XXV CONGRÉS Societat Catalano-Balear de Cirurgia Maxil·lofacial i Oral

Avances en el tratamiento del cáncer de la cavidad orofaríngea

Generalitat de Catalunya
Departament de Salut

ICO Institut Català d'Oncologia

VPH i càncer de cap i coll. Una epidèmia per arribar?

27 gener 2017

XXV congrés Societat Catalano-Balear de Cirurgia Maxil.lofacial i Oral

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Unitat d'Infeccions i Càncer
Programa de Recerca en Epidemiologia del Càncer
Institut Català d'Oncologia

Ens arribarà l'epidèmia?

Es preveu un **augment de casos de càncer d'orofaringe VPH relacionats en els propers anys**,

el **com i quan** no està del tot clar depèn de diversos factors!

Continguts

1. Virus del Papil-loma Humà (VPH)
2. Associació VPH-Càncer de cap i coll
3. Tendència d'incidències dels càncers de cap i coll VPH i no VPH relacionats
4. Factors que poden influir en el canvi de tendències

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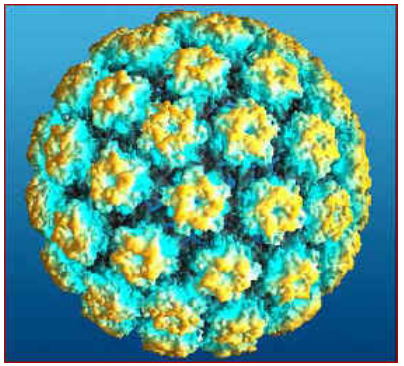
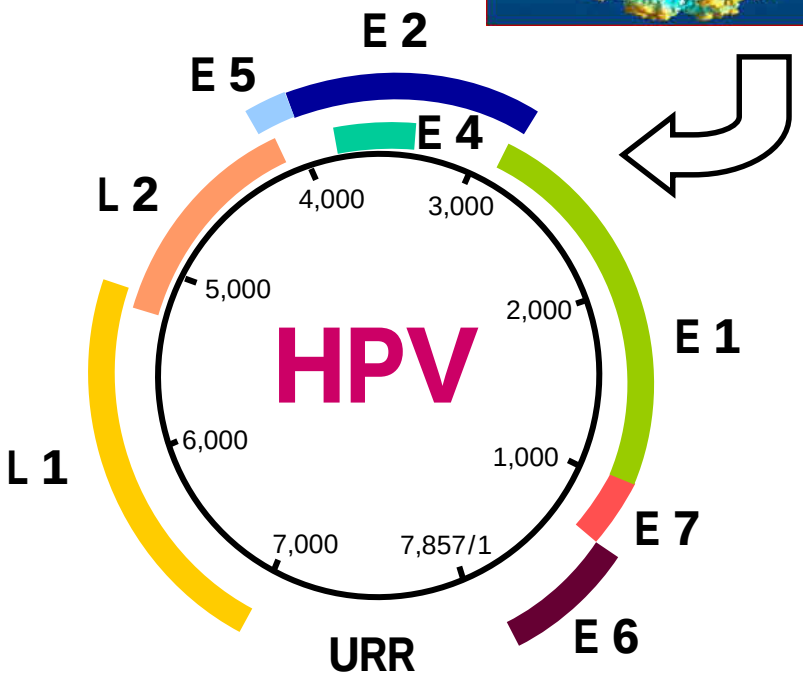
Human Papillomavirus

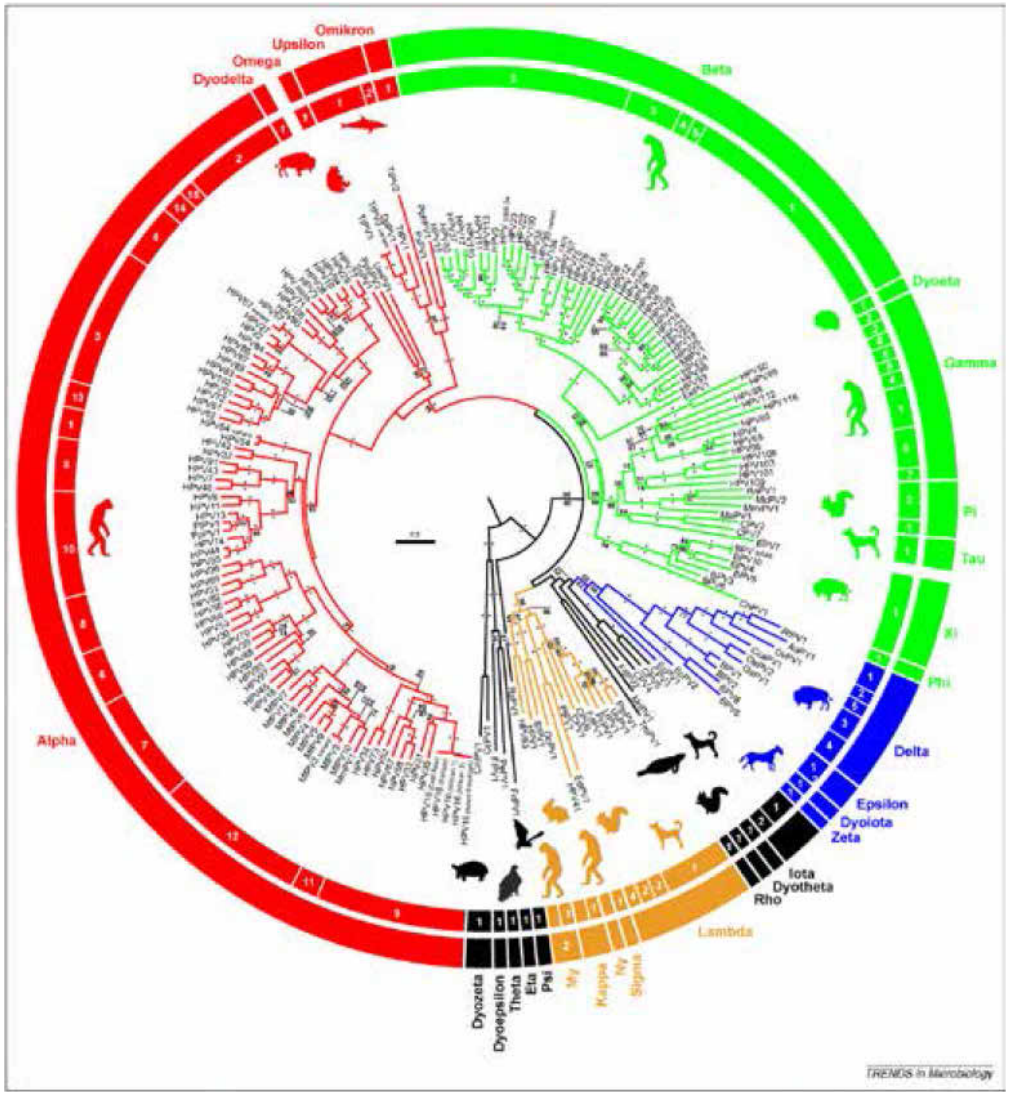


- Papillomaviridae family
- EXT.: Capsid proteins (L1/L2)
- INSIDE:
  - Double stranded DNA virus
  - Size: 8,000 bp
  - Well characterized viral genome
  - Early genes: E6/E7
  - Late genes: L1/L2



L1 and L2: capsid genes; URR: Upstream regulatory region
Reprinted from Macmillan Publishers Ltd: Nature Reviews Immunology 2004; 4(1): 46-54.
Vaccine, Vol 24 Supplement 3, 2006. Chapter 1, Figure 1

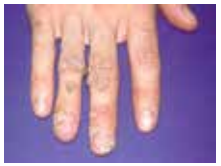
HPV - phylogeny



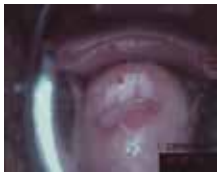
Bravo IG et al. Trends in Microbiology. 2010

HPV - types

>100 HPV types



§ Skin types (warts, non-melanoma skin cancer, …)



§ Mucosal types, classified in different groups regarding their association with cancer:

Table 2: Human papillomavirus (HPV) types assessed by the IARC Monograph Working Group

	Group	HPV types	Comments
	Alpha HPV types		
High risk	1	16	Most potent HPV type, known to cause cancer at several sites
High risk	1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
Probable/possible high risk	2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
Probable/possible high risk	2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
Probable/possible high risk	2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
Low risk	3	6, 11	..

**IARC Monograph 100B. Human carcinogens-Biological agents; The Lancet Oncology. 2009*

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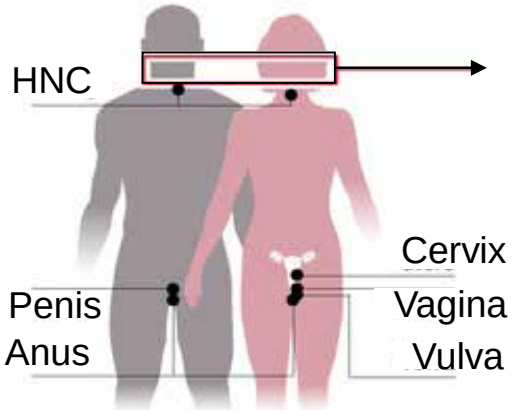
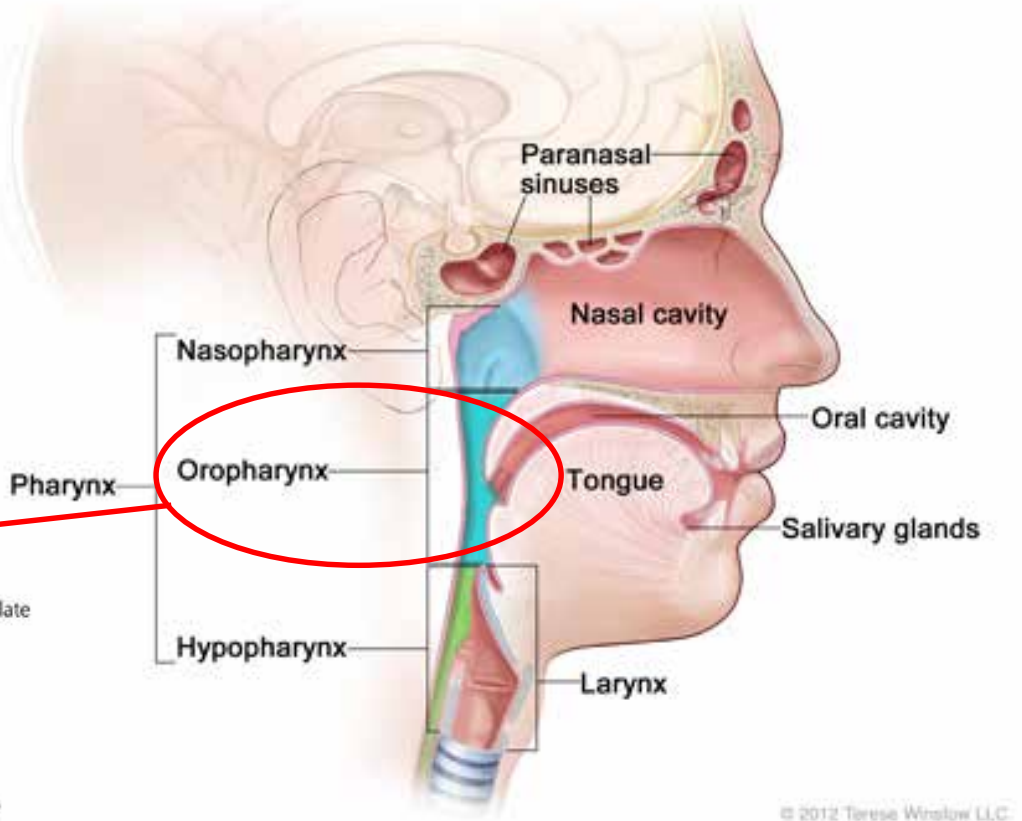
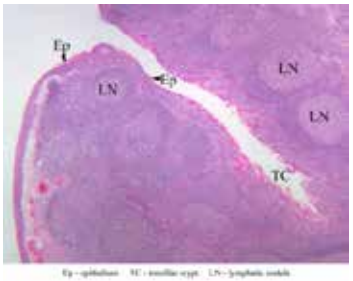
HPV - human carcinogen

