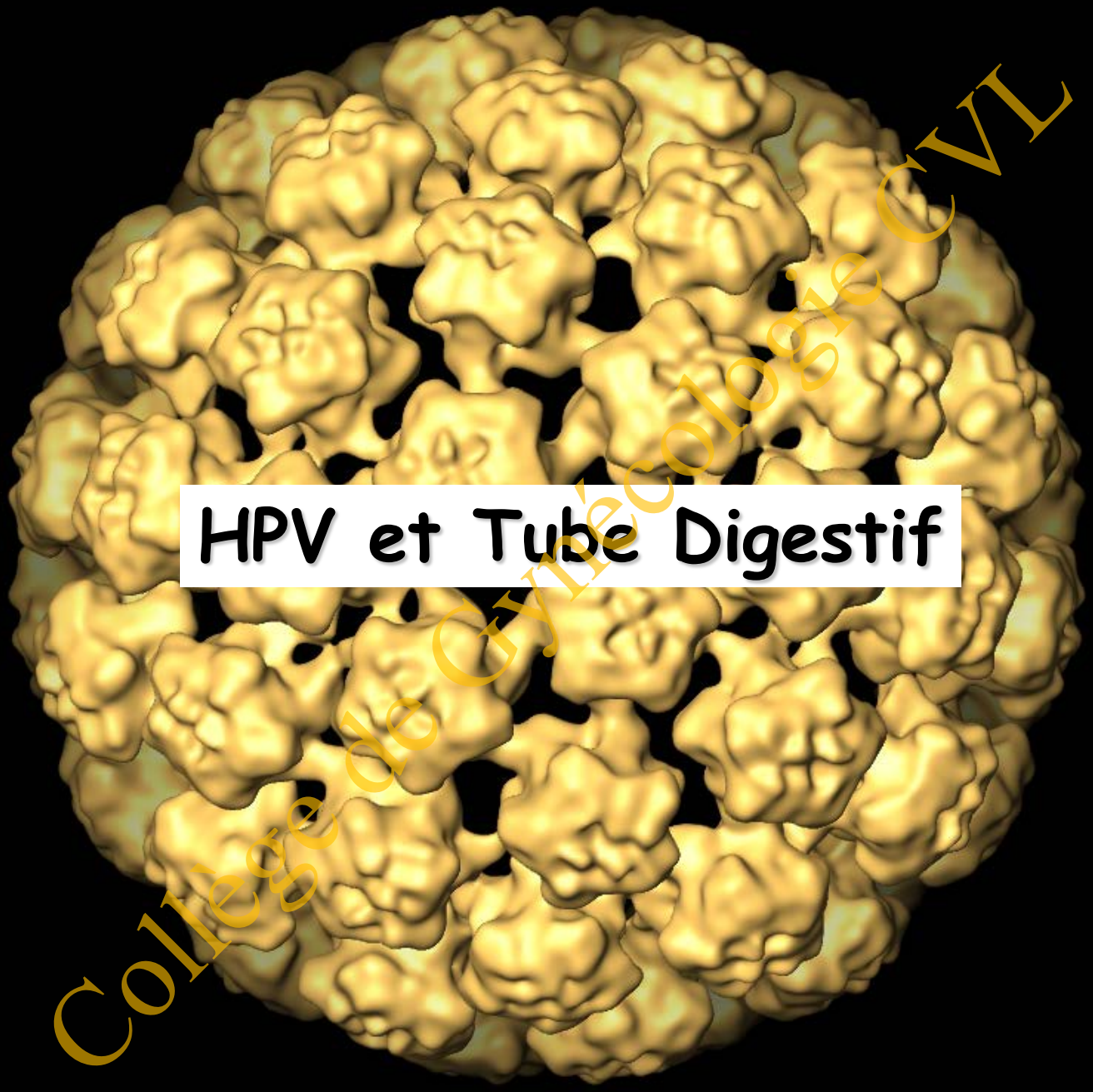
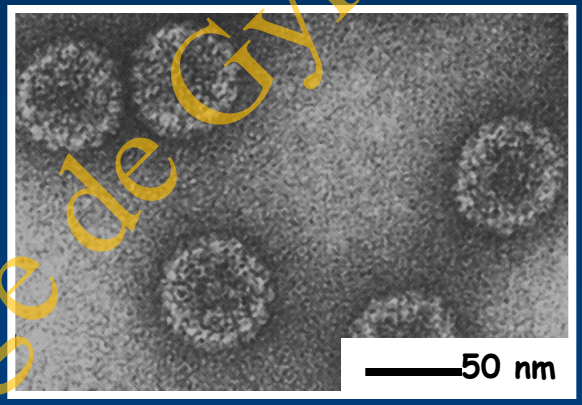


HPV et Tube Digestif

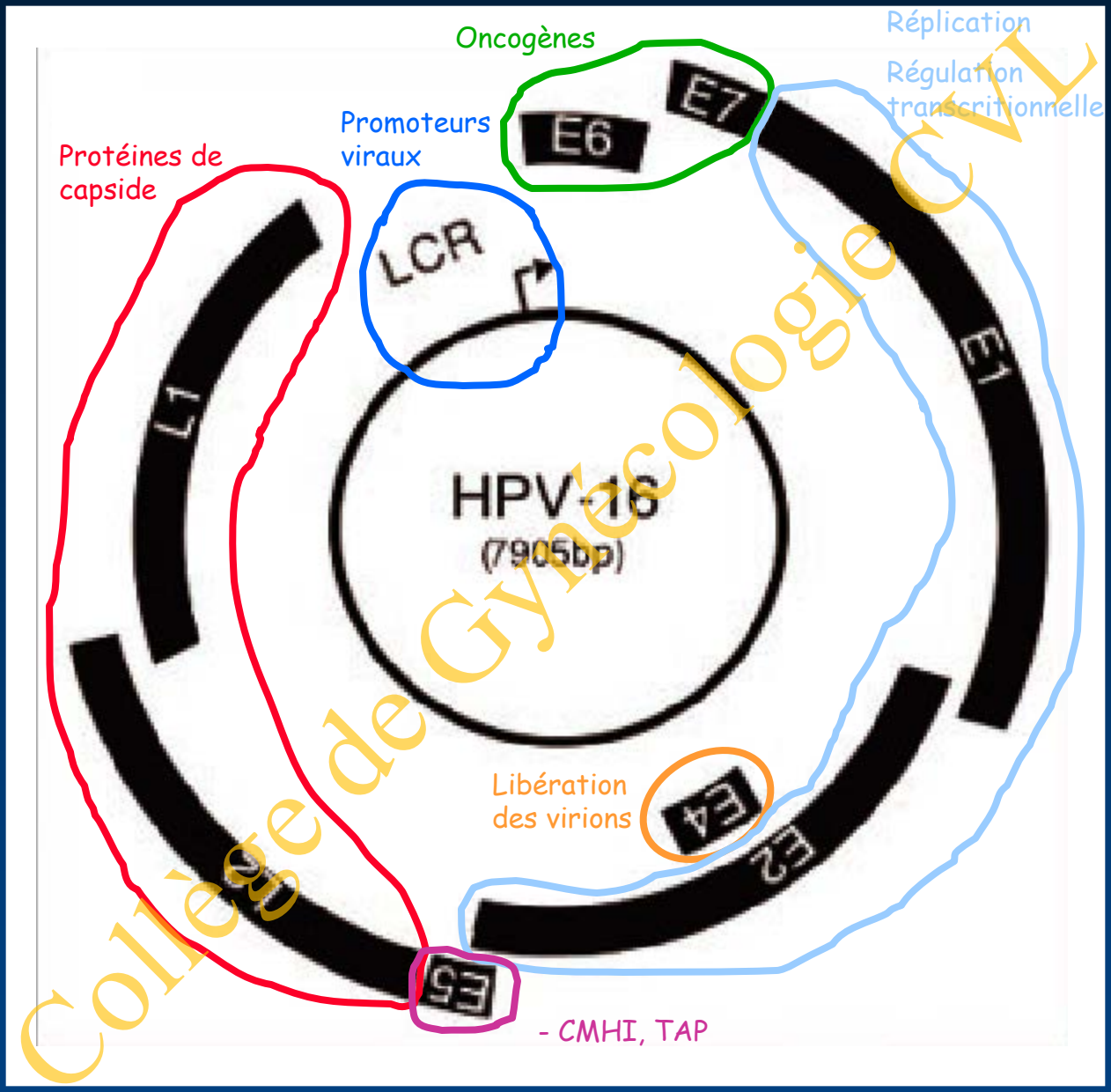
Pr Antoine Touzé, UMR INRA 1282 Infectiologie et Santé Publique, Equipe Virologie et Immunologie Moléculaire

Papillomaviridae

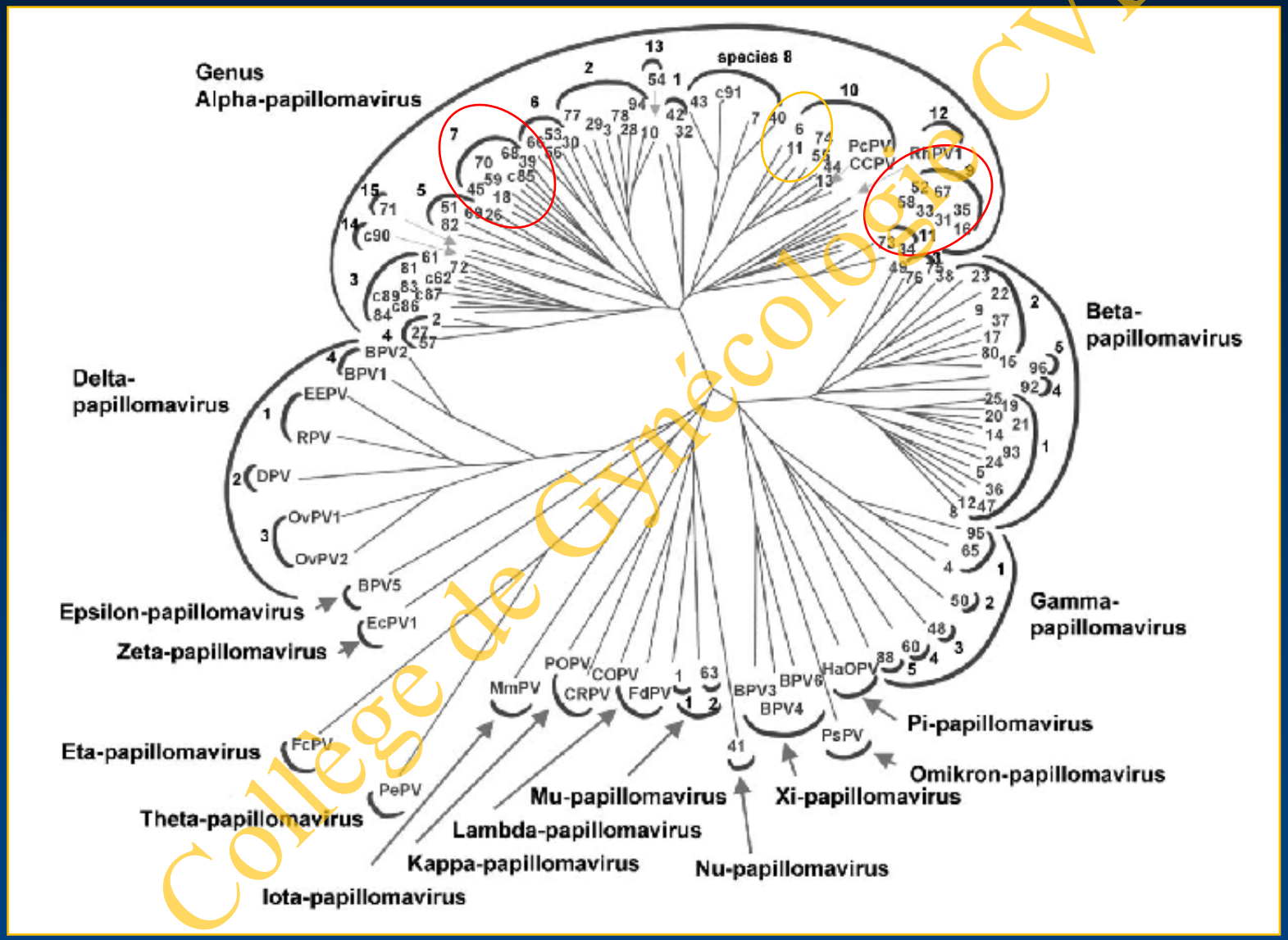
- Petits virus nus à ADN db circulaire, 50-55 nm
- Capside à symétrie icosaédrique T=7; L1 et L2
- Non cultivable in vitro
- Plus de 100 types humains
- virus épithéliotropes (peau, muqueuses) non lytiques
- Certains HPV sont associés au cancer du col utérin



