VACCINAZIONE HPV: SITUAZIONE E PROSPETTIVE

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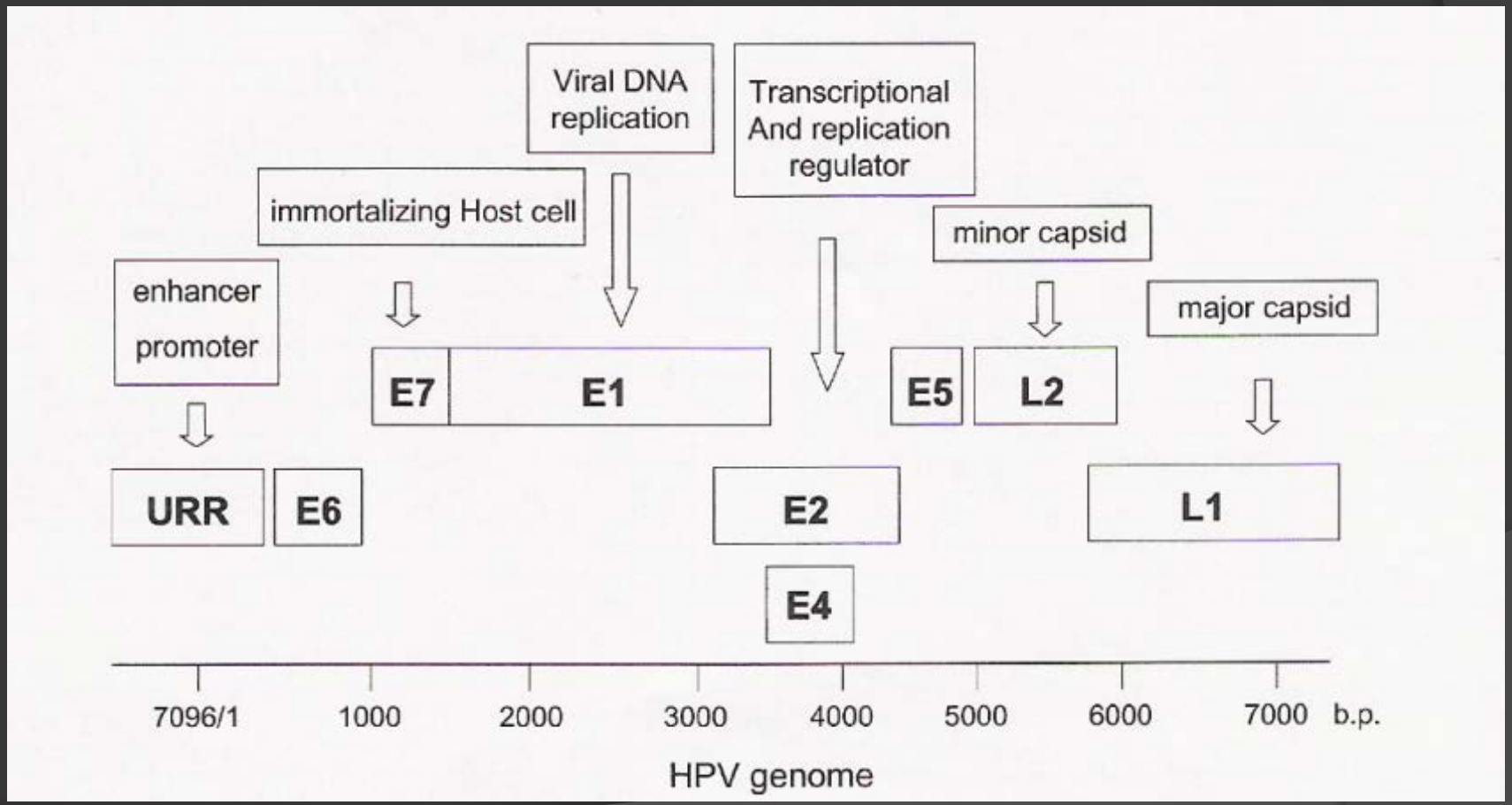
Obbiettivi della Presentazione

- **Caratterizzazione del virus e vie di diffusione**
- **Infezione da HPV nei due sessi e rischi connessi all'infezione**
- **Trasmissione orizzontale e verticale del virus**
- **Vaccinazione**

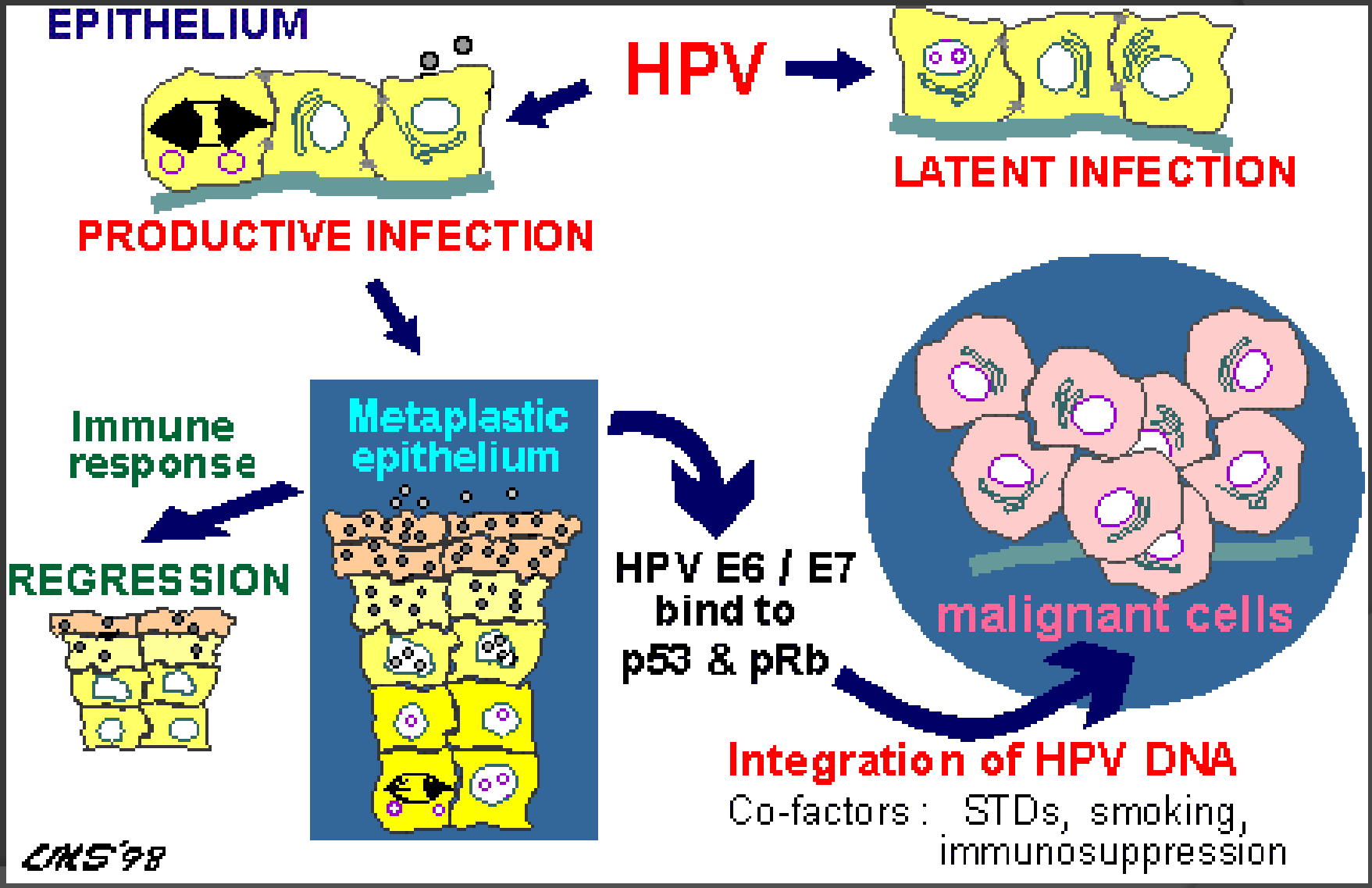
HPV E’ UNA PATOLOGIA TRASMISSIBILE PER CONTATTO SESSUALE

- Più di 100 genotipi identificati basati sulla sequnza genetica della proteina capsidica esterna L1
- 40 genotipi capaci di infettare l’epitelio mucoso e sessualmente trasmissibili
- Circa altri 60 ceppi causano verruche ai piedi, alle mani ed altre parti del corpo

