



EPIDEMIOLOGIA DEL CANCRO ANALE

Maria Benevolo

UOC Anatomia, Istologia Patologica e Citodiagnostica

Istituto Nazionale Tumori Regina Elena

INCIDENZA CARCINOMA ANALE

- ✓ 0.3-0.8 casi/100.000 uomini
- ✓ 0.5-1.0 cases/100.000 donne

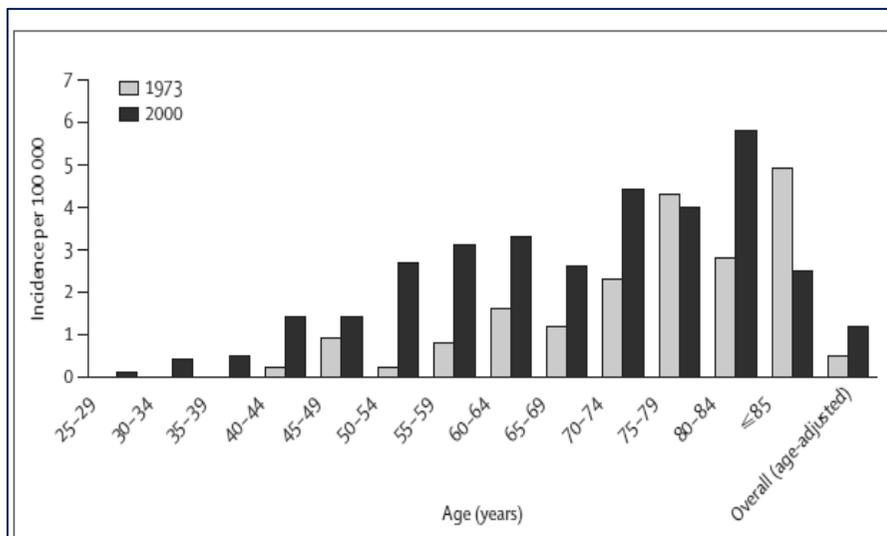
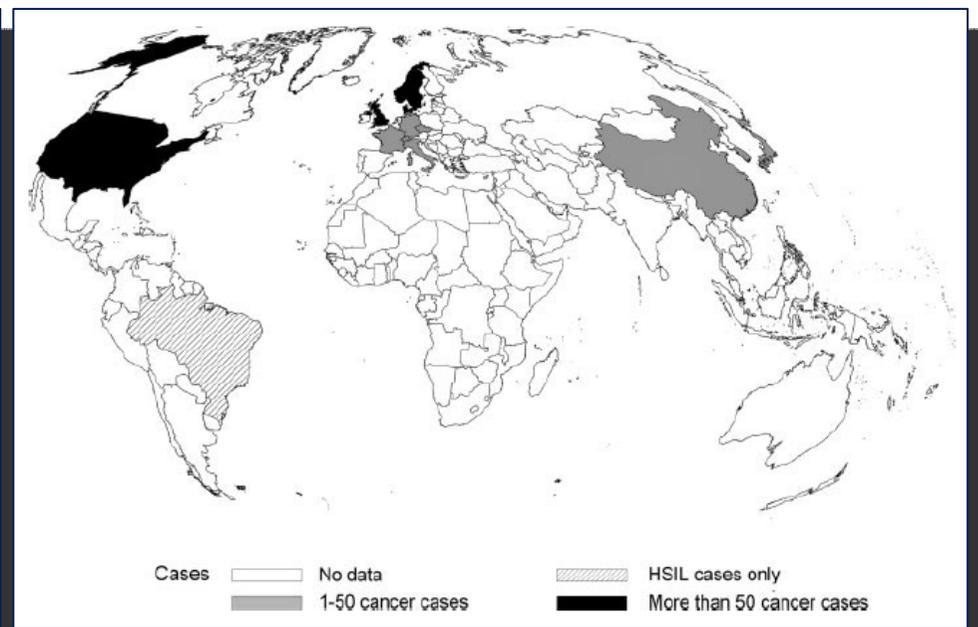


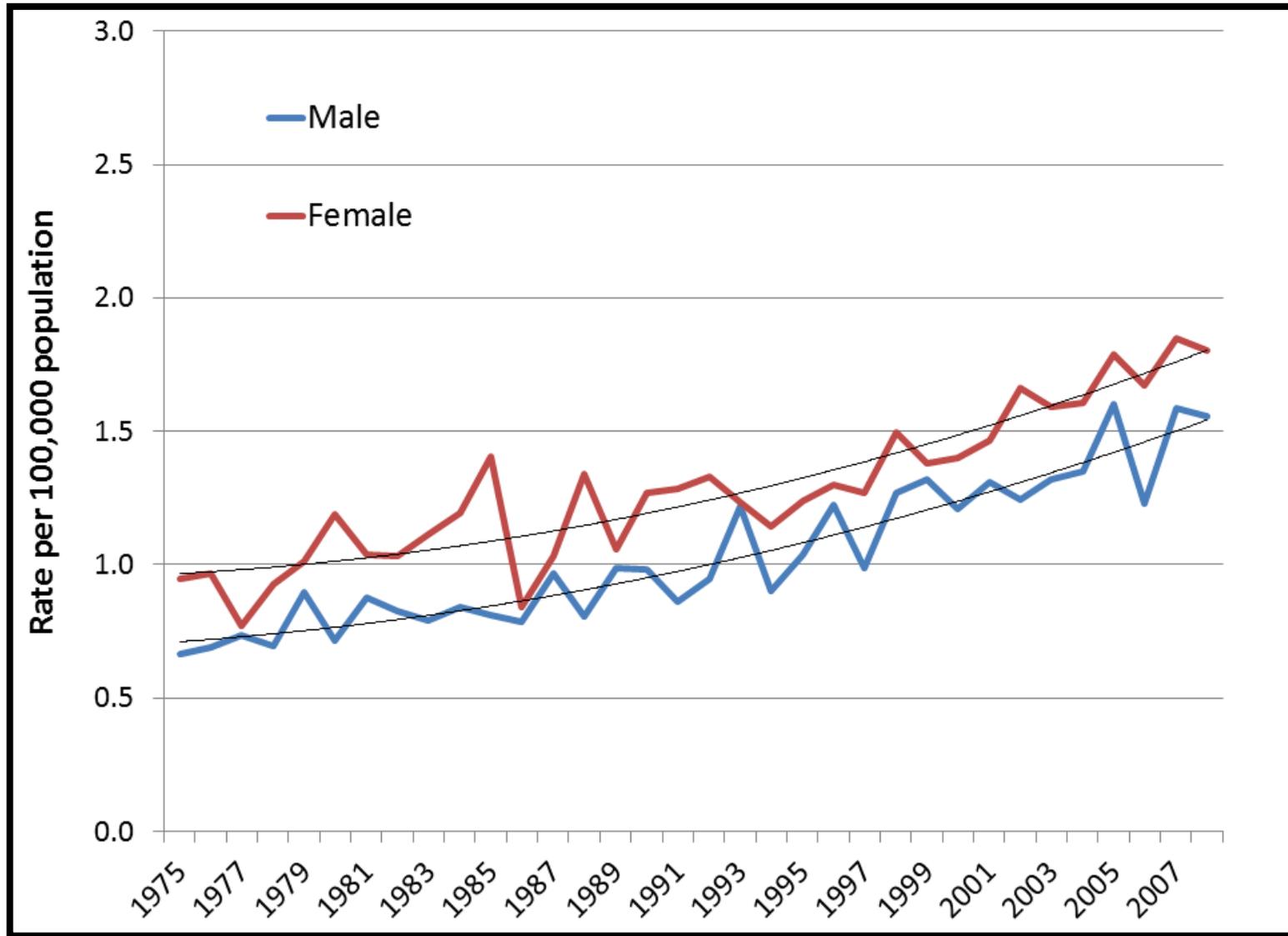
Figure 4: Anal cancer incidence in US men (1973 and 2000) by age group
Data from the US National Cancer Institute.⁴⁹



