



## Anal HPV genotypes and related dysplastic lesions in Italian and foreign born high-risk males

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### ABSTRACT

Anal intraepithelial neoplasia and anal cancer are closely related to infection from high-risk Human Papilloma Virus (HPV) genotypes. Since HPVs involved in disease progression are reported to vary by geographical regions, this study focuses on HPV genotypes spectrum in 289 males attending a Sexual Transmitted Diseases (STD) unit according to their nationality. Anal cytology, Digene Hybrid Capture Assay (HC2) and HPV genotyping were evaluated in 226 Italian (IT) and 63 foreign born (FB) subjects, recruited between January 2003 and December 2006. FB people were younger (median 32y-IQR 27–35 vs 36y-IQR 31–43, respectively; Mann–Whitney test  $p < 0.0001$ ) and had a higher rate of abnormal results ( $\geq$  atypical squamous cells of undetermined significance (ASCUS)) on anal cytology (95.0% vs 84.04%) ( $p = 0.032$ ; OR 3.61; 95% CI 1.04–1.23). HPV-16 is by far the most common genotype found in anal cytological samples independently from nationality while differences in distribution of other HPV genotypes were observed. The probability of infection from high-risk HPVs was higher in FB (OR 1.69; 95% CI 1.07–2.68) and is due to a higher rate of HPV-58 (OR 4.98; 95% CI 2.06–12.04), to a lower rate of HPV-11 (OR 0.35; 95% CI 0.16–0.77), to the presence of other high-risk genotypes (HPV-45, HPV-66, HPV-69). Multiple infections rate was high and comparable between IT and FB people. The relative contribution of each HPV genotype in the development of pre-neoplastic disease to an early age in the FB group cannot be argued by this study and more extensive epidemiological evaluations are needed to define the influence of each genotype and the association with the most prevalent high-risk HPVs on cytological intraepithelial lesions development.

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### 1. Introduction

Anal carcinoma is relatively rare in the general population but it is increasingly reported especially in high-risk people like HIV infected persons and men who have sex with men (MSM) [1–6].

HPV is found in about 90% of anal cancers in males and females and the oncogenic process, arising from the infection by high-risk HPV genotypes, even if less characterised both for evolution time and for the HPV genotypes involved in the oncogenesis, is similar to that described for cervical cancer in females [7,8]. HPV-16 and HPV-18 are the most common high-risk types involved in cervical and anal cancers worldwide [9] but several other HPV genotypes are classified as high risk in the de Villiers classification [10] due to their association with the development of genital cancers [11].

The recently commercialized preventive HPV vaccines are primarily directed against the most prevalent HPV genotypes involved in oncogenesis (HPV-16 and HPV-18) or in genital warts (HPV-6 and HPV-11) but viral characterization of infections in high-risk groups could be helpful in predicting the potential of preventive vaccines also after sexual debut and are needed to monitor if there is an impact of vaccine pressure in countries where vaccine programs are beginning.

Since the relative distribution of HPV genotypes has been reported to vary by geographical region [12], the aim of this cross-sectional study is the evaluation of HPV genotypes spectrum in a cohort of high-risk males attending an Sexually Transmitted Disease (STD) unit according to their nationality.

### 2. Methods

From January 2003 to December 2006, all consenting male out-patients attending the STD unit of the II Division of Infectious Disease, L Sacco Hospital Milan, Italy, independently from their HIV serostatus, were evaluated for HPV infection and related lesion of the anal canal.

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**Table 1**  
Risk factors for STD (in bold statistically significant differences).

	Total	Foreign born	Italian	<i>p</i>
Patients [# (%)]	289	63	226	
Drug addiction	240	42	198	0.69 <sup>a</sup>
Actual/previous	12 (5.0)	1 (2.4)	11 (5.69)	
Never	228 (95.0)	41 (97.6)	187 (94.4)	
Sexual habits	255	62	193	<b>0.0064<sup>b</sup></b>
Heterosexual	27 (10.6)	2 (3.2)	25 (12.9)	
Homosexual	197 (77.2)	57 (91.9)	140 (72.5)	
Bisexual	31 (12.2)	3 (4.8)	28 (14.5)	
Sex workers	289	63	226	<b>&lt;0.0001<sup>a</sup></b>
Yes	10 (3.5)	10 (15.9)	0 (0)	

<sup>a</sup> Fisher's exact test.<sup>b</sup>  $\chi^2$ -test.

High-resolution anoscopy was performed as primary screening procedure in all patients divided in two groups for the purpose of the study: Italian (IT) and foreign born (FB) persons.

Cytological brushing of the anal canal was performed through Cervex brush (Cytobrush PlusdMedscand Medical AB, Sweden) and evaluated according to the 2001 Bethesda System for cervical cytological reporting [13].