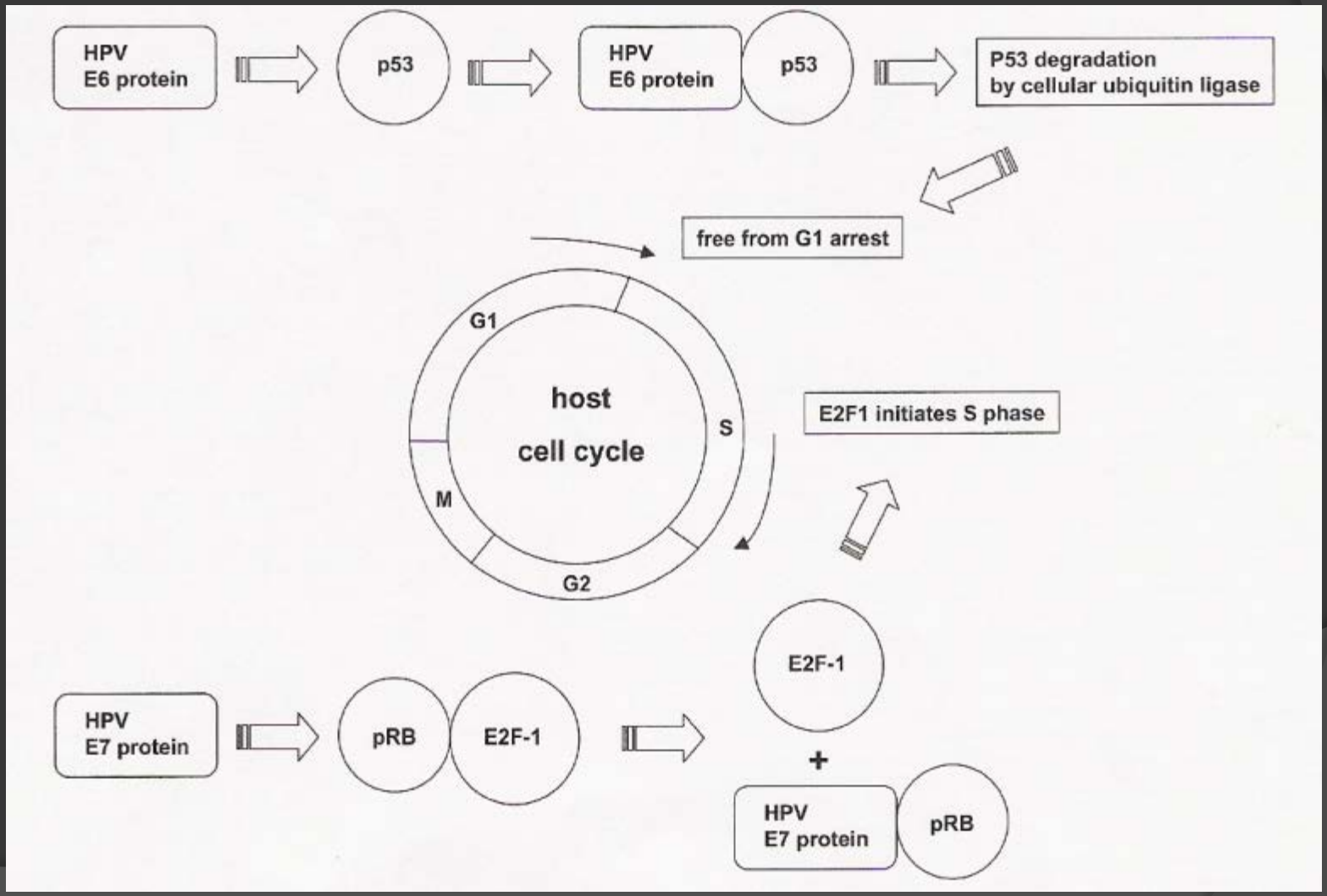
Genoma di HPV



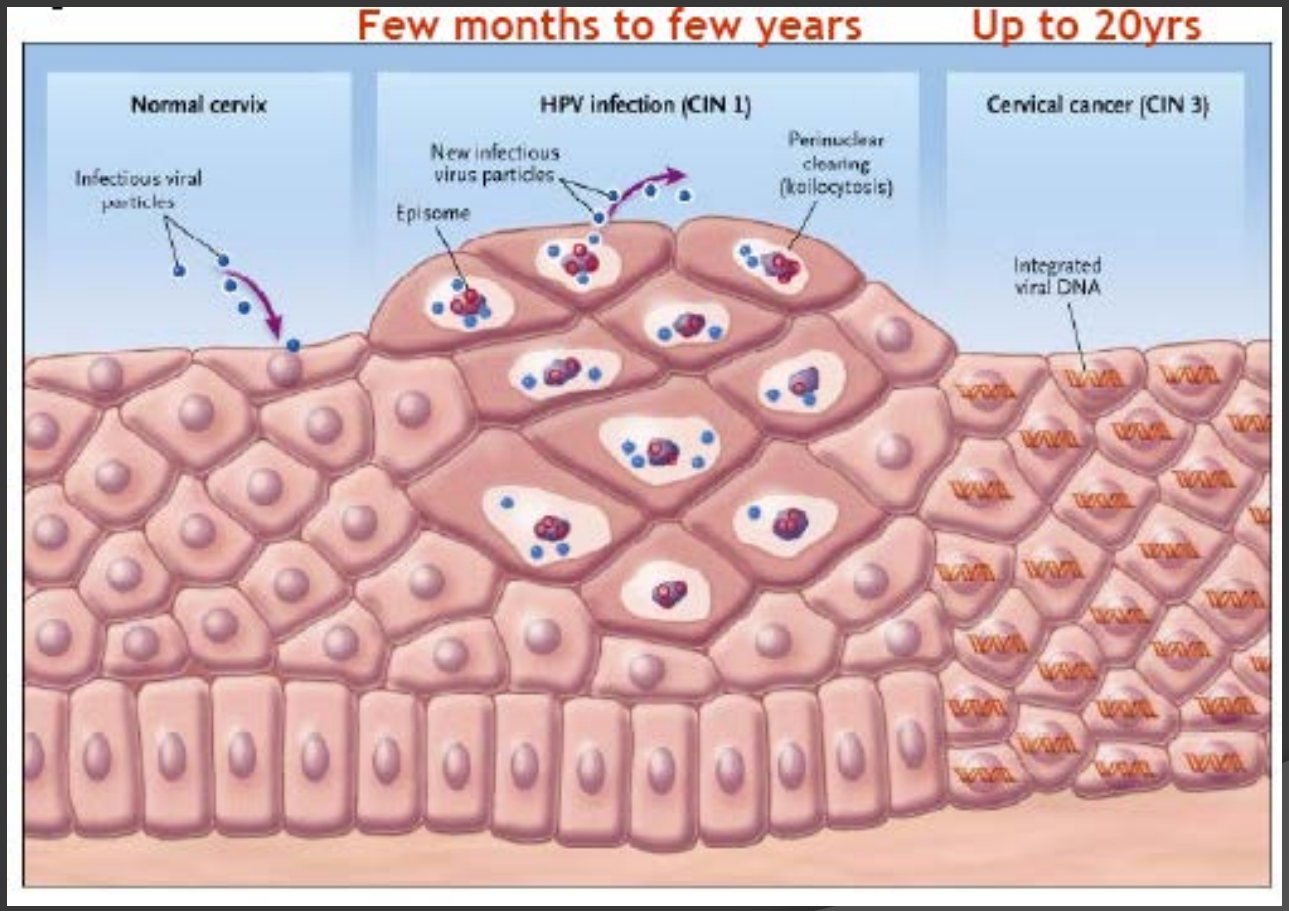
HPV Infection Mechanisms



Trasformazione da HPV: meccanismi di attivazione genica



Quanto tempo fra infezione e trasformazione?