Partridge *et al*, 2006

Hoots *et al*, 2009

Trend di incidenza del carcinoma anale US (1975-2008)



Nielsen et al, *IJC* 2012

Incidence of anal cancer by cancer registry and sex (last update 13/12/2013)

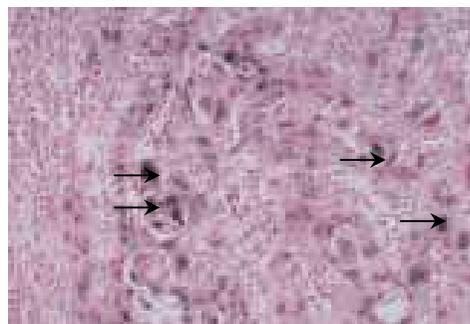
Age standardized rate range:

**Male 0.3-1.3
Female 0.1-1.8**

Country / Registry	Period	Male			Female		
		N cases ^a	Crude rate ^b	ASR ^b	N cases ^a	Crude rate ^c	ASR ^c
Italy							
Biella Province	2003-2007	9	2.0	0.8	15	3.1	1.1
Ferrara Province	2003-2007	21	2.5	0.9	23	2.5	0.7
Florence and Prato Provinces	2003-2005	42	2.4	0.9	46	2.5	1.0
Genova Province	2003-2006	44	2.7	1.3	72	3.9	1.4
Brescia Province	2003-2006	16	0.8	0.4	43	2.0	0.9
Modena Province	2003-2007	18	1.1	0.4	30	1.8	0.8
Naples	2003-2007	6	0.4	0.3	9	0.6	0.4
Parma Province	2003-2007	12	1.2	0.6	17	1.6	0.6
Ragusa Province	2003-2007	9	1.2	0.6	18	2.3	1.2
Reggio Emilia Province	2003-2007	9	0.7	0.4	22	1.8	0.7
Romagna Region	2003-2007	59	2.1	1.1	78	2.6	1.2
Salerno Province	2003-2007	33	1.2	0.7	24	0.9	0.5
Sassari Province	2003-2007	6	0.5	0.3	13	1.1	0.5
Sondrio	2003-2007	8	1.8	1.0	17	3.7	1.8
Syracuse Province	2003-2007	10	1.0	0.6	4	0.4	0.1
Latina	2003-2007	20	1.6	0.7	37	2.8	1.3
Umbria Region	2003-2007	26	1.2	0.7	40	1.8	0.8
Lombardy, Milan	2003-2006	22	0.9	0.5	58	2.1	1.0
Lombardy, Varese Province	2003-2007	31	1.5	0.8	41	1.9	0.8
Veneto Region	2003-2006	58	1.3	0.6	72	1.5	0.7
Alto Adige	2003-2006	11	1.2	0.7	31	3.2	1.5
Catania and Messina	2003-2005	20	0.8	0.5	24	0.9	0.5
Catanzaro	2003-2007	7	1.2	0.5	9	1.5	0.7
Friuli-Venezia Giulia	2003-2007	41	1.4	0.6	78	2.5	0.8
Lombardy, Como Province	2003-2007	19	1.4	0.8	29	2.0	0.9
Lombardy, Lecco Province	2003-2007	6	0.8	0.4	9	1.1	0.4
Lombardy, Mantova Province	2003-2005	7	1.2	0.5	5	0.8	0.3
Nuoro	2003-2007	4	0.7	0.4	7	1.1	0.4
Palerme	2003-2006	27	1.1	0.7	24	0.9	0.5
South Lombardy	2003-2005	5	0.5	0.3	19	1.7	0.7
Trapani	2003-2006	13	1.6	0.9	11	1.2	0.6
Trento	2003-2006	8	0.8	0.4	14	1.4	0.5
Torino	2003-2007	45	2.1	1.0	65	2.8	1.3

FATTORI di RISCHIO per il CARCINOMA ANALE

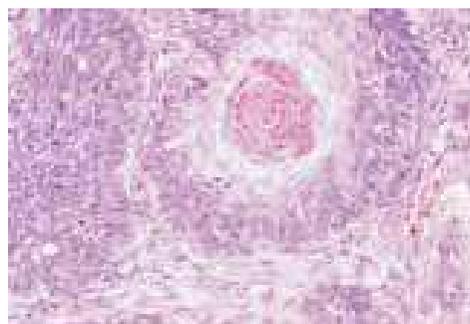
- Infezione da HPV
- Genotipi HPV
- Storia di rapporti anali recettivi
- N. partner sessuali
- Storia di condilomi anogenitali
- Immunosoppressione
- Età > 50 anni
- Fumo



Ibridazione in situ
(HPV16/18)