HPV DNA detection was performed by Hybrid Capture 2 HPV test (HC2; Digene, Gaithersburg, MD) both for high- and low-risk HPV genotypes (HR and LR) and by polymerase chain reaction (PCR): viral DNA was extracted from cell pellets by using a commercial kit (QIAamp® DNA Mini Kit, QIAGEN, GmbH, Germany) according to the manufacturer's instructions.

The quality and competence of the extracted DNA were tested by amplifying a 268 bp fragment of the ubiquitous gene of  $\beta$ -globin with the primers GH20/PC04. HPV DNA sequences were detected using the consensus primer set MY09/MY11 PCR assay,

**Table 2**  
Epidemiological and baseline clinical data of 289 males at time of the study (in bold statistically significant differences).

	Total	Foreign born	Italian	<i>p</i>
Patients (#)	289	63	226	
Age (mean $\pm$ S.D.)	36.4 $\pm$ 9.2	32.6 $\pm$ 7.2	37.4 $\pm$ 9.4	<b>&lt;0.0001<sup>c</sup></b>
HIV serostus (#)	266	58	208	
Pos. (%)	245 (92.1)	55 (94.83)	190 (91.35)	0.58 <sup>d</sup>
Neg. (%)	21 (7.9)	3 (5.17)	18 (8.65)	
CD4 cell/ $\mu$ L (median and IQR)	469.5 (329.5–636)	493.0 (351–721)	468.0 (320–605.5)	0.208 <sup>c</sup>
HIV RNA copies/ $\mu$ L	2.27 (1.69–4.05)	2.21 (1.69–3.6)	2.28 (1.69–4.18)	0.359 <sup>c</sup>
log <sub>10</sub> (median and IQR)				
Antiretroviral T	218	46	172	
No	63 (28.9)	9 (19.56)	54 (31.39)	
Non-HAART	5 (2.29)	0	5 (2.91)	0.12 <sup>e</sup>
HAART	150 (68.81)	37 (80.43)	113 (65.7)	
Anal cytology (#)	273	60	213	0.073 <sup>e</sup>
Neg. (%)	37 (13.55)	3 (5.0)	34 (13.96)	
LSIL (%)	195 (71.43)	46 (76.67)	149 (69.95)	<b>Any lesion vs neg.: 0.032<sup>d</sup> OR 3.61 (95% CI 1.04–1.23)</b>
HSIL (%)	35 (12.82)	11 (18.33)	24 (11.27)	
ASCUS (%)	6 (2.2)	0	6 (2.81)	
Inadequate	2 (0.37)	0	2 (0.94)	
Any lesion (%)	236 (86.45)	57 (95.0)	179 (84.04)	
Anoscopy (#)	203	45	158	
Neg. (%)	81 (39.9)	19 (42.22)	62 (39.24)	0.73 <sup>d</sup>
Pos. <sup>a</sup> (%)	122 (60.1)	26 (57.78)	96 (60.76)	
Histology (#)	156	31	125	
Neg. (%)	40 (25.64)	7 (22.58)	33 (26.4)	0.794 <sup>e</sup>
AIN1 (%)	103 (66.02)	22 (70.97)	81 (64.8)	0.819 <sup>d</sup> (any lesion vs neg)
AIN 2–3 (%)	10 (6.41)	2 (6.45)	8 (6.4)	
Ca (%)	3 (1.92)	0	3 (2.4)	
Any lesion	116 (74.36)	24 (77.42)	92 (73.6)	
Cyto/histology <sup>b</sup> (#)	276	60	216	
Neg. (%)	32 (11.6)	3 (5.0)	29 (11.79)	0.143 <sup>e</sup>
LSIL/AIN1 (%)	196 (71.01)	45 (75.0)	151 (69.91)	
HSIL/AIN2–3 (%)	40 (14.5)	12 (20.0)	28 (12.96)	
Ca (%)	3 (1.09)	0	3 (1.39)	
ASCUS (%)	5 (1.81)	0	5 (2.31)	
Any lesion (%)	244 (88.4)	57 (95.0)	187 (86.57)	
HC2 (#)	271	60	211	
Neg. (%)	19 (7.01)	2 (3.33)	17 (8.06)	0.467 <sup>e</sup>
LR (%)	32 (11.81)	6 (10.0)	26 (12.32)	
HR (%)	51 (18.82)	14 (23.33)	37 (17.53)	
HR/LR (%)	169 (62.36)	38 (63.33)	131 (62.08)	
HR or HR/LR	220 (81.18)	52 (86.67)	168 (79.62)	

<sup>a</sup> Positive results on anoscopic examination = presence of acetic white lesions or warts.<sup>b</sup> In case of discordant results between cytology and histology, the most severe result was considered.<sup>c</sup> Mann–Whitney test.<sup>d</sup> Fisher's exact test.<sup>e</sup>  $\chi^2$ -test.

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