HPV è determinante per la genesi del carcinoma cervicale

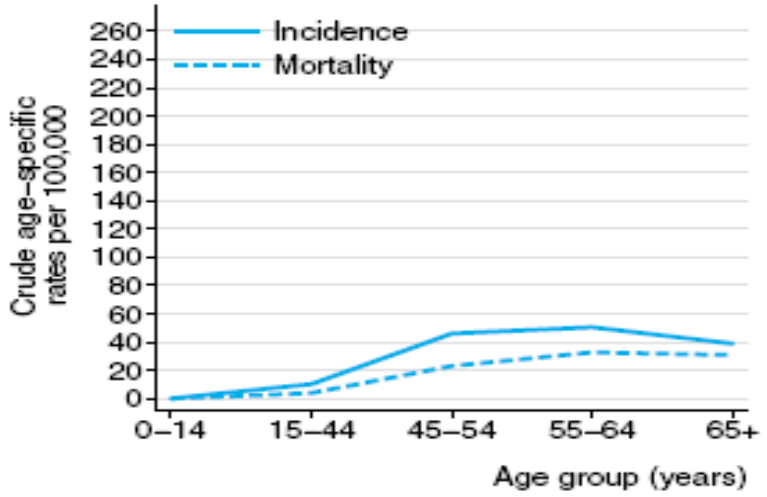
Harald Zur Hausen

- Nel 1977 capì che numerosi genotipi di HPV potevano essere correlati al carcinoma cervicale
- Nel 1984 cominciò a sviluppare l'idea di un vaccino per HPV
- Nel 2008 ha vinto il premio Nobel per la medicina

Limiti del carcinoma cervicale

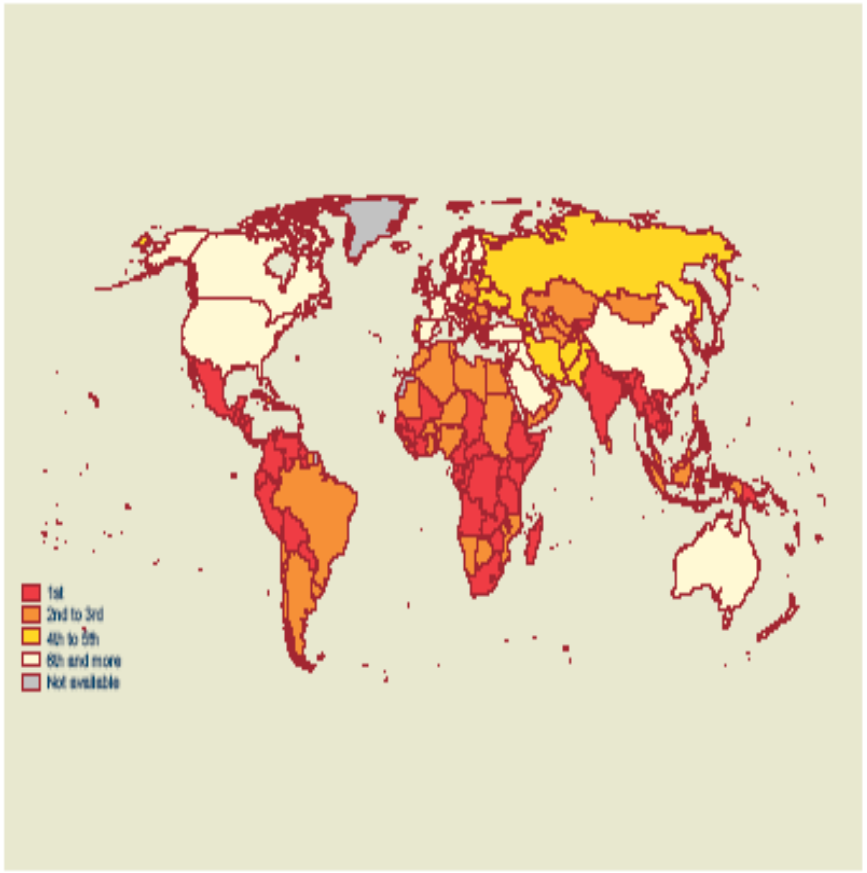
	Incidence	Mortality
Crude rate	16.2	8.9
Age-standardized rate	16.2	8.9
Cumulative risk (%). Age period 0-64 years	1.3	0.7
SIR/SMR	100	100
Annual number of new cases/deaths	493243	273505
Ranking of cervical cancer (all ages)†	2nd	3rd
Ranking of cervical cancer (15-44 years)†	2nd	2nd

Rates are per 100,000 women.
SIR/SMR: Standardized Incidence/Mortality Ratio.
†Ranking among all cancers.