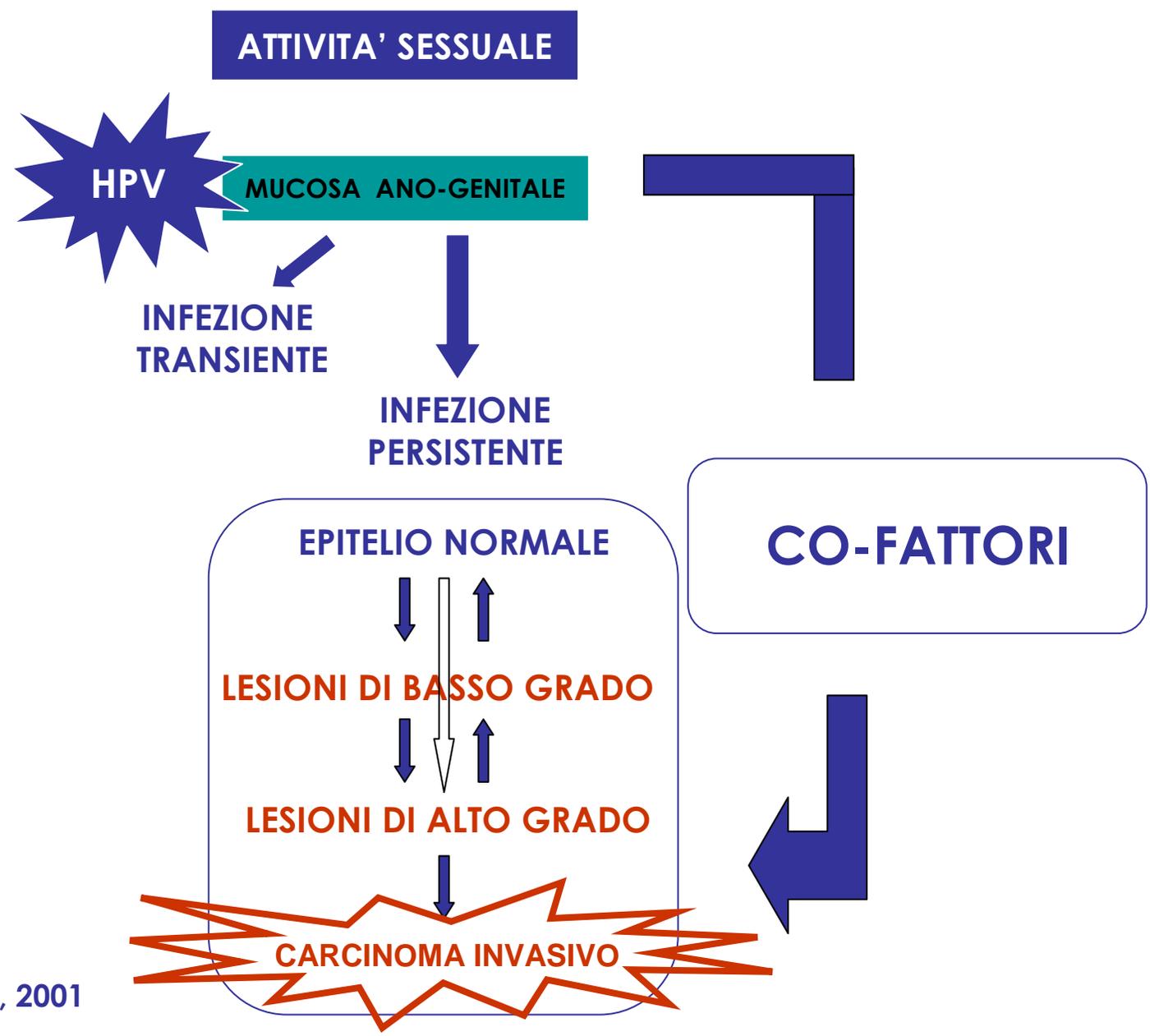


Carcinoma
squamoso anale
cheratinizzante,
ben differenziato



Carcinoma squamoso
anale con elementi
basaloidi

STORIA NATURALE DELLA CARCINOGENESI ANO-GENITALE



Franco et al, 2001



HPV INFECTION IN ANAL CANCER

Table 19: Prevalence of HPV in anogenital cancers other than the cervix in the World

	HPV prevalence		HPV 16/18 prevalence	
	No. tested	% (95% CI)	No. tested	% (95% CI)
Anal cancer	1197	75.8 (73.2-78.2)	1164	73.3 (70.6-75.8)
Vulvar cancer	1664	40.5 (38.1-42.9)	1604	36.1 (33.7-38.5)
Vaginal cancer	172	73.3 (66.0-79.7)	172	57.6 (49.8-65.0)
Penile cancer	1669	49.1 (46.7-51.5)	1669	37.5 (35.2-39.9)

Note: HPV prevalence is highly variable according to the histology, refer to specific sections in 4.2 for details
 Data sources: See references in Section 8.



Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide

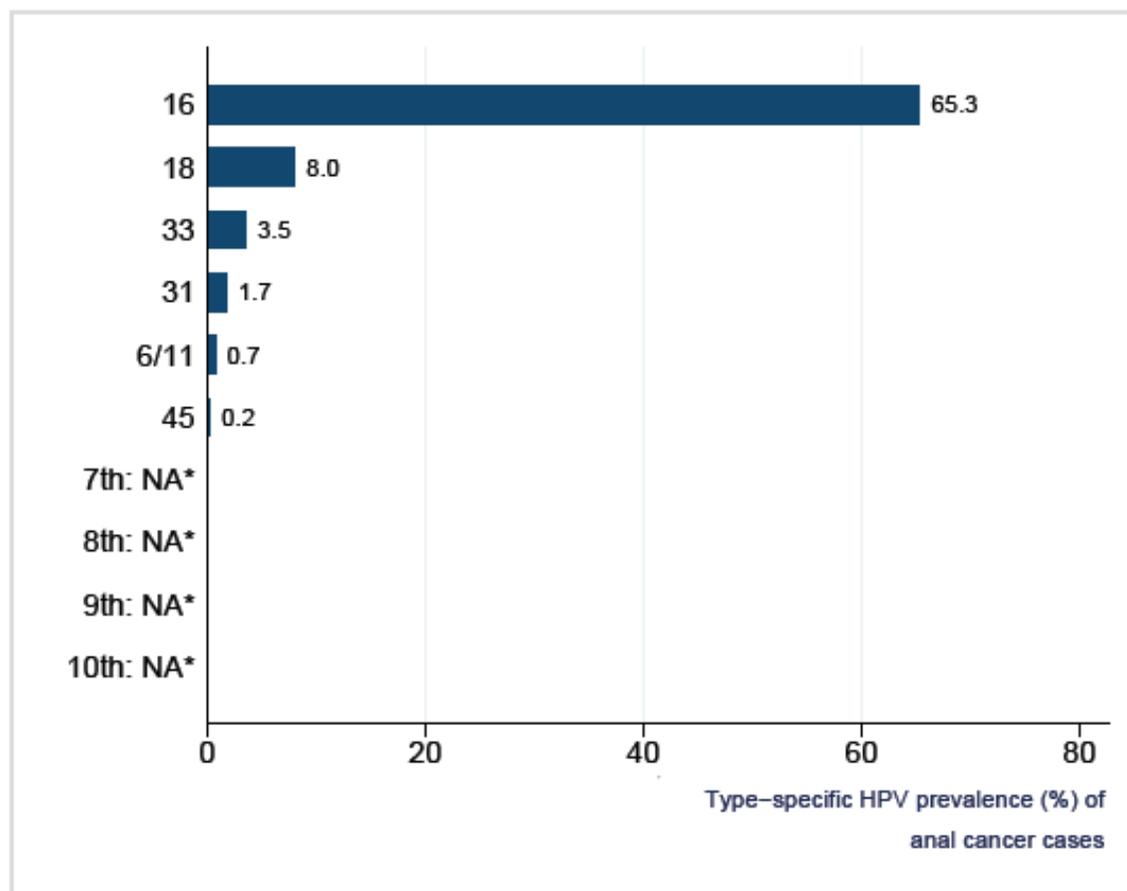
Laia Alemany^{1,2}, Maëlle Saunier¹, Isabel Alvarado-Cabrero³, Beatriz Quirós¹, Jorge Salmeron³, Hai-Rim Shin⁴, Edyta C. Pirog⁵, Núria Guimerà⁶, Gustavo Hernandez-Suarez⁷, Ana Felix⁸, Omar Clavero¹, Belen Lloveras⁹, Elena Kasamatsu¹⁰, Marc T. Goodman^{11,12}, Brenda Y. Hernandez¹¹, Jan Laco¹³, Leopoldo Tinoco¹⁴, Daan T. Geraets⁶, Charles F. Lynch¹⁵, Vaclav Mandys¹⁶, Mario Poljak¹⁷, Robert Jach¹⁸, Josep Verge¹⁹, Christine Clavel²⁰, Cathy Ndiaye²¹, JoEllen Klaustermeier^{1,2}, Antonio Cubilla¹⁰, Xavier Castellsagué¹, Ignacio G. Bravo¹, Michael Pawlita²², William G. Quint⁶, Nubia Muñoz²³, Francesc X. Bosch¹, and Silvia de Sanjose^{1,2} on behalf of the HPV VVAP Study Group