HPV-related cancers



Head and neck regions





Tonsil
(Hematoxylin-Eosin)

Oropharynx

**IARC Monograph 100B. Human carcinogens-Biological agents; The Lancet Oncology. 2009*

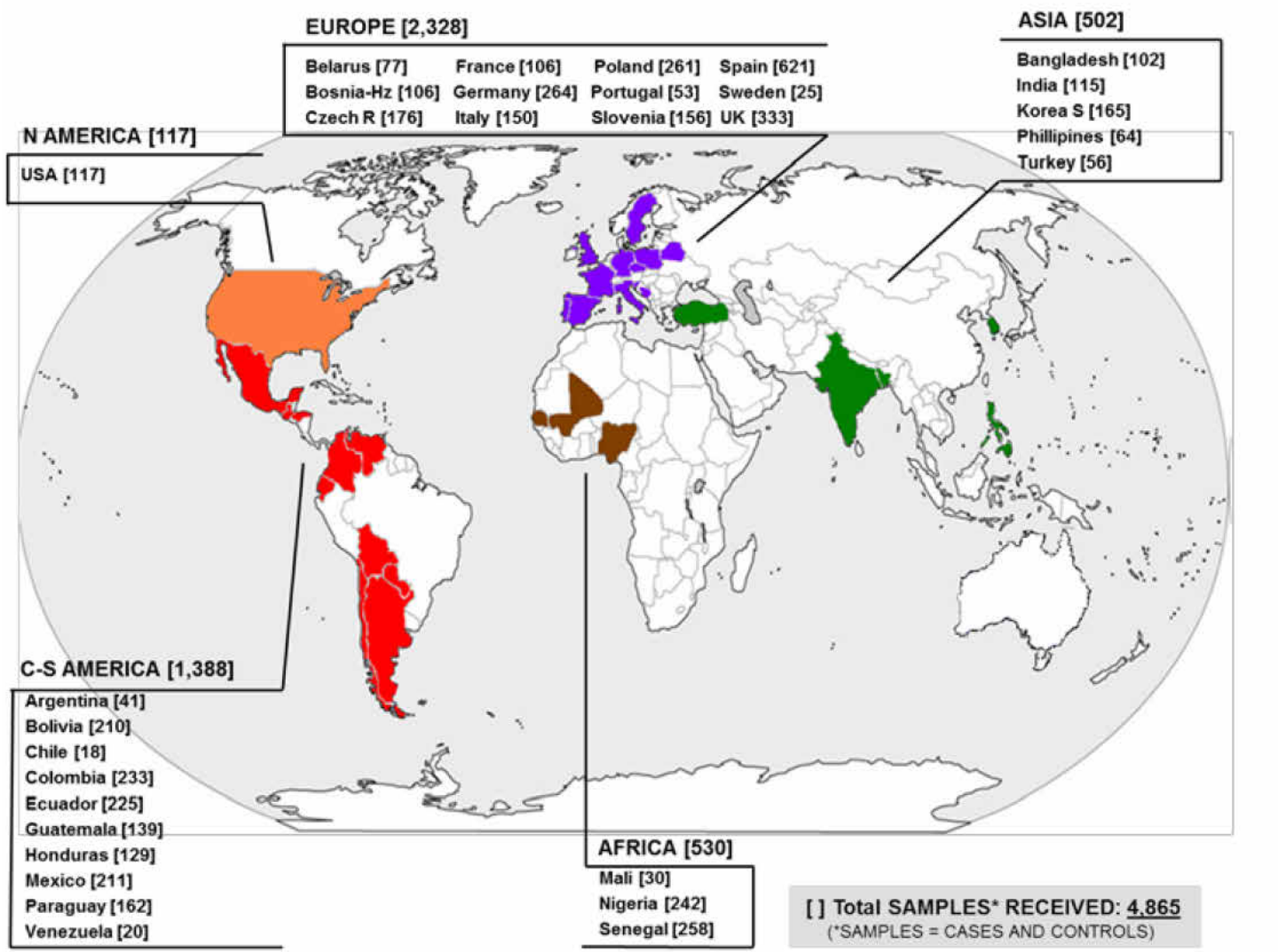
HPV attributable fractions (I)

- Prevalence of HPV DNA in cancer, systematic reviews:

DATA	Oral cavity	Oropharynx	Larynx
Kreimer AR et al, CEBP, 2005	23.5	35.6	24.0
De Martel C et al, Lancet Oncol, 2012*	-	25.6	-
Ndiaye C/Mena M et al, Lancet Oncol, 2014	24.2	45.8	22.1

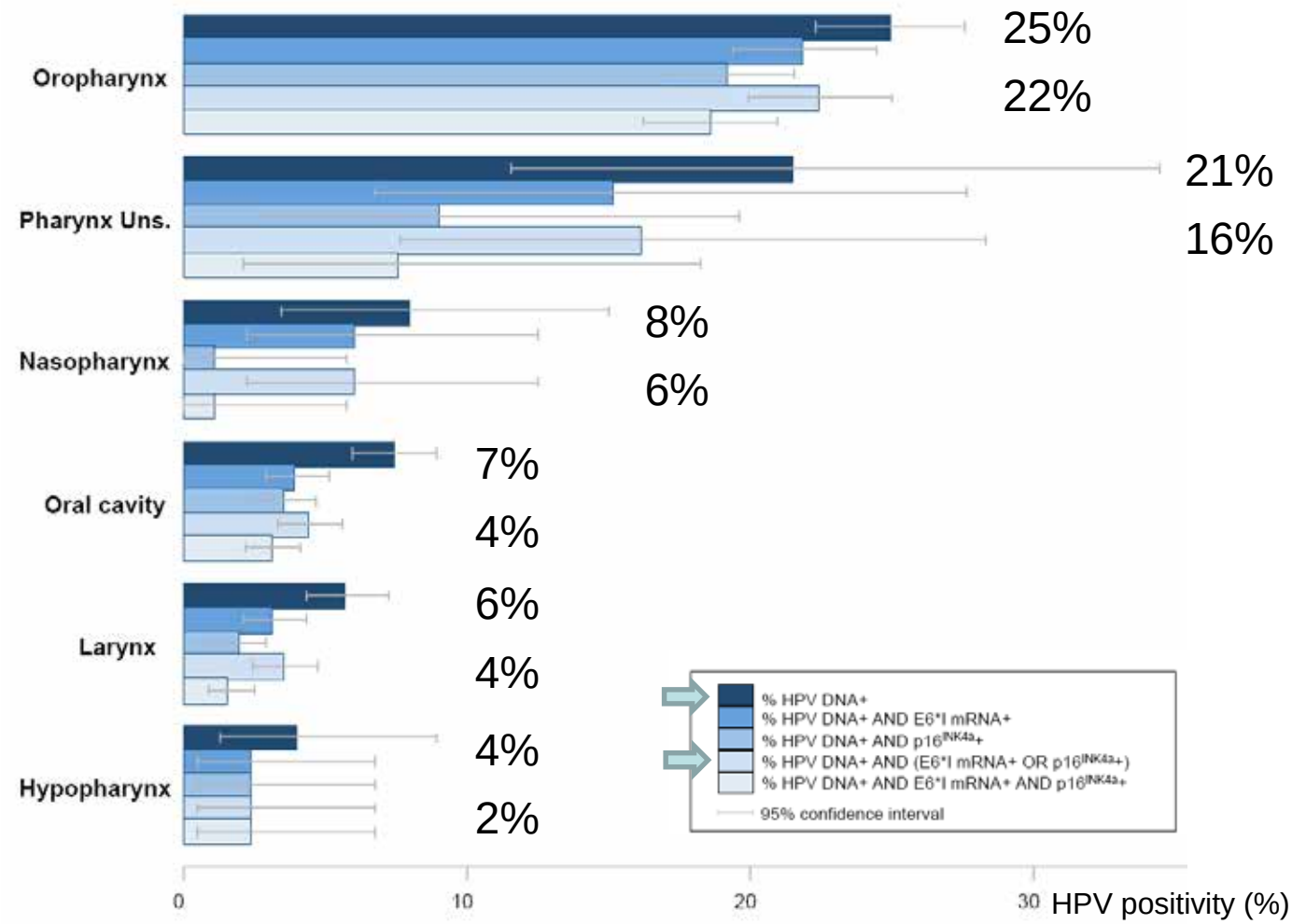
*(*DNA and mRNA; Geographical variability: 56% North America, 52% Japan, 45% Australia, 39% North-Western Europe, 38% Eastern Europe, 17% Southern Europe, 13% Rest)*