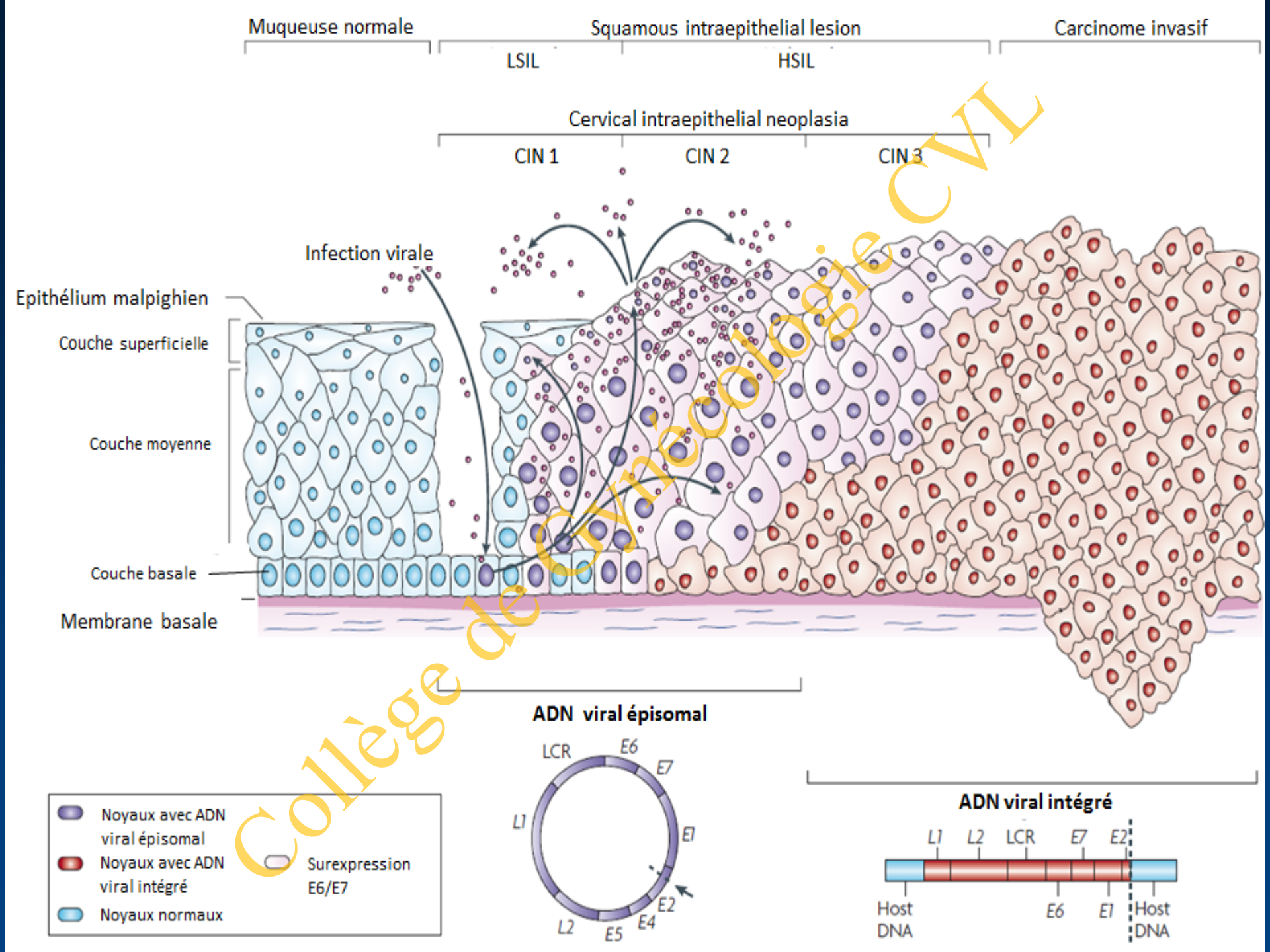
Papillomavirus Bovin de type 1



Taxonomie

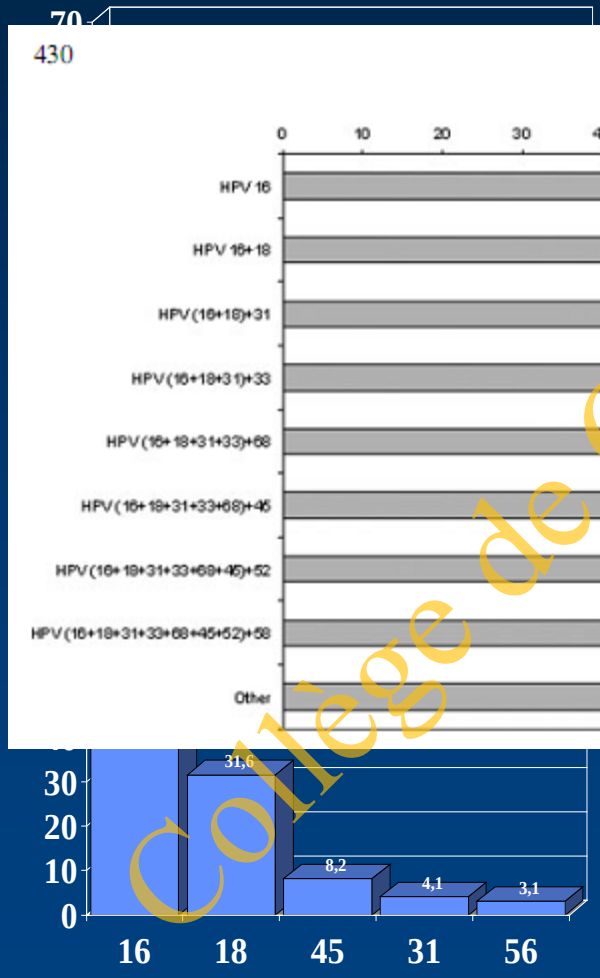


E.-M. de Villiers et al. / Virology 324 (2004) 17–27

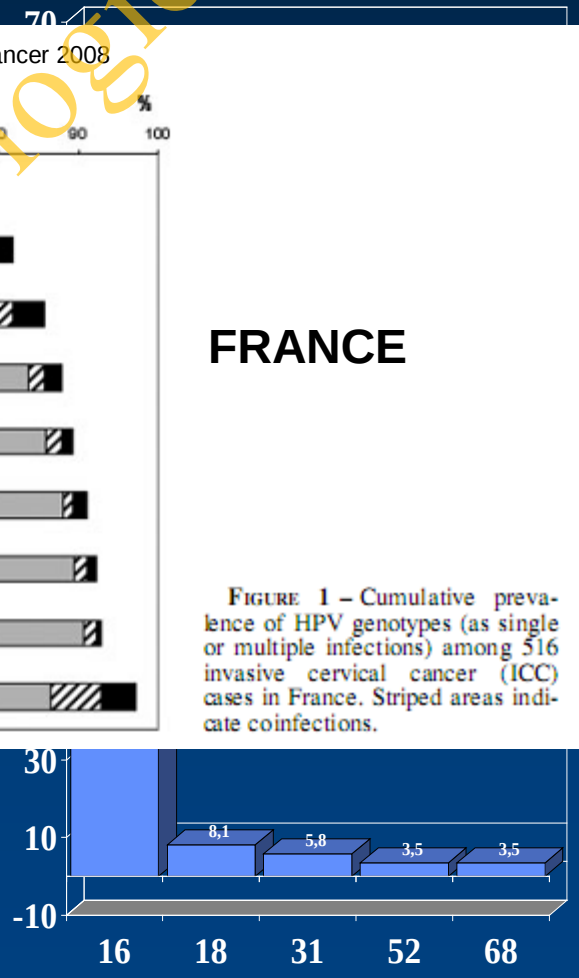


Prevalences in cervical cancer according to region

% **Africa**



% **Latin america**

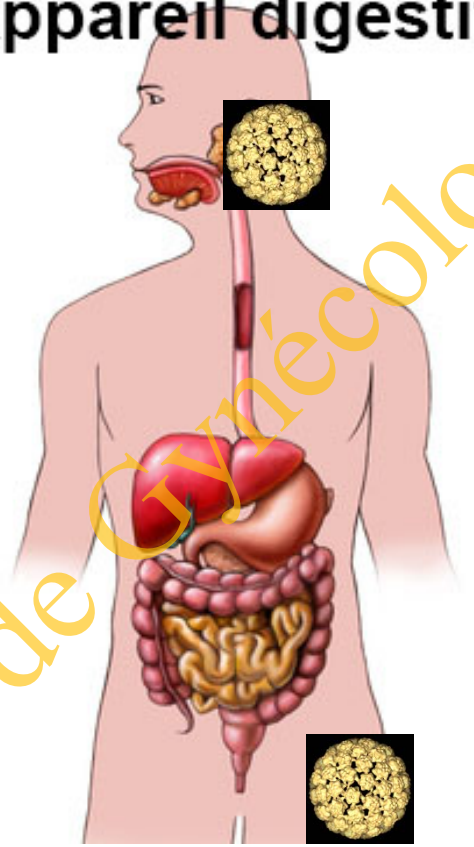


FRANCE

FIGURE 1 – Cumulative prevalence of HPV genotypes (as single or multiple infections) among 516 invasive cervical cancer (ICC) cases in France. Striped areas indicate coinfections.

IARC

Appareil digestif



Vaccine 30S (2012) F12–F23

Contents lists available at SciVerse ScienceDirect

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journal homepage: www.elsevier.com/locate/vaccine

Review

Global Burden of Human Papillomavirus and Related Diseases

David Forman[a,*], Catherine de Martel[b], Charles J. Lacey[c], Isabelle Soerjomataram[a], Joannie Lortet-Tieulent[a], Laia Bruni[d], Jerome Vignat[b], Jacques Ferlay[a], Freddie Bray[a], Martyn Plummer[b], Silvia Franceschi[b]

Table 4
Estimated number of new cancer cases[a] occurring in 2008 attributable to HPV by anatomic site.

HPV-RELATED CANCER SITE	Number of new cases in 2008	Number attributable to HPV	PAF (%)	Number attributable to infection by gender		Number attributable to infection by age group		
				Males	Females	<50 years	50 to 69 years	70+ years
Cervix uteri	530,000	530,000	100.0	0	530,000	250,000	220,000	59,000
Vulva	27,000	12,000	43.0	0	12,000	1,700	3,900	6,000
Anus	27,000	24,000	88.0	11,000	13,000	5,100	10,000	8,300
Penis	22,000	11,000	50.0	11,000	0	2,500	4,800	3,500
Vagina	13,000	9,000	70.0	0	9,000	2,000	4,000	3,100
Oropharynx[b]	85,000	22,000	25.6	17,000	4,400	4,300	13,000	4,600
TOTAL HPV RELATED SITES	700,000	610,000	86.3	39,000	570,000	270,000	260,000	85,000

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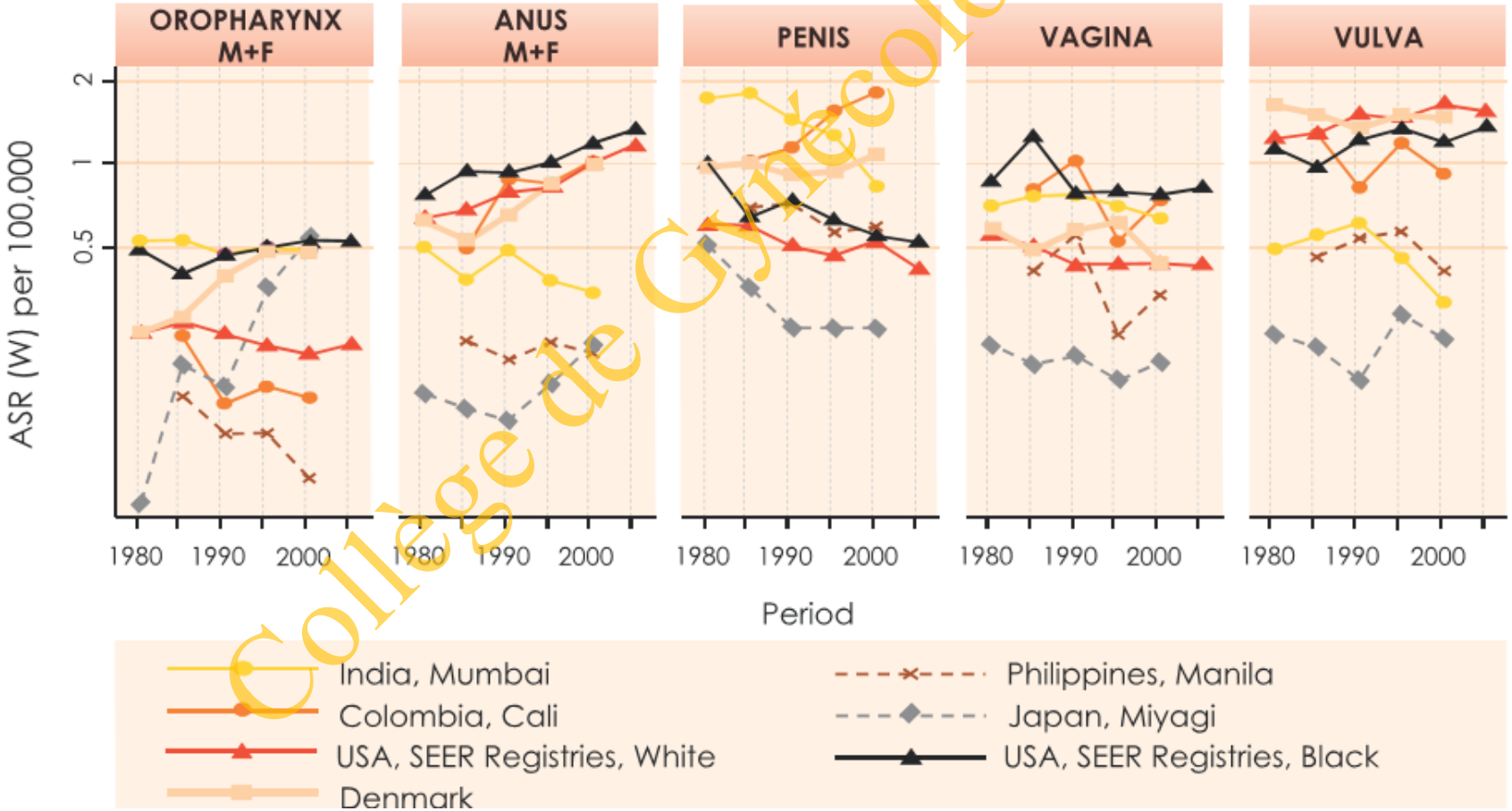

Historique

Br J Oral Surg. 1983 Jun;21(2):147-53.

Immunohistochemical demonstration of human papilloma virus (HPV) antigens in oral squamous cell lesions.

Syrjänen KJ, Pyrhönen S, Syrjänen SM, Lamberg MA.

Abstract

Six oral squamous cell tumours classified as focal epithelial hyperplasia (FEH), Condyloma acuminatum (CA) and squamous cell papilloma (SQP) were subjected to indirect immunoperoxidase staining with anti-human papillomavirus (anti-HPV) antiserum to demonstrate the possible presence of HPV antigens in these lesions. The results are discussed in the light of the observations on HPV-lesions elsewhere in the body (in uterine cervix), and a suggestion is made to adopt the name condyloma for all those tumours where HPV aetiology can be established by ultrastructural or immunohistochemical means.

Int J Cancer. 1986 Nov 15;38(5):671-6.

Rearranged HPV 16 molecules in an anal and in a laryngeal carcinoma.

Scheurlen W, Stremlau A, Gissmann L, Höhn D, Zenner HP, zur Hausen H.

Abstract

By hybridization under stringent conditions, one out of two anal carcinomas and one out of 36 laryngeal carcinomas were shown to harbor HPV 16 DNA in high copy number. Further analysis of both tumor DNAs indicated a rearrangement of the viral DNA in the tumor cells. HPV 16 DNA in the anal carcinoma could chiefly be found episomally in two different forms: a minority as 7.9-kb oligomeric episomes with no apparent modifications; as 10.7-kb rear-ranged oligomeric episomes with a duplication of the part of the viral genome encoding the open reading frames (ORF) E7, E1 and parts of E6 and E2. In the laryngeal carcinoma, integrated and episomal HPV 16 DNA molecules of 7.9 kb were present, together with rearranged molecules of approximately 18 kb with multiple duplications of the ORF E4 and parts of the ORFs E2, E5, L1 and L2. Possible consequences for transcription of the modified viral genomes are discussed.