Table 1. Sample description and HPV DNA prevalence in AIN 2/3 and invasive anal cancer cases

Region	AIN 2/3					Invasive anal cancer							
			HPV prevalence					HPV prevalence			PR		
	n	%	n	%	95 CI	n	%	n	%	95% CI	PR	95% CI	p-Value
Europe	23	53.5	22	95.7	[78.1–99.9]	169	34.1	148	87.6	[81.6–92.1]	0.86	[0.75–0.97]	0.017
North America ¹	–	–	–	–	–	96	19.4	92	95.8	[89.7–98.9]	1	–	–
Latin America	12	27.9	12	100.0	[73.5–100.0*]	157	31.7	142	90.4	[84.7–94.6]	0.88	[0.77–0.99]	0.042
Africa	1	2.3	1	100.0	[2.5–100.0*]	21	4.2	13	61.9	[38.4–81.9]	0.60	[0.42–0.87]	0.006
Asia and Oceania	7	16.3	6	85.7	[42.1–99.6]	53	10.7	43	81.1	[68.0–90.6]	0.81	[0.68–0.97]	0.021
TOTAL	43	100.0	41	95.3	[84.2–99.4]	496	100.0	438	88.3	[85.1–91.0]	–	–	–



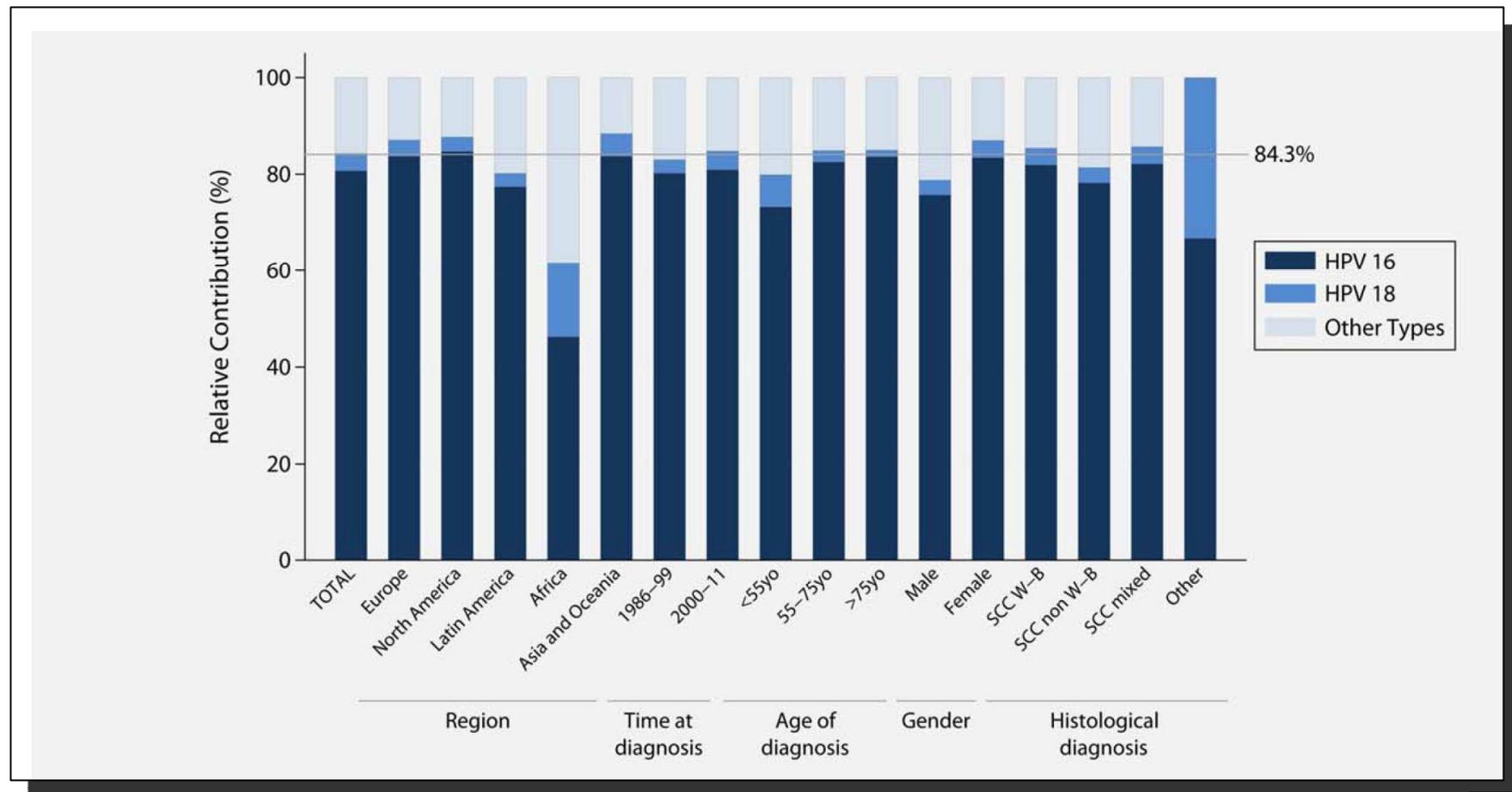
Ten most frequent HPV types among anal cancer cases in the world