ICO international survey, HPV in HNCs



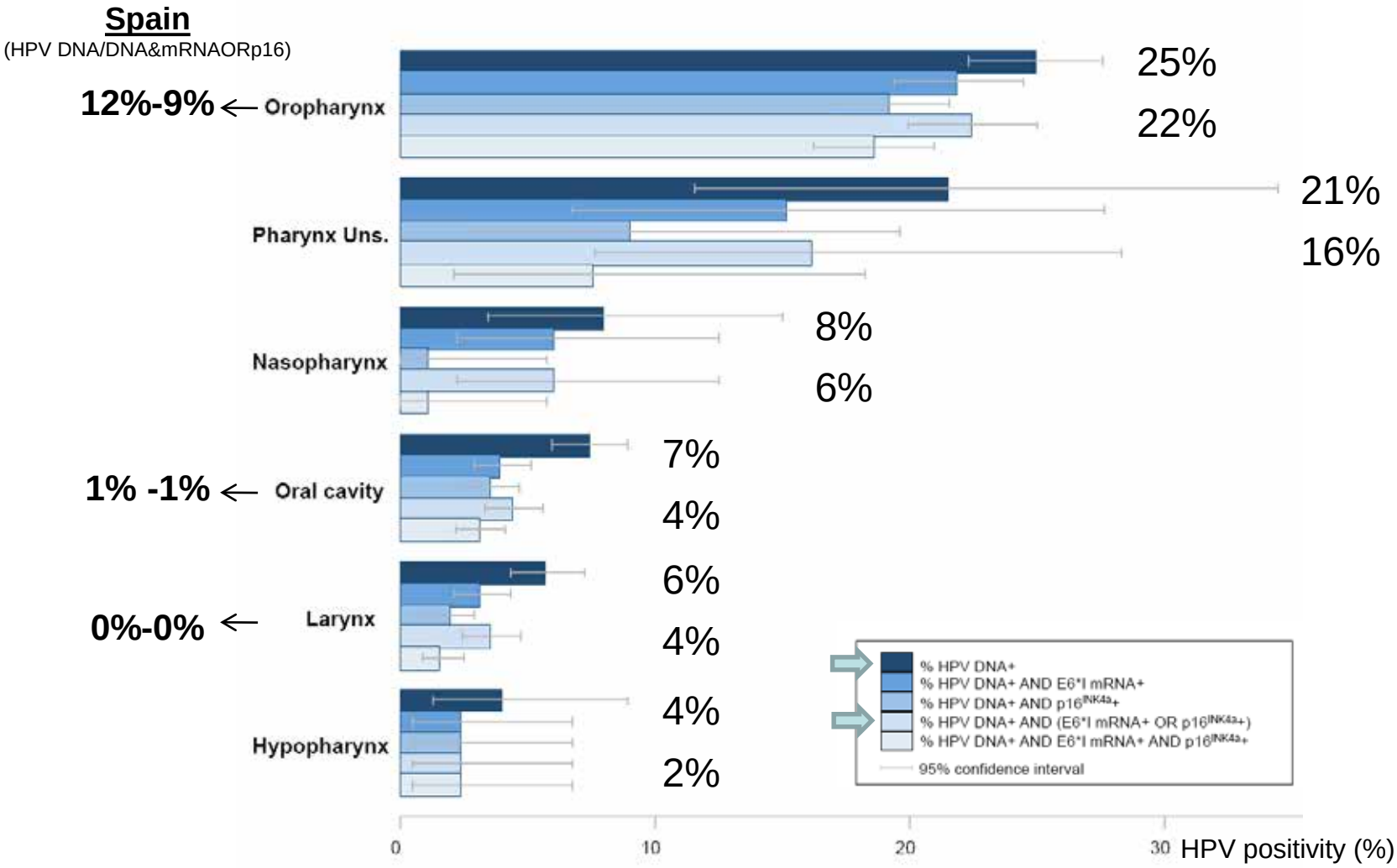
Updated: November, 2013

HPV attributable fractions (II) – ICO International survey in HNCs, 3680 cases



Castellsagué X /Alemany L et al; JNCI (accepted)

HPV attributable fractions (II) – ICO International survey in HNCs, 3680 cases



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Incidence trends in HNCs by site

Selection of studies evaluating incidence trends: Annual Percent Change

Study	Country	Years	Trends in Oropx cancer	Trends in Other HNC
Hocking JS, 2011	Australia	1982-2005	**INCREASE**	**DECREASE (M)**/STABLE (W)
Auluck A, 2010	Canada	1980-2006	**INCREASE**	**DECREASE (M)**/STABLE (W)
Blomberg M, 2010	Denmark	1978-2007	**INCREASE**	**INCREASE**
Reddy VM, 2010	England	1985-2006	**INCREASE**	**INCREASE**
Ioka A, 2005	Japan	1965-1999	INCREASE	INCREASE (M)/STABLE (W)
Braakhius BJ, 2009	The Netherlands	1989-2006	**INCREASE**	STABLE (M)/**INCREASE (W)**
Mork J, 2010	Norway	1981-2005	**INCREASE**	DECREASE
Hammarstedt L, 2006	Sweden	1970-2002	INCREASE	-
Chaturvedi A, 2008	USA	1973-2004	**INCREASE (M)**/ DECREASE (W)	DECREASE

Gillison ML et al. Vaccine. 2012; In bold letters p<0.05; If not specified, findings for both sexes are in the same direction (M:Men, W:Women)

Incidence trends in HNCs by site

Published Ahead of Print on November 18, 2013 as 10.1200/JCO.2013.50.3870
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.3870

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Worldwide Trends in Incidence Rates for Oral Cavity and Oropharyngeal Cancers

Anil K. Chaturvedi, William F. Anderson, Joannie Lortet-Tieulent, Maria Paula Curado, Jacques Ferlay, Silvia Franceschi, Philip S. Rosenberg, Freddie Bray, and Maura L. Gillison

Methods

We used data from the *Cancer Incidence in Five Continents* database Volumes VI to IX (years 1983 to 2002). Using age-period-cohort modeling, incidence trends for OPCs were compared with those of OCCs and lung cancers to delineate the potential role of HPV vis-à-vis smoking on incidence trends. Analyses were country specific and sex specific.

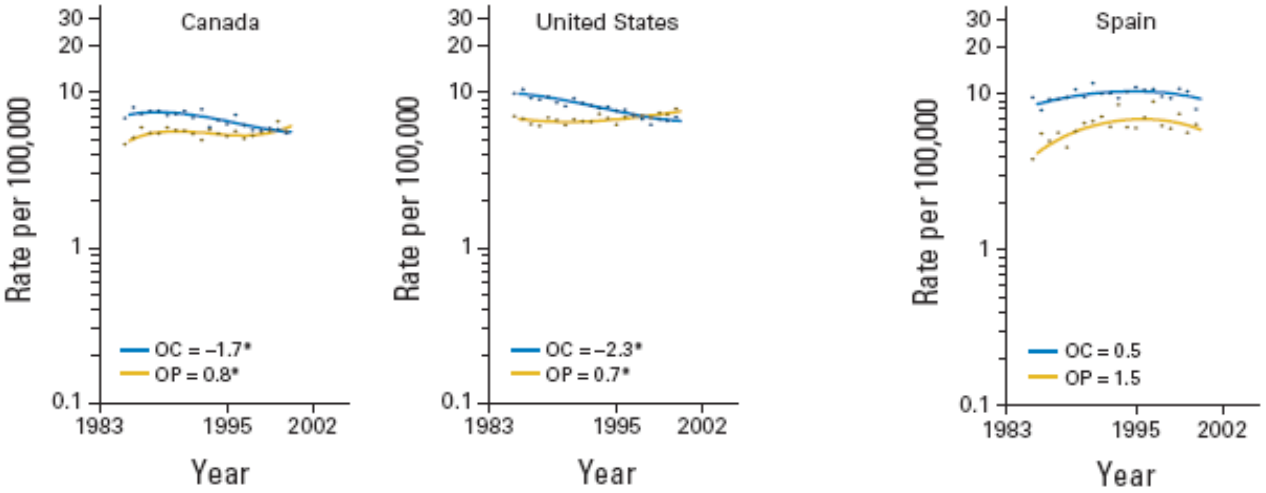
Conclusion

OPC incidence significantly increased during 1983 to 2002 predominantly in developed countries and at younger ages. These results underscore a potential role for HPV infection on increasing OPC incidence, particularly among men.

Chaturvedi A et al. J Clin Oncol. 2013

Incidence trends in HNCs by site

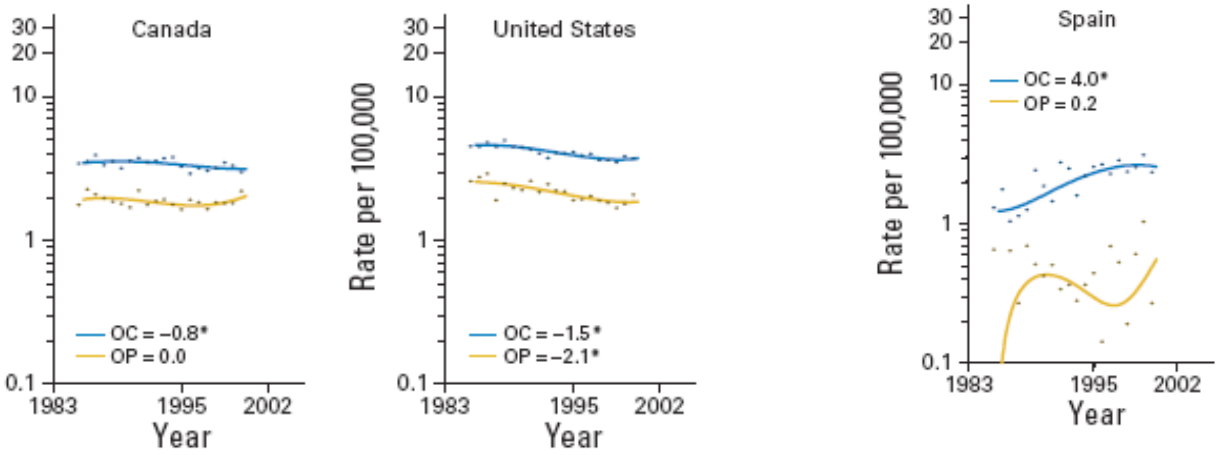
Men



- Yellow - Oropharynx
- Blue - Oral Cavity

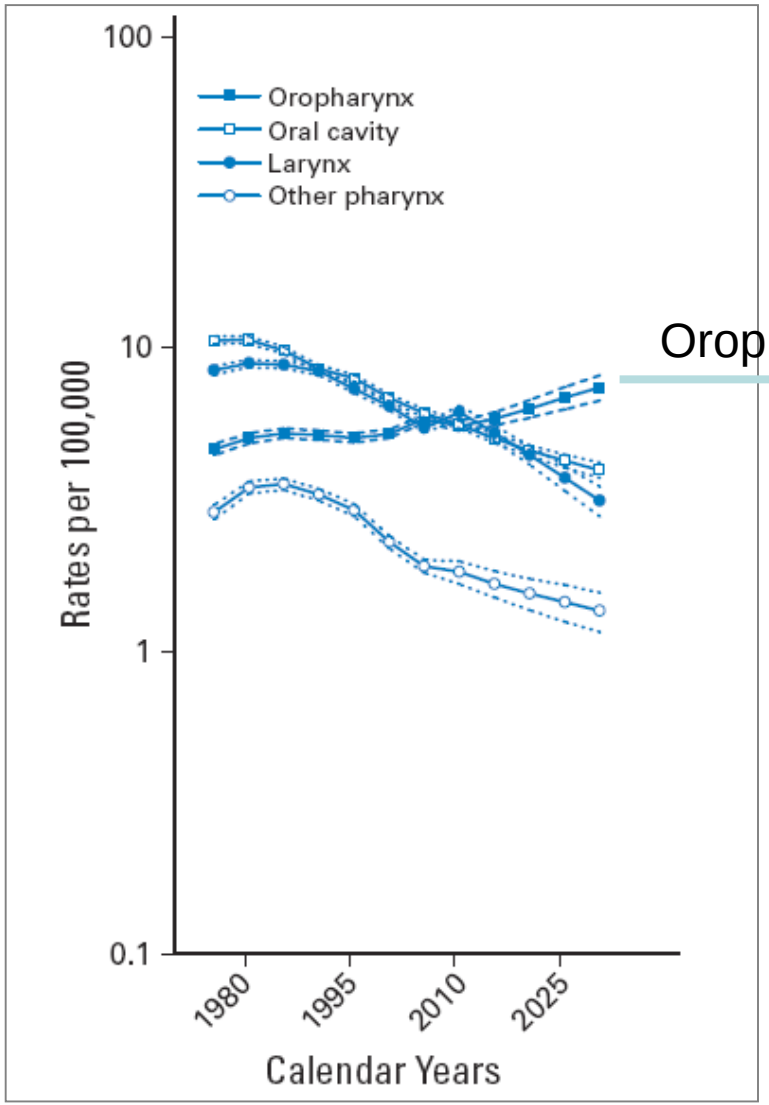
APC (Annual Percentage Changes; *p<0.05)