HPV et Head and Neck Carcinoma

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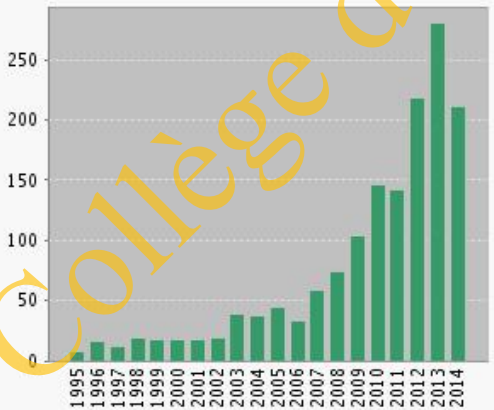
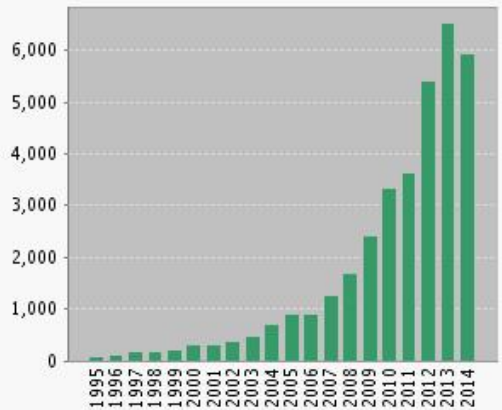
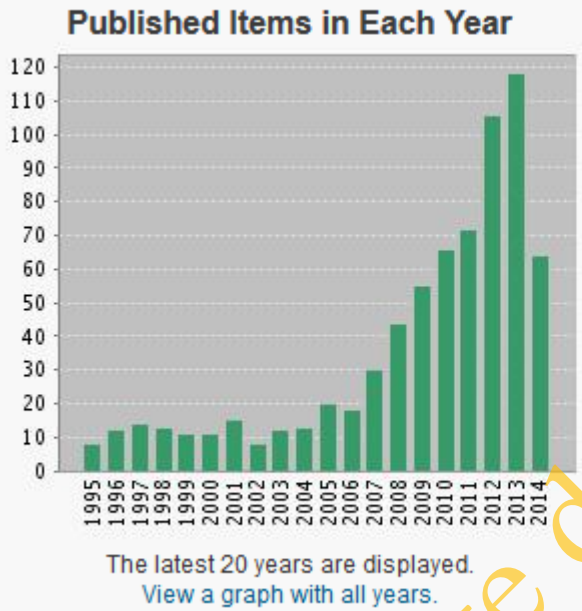
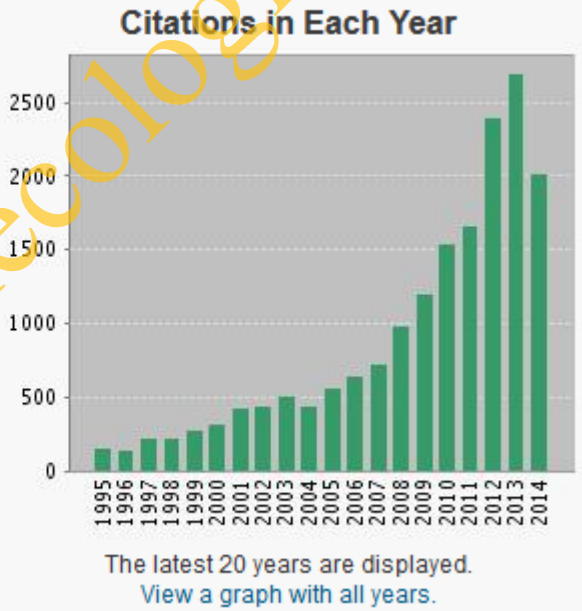


Citations in Each Year



HPV and anal cancer





Cancers tête et cou

- HNCs- 6.5% des cancers dans le monde 6ième cancer (4ième en France)
  - Incidence 38/100,000 /an (U.S.) **en augmentation** (Chaturvedi, JCO, 2011)
  - Age médian= 60
  - 2/3 H : 1/3 F
  - 14,697 cas en 2007 (11,158 hommes)
  - 95% sont des HNSCC
  - 75-80% dus à l'alcool et au tabac
  - 15-25 % dus aux HPV

Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers

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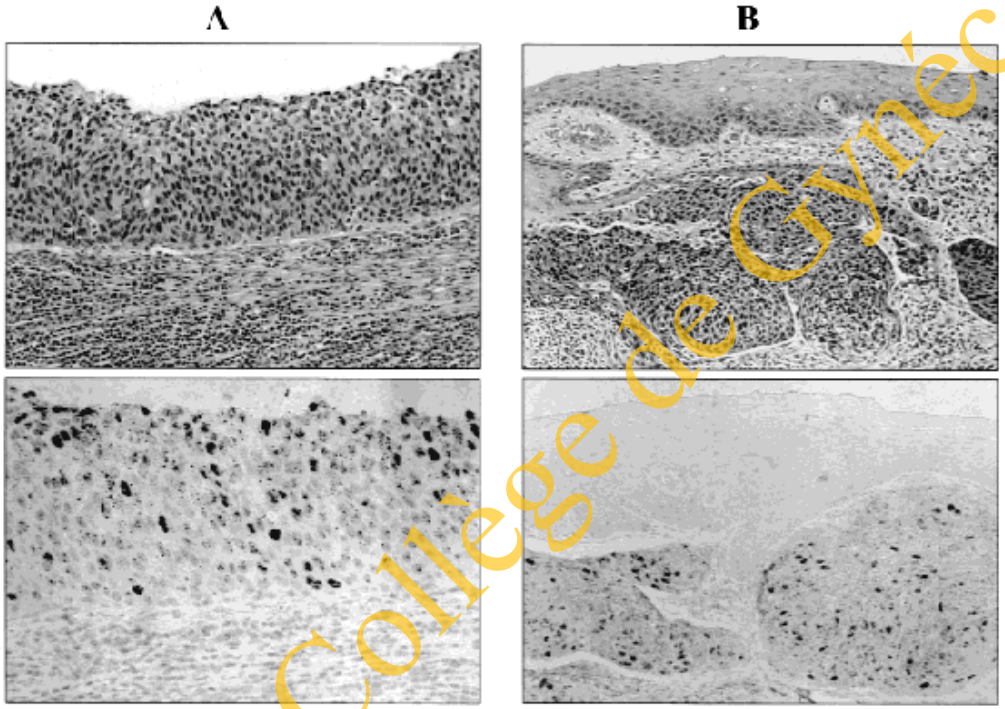
Journal of the National Cancer Institute, Vol. 92, No. 9, May 3, 2000

- HPV dans 25 % des HNSCC
- 90% HPV16 pos, intégré



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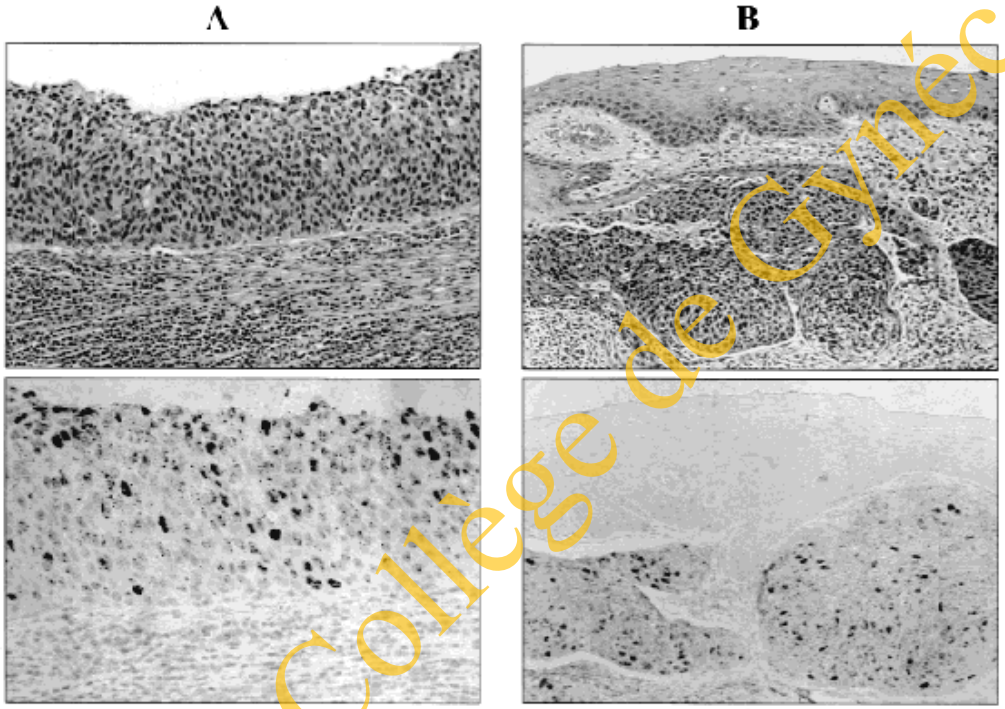

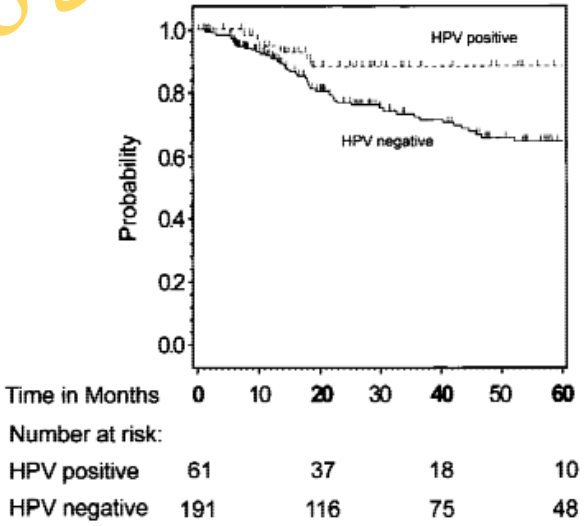

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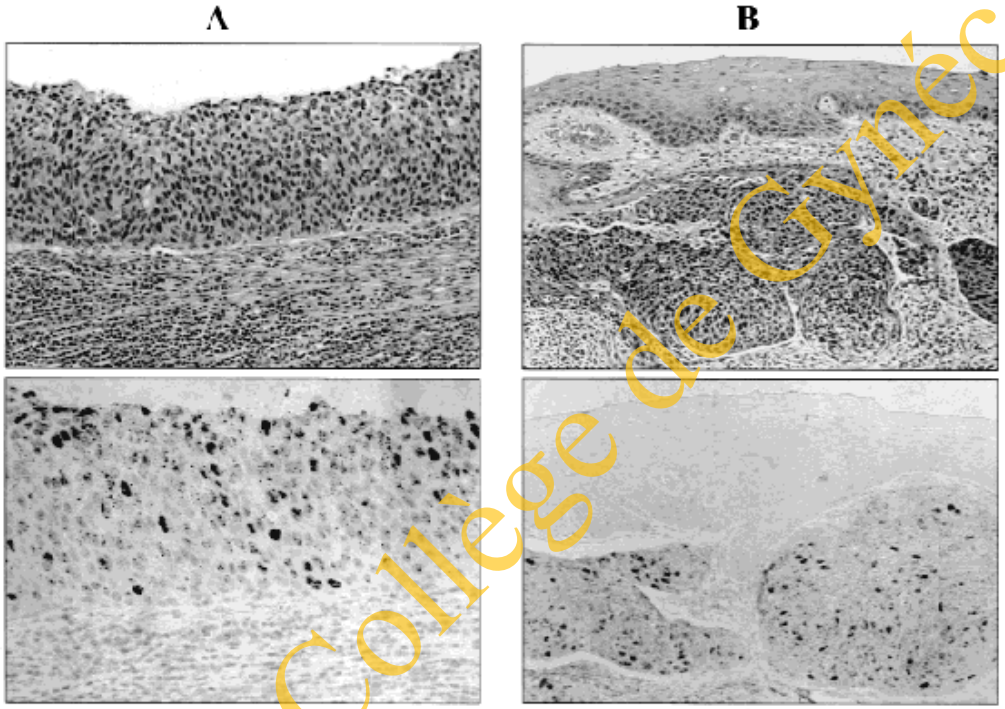

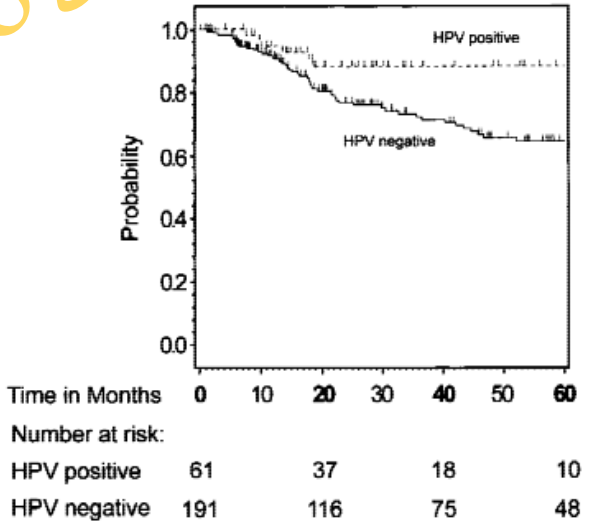

Ang et al. NEJM 2010 Radio + CisPt
Survie Globale à 3 ans
- 82.4% HPV pos
- 57.1% HPV neg

Journal of Clinical Virology 51 (2011) 100–104

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

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Jean Lacau St Guily[a,*], Anne-Carole Jacquard[b], Jean-Luc Prétet[c], Julie Haesebaert[b], Agnès Beby-Defaux[d], Christine Clavel[e], Gérard Agius[d], Philippe Birembaut[e], Claire Okaïs[b], Yann Léocmach[b], Benoît Soubeyrand[b], Pierre Pradat[f,g], Didier Riethmuller[c,h], Christiane Mougin[c], François Denis[i]

Table 1
Overall HPV prevalence and prevalence according to gender, area of residence, and carcinoma anatomical sites in (A) oropharyngeal carcinomas and (B) oral cavity carcinomas.

Oropharynx	*N*	HPV positive *n* (%)
A		
Overall HPV prevalence (%)	314	146 (46.5)
Gender		
Males	251	106 (42.2)
Females	63	40 (63.5)
Area of residence		
Paris area	69	42 (60.9)
West-Centre	50	25 (50.0)
North/North-East	94	37 (39.4)
South-East/Corsica	71	25 (35.2)
South-West	25	12 (48.0)
NA[a]	5	5 (100.0)
Carcinoma sub-localisation		
Tonsils	185	106 (57.3)
Base of tongue	43	13 (30.2)
Uvula and soft palate	22	3 (13.6)
Vallecula	16	4 (25.0)
Posterior wall	8	3 (37.5)
Lateral wall	3	0 (0.0)
Unspecified	37	17 (45.9)
Proportion of mono/multiple infections		
Mono-infections	314	138 (43.9)
Multiple infections	314	8 (2.5)
HPV negative	314	168 (53.5)

Cavité buccale

Overall HPV prevalence (%)	209	22 (10.5)
Gender		
Males	151	12 (7.9)
Females	58	10 (17.2)
Area of residence		
Paris area	33	6 (18.2)
West-Centre	33	3 (9.1)
North/North-East	72	5 (6.9)
South-East/Corsica	52	6 (11.5)
South-West	16	2 (12.5)
NA[a]	3	0 (0.0)
Carcinoma sub-localisation		
Floor of mouth	86	8 (9.3)
Oral tongue	80	5 (6.3)
Gingivae	21	5 (23.8)
Intermaxillary commissure	7	0 (0.0)
Cheeks	5	0 (0.0)
Hard palate	3	1 (33.3)
Lips	2	1 (50.0)
Unspecified	5	2 (40.0)
Proportion of mono/multiple infections		
Mono-infections	209	21 (10.0)
Multiple infections	209	1 (0.5)
HPV negative	209	187 (89.5)

[a] NA, non available.