*NA=Not available. No more types than shown were tested or were positive



CONTRIBUTO RELATIVO DEI DIVERSI GENOTIPI DI HPV NEI CASI DI CARCINOMA ANALE



Alemanly L. et al, IJC 2014



Table 20: Pooled estimate of HPV prevalence among anal cancer cases, by sex

Sex	No. tested	HPV prevalence	
		%	(95% CI)
Female	584	85.6	(82.5-88.4)
Male	255	74.1	(68.3-79.4)
Unspecified	358	60.9	(55.6-66.0)

Data sources:
See references in Section 8.

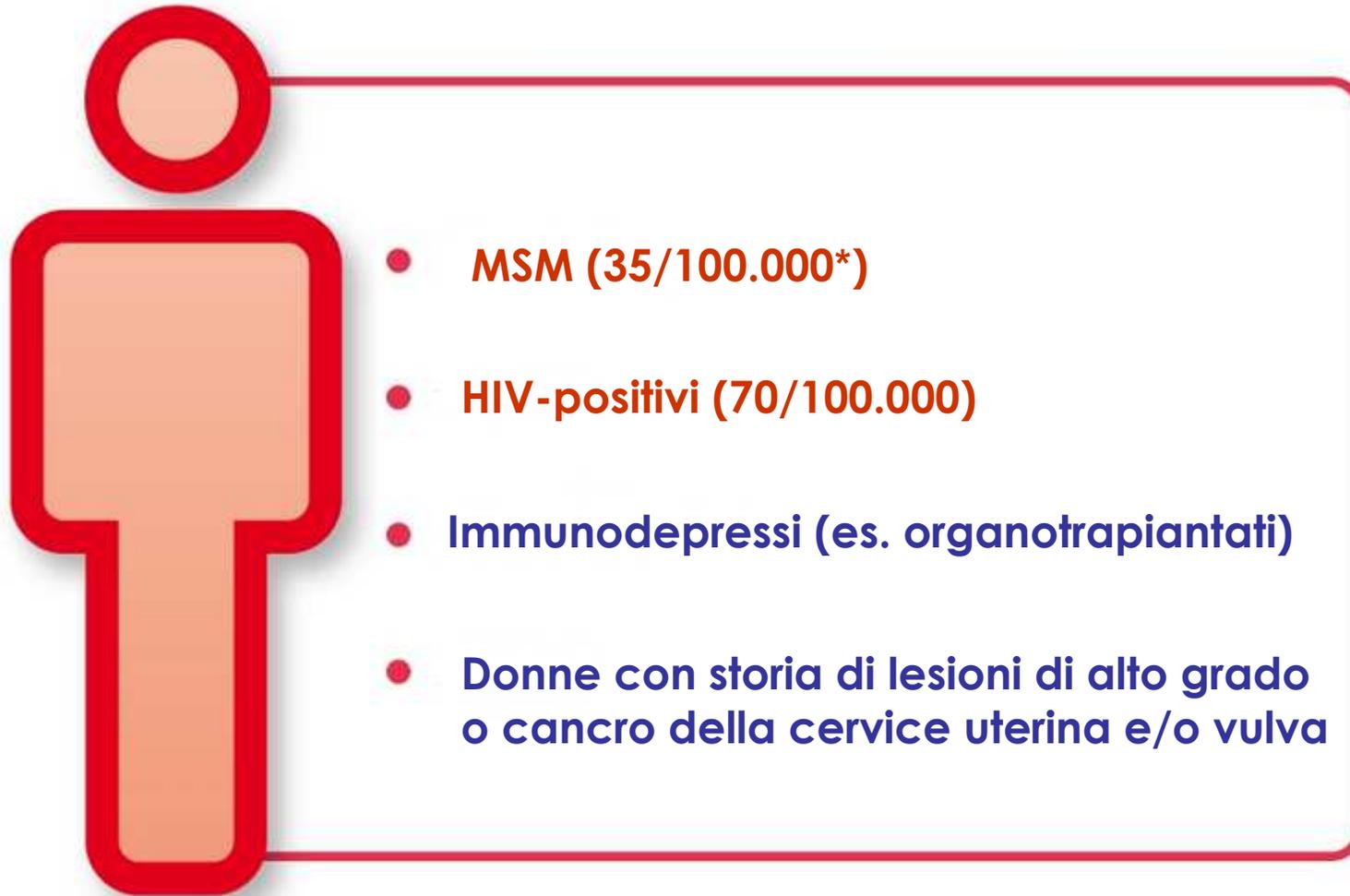
Table 21: Pooled estimate of HPV prevalence among men who have sex with men (MSM) and non-MSM with anal cancer

MSM	No. tested	HPV prevalence	
		%	(95% CI)
MSM	59	98.3	(90.9-99.9)
Non-MSM	135	68.9	(60.4-76.6)
Unspecified	61	62.3	(49.0-74.4)

Data sources:
See references in Section 8.



Popolazioni a rischio di carcinoma anale



* simile all'incidenza del carcinoma della cervice prima dell'introduzione del PAP-test

MSM HIV-positivi

Lack of regression of anal squamous intraepithelial lesions despite immune restoration under cART

Christophe Piketty^a, Béatrice Cochand-Priollet^b, Emilie Lanoy^{c,d},
Ali Si-Mohamed^e, Selma Trabelsi^{c,d}, Roland Tubiana^{c,d,f},
Pierre-Marie Girard^g, Laurence Weiss^{a,h}, Dominique Costagliola^{c,d,f},
the Valparaiso Study Group

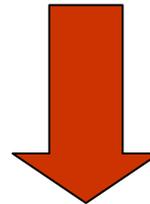
AIDS 2013, 27:401–406

HAART non previene l'acquisizione di nuove infezioni da HPV a livello ano-genitale e non diminuisce il tasso di persistenza dell'infezione