Women

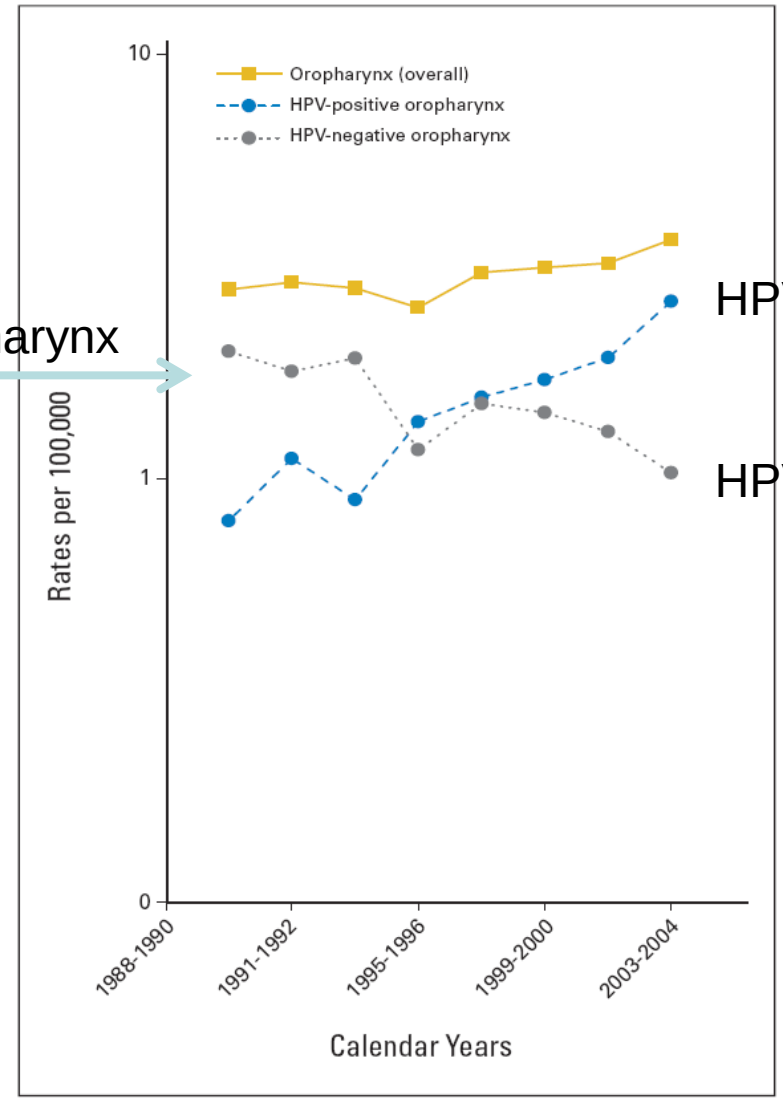


Chaturvedi A et al. J Clin Oncol. 2013

Trends of HPV positive cases (US)



Oropharynx



HPV+

HPV-

Chaturvedi A et al. J Clin Oncol. 2011

Trends of HPV positive cases

CLINICAL REVIEW

David W. Eisele, MD, *Section Editor*

PREVALENCE OF HUMAN PAPILLOMAVIRUS IN OROPHARYNGEAL AND NONOROPHARYNGEAL HEAD AND NECK CANCER—SYSTEMATIC REVIEW AND META-ANALYSIS OF TRENDS BY TIME AND REGION

Hisham Mehanna, PhD,[1] Tom Beech, MSc,[1] Tom Nicholson, MBChB,[1] Iman El-Hariry, MD, PhD,[2] Christopher McConkey, MSc,[3] Vinidh Paleri, MS FRCS(ORL-HNS),[4] Sally Roberts, DPhil[5]

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[3] Warwick Clinical Trials Unit, Warwick Medical School, Coventry, United Kingdom
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Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.22015

Mehanna H et al. Head and Neck. 2012

Trends of HPV positive cases in oropharyngeal cancers

Table 1. Synthesized human papillomavirus prevalence trends over time and by region.

Group	Overall prevalence (95% CI)	Midyear <2000 (95% CI)	Midyear 2000–2004 (95% CI)	Midyear 2005+ (95% CI)	Midyear NK	*p* value (midyear trend)	*p* value (year group trend)
OPC							
All regions	47.7 (42.9, 52.5)	40.5 (35.1, 46.1)	64.3 (56.7, 71.3)	72.2 (52.9, 85.7)	40.5 (31.1, 50.7)	<.0001	<.0001
	S = 102	S = 54	S = 22	S = 4	S = 22		
	n = 5396	*n* = 2690	*n* = 2037	*n* = 150	*n* = 519		
	0.89	0.82	0.9	0.8			
N. America	59.9 (54.7, 64.9)	50.7 (42.6, 58.7)	67.6 (61.7, 72.9)	69.7 (46.8, 85.7)	55.6 (41.4, 69.0)	0.0002	0.002
	S = 43	S = 19	S = 17	S = 2	S = 5		
	n = 2550	*n* = 696	*n* = 1678	*n* = 45	*n* = 131		
	0.8	0.73	0.79	0.76			
Europe	39.7 (32.8, 47.0)	35.3 (28.7, 42.5)	59.0 (30.2, 82.7)	73.1 (39.4, 91.9)	36.2 (24.3, 50.0)	0.07	0.004
	S = 46	S = 27	S = 4	S = 2	S = 13		
	n = 2278	*n* = 1704	*n* = 164	*n* = 105	*n* = 305		
	0.87	0.82	0.87	0.87			
Other, NK, and mixed regions	32.5 (23.9, 42.4)	32.2 (21.0, 45.9)	—	—	35.4 (18.5, 56.9)	0.46	—
	S = 13	S = 8	S = 1	S = 0	S = 4		
	n = 568	*n* = 290	*n* = 195	*n* = 0	*n* = 83		
	0.73	0.78					

Mehanna H et al. Head and Neck. 2012

Trends of HPV positive cases in non oropharyngeal cancers

Table 1. Synthesized human papillomavirus prevalence trends over time and by region.

Group	Overall prevalence (95% CI)	Midyear <2000 (95% CI)	Midyear 2000–2004 (95% CI)	Midyear 2005+ (95% CI)	Midyear NK	*p* value (midyear trend)	*p* value (year group trend)
Non-OPC							
All regions	21.8 (18.9, 25.1)	22.2 (18.4, 26.4)	17.2 (11.9, 24.4)	6.1 (0.7, 39.0)	26.3 (19.3, 34.8)	0.97	0.07
	S = 236	S = 140	S = 37	S = 5	S = 54		
	n = 13,972	*n* = 2260	*n* = 186	*n* = 2419			
	0.93	0.96	0.88	0.91			
N. America	12.8 (9.7, 16.6)	14.1 (10.1, 19.5)	9.8 (5.2, 17.5)	—	15.1 (7.3, 28.7)	0.03	0.08
	S = 62	S = 38	S = 13	S = 2	S = 9		
	n = 3803	*n* = 2212	*n* = 1204	*n* = 40	*n* = 347		
	0.86	0.87	0.85				
Europe	23.7 (19.4, 28.7)	23.6 (18.5, 29.5)	23.2 (12.7, 38.4)	11.7 (0.9, 67.0)	25.9 (16.3, 38.5)	0.27	0.66
	S = 90	S = 53	S = 14	S = 3	S = 20		
	n = 4625	*n* = 29490	*n* = 539	*n* = 146	*n* = 991		
	0.9	0.9	0.87	0.93			
Other, NK, and mixed regions	28.8 (22.5, 36.1)	28.6 (20.4, 38.5)	23.9 (14.5, 36.7)	—	31.7 (19.8, 46.7)	0.53	0.55
	S = 84	S = 49	S = 10	S = 0	S = 25		
	n = 5364	*n* = 3766	*n* = 517	*n* = 0	*n* = 1081		
	0.95	0.96	0.84				

Mehanna H et al. Head and Neck. 2012

Trends of HPV positive cases in oropharyngeal cancers, Spain (Asturias)

Table 3. Distribution of p16-positive and HPV G5+6+ PCR-positive OPSCC, heavy tobacco and alcohol use and tonsillar localization over two decades: 1990–1999 and 2000–2009

	1990–1999 $n = 166$	2000–2009 $n = 82$	p-value	
HPV positive	3 (1.8%)	5 (6.1%)	0.120	Fisher's exact
Tobacco > 50 pack-year	81 (49%)	24 (29%)	0.009	Pearson
Alcohol > 100 gr/day	106 (64%)	49 (60%)	0.991	Pearson
Tonsillar localization	104 (63%)	36 (44%)	0.006	Fisher's exact

Rodrigo JP et al. In J Cancer. 2013

Trends of HPV positive cases in oropharyngeal cancers, World and in Spain (%)

Period of diagnosis	World (n=1,090)		Spain* (n=579)
	HPV DNA – 24.9%	HPV DNA & (p16 OR mRNA) – 22.4%	HPV DNA – 11.1%
1991-94	**10.8**	**7.2**	9.8
1995-99	**10.1**	**10.1**	7.4
2000-04	**21.4**	**18.7**	8.7
2005-09	**29.9**	**26.1**	13.8
2010-12	**34.0**	**32.7**	11.9

Castellsague X/Alemany L, JNCI (accepted); Mena M, in preparation; in bold p-trend <0.05

*H.Sant Pau (de Martel M, Oral Oncol 2017) – 1991-98:8%; 1999-06:11%; 2007-14: 19%