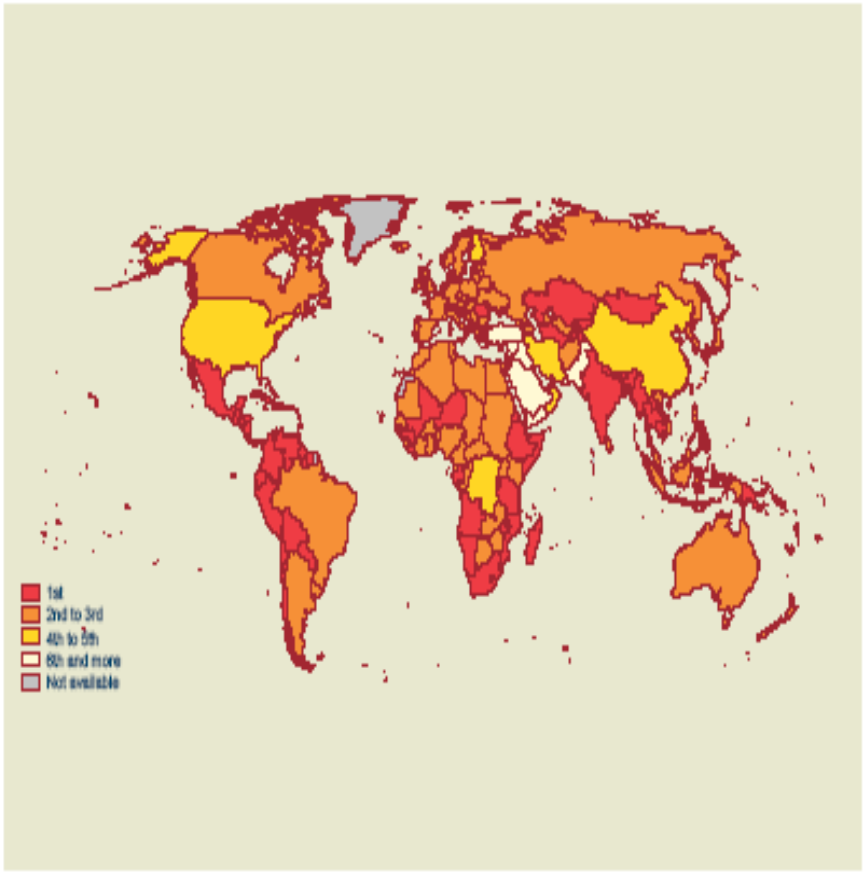


Limiti del carcinoma cervicale

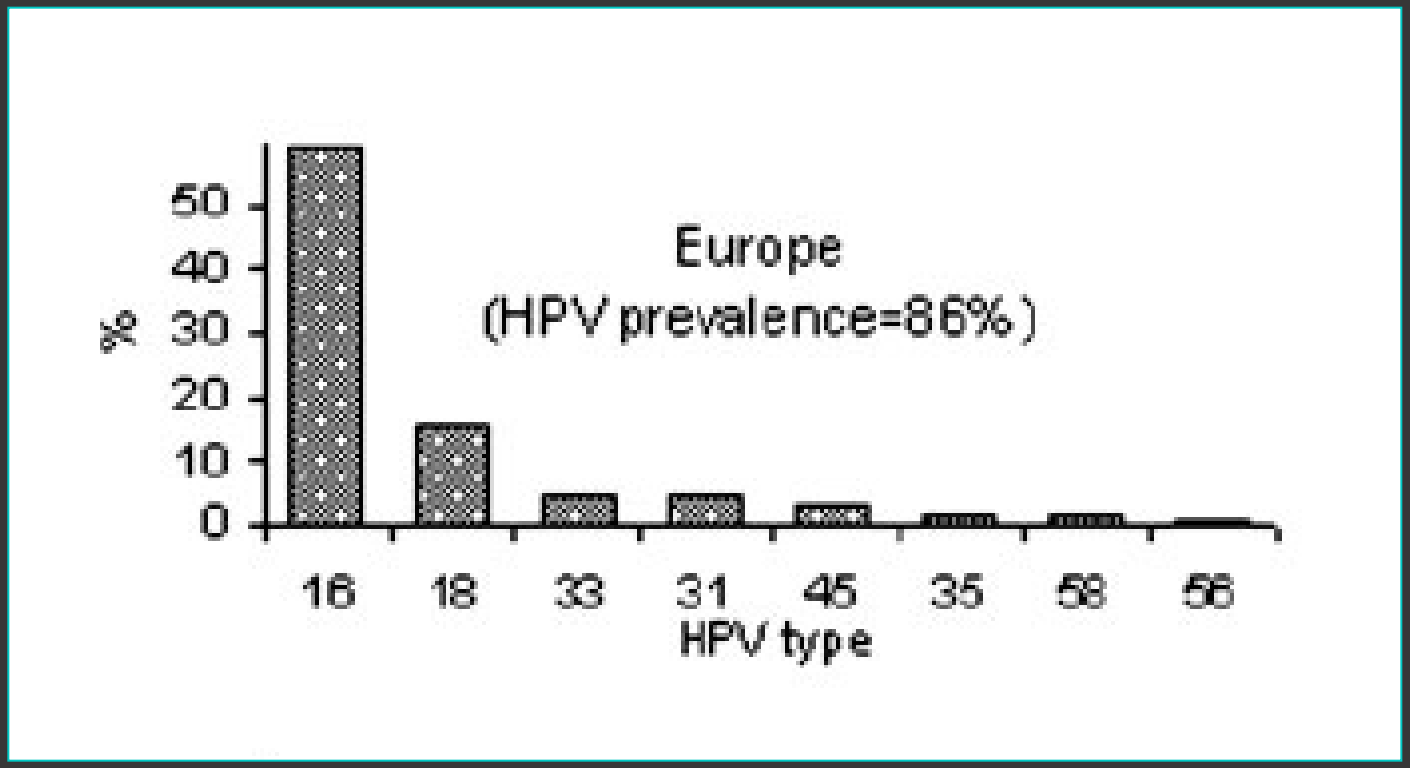
WOMEN ALL AGES



WOMEN 15-44 YEARS



Carcinoma Cervicale : Metanalisi Epidemiologica Europea



Asia 38%
Europa 30%
Centro e Sud America 10%

Nord America 9%
Africa 9%
Oceania 3%.

Smith JID 2008

=

L’ infezione da HPV è comunemente riconosciuta come la causa di carcinoma cervicale nelle donne e altre neoplasie nei due sessi

INFEZIONE da HPV

UOMO

VETTORE

Sintomi clinici scarsi o assenti

Trasmissione sessuale

BERSAGLIO

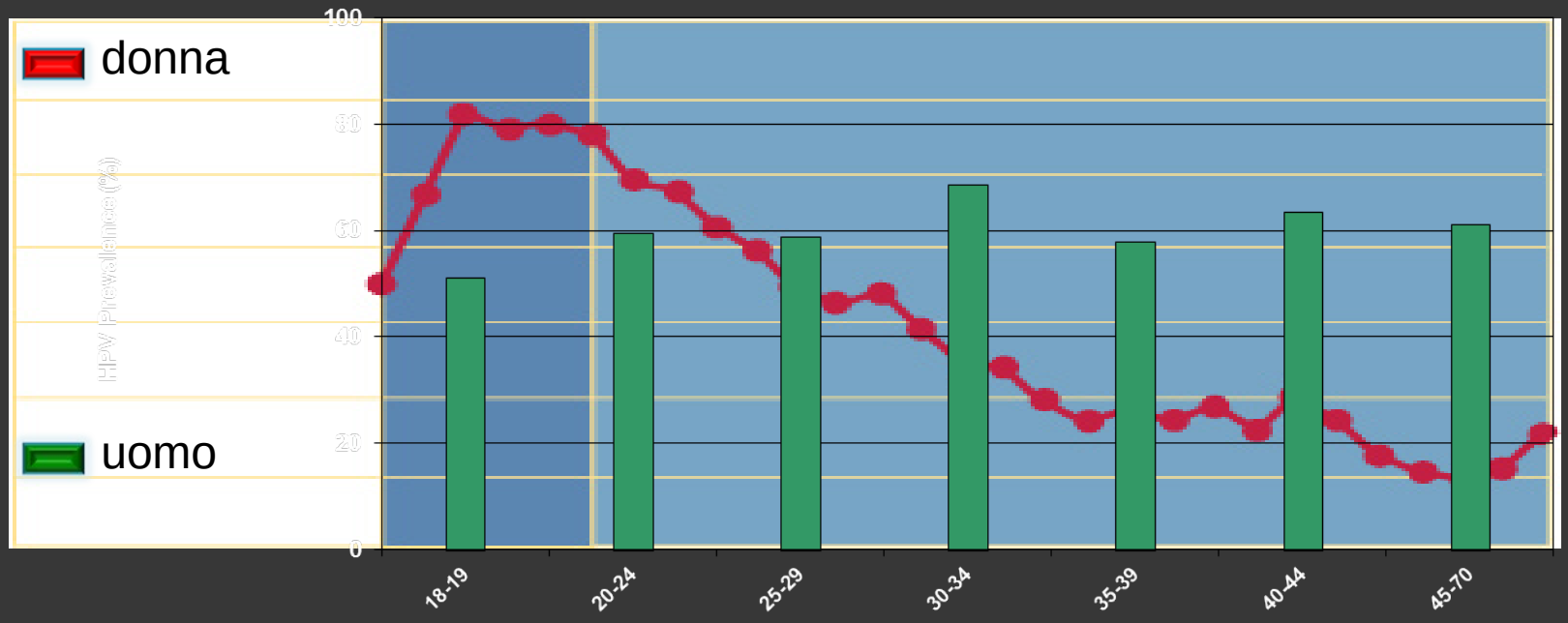
Sintomi o evidenze cliniche significativi

Altre modalità di presentazione ancora sconosciute

Correlazione con

Neoplasie uro-genitali?