Incidenza annuale di cancro anale tra MSM HIV-positivi:

pre-HAART: 21.8 per 100.000

post HAART: 77.8 per 100.000



Machalek DA, *Lancet Oncol* 2012

DIFFERENZE TRA IL CANCRO CERVICALE E QUELLO ANALE

Key Differences	Cervical Cancer	Anal Cancer
Population affected	Women	Men and Women
Incidence	Decreasing	Increasing
Prevalence: General population ¹	8.1/100,000 (includes unscreened)	1.6/100,000
Prevalence: HIV positive ²	5.6/100,000	34.6/100,000
Median age at Cancer Diagnosis/Death ¹	48 y/57 y	60 y/65 y
HPV types in cancer (cervix ⁷⁵ , anus ²⁰)	Type 16: 53.5% Type 18: 17.2%	Type 16: 65.6% Type 18: 5.1%
HPV prevalence	Peaks in 3 rd decade	High (50-60%) prevalence over all ages in HIV-negative MSM
Histologic type	Squamous and glandular	Squamous
National screening guidelines	Yes	No (limited guidelines in NY state only)
Palpation useful for detection of early invasion	No	Yes, DARE
Cytologic screening efficacious	Yes	Probable, not proven
HR-HPV testing for triage of ASC-US	Yes	Not clear, probably not
HR-HPV testing useful in primary screening	Yes, in women ≥ 30 y, with Pap	No
Management	Colposcopy	HRA
Availability of trained, experienced cytopathology and clinical personnel	Widespread	Very limited
Treatment: high-grade	Ablative: cryotherapy, laser Excision: LEEP in office	Ablative: IRC, fulguration Excision: Usually in OR
Treatment: cancer		
Early	Conization (microinvasion)	Not defined
Late	Surgical +/- CMT	Standard: CMT

SCREENING PER IL CARCINOMA ANALE: PERCHE'?

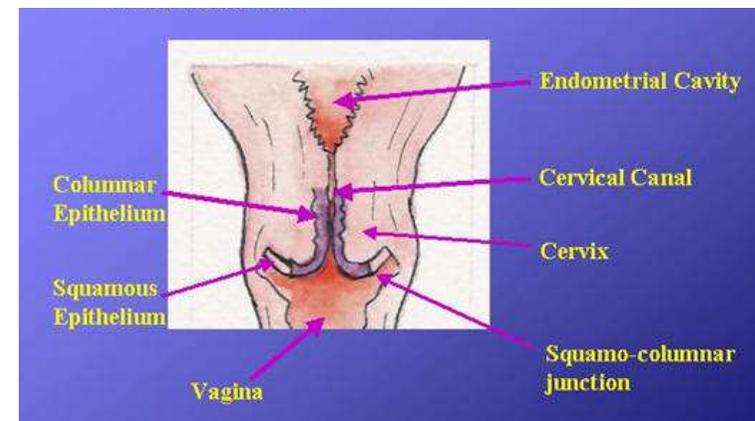
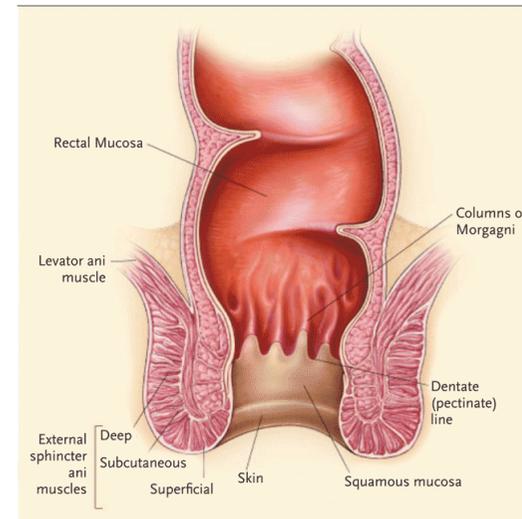
E' biologicamente simile al carcinoma della cervice uterina (zona di trasformazione=target HPV)

✓ E' preceduto dallo sviluppo di lesioni pre-tumorali (High-grade anal Intraepithelial neoplasia, AIN)

✓ In termini di tempo, la progressione da AIN di alto grado a cancro anale sembra essere simile a quella da CIN a cancro cervicale

✓ Progression-rate più bassa

✓ Clearance HPV più rapida



SCREENING PER IL CARCINOMA ANALE: CHI?

- **Tutti MSM HIV-positivi**
- **Tutti MSM HIV-negativi > 40 ys**
- **Tutti gli individui immunocompromessi**
- **Tutte le donne e gli uomini HIV-positivi**
- Le donne con lesioni HG/cancro vulvare o cervicale?
- Tutti gli individui con storia di condilomi ano-genitali?



NY State Department of Health
AIDS Institute: guidelines for AC screening (2007)

Pap Test ANNUALE per individui HIV-infetti:

- ✓ MSM
- ✓ Pazienti con storia di condilomatosi ano-genitale
- ✓ Donne con storia di lesioni cervicali/vulvari



No linee guida per lo screening del carcinoma anale

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali alla gestione diagnostico-clinica delle persone con infezione da HIV-1

Novembre 2013

Su mandato del *Ministro della Salute*

Tabella 3- Programmi di Screening oncologici adattati/specifici per la popolazione HIV-positiva.

TUMORE	POPOLAZIONE	PROCEDURE SCREENING	TEMPISTICA SCREENING	RACCOMANDAZIONE (FORZA/EVIDENZA)
Cervice uterina	Donne sessualmente attive >20 aa (E) ≥ 18 aa (A)	-PAP test convenzionale - PAP test su base liquida	Annuale se 2 esami consecutivi neg Se Pap test patologico	[A]
Ano	-MSM; -Tutti con storia di condilomi ano- genitali; -Donne con istologia genitale patologica ∞∞∞∞∞∞∞∞ MSM*	- Colposcopia -PAP test convenzionale - PAP test su base liquida Anoscopia ad alta risoluzione	*Annuale, se 2 esami consecutivi neg Se Pap test patologico	[AIII] [AII]

Raccomandazione: A = fortemente raccomandato

SCREENING CITOLOGICO

Bethesda 2001 guidelines (Darragh T et al, The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 2nd ed. New York: Springer-Verlag; 2004)

Reports:

NILM: negative for intraepithelial lesion or malignancy

ASC-US: atypical squamous cells of undetermined significance

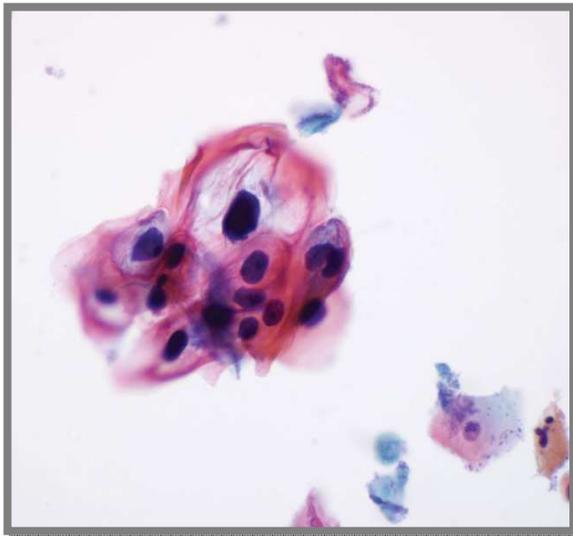
ASC-H: atypical squamous cells—cannot exclude HSIL

L-SIL: low-grade squamous intraepithelial lesion

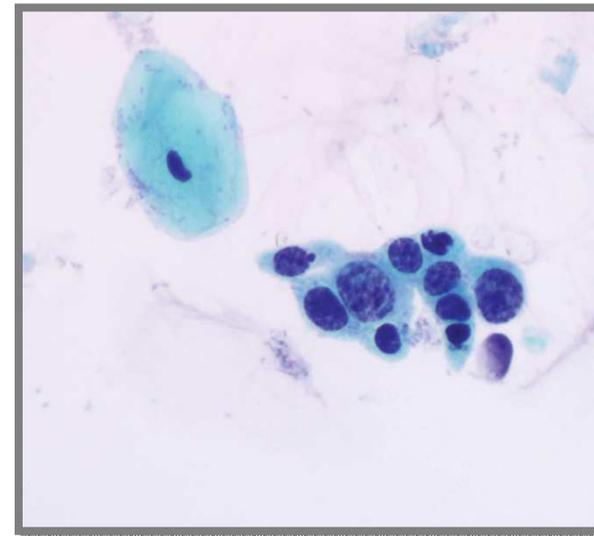
H-SIL: high-grade squamous intraepithelial lesions

SCC: squamous cell carcinoma

L-SIL



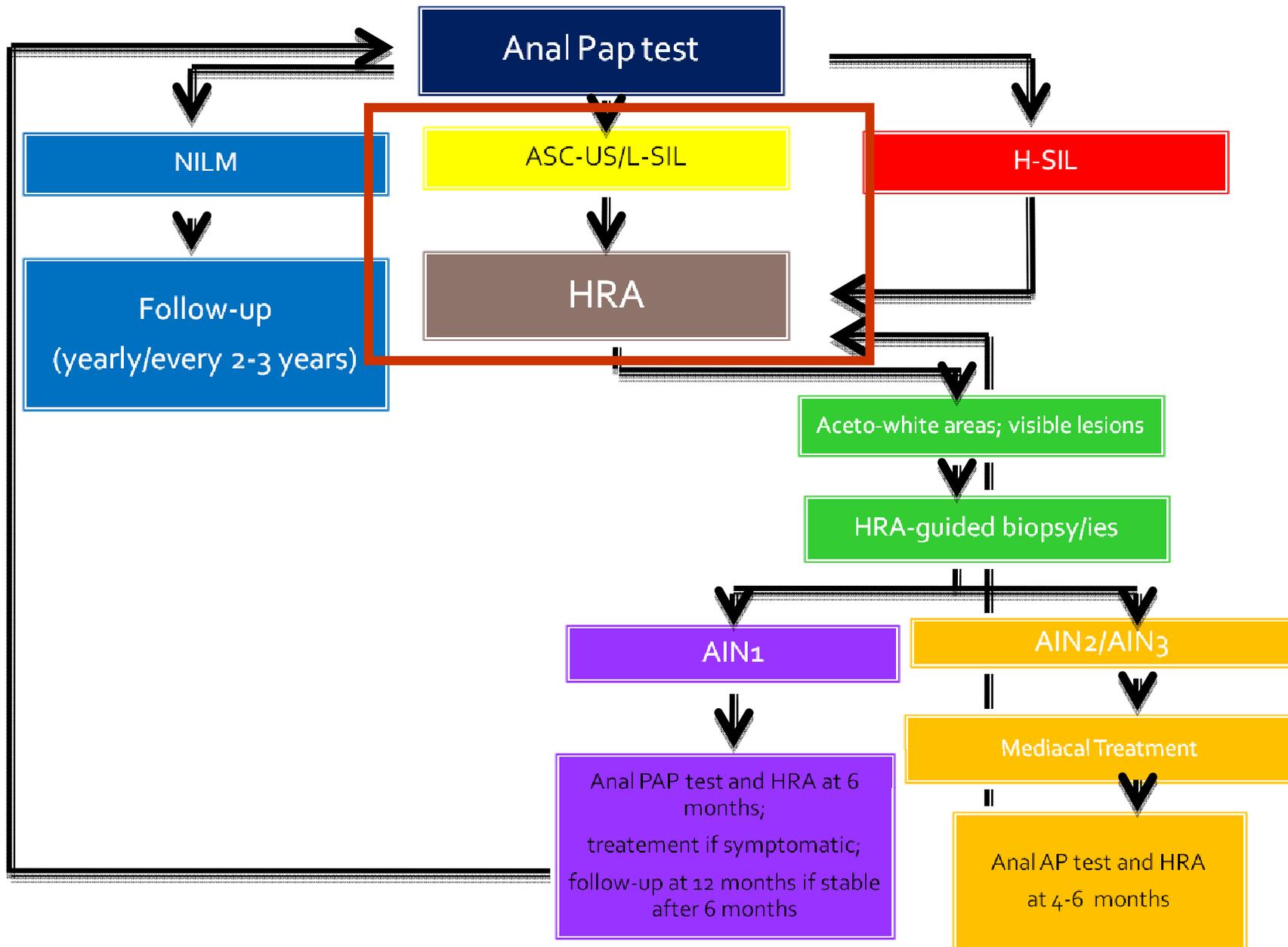
H-SIL



CITOLOGIA ANALE

- **Sensibilità (ASCUS+) : 42-98%**
- **Specificità (ASCUS+) 16-96%**
- **La prevalenza di high-grade AIN osservata è notevolmente più bassa con diagnosi citologica rispetto a quella istologica**
- **Sensibilità più alta in MSM HIV-positivi rispetto a HIV-negativi**

