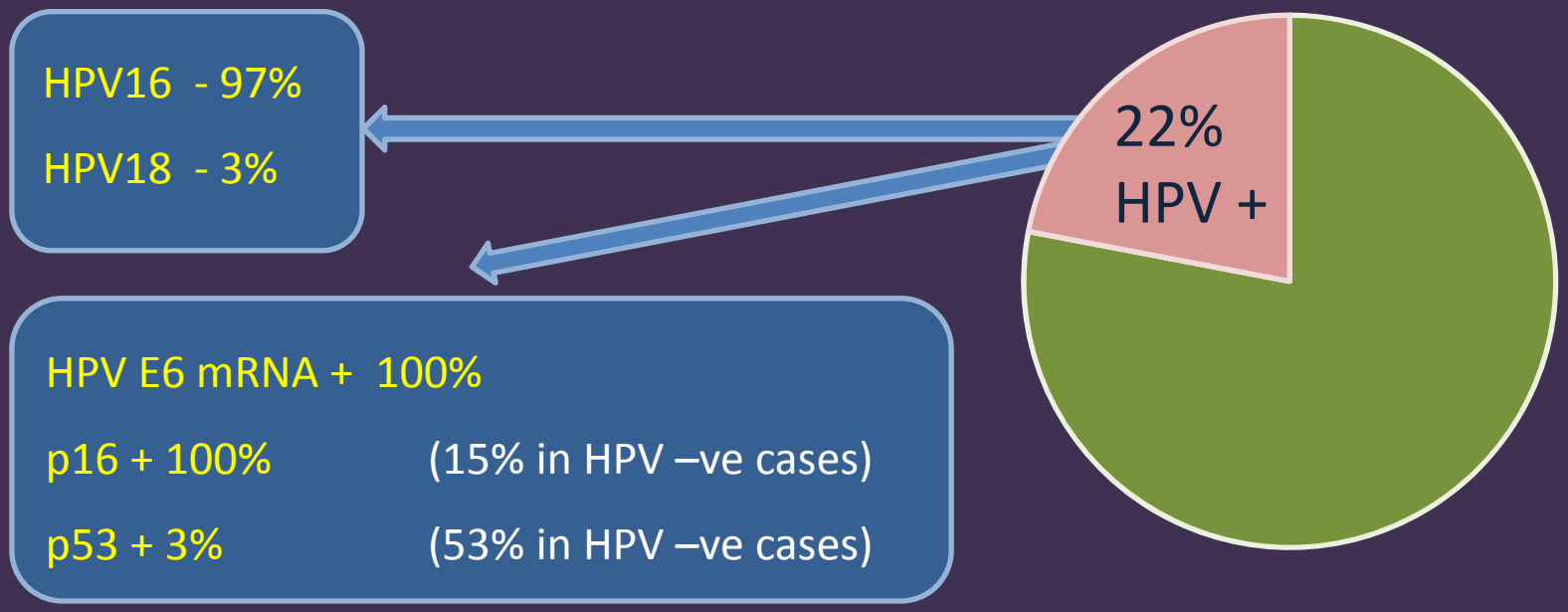



What proportion of oropharyngeal cancers are associated with HPV ?

2005-2009

9 HA hospitals

141 oropharyngeal squamous cell carcinoma



Unpublished preliminary data

Features of HPV + oropharyngeal squamous cell carcinoma

	HPV + N = 31	HPV - N = 110	P - value
< 50 yr	29%	11%	0.01
Female	26%	9%	0.01
Non-smoker	45%	14%	< 0.01
Non-drinker	59%	25%	< 0.01