Prevalenza dell’ infezione da virus HPV nella popolazione maschile e femminile nel corso della vita



adattato da Giuliano A, et al. CEBP 2008

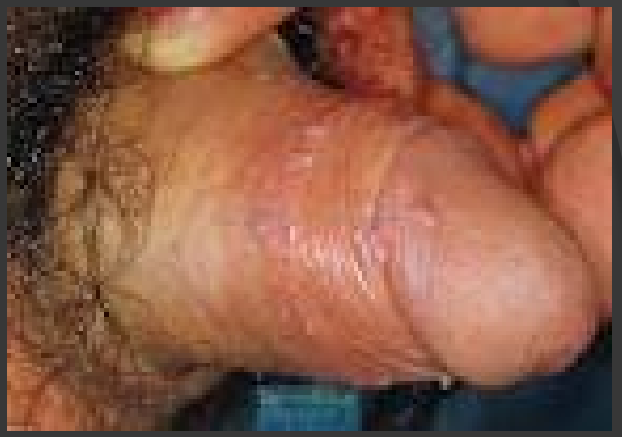
De Vuyst H et al. *Eur J Cancer* 2009; 45: 2632-2639

Che cosa sappiamo su HPV nel maschio?

- Il maschio è un importante vettore di malattia
- L'evidenza della patologia nel maschio è rappresentata dal Condiloma
- Esistono categorie di maschi "a rischio" per patologie neoplastiche (omosessuali, immunodepressi, affetti da HIV)
- Esistono delle metodiche di "prevenzione" (condom, circoncisione)

Il maschio è un importante vettore della malattia

I Condilomi rappresentano la più importante evidenza clinica nel maschio



- Sono associati a sintomatologia locale
- Genotipi generalmente coinvolti : 6 e 11 (90% dei casi)
- Altri genotipi: 16,31,33,35,39

Conferenza di Consenso sulle patologie da HPV umano nel maschio, Roma 2010

Il maschio è un importante vettore della malattia

- E’ necessario il contatto sessuale con un partner infetto per la trasmissione del virus
- Forte correlazione fra numero dei partners e riscontro di infezione nella donna
- La circoncisione riduce il rischio di trasmissione virale alla donna

Associations between Male Anogenital Human Papillomavirus Infection and Circumcision by Anatomic Site Sampled and Lifetime Number of Female Sex Partners

Carrie M. Nielson,[1] Melody K. Schiaffino,[2] Eileen F. Dunne,[3] Jason L. Salemi,[2] and Anna R. Giuliano[2]

[1]Oregon Health and Science University, Portland; [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [3]Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

(See the editorial commentary by Gray et al. and the articles by Auvert et al. and Warner et al., on pages 1–3, 14–9, and 59–65, respectively.)

Background. Male circumcision may lower men's risk of human papillomavirus (HPV) infection and reduce transmission to sex partners. Reported associations between circumcision and HPV infection in men have been inconsistent.

Methods. Four hundred sixty-three men in 2 US cities were tested at 6 anogenital sites and in semen for 37 types of HPV. Men were eligible if they reported sex with a woman within the past year, no history of genital warts or penile or anal cancer, and no current diagnosis of a sexually transmitted infection. Participants completed a self-administered questionnaire. Circumcision status was assessed by the study clinician. Logistic regression was used to examine associations between circumcision and HPV detection at each site and in semen, with adjustment for potential confounders.

Results. Seventy-four men (16.0%) were uncircumcised. Adjusted odds ratios (AORs) for any HPV genotype and circumcision were 0.53 (95% confidence interval [CI], 0.28–0.99) for any anatomic site/specimen, 0.17 (95% CI, 0.05–0.56) for the urethra, 0.44 (95% CI, 0.23–0.82) for the glans/corona, and 0.53 (95% CI, 0.28–0.99) for the penile shaft. AORs were <1.0 but not statistically significant for the scrotum, semen, anal canal, and perianal area.

Conclusions. Circumcision may be protective against HPV infection of the urethra, glans/corona, and penile shaft.

463 p.ti

16% non Circoncisi

J. Infect. Dis. 2009

ORIGINAL RESEARCH ARTICLE

Multiple-type human papillomavirus infection in younger uncircumcised men

A Nielsen MSc PhD*, **C Munk** MD PhD*, **H O Jørgensen** MD†, **J F Winther** MD DMSc§, **A J C van den Brule** PhD‡ **and S K Kjaer** MD PhD*,**

*Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen; †Danish Armed Forces Health Services, Roskilde; §Survivorship, Danish Cancer Society Research Center, Copenhagen, Denmark; ‡Laboratory for Molecular Diagnostics, Jeroen Bosch Hospital,'s-Hertogenbosch, The Netherlands; **Gynaecological Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

International Journal of STD & AIDS 2013; **24**: 128–133. DOI: 10.1177/0956462412472294

Table 1 Human papillomavirus status of the β-globin-positive study participants (*N* = 350)

HPV status	*n*	Prevalence (95% CI)
Overall		
HPV negative	233	66.6 (61.6–71.5)
HPV positive	117	33.4 (28.5–38.4)
HR types	54	15.4 (11.8–19.6)
LR types	23	6.6 (4.2–9.7)
HR and LR types	18	5.1 (3.1–8.0)
Single type	56	16.0 (12.2–19.8)
Multiple types	39	11.1 (7.9–14.4)
Unknown types	22	6.3 (3.7–8.8)

…conflicting results!!!

Albero et al. BMC Infectious Diseases 2013, 13:18
http://www.biomedcentral.com/1471-2334/13/18

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Male circumcision and prevalence of genital human papillomavirus infection in men: a multinational study

Ginesa Albero[1,2,3], Luisa L Villa[4], Eduardo Lazcano-Ponce[5], William Fulp[6], Mary R Papenfuss[6], Alan G Nyitray[6], Beibei Lu[6], Xavier Castellsagué[1,2], Martha Abrahamsen[6], Danélle Smith[6], F Xavier Bosch[1], Jorge Salmerón[7], Manuel Quiterio[5] and Anna R Giuliano[6*]

Table 2 Association between male circumcision and genital HPV detection in men

	Any HPV (n = 3969)		Oncogenic HPV (n = 2503)		Non-Oncogenic HPV (n = 2219)		Unclassified HPV (n = 1889)	
	Univariate PR (95% CI)	Multivariable[1] PR (95% CI)	Univariate PR (95% CI)	Multivariable[1] PR (95% CI)	Univariate PR (95% CI)	Multivariable[1] PR (95% CI)	Univariate PR (95% CI)	Multivariable[1] PR (95% CI)
Circumcision								
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.99 (0.94 - 1.04)	0.96 (0.91 - 1.01)	0.98 (0.90 - 1.07)	0.95 (0.87 - 1.03)	**0.87 (0.78 - 0.97)**	**0.85 (0.76 - 0.95)**	**1.21 (1.05 – 1.39)**	1.07 (0.92 – 1.24)