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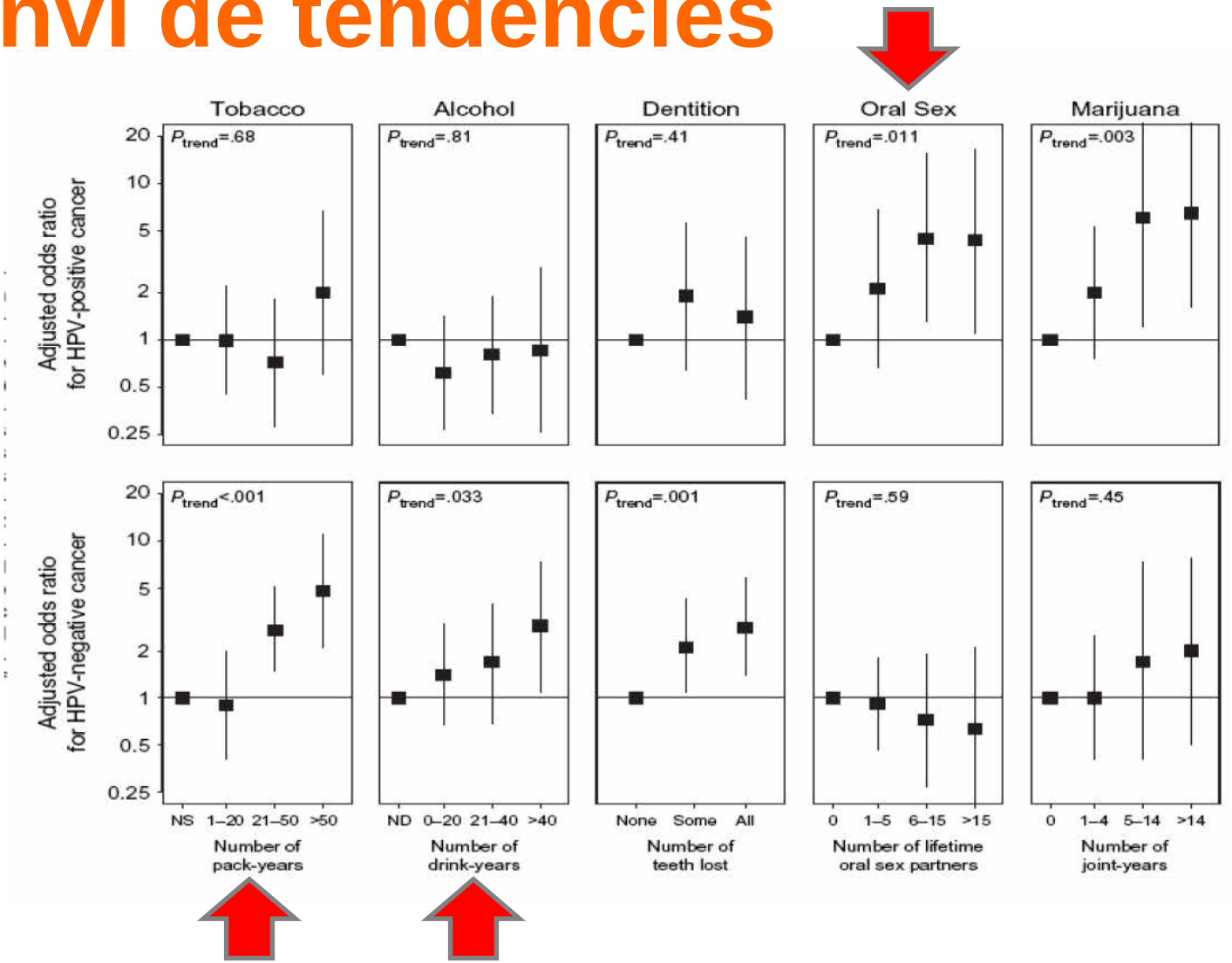
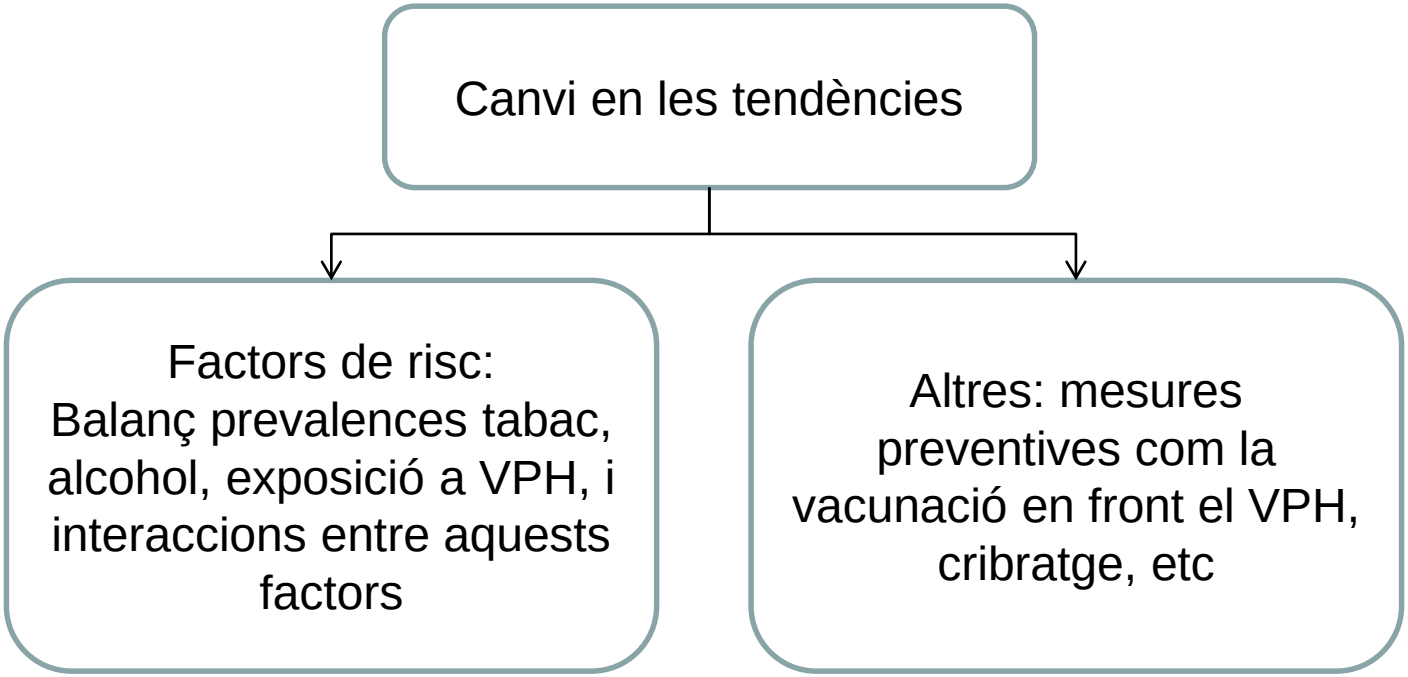
Factors que poden determinar canvi de tendències