Journal of Clinical Virology 51 (2011) 100–104

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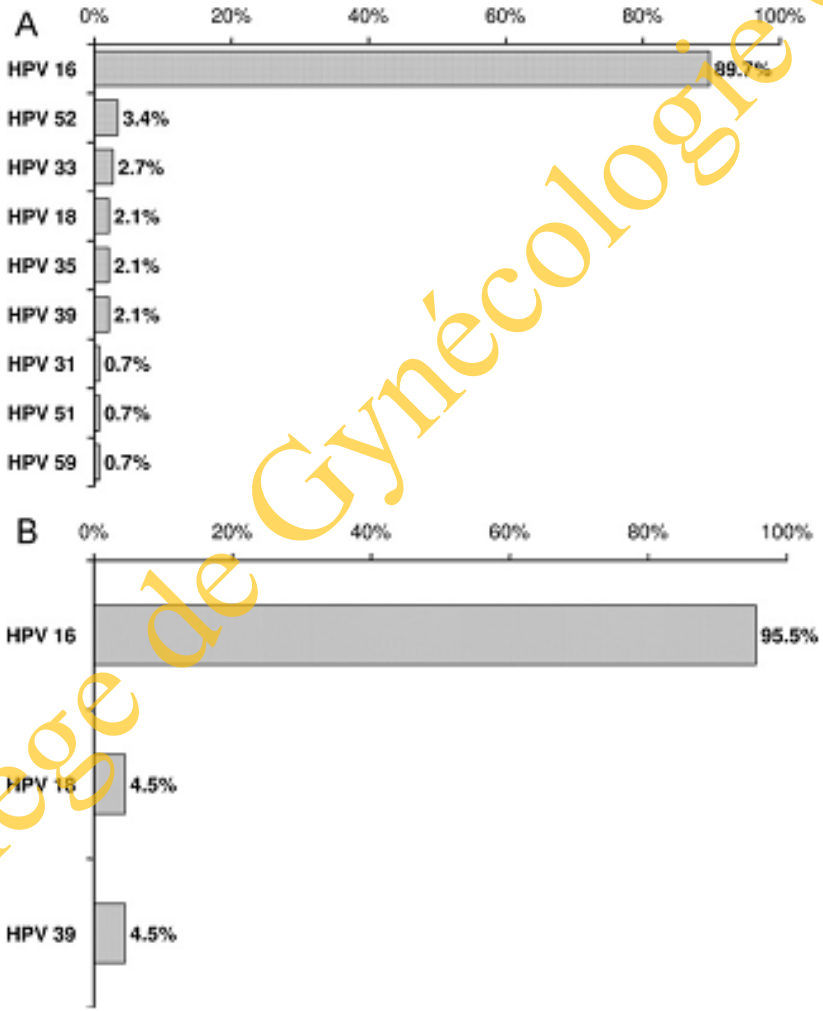
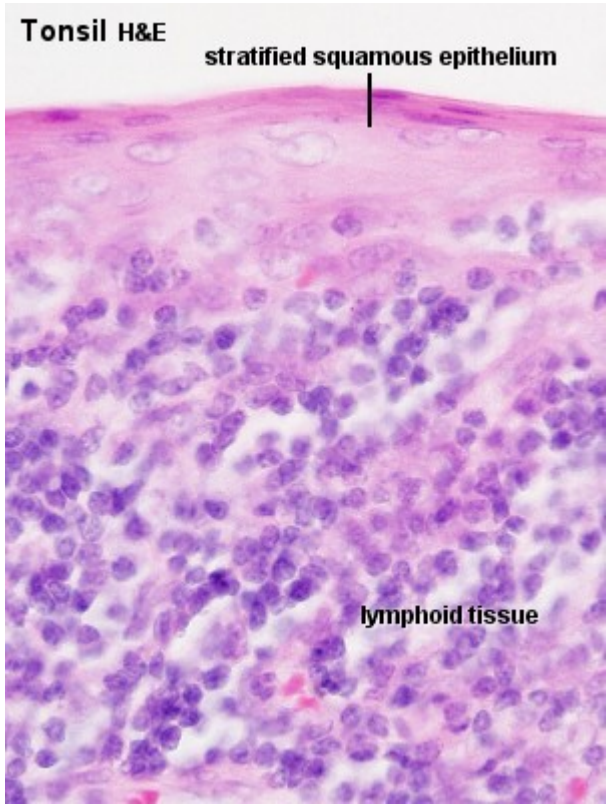
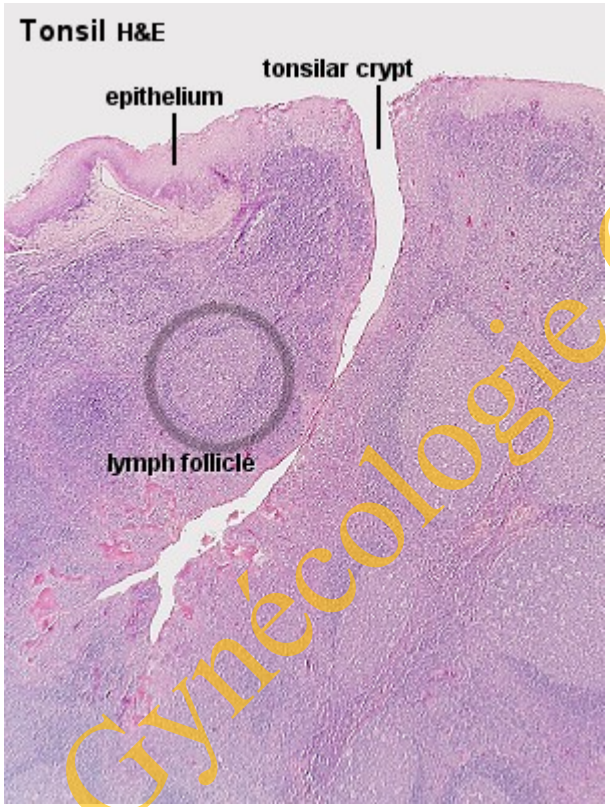
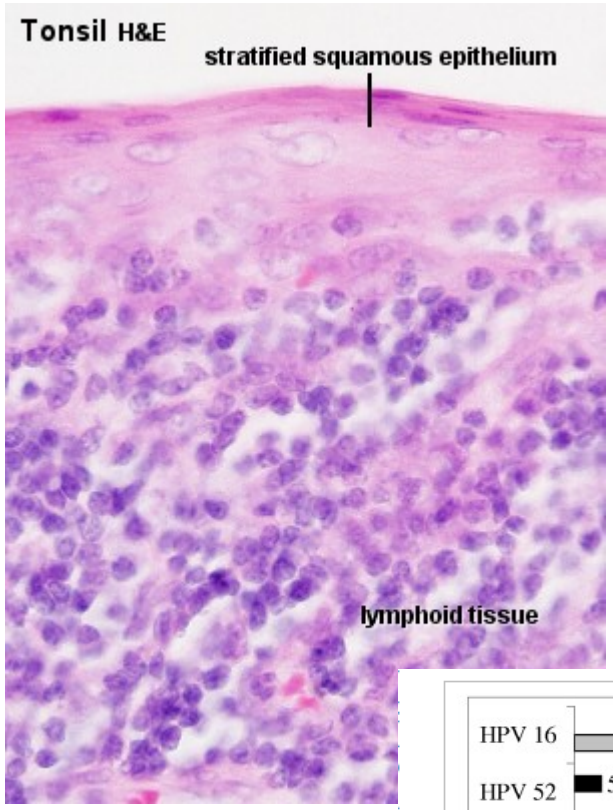
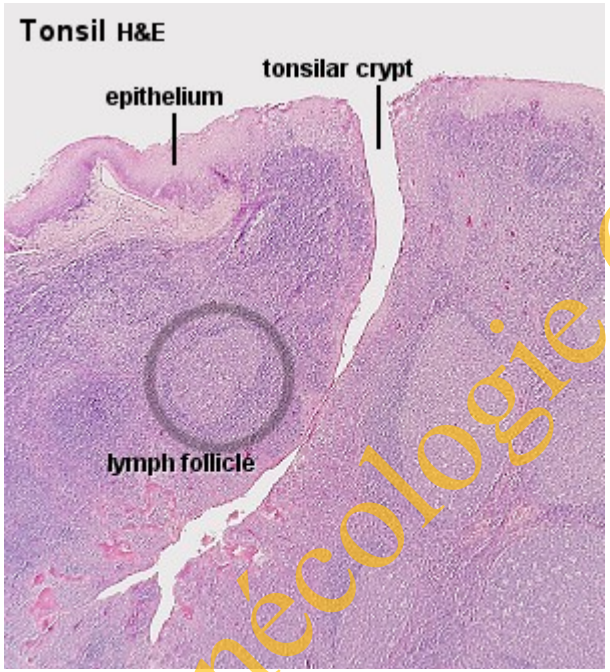


Fig. 1. HPV genotype distribution among HPV positive samples of oropharyngeal ($n = 146$) (A) and oral cavity ($n = 22$) (B) invasive carcinomas.

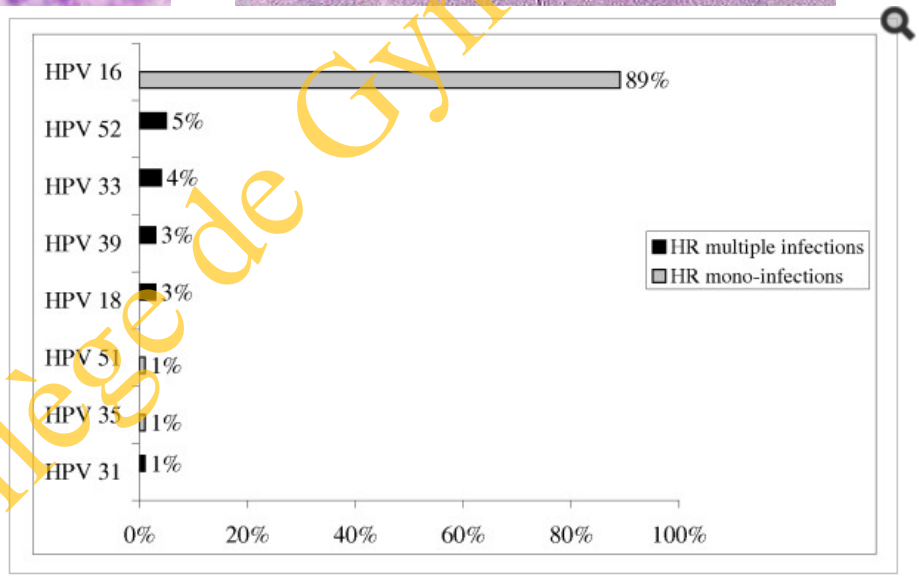








HPV prevalence 57%



HR HPV distribution among tonsil HPV positive cases (n = 106).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

N Engl J Med 2007;356:1944-56.

Table 3. Association of Oropharyngeal Cancer with Exposure to HPV and with Biomarkers of Cancer Associated with HPV-16.

Measure of HPV Exposure or Disease	Prevalence		Odds Ratio (95% CI)	
	Case Patients (N=100)	Control Patients (N=200)	Unadjusted	Adjusted*
	number (percent)			
HPV-16 L1 serologic status				
Seronegative	43 (43)	186 (93)	1.00	1.00
Seropositive	57 (57)	14 (7)	17.6 (8.8–34.5)	32.2 (14.6–71.3)
Oral HPV-16 infection†				
Negative	68 (68)	192 (96)	1.00	1.00
Positive	32 (32)	8 (4)	11.3 (5.0–25.7)	14.6 (6.3–36.6)
Any oral HPV infection‡				
Negative	63 (63)	189 (94)	1.00	1.00
Positive	37 (37)	11 (6)	10.0 (4.8–20.7)	12.3 (5.4–26.4)
HPV-16 E6 or E7 serologic status				
Seronegative for E6 and E7	36 (36)	192 (96)	1.00	1.00
Seropositive for E6 or E7	64 (64)	8 (4)	33.3 (16.2–68.6)	58.4 (24.2–138.3)
HPV-16 DNA in tumor				
Absent	28 (28)	—	—	—
Present	72 (72)	—	—	—

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N Engl J Med 2007;356:1944-56.

Table 2. Associations of Oropharyngeal Cancer with Sexual Behaviors.*

Sexual Behavior	Patients with Oropharyngeal Cancer (N=100)	Control Patients (N=200)	Adjusted Odds Ratio (95% CI)†	
			All Patients	HPV-16+ Patients‡
	number (percent)			
Lifetime no. of vaginal-sex partners				
0–5	31 (31)	108 (54)	1.0	1.0
6–25	41 (41)	63 (32)	2.2 (1.2–4.0)	2.7 (1.4–5.5)
≥26	28 (28)	29 (14)	3.1 (1.5–6.5)§	4.2 (1.8–9.4)¶
Lifetime no. of oral-sex partners				
0	12 (12)	38 (19)	1.0	1.0
1–5	46 (46)	110 (55)	1.9 (0.8–4.5)	3.8 (1.0–14.0)
≥6	42 (42)	52 (26)	3.4 (1.3–8.8)‖	8.6 (2.2–34.0)**
Anal sex				
No	55 (55)	129 (64)	1.0	1.0
Yes	45 (45)	71 (36)	1.3 (0.8–2.2)	1.6 (0.9–2.8)
Casual-sex partner††				
No	42 (42)	120 (60)	1.0	1.0
Yes	58 (58)	80 (40)	1.7 (1.0–3.0)	2.4 (1.2–4.7)
Age at first intercourse				
18 yr or older	30 (30)	87 (44)	1.0	1.0
17 yr or younger	70 (70)	113 (56)	1.3 (0.7–2.3)	2.1 (1.1–3.6)
Condom use				
Usually or always	28 (28)	90 (45)	1.0	1.0
Never or rarely	72 (72)	110 (55)	2.2 (1.2–3.8)	2.1 (1.1–4.0)
Sex with same-sex partner				
No	92 (92)	186 (93)	1.0	1.0
Yes	8 (8)	14 (7)	1.0 (0.4–2.6)	1.1 (0.3–3.3)
Sexual partner with history of HPV-associated cancer‡‡				
No	86 (86)	190 (95)	1.0	1.0
Yes	3 (3)	2 (1)	3.0 (0.5–20.5)	3.9 (0.6–25.8)
Unsure	11 (11)	8 (4)	2.3 (0.8–6.5)	2.8 (0.9–8.5)

Oral Sexual Behaviors Associated with Prevalent Oral Human Papillomavirus Infection

Gypsyamber D'Souza,[1] Yuri Agrawal,[2] Jane Halpern,[3] Sacared Bodison,[4] and Maura L. Gillison[5]

The Journal of Infectious Diseases 2009; 199:1263–9

Table 2. Associations between factors of interest and oral human papillomavirus (HPV) infection among 210 college-aged men.