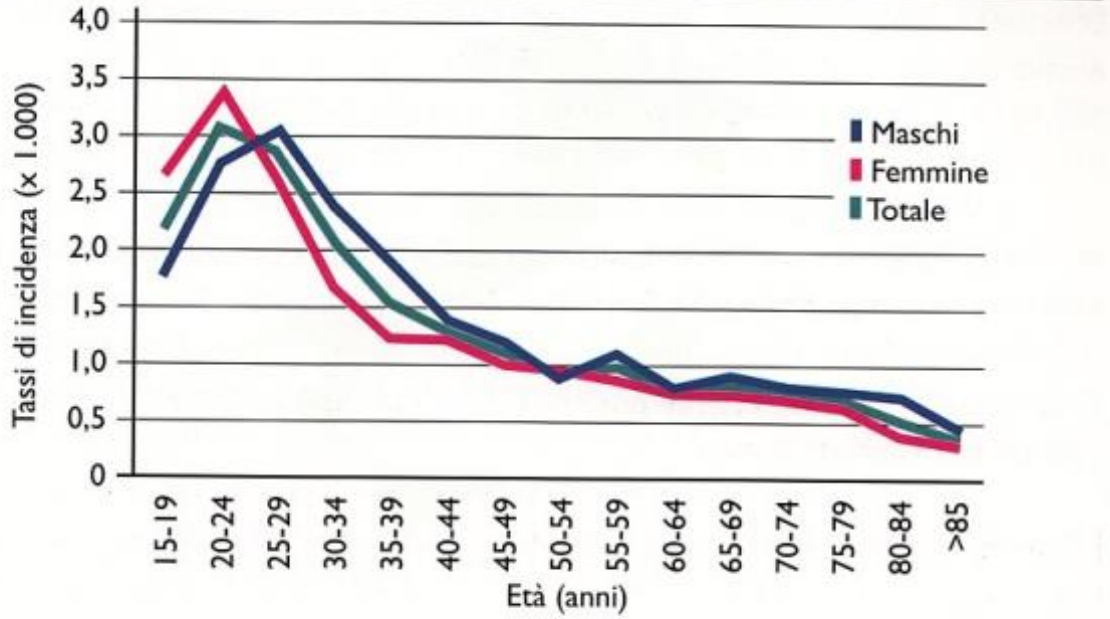
NOTE. *PR*, prevalence ratio; *CI*, confidence interval. Numbers in bold correspond to statistically significant point estimates.
[1]Adjusted for race, marital status, lifetime female sexual partners, female sexual partners in past 3–6 months and male anal sexual partners in the past 3 months.

- 4072 soggetti 18-70 aa. Selezionati in Brasile, Messico e USA.
- Ricerca HPV DNA/PCR su cellule esfoliate da varie zone del glande

- **Nessuna associazione significativa fra circoncisione e infezione da HPV eccetto che per i genotipi non oncogenici**

Sito	N. soggetti (incidenza cumulativa [IC95%], %)	
	Tutti i tipi di HPV genitale	Tutti i tipi di HPV genitale ad alto rischio*
Tutti i siti genitali	72 (62,4 [52,6-72,2])	59(47,9 [38,6-58,0])
Glande	49 (44,3 [34,8-55,0])	38 (32,3 [24,1-42,5])
Asta	49 (45,4 [35,8-56,2])	41 (35,7 [27,0-46,0])
Scroto	46 (43,6 [34,0-54,7])	39 (33,8 [25,3-44,1])
Urina	8 (8,6 [4,6-16,9])	7 (7,0 [3,3-14,5])
Unghie	30 (31,9 [22,5-44,0])	26 (25,8 [17,4-37,2])

Tassi di incidenza di condilomi (x 1.000) stratificati per età e sesso (anno 2006)



Fonte: Marra, 2009 [3].

Conferenza di Consenso sulle patologie da HPV umano nel maschio, Roma 2010

I TIPI VIRALI HPV 16 AND 18 SONO ASSOCIATI A LA MAGGIORE QUANTITÀ DI LESIONI PRE-CANCEROSE

	HPV (tutti tipi) Prevalenza	Cancri 16/18 HPV+
Cancro del collo dell'utero	>99%	70-75%
Cancro Anale	84%	> 90%
Cancro della Vagina	70%	80-90%
Cancro della Vulva	40%	> 90%
Cancro del Pene*	47%	> 80%
Cancri Testa e collo		
Cancro dell'orofaringe	36%	> 95%
Cancro della cavita orale	23%	> 95%

E più del 90% dei condilomi genitali sono causati dai tipi HPV 6 e 11 e quasi tutti i casi di Papillomatosi respiratoria ricorrente (RRP)

[1]DE Vuyst Eur J Cancer 2009; [2] De Vuyst Int J Cancer 2009; [3] Miralles-Guri J Clin Pathol 2009;
[4] Kreimer Cancer Epidemiol Biomarkers Prev 2005; [5] von Krogh Eur J Dermatol 2001

IN EUROPA
NUMERO MEDIO ANNUO PREVISTO DI NUOVI CASI DI CANCRO POTENZIALMENTE CORRELATI AD HPV PER SESSO

Localizzazione	Numero atteso di nuovi casi di cancro, indipendentemente dallo stato HPV		Numero atteso di nuovi casi di cancro attribuibile a HPV		Numero atteso di nuovi casi di cancro attribuibili a HPV16/18	
	Maschio	**Femmine**	**Maschio**	**Femmine**	**Maschio**	**Femmine**
Collo dell'utero	**-**	30, 517	**-**	30,517	**-**	23,254
Vagina	**-**	1,869	**-**	1,306	**-**	1,146
Vulva	**-**	7,384	**-**	2,983	**-**	2,702
Testa e collo	**67,354**	13,448	**14,098**	2,715	**12,707**	2,531
Ano	**2,162**	3,727	**1,821**	3,141	**1,699**	2,929
Pene	**3,178**	-	**1,484**	-	**1,091**	-
Totale	**72,694**	56,945	**17,403**	40,662	**15,497**	**32,562**

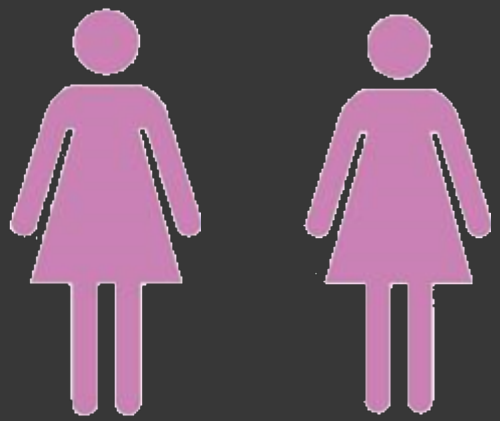
Adapted form Hartwig , Castelsagueet al. submitted to BMC

IL CANCRO HPV-CORRELATO HA UN IMPATTO IN ENTRAMBI SESSI

32,562 casi in Europa/anno
HPV 16/18-correlati nella donna

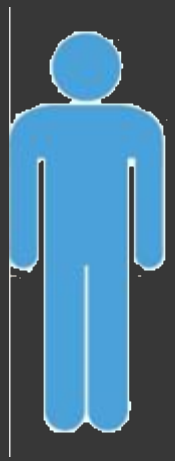
VS

15,497 casi in Europa/anno
HPV 16/18-correlati nel maschio



Per ogni due casi di cancro HPV 16/18 correlato nelle femmine in Europa, ci sarà un caso nei maschi:

2:1



Adapted from: Hartwig S, Syrjanen S, Dominiak-Felden G, Brotons M, Castelsague X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. BMC Cancer 2012,12:30 doi:10.1186/1471-2407-12-30

ULTIMI DATI USA - SUL BURDEN OF DISEASE MMWR 2012

- Intorno a 33,369 cancri annuali USA HPV correlati
- **21,290** nelle femmine,
- **12,080** nei maschi:
  - Primo posto - Cancro cervicale un totale di **11, 967 casi**.
  - Secondo posto – cancro testa-collo 11,726 (2,370 femmine - 9,356 maschi)
- Cancro anale più casi nelle femmine
- 1/3 dei cancri totali HPV correlati sono nel maschio

MMWR Aprile 2012

Morbidity and Mortality Weekly Report

Human Papillomavirus–Associated Cancers — United States, 2004–2008

Oncogenic human papillomavirus (HPV) has a causal role in nearly all cervical cancers and in many vulvar, vaginal, penile, anal, and oropharyngeal cancers (*1*). Most HPV infections clear within 1–2 years, but those that persist can progress to precancer or cancer. In the United States, public health prevention of cervical cancer includes both secondary prevention through cervical cancer screening and primary prevention through HPV vaccination. Transmission of HPV also can be reduced through condom use and limiting the number of sexual partners. Two vaccines (bivalent and quadrivalent) are available to protect against HPV types 16 and 18, which are responsible for 70% of cervical cancers. HPV 16 also is the most common HPV type found in the other five cancers often associated with HPV (*2*). To assess the incidence of HPV-associated cancers (i.e., cancers at specific anatomic sites and with specific cell types in which HPV DNA frequently is found), CDC analyzed 2004–2008 data from the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) program. During 2004–2008, an average of 33,369 HPV-associated cancers were diagnosed annually (rate: 10.8 per 100,000 population), including 12,080 among males (8.1 per 100,000) and 21,290 among females (13.2). Multiplying the counts for HPV-associated cancers by percentages attributable to HPV (*3*), CDC estimated that approximately 26,000 new cancers attributable to HPV occurred each year, including 18,000 among females and 8,000 among males. Population-based cancer registries are important surveillance tools to measure the impact on cancer rates of public health interventions such as vaccination and screening.