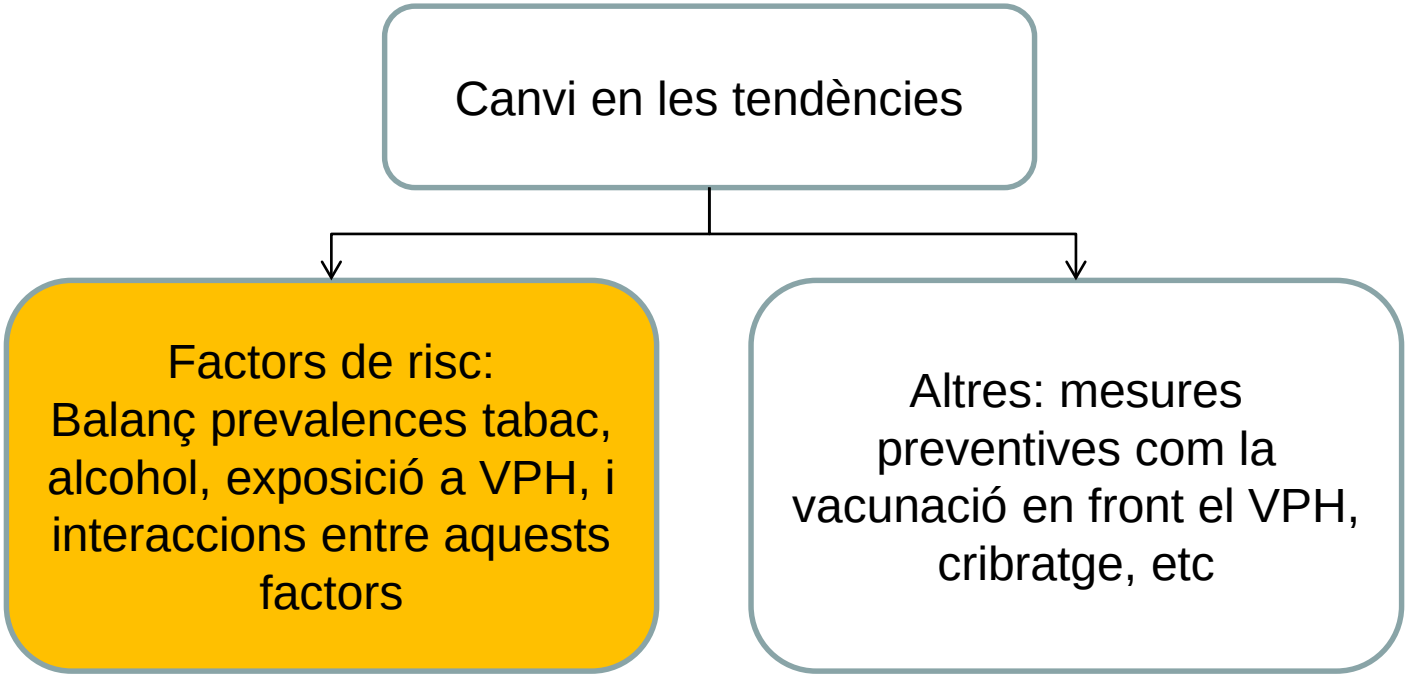


Gillison, M et al. J Natl Cancer Inst. 2008

Factors que poden determinar canvi de tendències

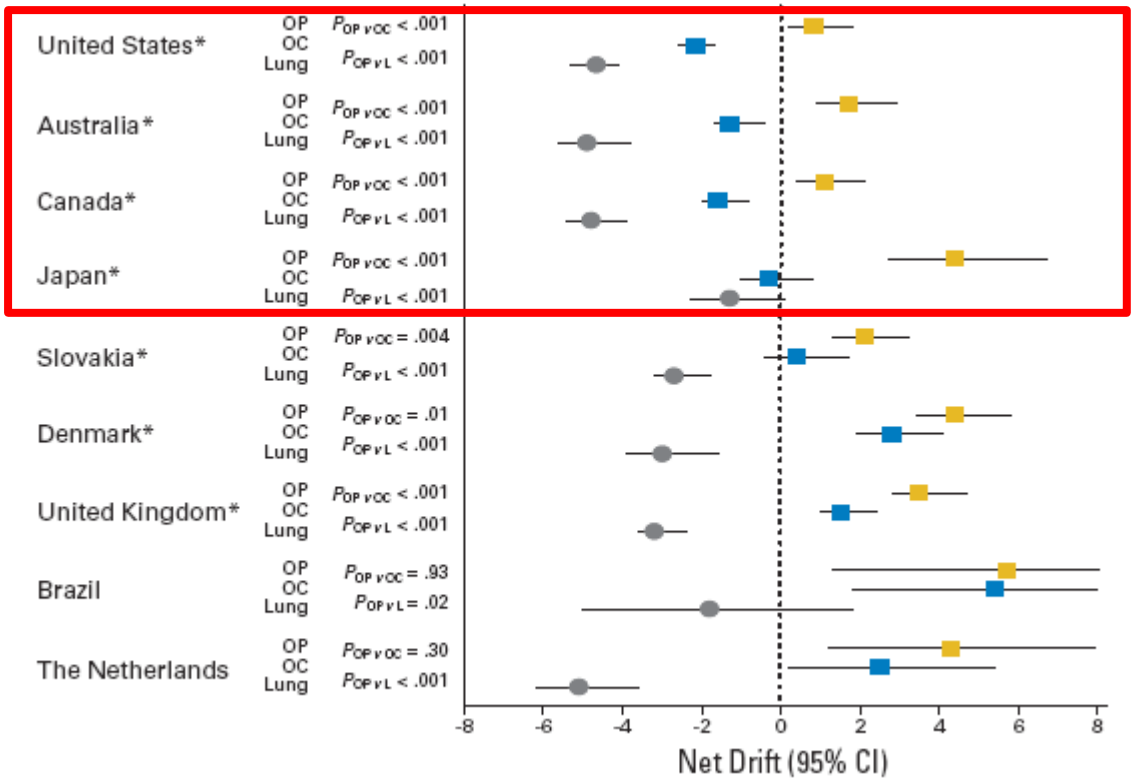


Factors que poden determinar canvi de tendències



Variació prevalences tabac

Homes

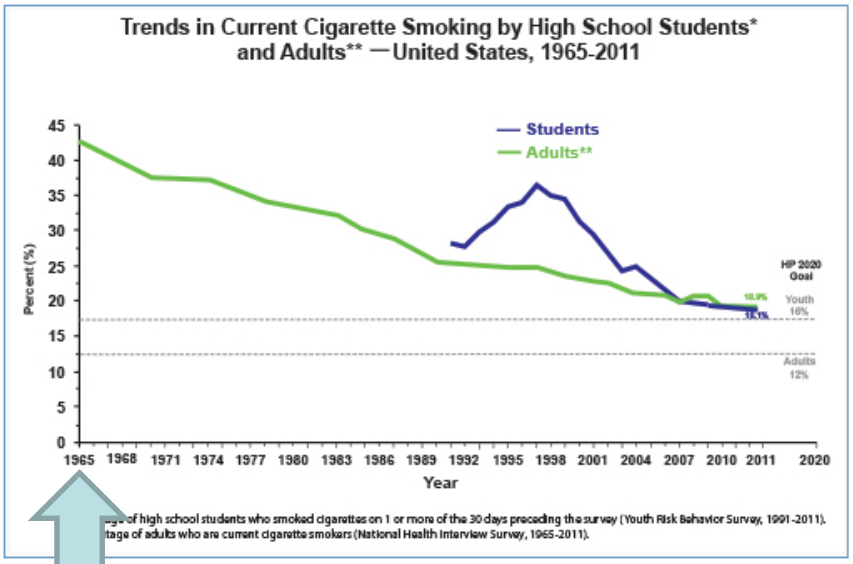


- Yellow - Oropharynx
- Blue - Oral Cavity
- Grey - Lung

Chaturvedi A et al. J Clin Oncol. 2013

Variació prevalences tabac

Estats Units



Espanya

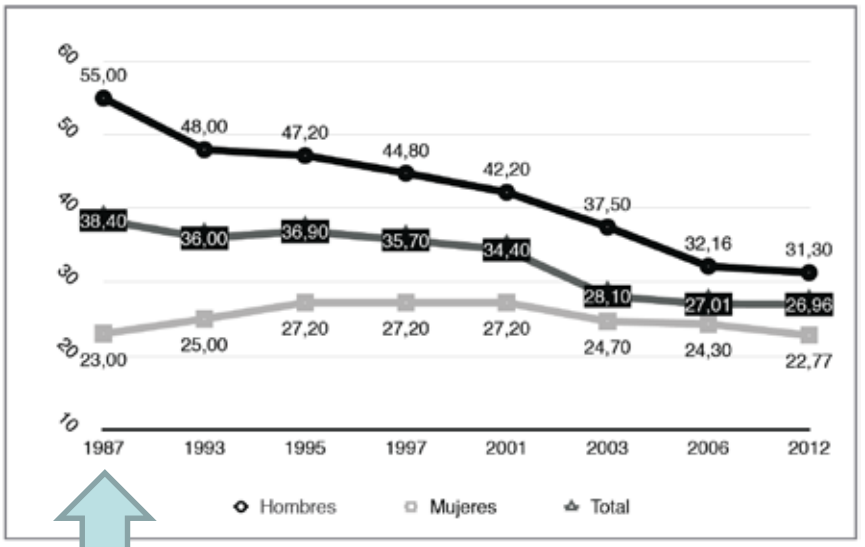


Figura 2. ución del consumo de tabaco en España según sexo 1987-2012. Fuente: INE, 2013.

CDC

Antoni Baena García (tesis doctoral)

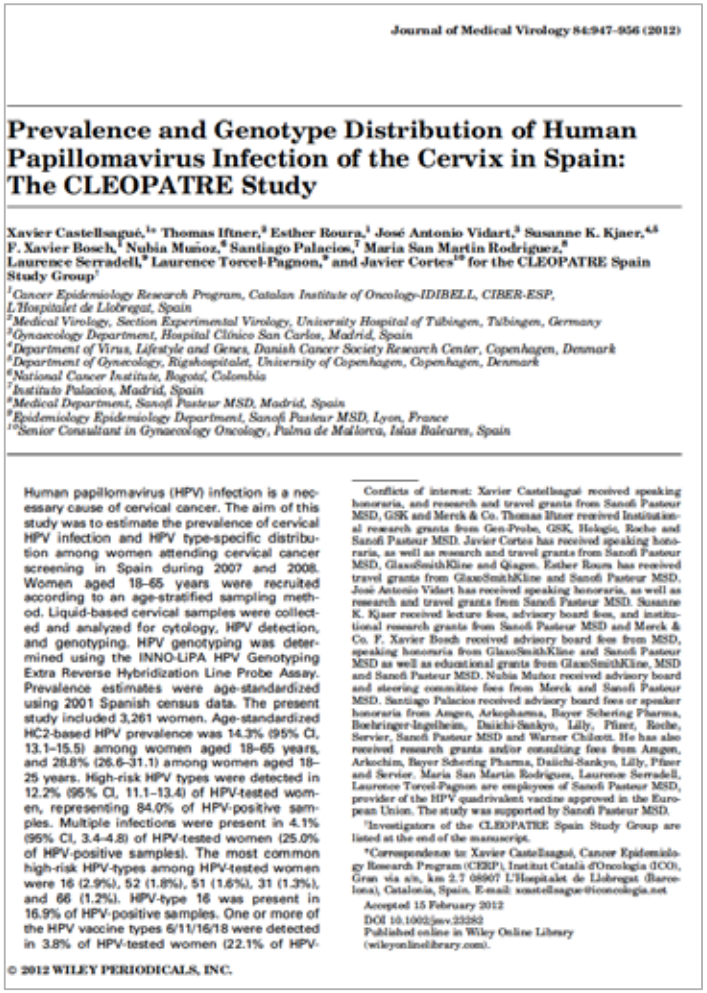
1965 ⟷ 1987

20 anys de diferència!

Interaccions entre factors de risc, tabac i VPH en estudis casos-control

- **No modificació de l'efecte** *(Herrero R et al, 2003; D'Souza G et al, 2007)*
- **Interacció positiva** *(Schwartz SM et al, 1998; Smith E et al, 2010)*
- **Interacció negativa** *(Applebaum K et al, 2007; Ji X et al, 2008; Ribeiro KB et al, 2011; Kreimer AR et al, 2013; Anantharaman D et al, 2013)*

Variació exposició al VPH



Journal of Medical Virology 84:947–956 (2012)

Prevalence and Genotype Distribution of Human Papillomavirus Infection of the Cervix in Spain: The CLEOPATRE Study

Xavier Castellsagué,[1]* Thomas Iftner,[2] Esther Roura,[1] José Antonio Vidart,[3] Susanne K. Kjaer,[4,5] F. Xavier Bosch,[1] Nubia Muñoz,[6] Santiago Palacios,[7] Maria San Martin Rodriguez,[8] Laurence Serradell,[9] Laurence Torcel-Pagnon,[9] and Javier Cortes[10] for the CLEOPATRE Spain Study Group[†]

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[3]*Gynaecology Department, Hospital Clínico San Carlos, Madrid, Spain*
[4]*Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark*
[5]*Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[6]*National Cancer Institute, Bogotá, Colombia*
[7]*Instituto Palacios, Madrid, Spain*
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Human papillomavirus (HPV) infection is a necessary cause of cervical cancer. The aim of this study was to estimate the prevalence of cervical HPV infection and HPV type-specific distribution among women attending cervical cancer screening in Spain during 2007 and 2008. Women aged 18–65 years were recruited according to an age-stratified sampling method. Liquid-based cervical samples were collected and analyzed for cytology, HPV detection, and genotyping. HPV genotyping was determined using the INNO-LiPA HPV Genotyping Extra Reverse Hybridization Line Probe Assay. Prevalence estimates were age-standardized using 2001 Spanish census data. The present study included 3,261 women. Age-standardized HC2-based HPV prevalence was 14.3% (95% CI, 13.1–15.5) among women aged 18–65 years, and 28.8% (26.6–31.1) among women aged 18–25 years. High-risk HPV types were detected in 12.2% (95% CI, 11.1–13.4) of HPV-tested women, representing 84.0% of HPV-positive samples. Multiple infections were present in 4.1% (95% CI, 3.4–4.8) of HPV-tested women (25.0% of HPV-positive samples). The most common high-risk HPV-types among HPV-tested women were 16 (2.9%), 52 (1.8%), 51 (1.6%), 31 (1.3%), and 66 (1.2%). HPV-type 16 was present in 16.9% of HPV-positive samples. One or more of the HPV vaccine types 6/11/16/18 were detected in 3.8% of HPV-tested women (22.1% of HPV-

Conflicts of interest: Xavier Castellsagué received speaking honoraria, and research and travel grants from Sanofi Pasteur MSD, GSK and Merck & Co. Thomas Iftner received Institutional research grants from Gen-Probe, GSK, Hologic, Roche and Sanofi Pasteur MSD. Javier Cortes has received speaking honoraria, as well as research and travel grants from Sanofi Pasteur MSD, GlaxoSmithKline and Qiagen. Esther Roura has received travel grants from GlaxoSmithKline and Sanofi Pasteur MSD. José Antonio Vidart has received speaking honoraria, as well as research and travel grants from Sanofi Pasteur MSD. Susanne K. Kjaer received lecture fees, advisory board fees, and institutional research grants from Sanofi Pasteur MSD and Merck & Co. F. Xavier Bosch received advisory board fees from MSD, speaking honoraria from GlaxoSmithKline and Sanofi Pasteur MSD as well as educational grants from GlaxoSmithKline, MSD and Sanofi Pasteur MSD. Nubia Muñoz received advisory board and steering committee fees from Merck and Sanofi Pasteur MSD. Santiago Palacios received advisory board fees or speaker honoraria from Amgen, Arkopharma, Bayer Schering Pharma, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Pfizer, Roche, Servier, Sanofi Pasteur MSD and Warner Chilcott. He has also received research grants and/or consulting fees from Amgen, Arkochim, Bayer Schering Pharma, Daiichi-Sankyo, Lilly, Pfizer and Servier. Maria San Martin Rodrigues, Laurence Serradell, Laurence Torcel-Pagnon are employees of Sanofi Pasteur MSD, provider of the HPV quadrivalent vaccine approved in the European Union. The study was supported by Sanofi Pasteur MSD.