Factor	Prevalance of HPV,[b] total no. (%)[c]	Univariate analysis OR (95% CI)[d]	Univariate analysis *P*[e]	Multivariate analysis[a] OR (95% CI)[d]	Multivariate analysis *P*[e]
Demographic					
Race					
White	145 (3.5)	1.0			
Black	45 (2.2)	0.63 (0.07–5.5)			
Asian, Native American, or other	22 (0.0)	. . .			
Ethnicity					
Non-Hispanic	198 (3.0)	1.0			
Hispanic	12 (0.0)	. . .			
Age, years			.009		.021
18–19	110 (0.9)	1.0		1.0	
20–23	100 (5.0)	5.7 (0.65–50.0)		4.5 (0.51–41.0)	
Sexual behavior					
Sexual orientation					
Heterosexual	200 (2.5)	1.0		1.0	
Homo- or bisexual	10 (9.1)	4.3 (0.46–41.0)		15.6 (0.83–129.0)	
Oral sex partners,[f] no.					
In lifetime			.029		.031
0–9	203 (2.0)	1.0		1.0	
⩾10	7 (28.6)	20.0 (2.9–135.0)		7.4 (0.82–66.0)	
In past year			.033		.046
0–5	199 (2.0)	1.0		1.0	
⩾6	11 (18.2)	10.8 (1.7–67.0)		7.9 (1.05–59.0)	
Barrier use[g]					
Usually/always or no oral sex	97 (1.0)	1.0		1.0	
Rarely/ never	113 (4.4)	4.4 (0.51–39.0)		7.4 (0.65–85.0)	
People open-mouthed kissed, no.					
In lifetime			.083		.067
0–9	129 (0.8)	1.0		1.0	
⩾10	81 (6.2)	8.4 (0.97–73.0)		9.5 (0.76–118.0)	
In past year			.037		.023
0–5	144 (0.7)	1.0		1.0	
⩾6	66 (7.6)	11.7 (1.3–102.0)		17.4 (1.5–198.0)	
Vaginal sex partners, no.					
In lifetime			.44		.91
0–9	181 (2.2)	1.0		1.0	
⩾10	29 (6.9)	2.1 (0.24–19.0)		0.70[h] (0.07–7.6)	
In past year			.063		.27
0–5	184 (2.2)	1.0		1.0	
⩾6	26 (7.7)	3.8 (0.6–21.6)		1.5[g] (0.19–11.0)	
HSV-2 antibodies					
No	199 (3.0)	1.00		1.00	
Yes	11 (0.0)	. . .		. . .	

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Evaluation of Human Papillomavirus Antibodies and Risk of Subsequent Head and Neck Cancer

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J Clin Oncol 31.

Table 2. ORs by HPV16 Serology Status for Cancer of the Oral Cavity, Oropharynx, Larynx, and Esophagus

	Controls (n = 1,599)		Oral Cavity Cancer (n = 180)				Oropharynx Cancer (n = 135)				Larynx Cancer (n = 247)*				Esophageal Cancer (n = 300)			
Serology Status	No. of Participants	%	No. of Patients	%	OR	95% CI	No. of Patients	%	OR	95% CI	No. of Patients	%	OR	95% CI	No. of Patients	%	OR	95% CI
HPV16 oncoproteins																		
E6																		
Seronegative	1,590	99.4	178	98.9	1		88	65.2	1		244	98.8	1		299	99.7	1	
Seropositive	9	0.6	2	1.1	1.3	0.3 to 6.9	47	34.8	274	110 to 681	3	1.2	3.8	0.8 to 17.6	1	0.3	0.6	.1 to 5.2
E7																		
Seronegative	1,421	88.9	155	86.1	1		108	80.0	1		217	87.9	1		272	90.7	1	
Seropositive	178	11.1	25	13.9	1.2	0.7 to 1.9	27	20.0	2.4	1.5 to 3.9	30	12.1	0.9	0.5 to 1.4	28	9.3	0.7	0.5 to 1.2
HPV16 other early proteins																		
E1																		
Seronegative	1,536	96.1	165	91.7	1		113	83.7	1		226	91.5	1		283	94.3	1	
Seropositive	63	3.9	15	8.3	2.1	1.1 to 3.9	22	16.3	5.7	3.2 to 10.0	21	8.5	2.2	1.2 to 3.9	17	5.7	1.7	0.9 to 3.0
E2																		
Seronegative	1,527	95.5	170	94.4	1		102	75.6	1		234	94.7	1		286	95.3	1	
Seropositive	72	4.5	10	5.6	1.0	0.5 to 2.1	33	24.4	9.5	5.7 to 15.8	13	5.3	1.0	0.5 to 1.9	14	4.7	0.9	0.5 to 1.7
E4																		
Seronegative	1,437	89.9	165	91.7	1		120	88.9	1		218	88.3	1		276	92.0	1	
Seropositive	162	10.1	15	8.3	0.8	0.5 to 1.5	15	11.1	1.3	0.7 to 2.4	29	11.7	1.2	0.7 to 1.9	24	8.0	0.8	0.5 to 1.2
HPV16 late protein																		
L1																		
Seronegative	1,270	79.4	138	76.7	1		79	58.5	1		187	75.7	1		231	77.0	1	
Seropositive	329	20.6	42	23.3	1.2	0.8 to 1.7	56	41.5	3.1	2.1 to 4.5	60	24.3	1.3	0.9 to 1.8	69	23.0	1.1	0.8 to 1.6

NOTE. All ORs were adjusted for sex, age at enrollment (in 5-year age categories), country, tobacco (never, former, current), and alcohol use (never/ever and continuous values in gm/day at recruitment).
Abbreviations: HPV, human papillomavirus; OR, odds ratio.
*The larynx cancer category includes 31 participants with hypopharyngeal cancer.

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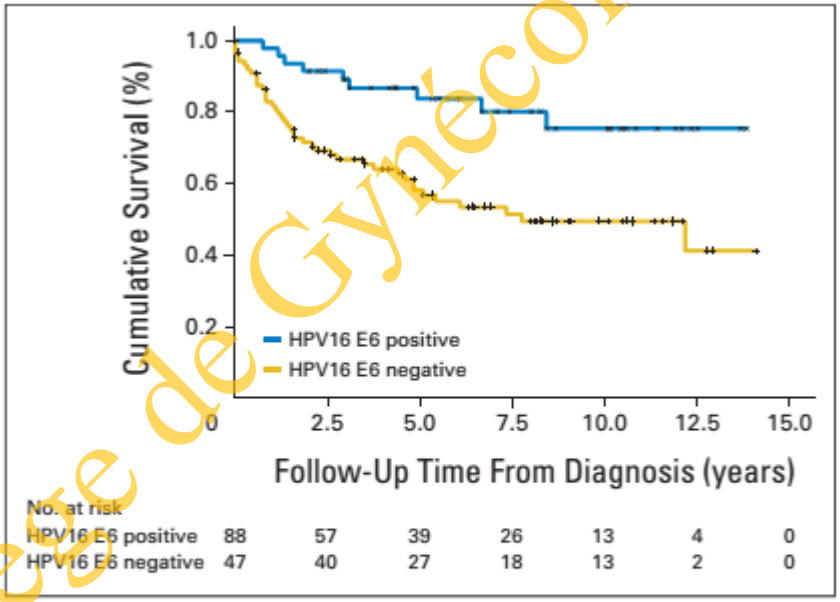
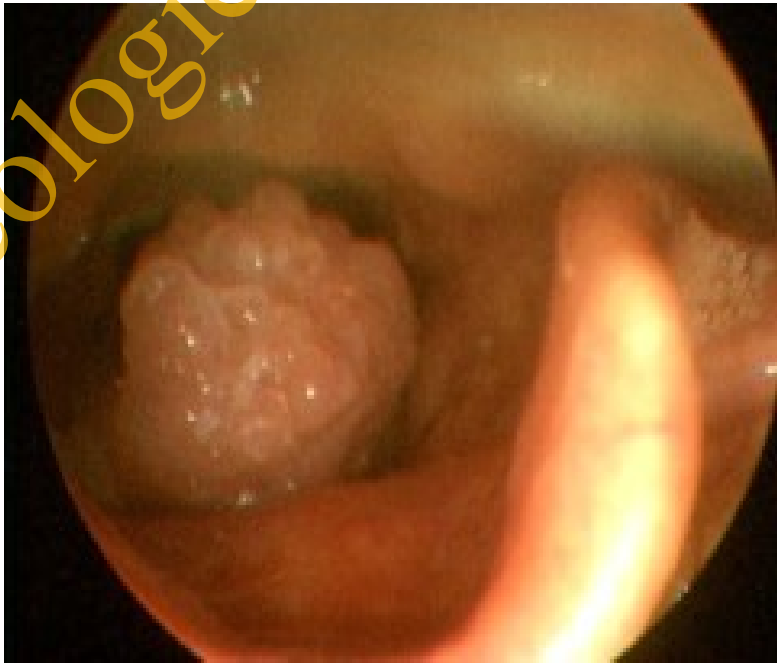


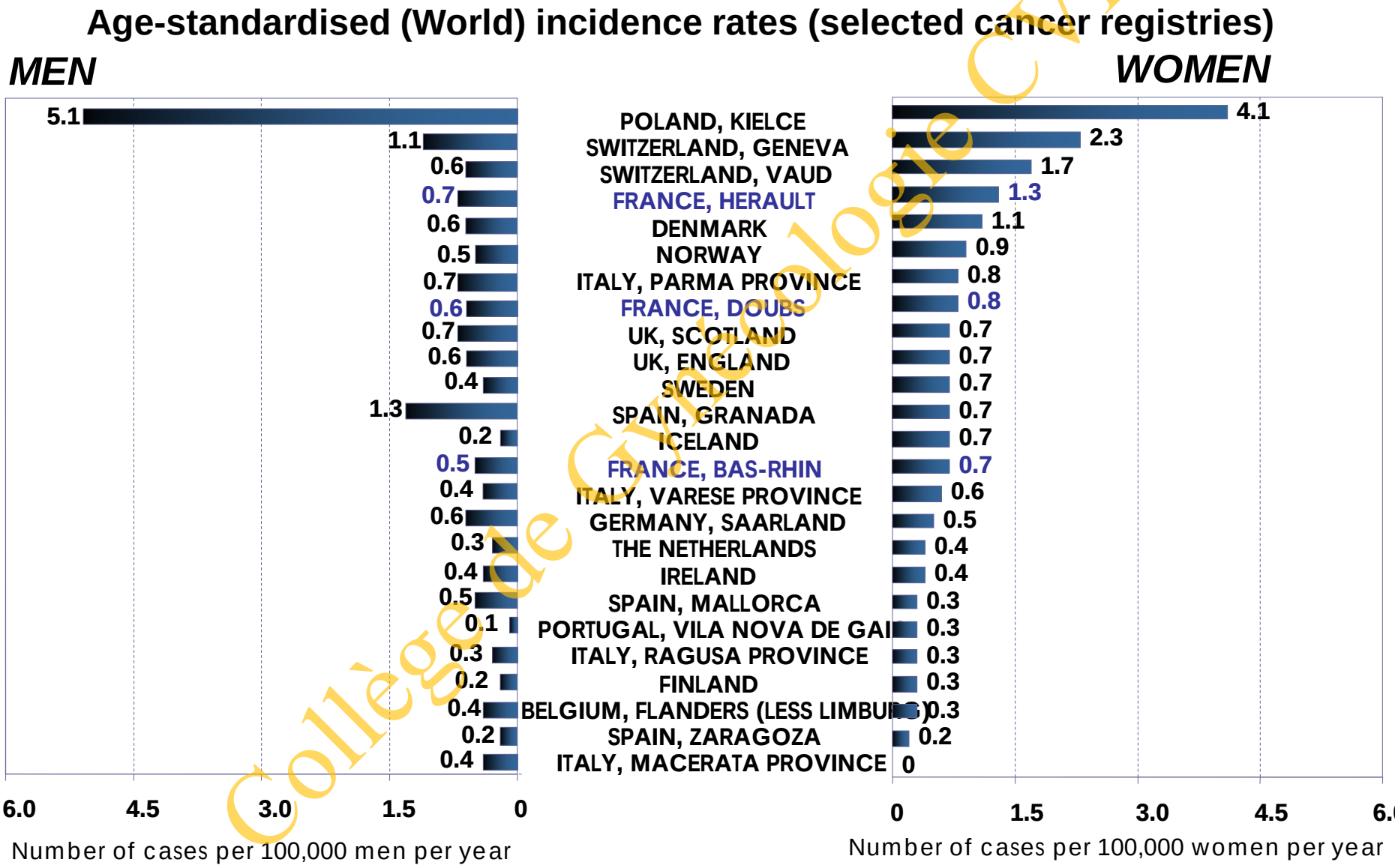
Fig 2. Cumulative survival of all-cause mortality among patients diagnosed with oropharyngeal cancer by prediagnostic human papillomavirus type 16 (HPV16) E6 serostatus. Patients who were seropositive (blue line; n = 47) and seronegative (gold line; n = 88) for HPV16 were compared for all-cause mortality. Numbers at the bottom of the figure indicate number of patients at the start of each time interval by HPV16 E6 serostatus.

HPV et Recurrent Respiratory Papillomatosis

- HPV- 6, 11
- 2 types: 3-4/100000
  - Juvenile : 5 ans
    - Mère avec lésion
  - Adulte : 20-40 ans
    - nb de partenaires/sexe oral



Cancer Anal en Europe



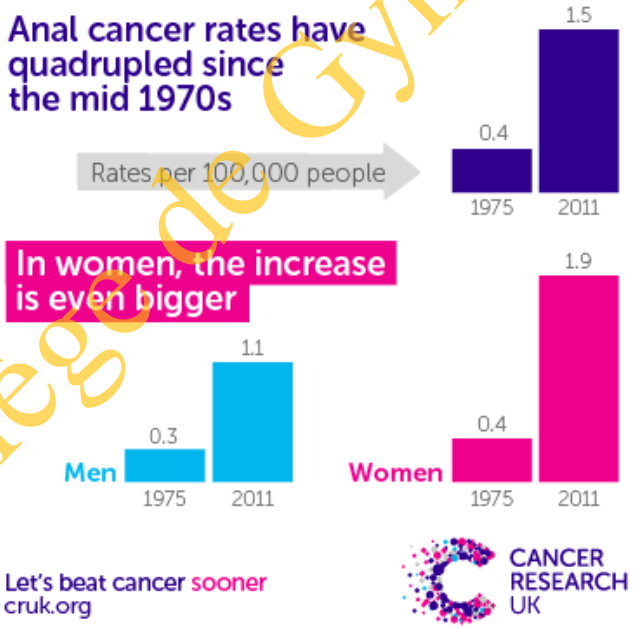
European Union except Cyprus, Greece, Hungary, Luxembourg (21 countries)+ Iceland, Norway, Switzerland (3 countries).