***Singolo pap test: sens. 75%, spec.90%**



PROGETTO SAIN

Screening delle lesioni intraepiteliali anali e delle infezioni anali da HPV



ISG

ISTITUTO DERMATOLOGICO

SAN GALLICANO

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

S.C. di Dermatologia Infettiva e Allergologica

A. Cristaudo, M. Giuliani, A. Latini, M. Colafigli,
M.Frasca, M.G. Donà

Laboratorio di Patologia Clinica e Microbiologia ISG



IRE

ISTITUTO NAZIONALE TUMORI

REGINA ELENA

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

UOC Anatomia Istopatologia Patologica e Citodiagnostica

E. Pescarmona, M. Benevolo, F. Marandino, F. Rollo, L. Ronchetti, V. Laquintana

UOC Gastroenterologia

PROGETTO SAIN

Screening delle lesioni intraepiteliali anali e delle infezioni anali da HPV

✓ 2009
✓ 675 MSM

MSM HIV-positivi



N=198
Età mediana: 41 (IQR 33-47)
92.2% Caucasici

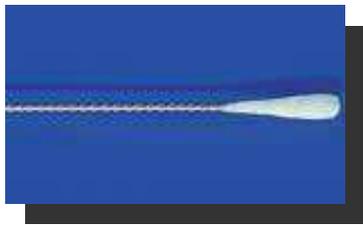
MSM HIV-negativi



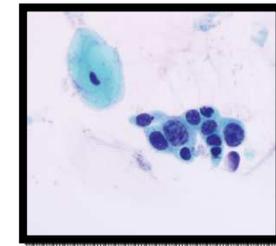
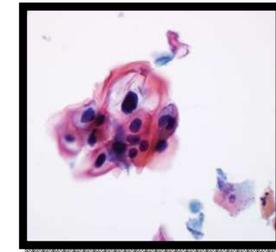
N=477
Età mediana: 32 (IQR 27-39)
97.0% Caucasici

MATERIALI E METODI

Campione citologico ANALE



Citologia su strato sottile



Linee guida
Bethesda 2001
(Darragh et al, 2004)

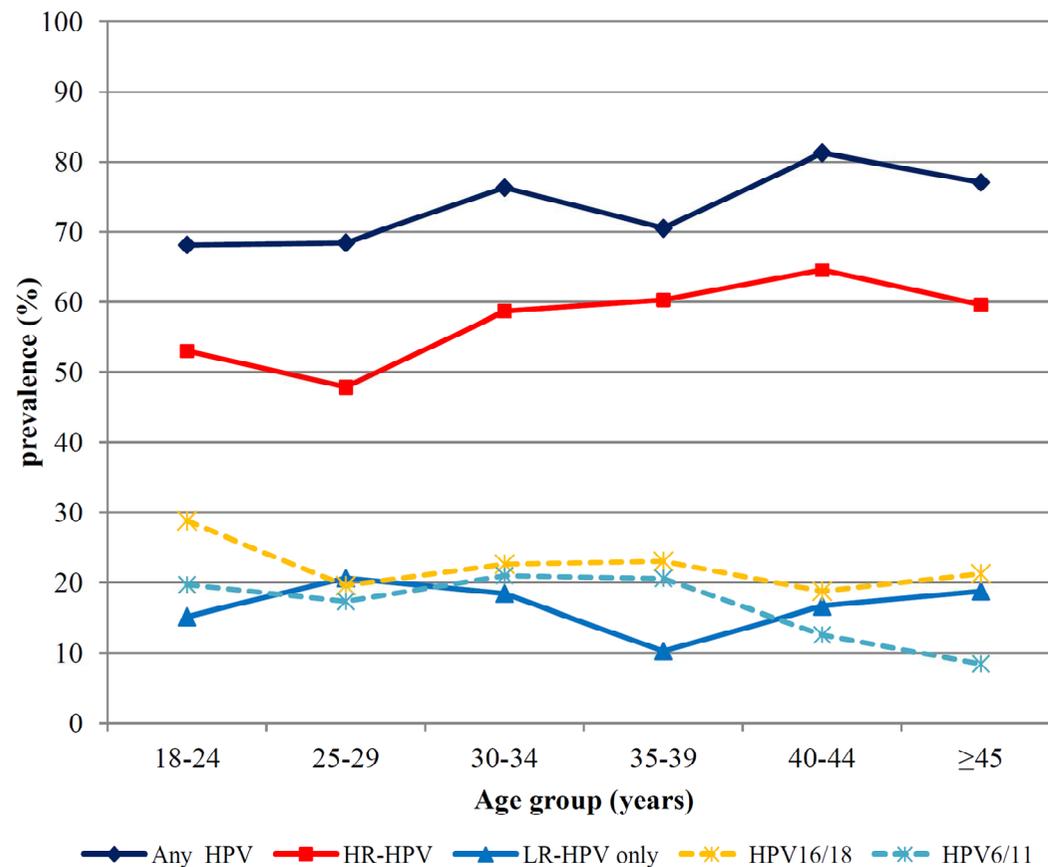
Test HPV DNA

LINEAR ARRAY
HPV Genotyping Test®
(37 genotipi mucosali)

Anal human papillomavirus infection prevalence in men who have sex with men is age independent: a role for recent sexual behavior?

Maria Gabriella Donà^{*1}, Alessandra Latini¹, Maria Benevolo², Domenico Moretto³, Antonio Cristaudo¹ & Massimo Giuliani¹

L'infezione anale da HPV è comune in tutte le età indipendentemente dal genotipo



ABNORMAL CYTOLOGY (ASCUS+) ASSOCIATIONS

	Abnormal cytology n/N (%)	COR (95% CI)
HPV infection		
Negative	10/83 (12.0)	1.00
Any HPV	79/216 (36.6)	4.21 (1.97-9.23)
LR-HPV only	20/52 (38.5)	4.56 (1.78-11.90)
Any HR-HPV	59/164 (36.0)	4.10 (1.88-9.17)
HPV 16 and/or 18	30/69 (43.5)	5.62 (2.33-13.81)
HR-HPV other than 16 and/or 18	29/95 (30.5)	3.21 (1.37-7.67)
Multiple HPV infection		
No	21/77 (27.3)	1.00
Yes	58/139 (41.7)	1.91 (1.00-3.66)

No association with:

- ✓ Age
- ✓ Education
- ✓ Income
- ✓ Age at 1° intercourse
- ✓ Lifetime n. partners
- ✓ Recent n. partners
- ✓ Receptive anal sex
- ✓ Condom use
- ✓ STI history

VACCINE EFFICACY IN MALES (quadrivalent Gardasil)

- Trial in 4065 men ages 16-26 from 18 countries and 602 HIV-negative MSM (Giuliano A, N Engl J Med 2011)
- Significant protection against HPV6,11, 16 or 18 external genital lesions (primary endpoint)
- Protection against AIN (any grade) and anal cancer
- 2009: FDA approval for AIN and anal cancer prevention
- 2014, June: EMA approval for anal cancer prevention