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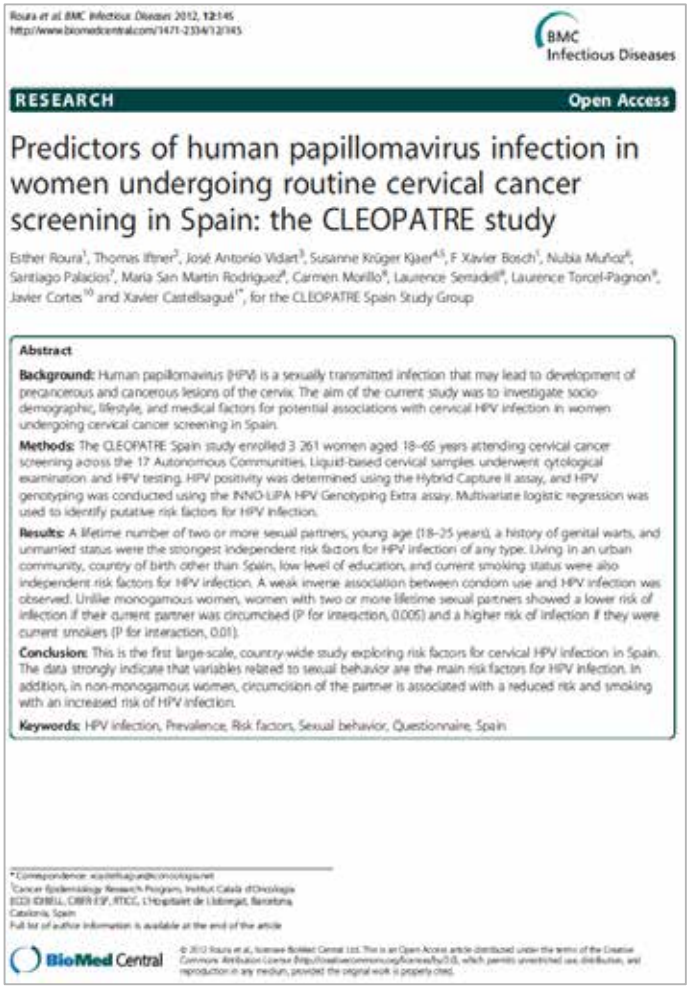

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BMC Infectious Diseases

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Predictors of human papillomavirus infection in women undergoing routine cervical cancer screening in Spain: the CLEOPATRE study

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Abstract

Background: Human papillomavirus (HPV) is a sexually transmitted infection that may lead to development of precancerous and cancerous lesions of the cervix. The aim of the current study was to investigate socio-demographic, lifestyle, and medical factors for potential associations with cervical HPV infection in women undergoing cervical cancer screening in Spain.

Methods: The CLEOPATRE Spain study enrolled 3 261 women aged 18–65 years attending cervical cancer screening across the 17 Autonomous Communities. Liquid-based cervical samples underwent cytological examination and HPV testing. HPV positivity was determined using the Hybrid Capture II assay, and HPV genotyping was conducted using the INNO-LiPA HPV Genotyping Extra assay. Multivariate logistic regression was used to identify putative risk factors for HPV infection.

Results: A lifetime number of two or more sexual partners, young age (18–25 years), a history of genital warts, and unmarried status were the strongest independent risk factors for HPV infection of any type. Living in an urban community, country of birth other than Spain, low level of education, and current smoking status were also independent risk factors for HPV infection. A weak inverse association between condom use and HPV infection was observed. Unlike monogamous women, women with two or more lifetime sexual partners showed a lower risk of infection if their current partner was circumcised (P for interaction, 0.005) and a higher risk of infection if they were current smokers (P for interaction, 0.01).

Conclusion: This is the first large-scale, country-wide study exploring risk factors for cervical HPV infection in Spain. The data strongly indicate that variables related to sexual behavior are the main risk factors for HPV infection. In addition, in non-monogamous women, circumcision of the partner is associated with a reduced risk and smoking with an increased risk of HPV infection.

Keywords: HPV infection, Prevalence, Risk factors, Sexual behavior, Questionnaire, Spain

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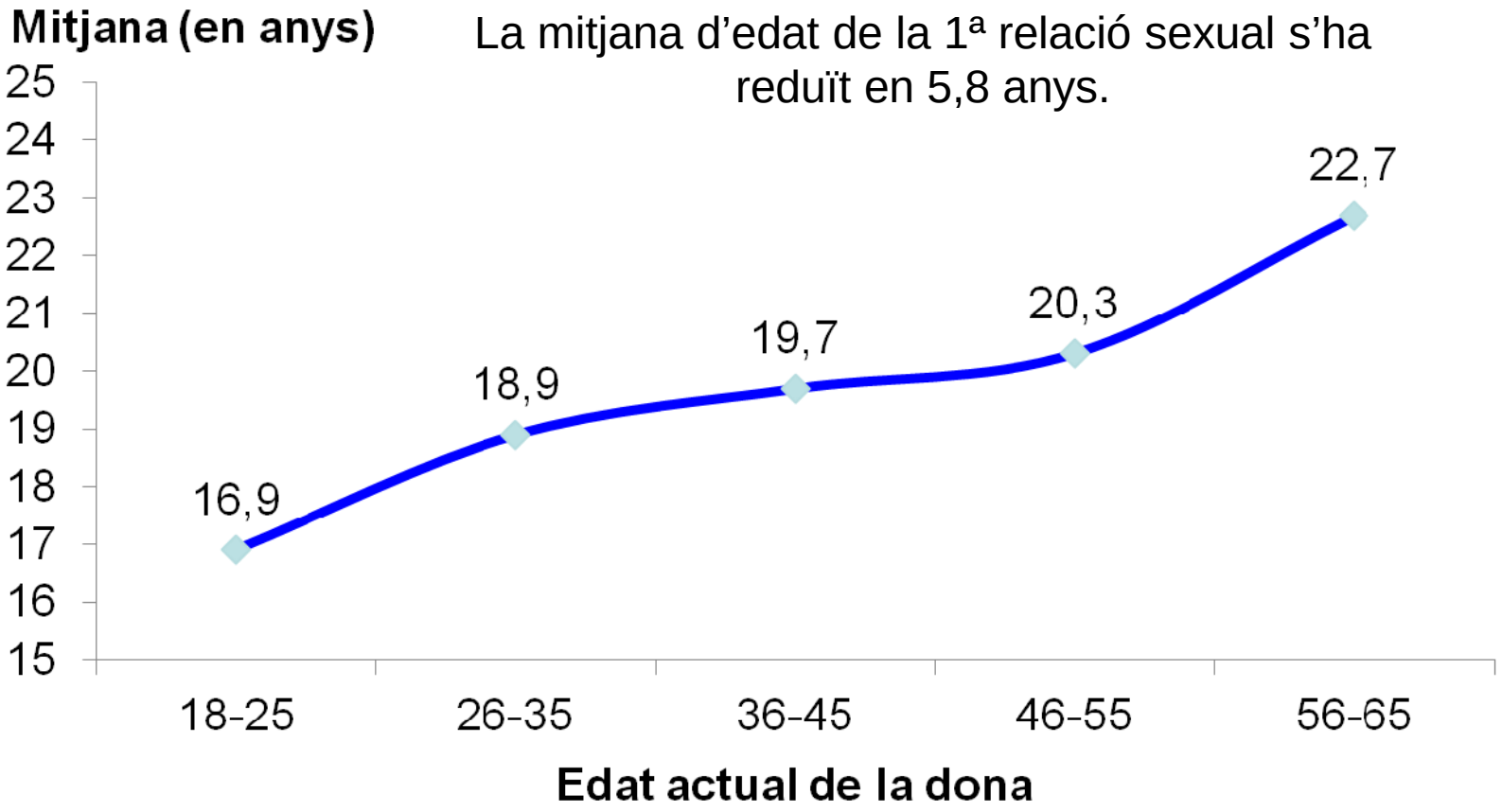
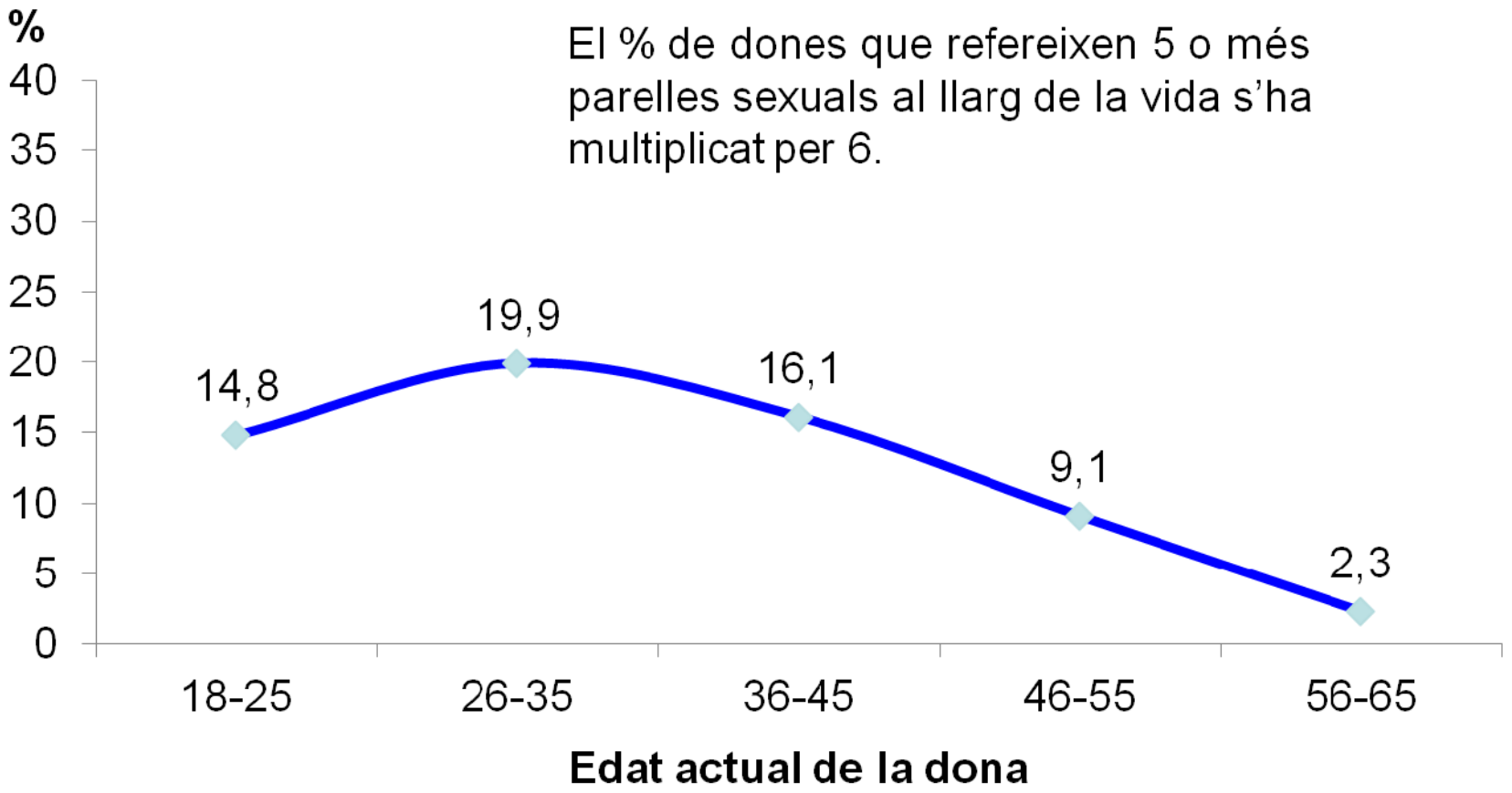
Mitjana de edat a la primera relació sexual segons edat actual de la dona

La mitjana d'edat de la 1ª relació sexual s'ha reduït en 5,8 anys.