CANCER INCIDENCE IN FIVE CONTINENTS VIII (IARC).

Epidémiologie du Cancer Anal

- **Incidence enFrance** ***(SEER Cancer Statistics)***
  - **1.43 / 100 000**
  - **866 new cases/year**
  - **1,5% cancers du TD**

- **More frequent in women (X4) than in men; 65 yrs**



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EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection

Anna R. Giuliano[1], Alan G. Nyitray[2], Aimée R. Kreimer[3], Christine M. Pierce Campbell[1], Marc T. Goodman[4], Staci L. Sudenga[1], Joseph Monsonego[5] and Silvia Franceschi[6]

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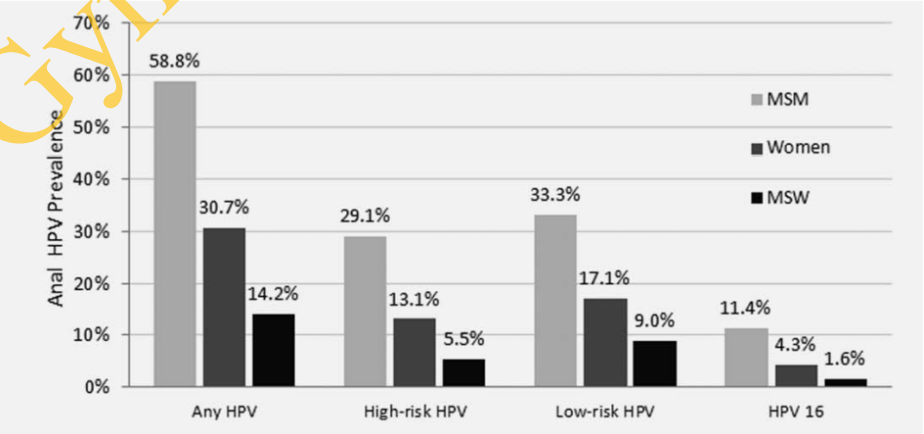

- **Very high incidence in HIV+ MSM:** *(Piketty et al, 2008)*
  - **75/100 000**

Epidémiologie du Cancer Anal

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- **More frequent in women (X4) than in men; 65 yrs**

- **Very high incidence in HIV+ MSM:** *(Piketty et al, 2008)*
  - **75/100 000**

- **Most cancers are epidermoid cancers (cloacogenic, adenocarcinoma)**

- **Chemoradiation & surgical excision or ablation**
  - **Considerable morbidity**
  - **Recurrence**

1ère cause de néoplasies anogénitales

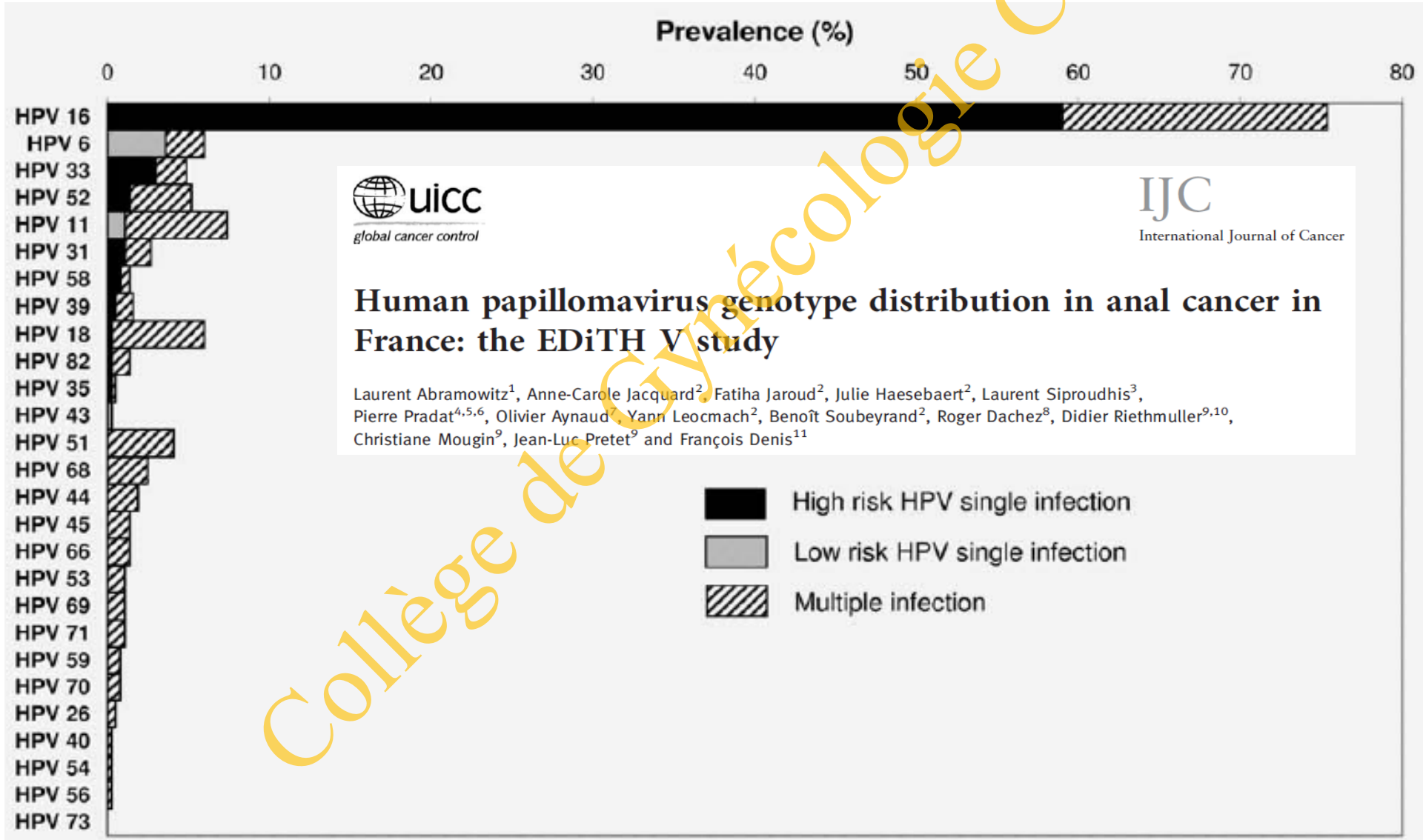
Classification des génotypes des HPV infectant les muqueuses anogénitales	
HPV à haut risque	**16, 18**, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82
Potentiellement à HR	55, 62, 64, 67, 69, 71, 83, 84, 89
HPV à bas risque	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

Etienney I 2013

Prévalence des HPV en cas de néoplasie intraépithéliale ou de carcinome anal	
HPV les plus prévalents en cas d'AIN 1	16 (37,2%), 6 (36,2%), 18 (21,3%), 11 (18,1%)
HPV les plus prévalents en cas d'AIN 2-3	**16** (59,8%), 18 (17,4%), 33 (13,6%), 58 (13,1%)
HPV les plus prévalents en cas de CE anal	**16** (73,4%), 18 (5,2%), 33 (4,8%)

De Vuyst H 2009

1ère cause de néoplasies anogénitales

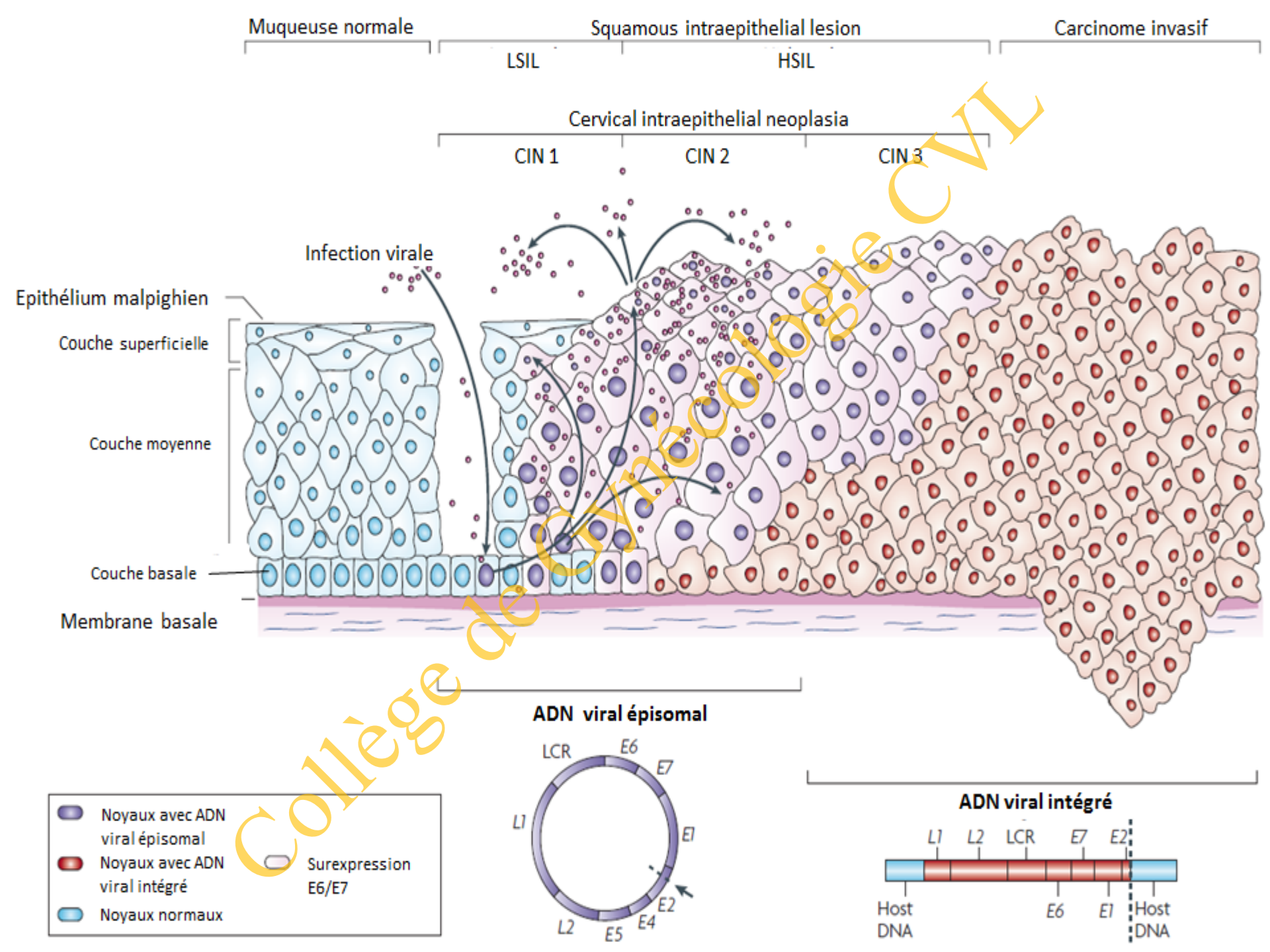


uicc
global cancer control

IJC
International Journal of Cancer

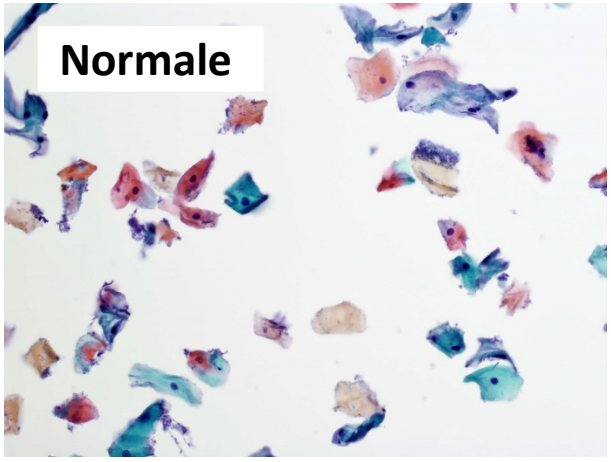
Human papillomavirus genotype distribution in anal cancer in France: the EDiTH V study

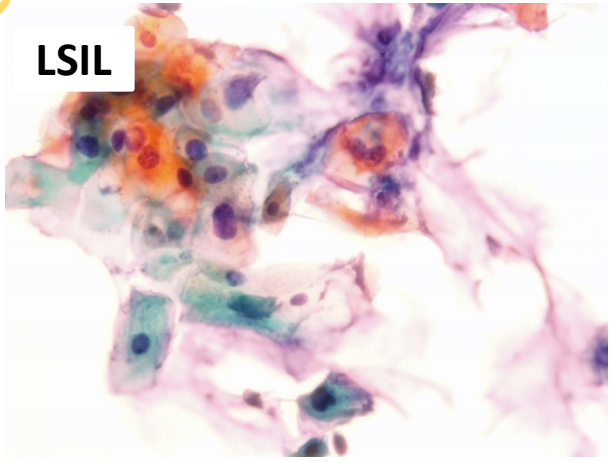
Laurent Abramowitz[1], Anne-Carole Jacquard[2], Fatiha Jaroud[2], Julie Haesebaert[2], Laurent Siproudhis[3], Pierre Pradat[4,5,6], Olivier Aynaud[7], Yann Leocmach[2], Benoît Soubeyrand[2], Roger Dachez[8], Didier Riethmuller[9,10], Christiane Mougin[9], Jean-Luc Pretet[9] and François Denis[11]