CDC analyzed NPCR and SEER data on cancers diagnosed during 2004–2008 in 50 states and the District of Columbia (data covering 100% of the U.S. population are now available through expansion of NPCR) (*4*). Case definitions based on expert consensus were used to examine the burden of invasive cancers at anatomic sites (cervix, vulva, vagina, penis, anus, and oropharynx [*5*]) and for cell types (carcinoma of the cervix and squamous cells for the other sites) in which HPV DNA is frequently found. Inclusion of oropharyngeal cancers as HPV-associated was further limited to specific sites where HPV is most likely to be found: base of tongue, tonsils, and "other oropharynx" (*5*).

Cancer data were analyzed by sex, age, race, Hispanic ethnicity, and state of residence. Race categories included white, black, Asian/Pacific Islander, and American Indian/Alaska Native; "all races" included other and unknown categories. American Indian/Alaska Native data were enhanced by linkage with Indian Health Service administrative records (*6*). Hispanic ethnicity included persons of any race who were identified as being Hispanic in the medical record or by use of an algorithm* (*6*). Age-adjusted incidence rates were calculated per 100,000 persons in SEER*Stat† and were standardized to the 2000 U.S. Standard Population. Significant differences in rates were limited to comparisons at $p<0.05$. Because HPV-associated cancers defined by cell type and specific anatomic site might include cancers not caused by HPV, and because cancer registries typically do not capture information on HPV infection status, for this analysis, the average annual number of HPV-associated cancers was multiplied by the percentage of each cancer type found attributable to HPV based on genotyping studies (*3*).

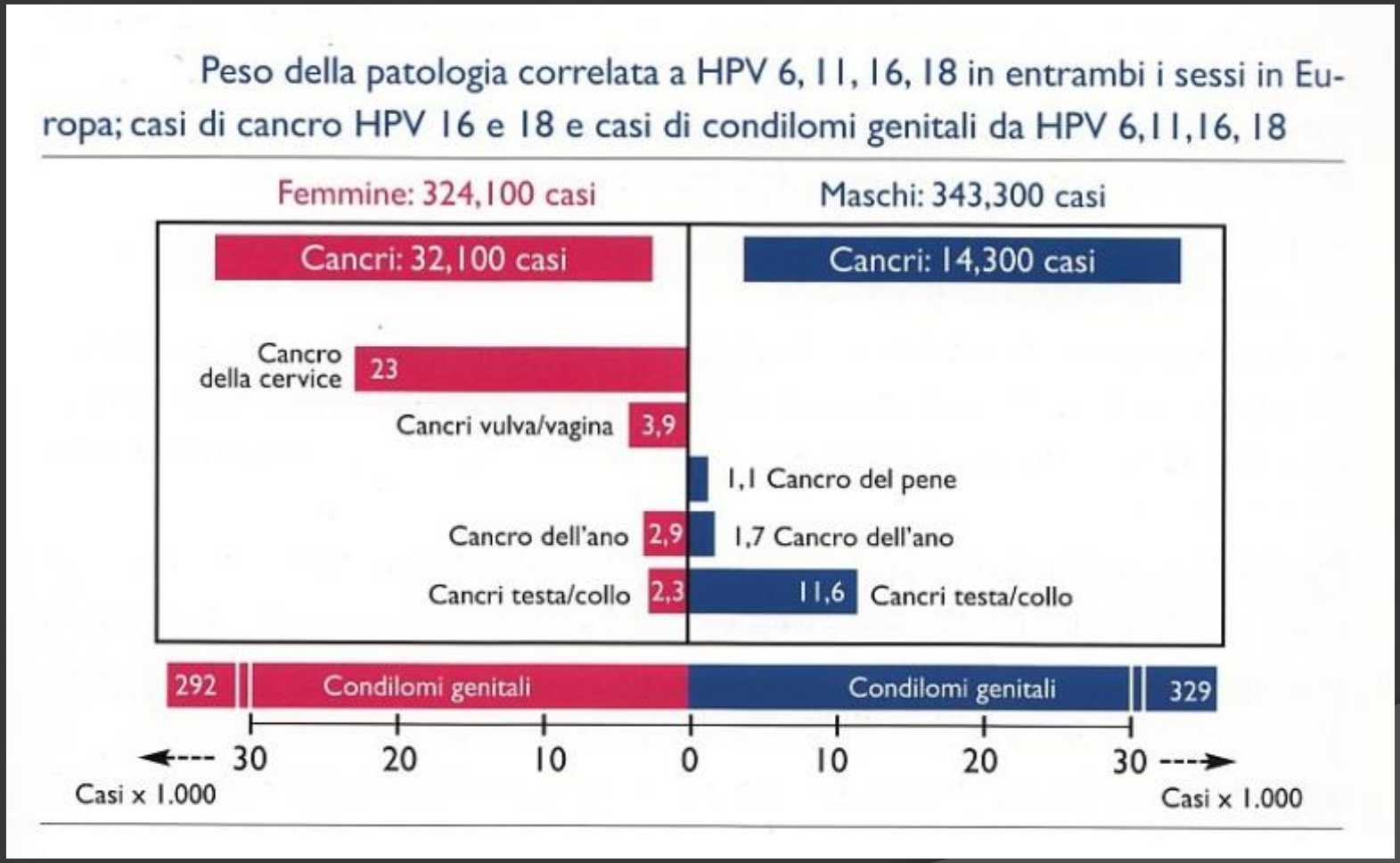
Overall, an average of 33,369 HPV-associated cancers (10.8 per 100,000 population) were diagnosed annually: 21,290 among females (13.2) and 12,080 among males (8.1). Cervical cancer was the most common of these cancers, with an average of 11,967 cases annually; oropharyngeal cancer was the second most common, with an average of 11,726 cases annually (2,370 among females and 9,356 among males) (Tables 1 and 2). The rate of anal cancer among females (1.8 per 100,000) was higher than among males (1.2). The rate of oropharyngeal cancer among males (6.2) was four times that among females (1.4). Rates of cervical and penile cancer were higher among blacks (9.9) and Hispanics (11.3), when compared with whites (7.4) and non-Hispanics (7.4); however, the rate of vulvar cancer was lower among blacks (1.4) and Hispanics (1.2) than among whites (1.9) and non-Hispanics (1.9). Anal cancer in females was highest among whites (2.0), whereas rates in males were highest among blacks (1.6). For both sexes, rates of oropharyngeal cancer were higher among whites (males: 6.4, females: 1.4) and blacks (males: 6.3, females: 1.4) than other races (Table 1).

Rates varied by state, with rates of HPV-associated cancers combined ranging from 8.5 per 100,000 (Utah) to 16.3 (West Virginia) among females, and from 4.9 (Utah) to 11.6 (District of Columbia) among males. Although rates varied by anatomic site, some states had lower or higher rates across cancer sites. Maryland, Colorado, and Utah had cancer rates in the lowest tertile for most or all HPV-associated cancers,

*The North American Association of Central Cancer Registries' Method to Enhance Hispanic/Latino Identification algorithm uses information on ethnicity from the medical record, information reported to the cancer registry, and information on surname (including maiden name, when available) to categorize patients as either Hispanic or non-Hispanic.