Inclou dones sexualment actives.

% de dones que refereixen 5 o més parelles sexuals al llarg de la vida



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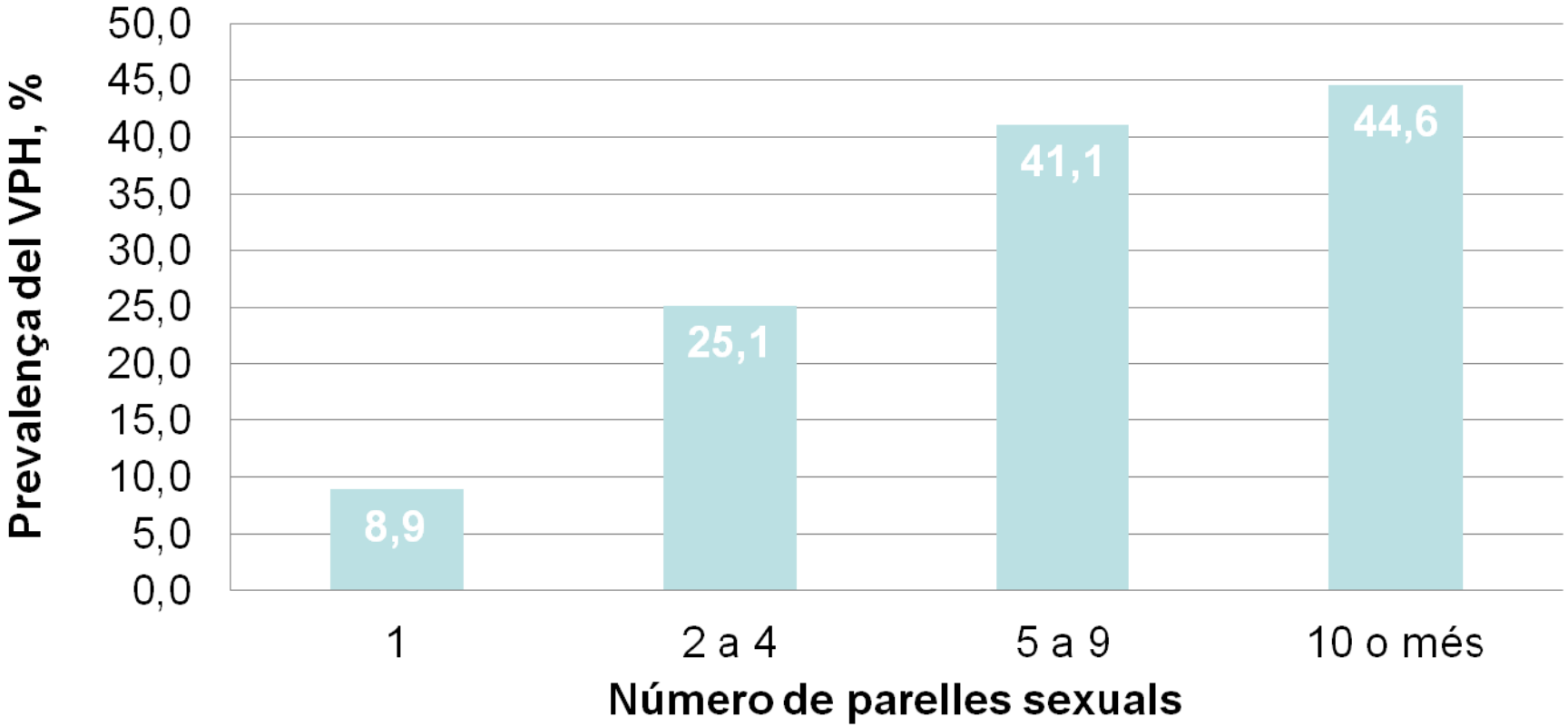
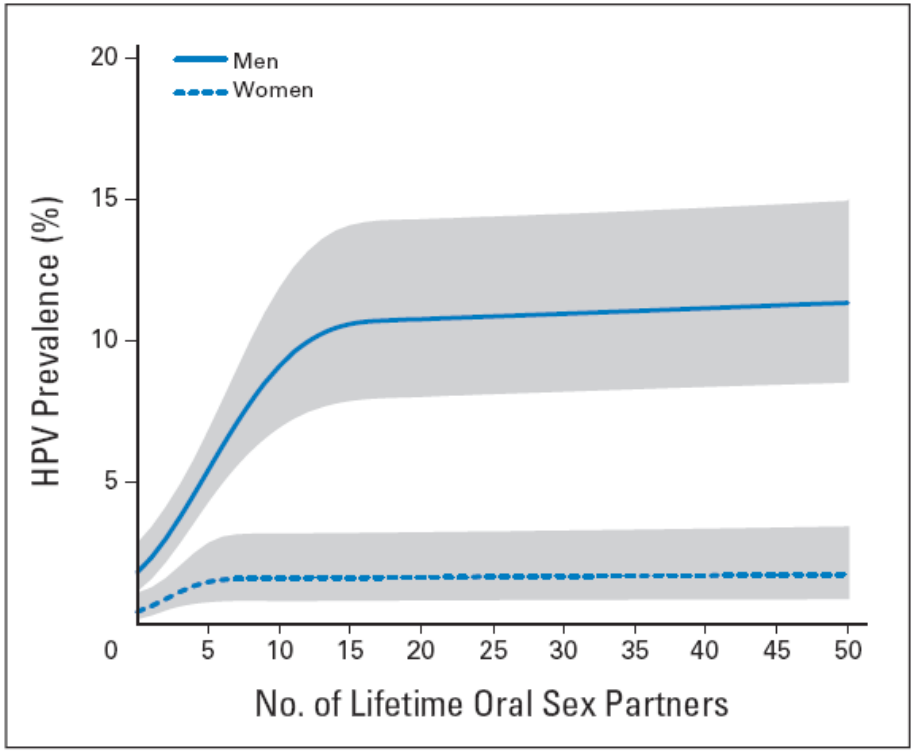
Prevalença del VPH cervical segons el número de parelles sexuals al llarg de la vida

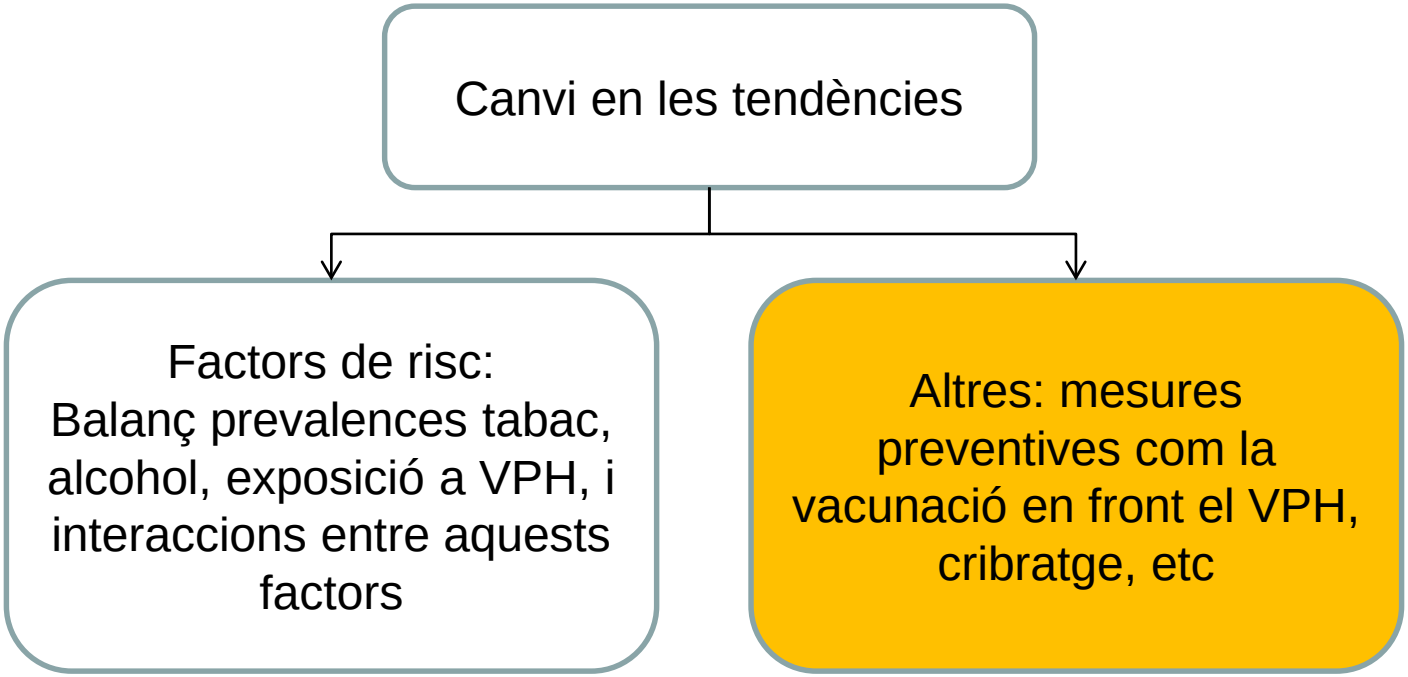


Prevalença del VPH oral segons el número de parelles sexuals al llarg de la vida



Gillison M et al. J Clin Oncol. 2015

Factors que poden determinar canvi de tendències



Conclusions

- Càncer d'orofaringe, localització més VPH relacionada
- Augment d'incidència dels càncers d'orofaringe en països desenvolupats i sobretot en homes
- Augment a expenses de l'augment de casos VPH positius
- Aquests canvis es podrien atribuir a la disminució de la prevalença d'altres factors de risc, com el tabac, i a l'augment de l'exposició al VPH per canvis de comportament sexual
- En el nostre contexte s'espera un augment de casos al llarg del temps, el que no tenim encara clara és la tendència concreta en quant a la pendent del canvi, etc

Agraïments

Al grup de treball de VPH i càncer de cap i coll de l'ICO i col-laboradors – DDL, DKFZ, IARC, H.Sant Pau, H.Mar, H.Parc Taulí, UFCC ICO-Bellvitge, centres col-laboradors de l'estudi internacional, Antoni Baena García