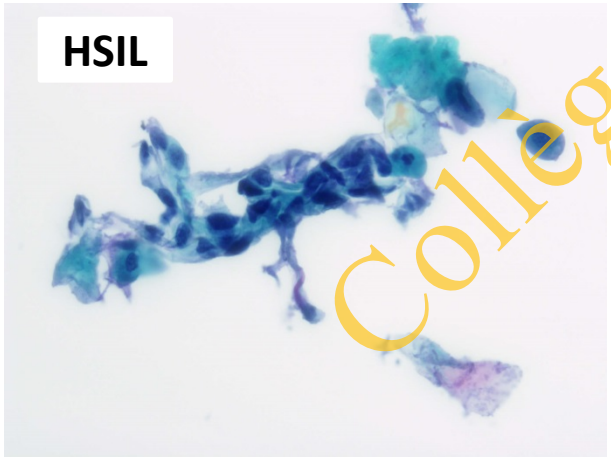


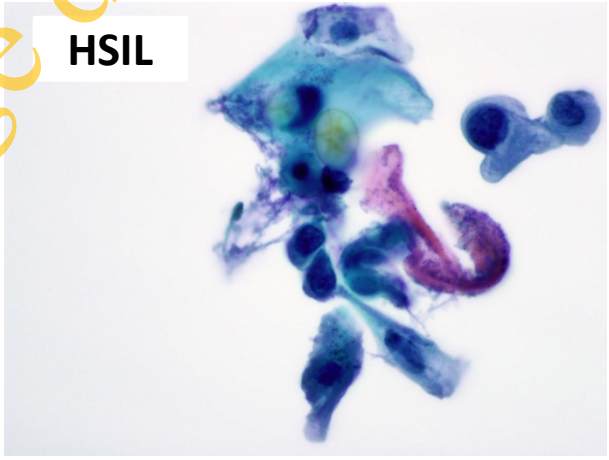
Dysplasie anale: terminologie

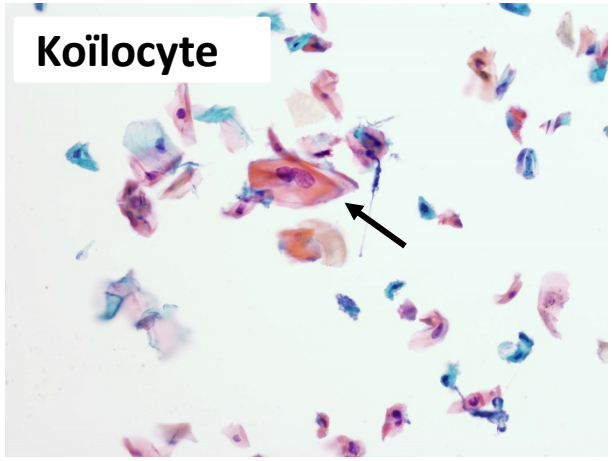
CYTOLOGIE





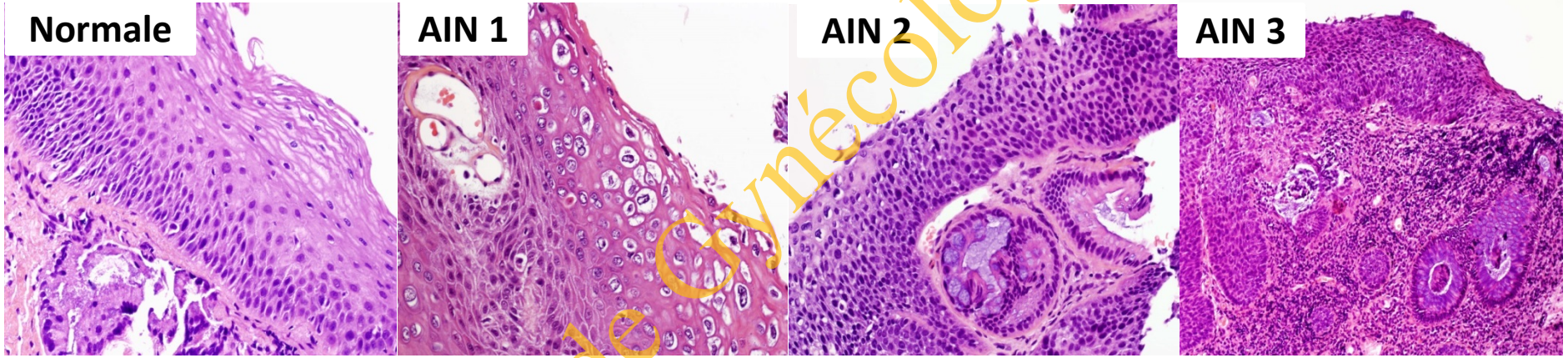






Dysplasie anale: terminologie

HISTOLOGIE



Correspondances des terminologies histologiques de la dysplasie du canal anal			
Dysplasie légère	AIN 1	Dysplasie de bas grade	AIN bas grade
Dysplasie modérée	AIN 2	Dysplasie de haut grade	AIN haut grade
Dysplasie sévère	AIN 3		
Carcinome *in situ*			

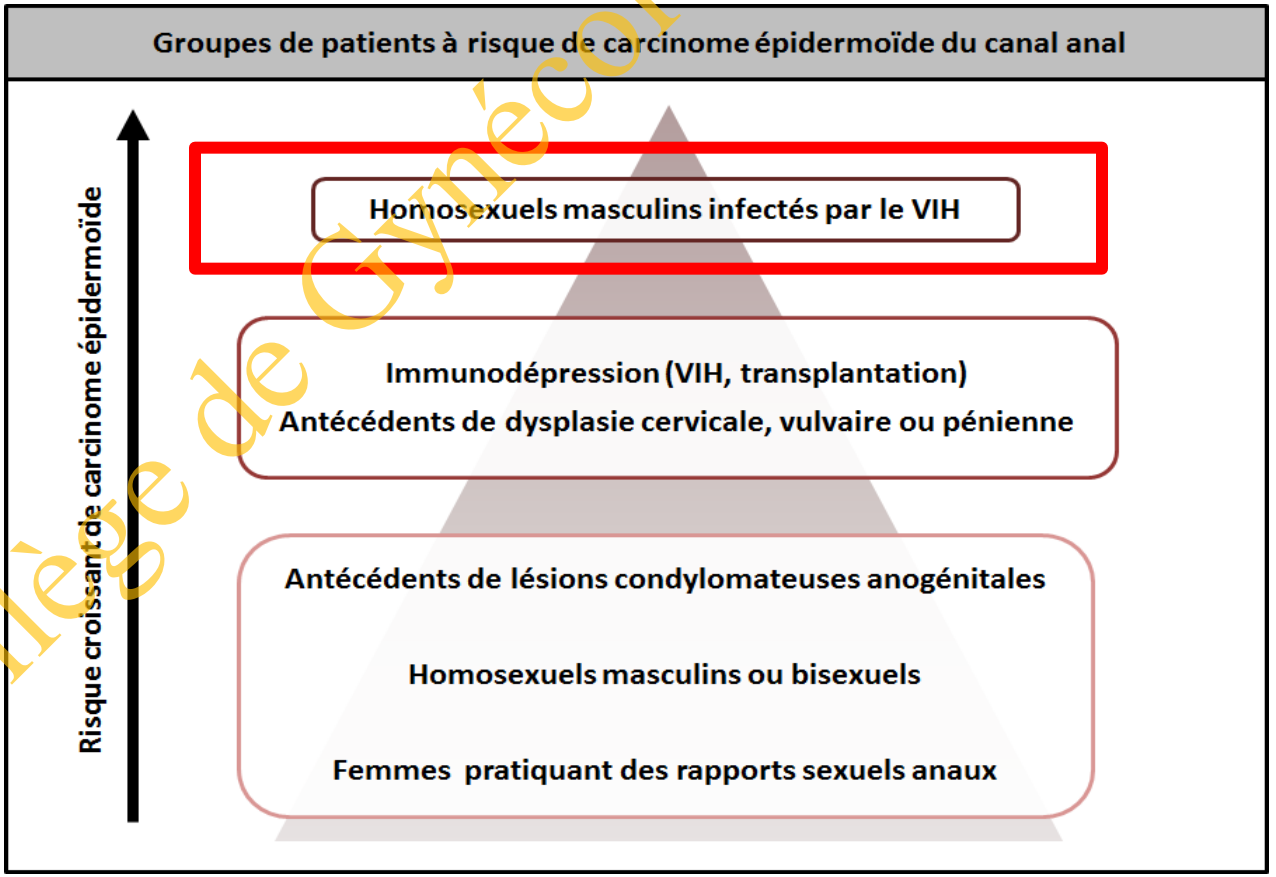
The Richart and Bethesda classification of anal dysplastic changes

Rare.....mais en progression depuis 20 ans

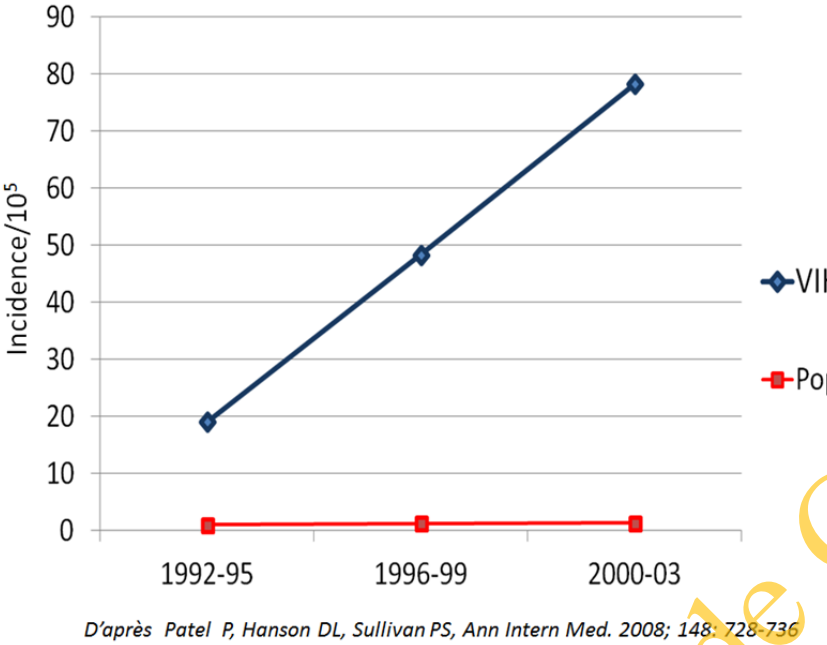
- **Progression: 2% par an**
- **2ème pic d'incidence**: 42,2 ans

Abramowitz L, Int J Cancer 2011
Sendagorta E, Actas Dermosifiliogr 2011
Piketty C, Aids 2008

Nb de partenaires sexuels (vie)
Cigarette
Greffe

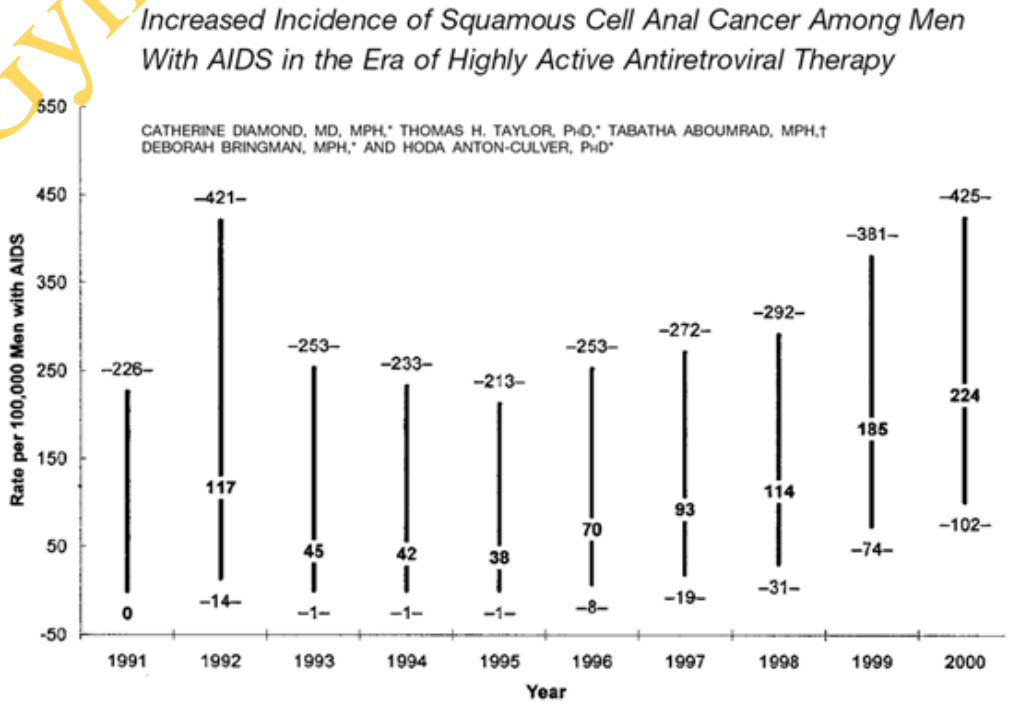


CE et VIH



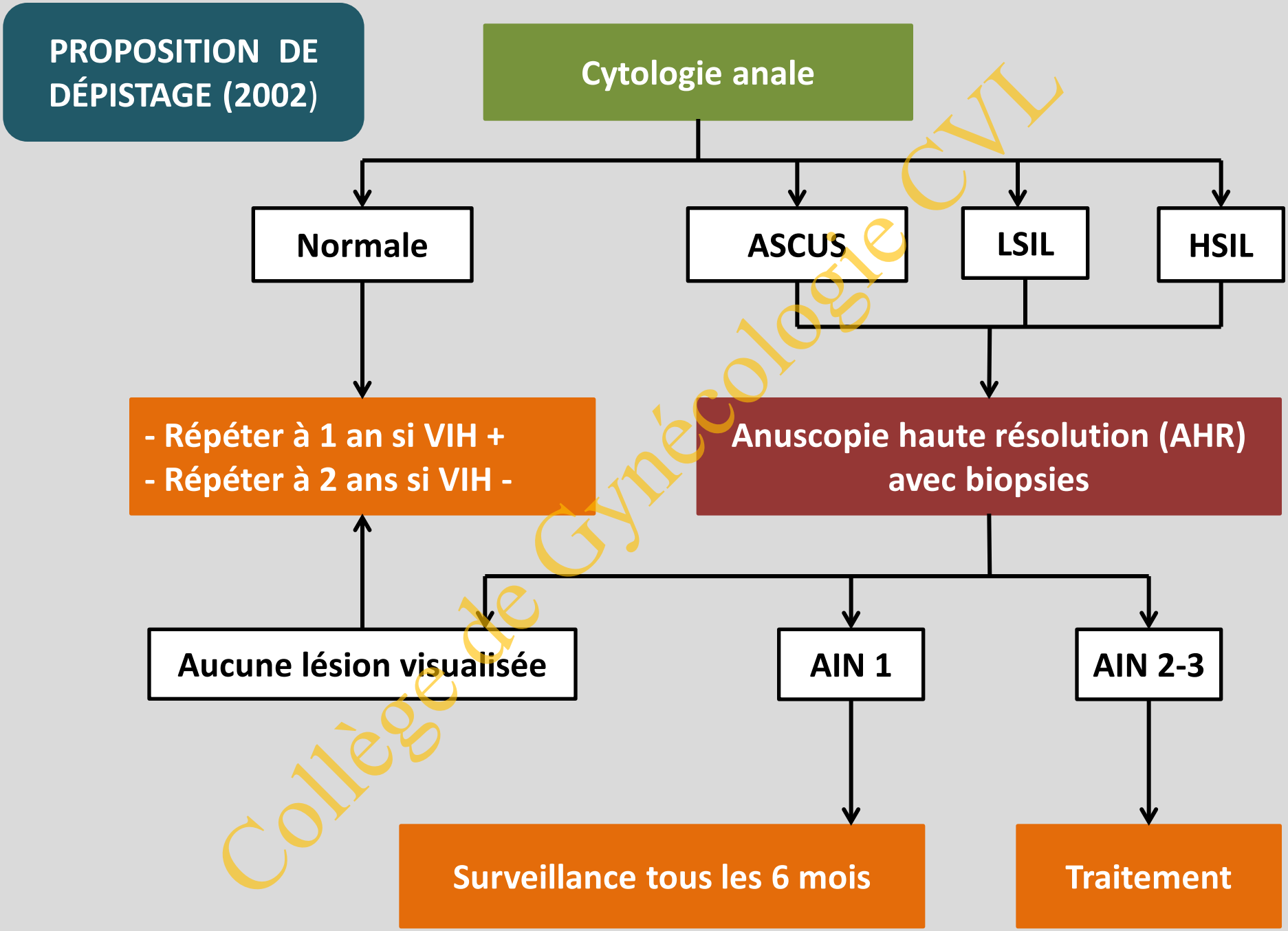
D'après Patel P, Hanson DL, Sullivan PS, Ann Intern Med. 2008; 148: 728-736