Unpublished preliminary data

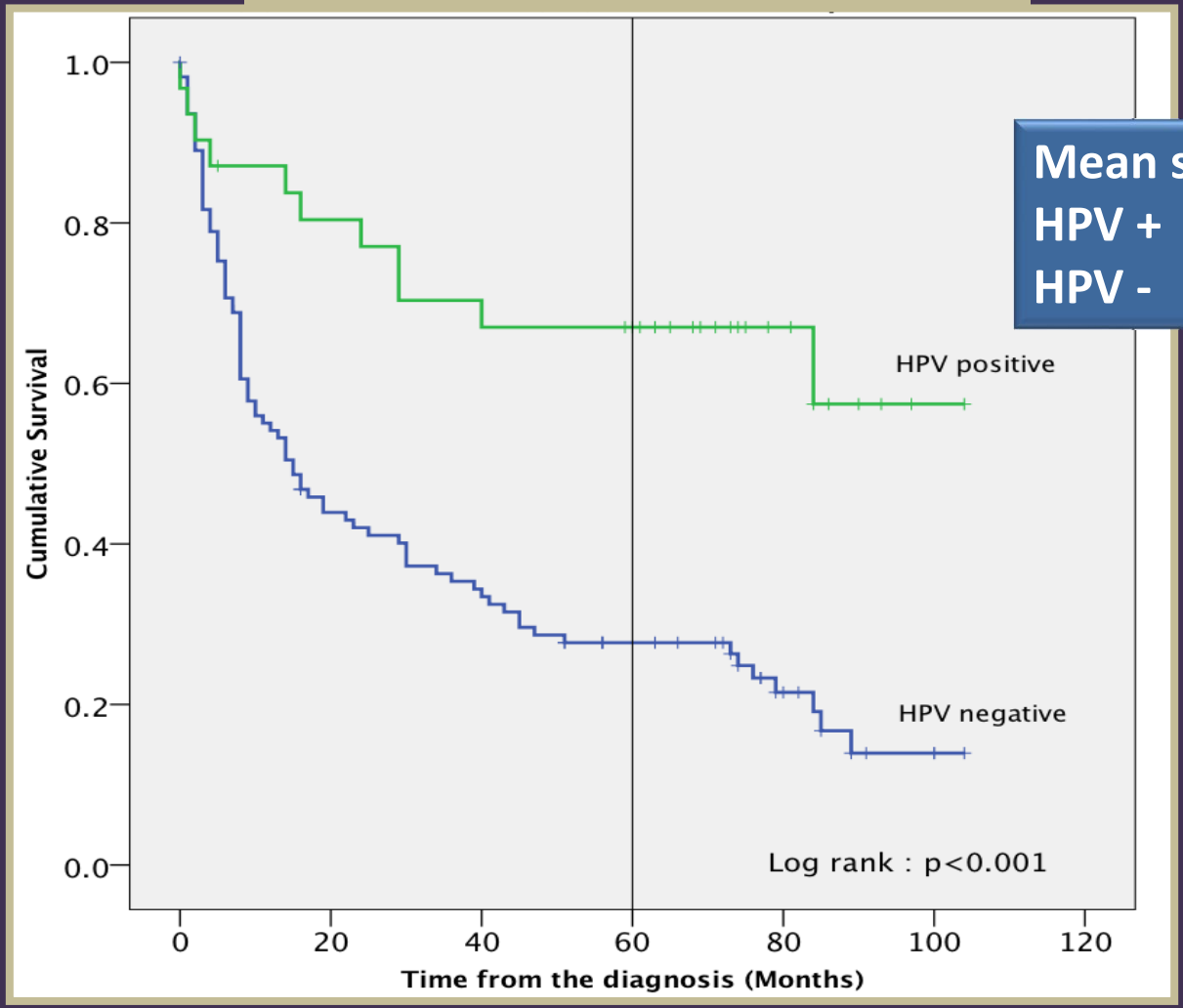
Features of HPV + oropharyngeal squamous cell carcinoma

	HPV + N = 31	HPV - N = 110	P - value
Early T stage (T1)	39%	11%	< 0.01
Basaloid differentiation	36%	7%	< 0.01
Lack keratinization	77%	45%	< 0.01
Lymphocyte infiltration	59%	25%	< 0.01

Unpublished preliminary data

Features of HPV + oropharyngeal squamous cell carcinoma

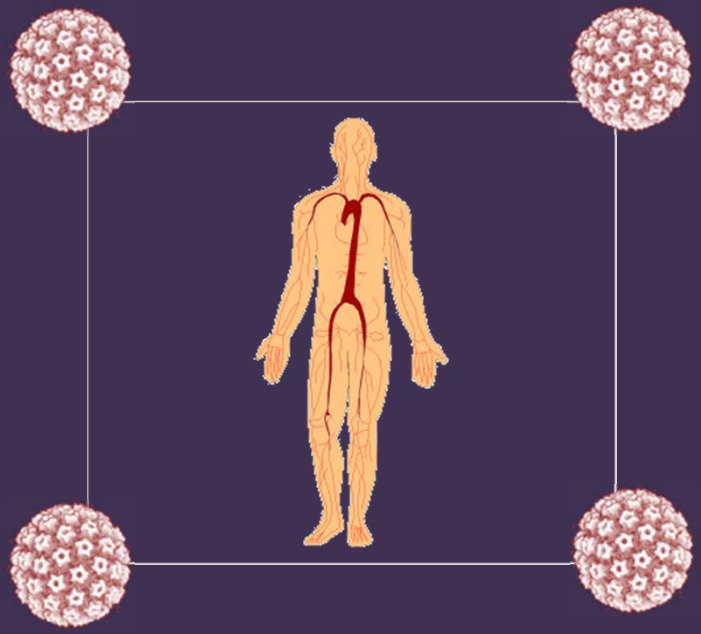
Overall survival of 141 OPSCC patients

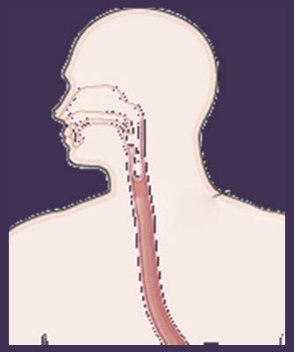


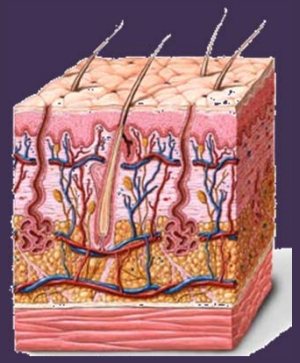
Mean survival:
HPV + 73 months
HPV - 36 months

Unpublished preliminary data

Oropharyngeal cancer (squamous cell carcinoma) in Hong Kong 2001-2011







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- Research Grant Council
- Research Fund for the Control of Infectious Diseases

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LS Tam
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SK Chan

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MC To

Pamela Youde Nethersole Eastern Hospital
WL Tang

United Christian Hospital
CY Leung

Laboratory Team & Students

2007

2014

The great father of HK pathologists

▲ *Dr Teoh: 2nd from left.*

Pathologue 2013; 22: 2