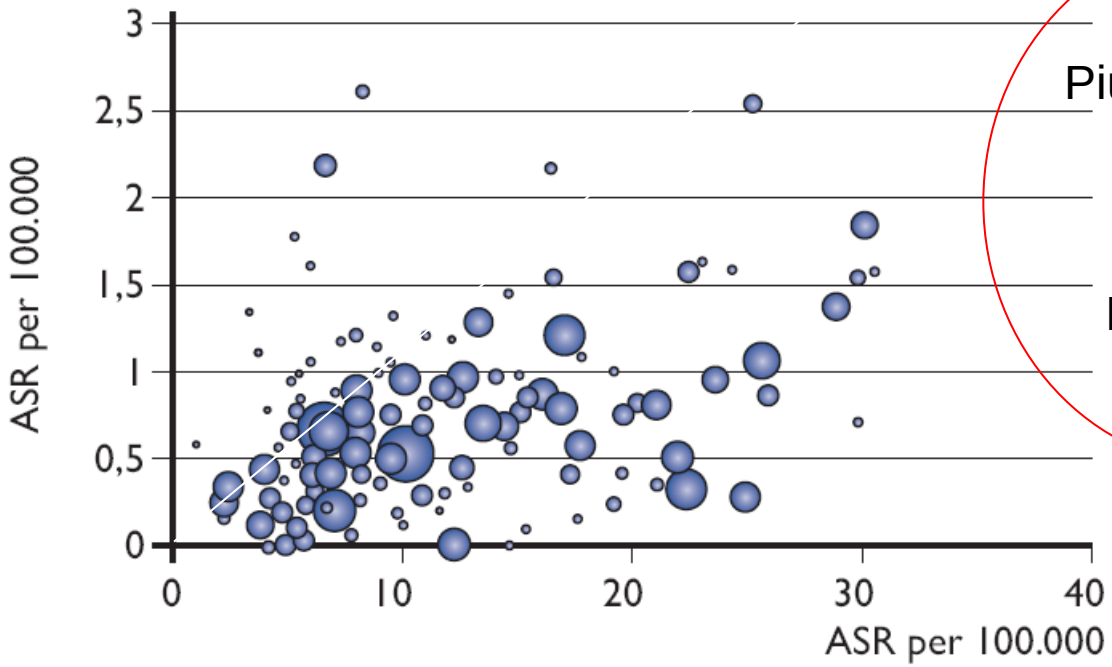
†Available at http://seer.cancer.gov/seerstat.

HPV HA UN IMPATTO ESTREMAMENTE RILEVANTE SIA NELLA FEMMINA CHE NEL MASCHIO



Conferenza di Consenso sulle patologie da HPV umano nel maschio, Roma 2010

Tassi di incidenza di cancro della cervice uterina (in ascissa) e di cancro del pene (in ordinata) standardizzati per età su dati mondiali nel periodo 1993-1997, ottenuti da tutti i Registri Tumori compresi nel volume VIII di *Incidenza di Cancro in 5 continenti*; la dimensione dei punti è ponderata in funzione degli anni-persona di osservazione di ogni registro (ASR=Age standardized rate)



Più femmine che maschi

PERCHE' ?

Fonte: Parkin, 2006 [21].

Possibili giustificazioni

- Quantità della superficie mucosa disponibile
- Grado di acidità ambientale
- Grado di aereobiosi
- Coinfezione come elemento favorente
- Altri fattori sconosciuti

- Presenza del virus in pari proporzioni nei due sessi senza evidenza di lesioni mucose ????

Sono state ipotizzate altre possibili malattie maschili HPV correlate ?

- **Mazzoli** e coll: HPV DNA nel seme di soggetti con prostatite non batterica (Congresso EAU Milano)
- **Foresta** e coll. : Spermatozoi infettati da HPV (PlosOne 2010)
- **Aatenyi-Agaba** e coll.: HPV nella congiuntiva e correlazione col ca.squamoso (Br.J.Cancer 2010)
- **Cai** e coll.: HPV DNA nei pazienti con tumore vescicale non muscolo invasivo e pazienti con IPB del gruppo di controllo (Oncol.Rep.2010)

HPV nei pazienti con prostatite

- 1,959 young male patients from several Italian regions attending our Centre for Prostatitis
- Period of study: Jan. 2005- Dec. 2008
- Age range : 19-43 (mean 31.3)

	MALE PATIENTS n°	HPV POSITIVE n°	HPV PREVALENCE %
2005	584	86	14.7
2006	446	123	27.5
2007	482	32	6.6
2008	447	149	33
TOTAL	1959	390	19.9

HPV negli spermatozoi

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PLoS one

Mechanism of Human Papillomavirus Binding to Human Spermatozoa and Fertilizing Ability of Infected Spermatozoa

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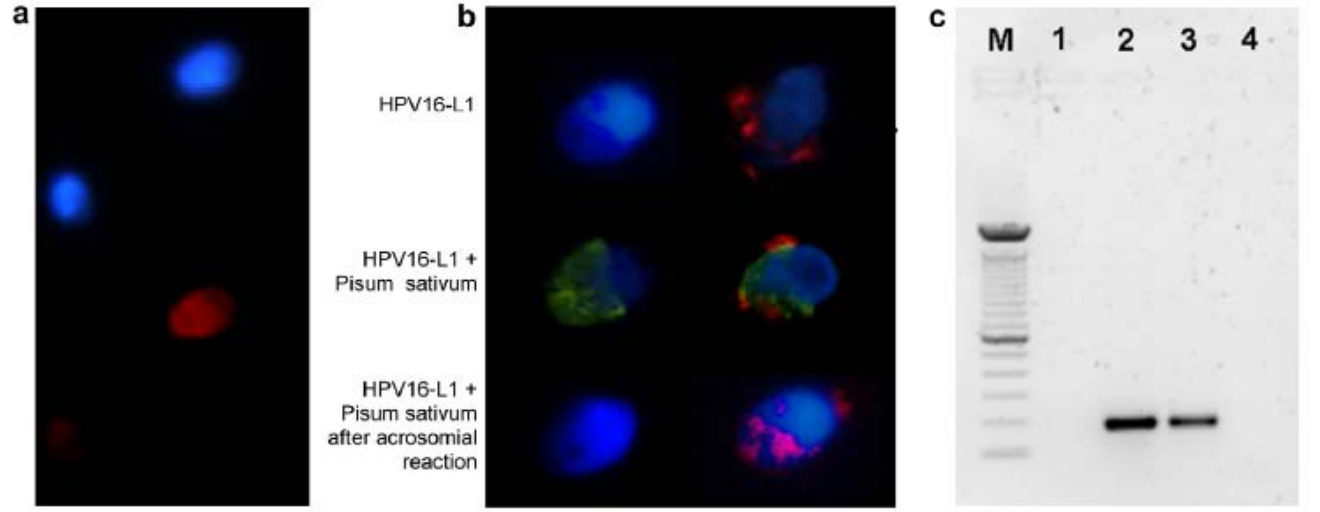

HPV e fertilità

- HPV è in grado di legarsi agli spermatozoi e rimanervi adeso riducendo la motilità (Foresta Fertil. Steril.2010)
- Uno studio recente ha evidenziato 25% dei soggetti con HPV nel seme (Foresta Fertil.Steril. 2010)
- Clearance spontanea in 6-12 mesi (84%)
- Passaggio di HPV da spermatozoo a oocita: possibile causa abortiva.
- HPV nel maschio: % abortiva 66,7% rispetto al 15% delle coppie sane (Perino Fertil. Steril. 2011)

HPV nella congiuntiva

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Human papillomavirus infection and squamous cell carcinoma of the conjunctiva

Clinical Studies

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