- RR: 29
- VIH+ MSM: 75-137/100000 hab./an



Sur-risque:

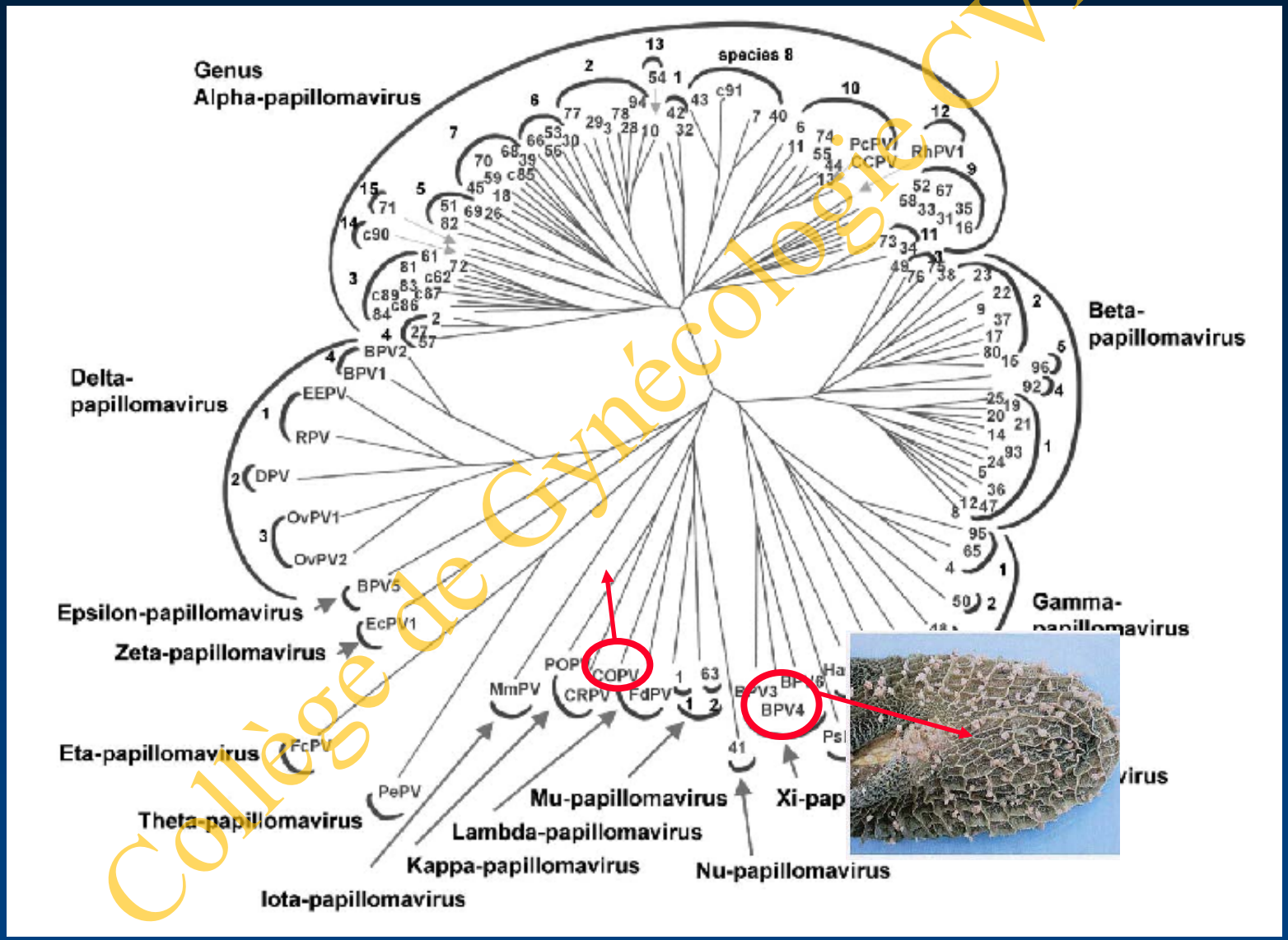
- 109 chez VIH MSM+
- 49 chez VIH MSM-
- 13 chez les femmes VIH



Prévention primaire ?

	Gardasil® Quadrivalent HPV 6, 11, 16, 18	**Cervarix®** Bivalent HPV 16, 18
Expression system	Yeast (*S. cerevisiae*)	Insect cell /baculovirus
Antigenic content	20 µg HPV-6 40 µg HPV-11 40 µg HPV-16 20 µg HPV-18	20 µg HPV-16 20 µg HPV-18
Adjuvant	Amorphous aluminium hydroxyphosphate sulfate (225 µg)	AS04 (Aluminium hydroxide 500 µg + 50 µg MPL)
Dose and injection	0,5 ml intramuscular	0,5 ml intramuscular
Regimen	0, 2 et 6 months	0, 1 et 6 months

Animal models



COPV model

1: Pathobiology. 1994;62(4):194-8.

A formalin-inactivated vaccine protects against mucosal papillomavirus infection: a canine model.

Bell JA, Sundberg JP, Ghim SJ, Newsome J, Jenson AB, Schlegel R.

Marshall Farms USA, Inc., North Rose, N.Y., USA.

A formalin-inactivated canine oral papilloma homogenate was used as a vaccine to prevent infection by the oncogenic, mucosotropic canine oral papillomavirus (COPV) in beagle dogs. Twenty-six dogs received 2 doses of phosphate-buffered saline intradermally and 99 dogs received 2 doses of the inactivated vaccine. One month after the second dose all dogs were challenged with infectious COPV by scarification of the oral mucosa. All of the control dogs developed papillomas by 6-8 weeks after challenge while none of the vaccinated dogs did. This vaccine has been used successfully in approximately 60,000 line bred beagles with no untoward effects and with long-lasting protection. These data demonstrate that a systemically administered, formalin-inactivated vaccine can protect against mucosal infection by COPV and suggest approaches for the development of human papillomavirus vaccines.

COPV model

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 11553–11557, December 1995
Immunology

Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas

JoAnn A. Suzich*†, Shin-je Ghim†‡, Frances J. Palmer-Hill*, Wendy I. White*, James K. Tamura*§, Judith A. Bell¶, Joseph A. Newsome‡, A. Bennett Jenson‡, and Richard Schlegel‡

*MedImmune, Inc., Gaithersburg, MD 20878; ‡Georgetown University Medical Center, Washington, DC 20007; and ¶Marshall Farms, Rose, NY 14516

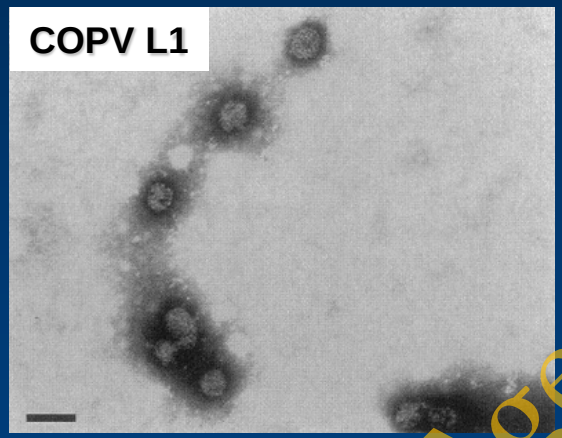


Table 1. COPV vaccine study

Group	Immunogen	L1, μg per dose	Total protein, μg per dose	No. of dogs with warts
1	Wart extract vaccine	0.01–0.1	1	0/7
2	PBS	—	—	7/7
3	Baculovirus/Sf9 nuclear protein	—	860	6/7
4	Crude COPV L1 VLPs	20	860	0/7
5	Enriched COPV L1 VLPs	20	120	0/7
6	SDS-denatured COPV L1 VLPs	20	120	7/7
7	HPV-11 L1 VLPs	20	30	7/7

Dogs (seven per group) were immunized by intradermal injection at week 0 and week 2. Immunogens were administered without adjuvant. All dogs were challenged with infectious COPV at week 4. Animals were followed for wart development for 13 weeks after challenge.

Table 2. Protection achieved with various dosages of COPV L1 VLPs

Group	L1, μg per dose	No. of dogs with warts
1	20	0
2	1	0
3	0.05	0
4	0.0025	2
5	0.000125	3
6	—	5

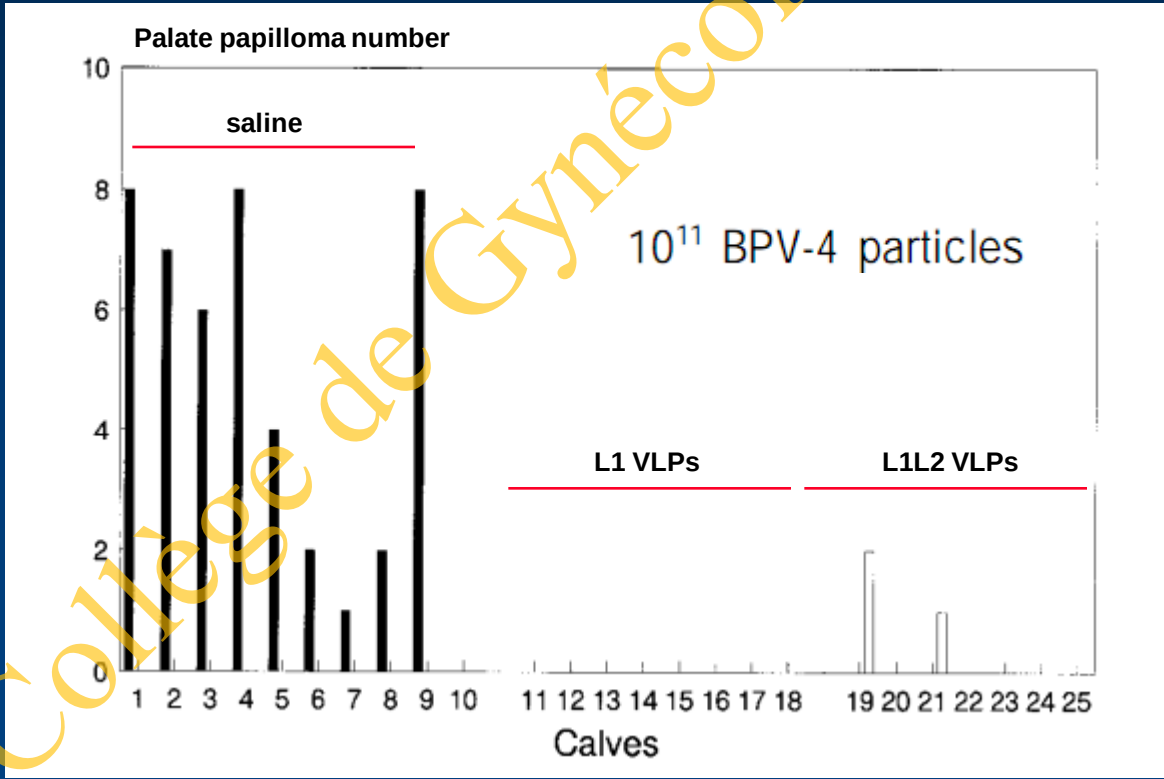
Dogs (five per group) were immunized by intradermal injection with crude COPV L1 VLPs at the indicated dosages. Group 6 was injected with PBS. All dogs received primary and booster immunizations at weeks 0 and 2, respectively, and were challenged with infectious COPV at week 4. Animals were followed for wart development for 10 weeks after challenge.

BPV-4 model

VIROLOGY 219, 37–44 (1996)
ARTICLE NO. 0220

Virus-like Particles of Bovine Papillomavirus Type 4 in Prophylactic and Therapeutic Immunization

R. KIRNBAUER,* L. M. CHANDRACHUD,† B. W. O'NEIL,† E. R. WAGNER,‡ G. J. GRINDLAY,‡ A. ARMSTRONG,* G. M. McGARVIE,‡ J. T. SCHILLER,§ D. R. LOWY,§ and M. S. CAMPO‡,[1]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2011;365:1576-85.

HPV Vaccine against [illegible] and Anal Intraepithelial Neoplasia

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Table 2. Vaccine Efficacy against HPV-6, 11, 16, or 18–Related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in the Per-Protocol Efficacy Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)†
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
AIN due to any HPV type‡	129	12	299.4	4.0	126	28	315.2	8.9	54.9 (8.4 to 79.1)
HPV-6, 11, 16, or 18	194	5	381.1	1.3	208	24	411.6	5.8	77.5 (39.6 to 93.3)
HPV-16 or 18	192	2	382.2	0.5	205	10	408.8	2.4	78.6 (–0.4 to 97.7)
AIN due to a specific HPV type									
HPV-6	141	3	275.2	1.1	144	10	298.5	3.4	67.5 (–26.4 to 94.2)
HPV-11	141	0	279.2	0.0	144	6	298.2	2.0	100 (9.3 to 100)
HPV-16	167	2	330.6	0.6	170	6	341.9	1.8	65.5 (–92.8 to 96.6)
HPV-18	173	0	345.3	0.0	193	4	387.4	1.0	100 (–70.0 to 100)
By lesion type									
AIN grade 1	194	4	383.1	1.0	208	16	413.8	3.9	73.0 (16.3 to 93.4)
Condyloma acuminatum	194	0	386.8	0.0	208	6	418.2	1.4	100 (8.2 to 100)
Flat lesion	194	4	383.1	1.0	208	11	416.7	2.6	60.4 (–33.5 to 90.8)
AIN grade 2 or 3	194	3	383.9	0.8	208	13	417.2	3.1	74.9 (8.8 to 95.4)
Grade 2	194	2	384.5	0.5	208	9	418.6	2.2	75.8 (–16.9 to 97.5)
Grade 3	194	2	385.4	0.5	208	6	419.7	1.4	63.7 (–103.0 to 96.4)
Anal cancer	194	0	386.8	0.0	208	0	421.1	0.0	NA

* The per-protocol efficacy population consisted of participants who were seronegative and had HPV DNA–negative swab and biopsy specimens on day 1 for relevant vaccine types, were negative for vaccine-type DNA through month 7, and did not have any protocol violations. To eliminate potential ascertainment bias, analyses in the per-protocol efficacy population excluded AIN diagnosed by the presence of perianal external lesions on high-resolution anoscopy. A participant may have been counted more than once if multiple lesions in different categories developed.

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FDA: Gardasil approved to prevent anal cancer

The U.S. Food and Drug Administration today approved the vaccine Gardasil for the prevention of anal cancer and associated precancerous lesions due to human papillomavirus (HPV) types 6, 11, 16, and 18 in people ages 9 through 26 years.

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