

Human Papillomavirus and Ano-genital Diseases

Gianluca Pellino

Gianluca Pellino, Division of General Surgery, Second University of Naples, Naples, 81031, Italy

Correspondence to: Gianluca Pellino, Division of General Surgery, Second University of Naples, 81031 Aversa (CE), Naples, Italy. gipe1984@gmail.com

Telephone: +039-81-8902291

Received: July 7, 2012 Revised: September 4, 2012

Accepted: September 8, 2012

Published online: January 21, 2013

ABSTRACT

Human Papillomaviruses (HPV) are responsible of a wide spectrum of diseases, from warts to carcinoma. The incidence of HPV infection is increasing during time. We are used to consider the disease as a “female matter”; however, once the burden of disease is carefully observed in men, a few considerations concerning screening and prophylactic approaches to male subjects may be wise.

© 2013 Thomson research. All rights reserved.

Key words: Human papillomavirus; Warts; HPV; Condyloma; Vaccination; Anal cancer

Pellino G. Human Papillomavirus and Ano-genital Diseases. *Journal of Gastroenterology and Hepatology Research* 2013; 2(1): 350-352
Available from: URL: <http://www.ghrnet.org/index./joghr/>

HPV: NOT ONLY A WOMEN'S ISSUE

Human Papillomaviruses (HPV) are members of the family “Papovaviridae”. There is no membrane envelope, the diameter ranges between 50 and 55 nm, with an icosahedral capsid of 72 capsomers and circular double-stranded DNA genome of approximately 7900 base pairs (bp).

There are more than one hundred members of HPVs, and they can be classified in 5 different genera: Alpha, Beta, Gamma, Mu e Nu^[1]. Alpha HPVs, identified only in men and primates, consist of high-risk, low-risk and cutaneous HPVs. Such classification reflects a different level of evolution, a different symptomatology and different correlated diseases: high-risk viruses, such as HPV 16 and HPV 18,

account for >70% of all cervix carcinomas (HPV 16 > 50% and HPV 18 approximately 20%), while low-risk HPVs, such as HPV 6 and HPV 11 are commonly associated with genital warts; cutaneous HPVs, such as HPV 2, cause vulgar warts, especially in children^[1]. Papillomaviruses Beta are responsible of asymptomatic or unapparent infections; Gamma, Mu and Nu genera are associated with cutaneous papillomas.

Papillomaviruses are host-specific and tissue-specific, needing a well differentiated keratinized squamous epithelium to complete a reproductive cycle. Two main HPV groups can be consequently identified: one consisting of HPV infecting skin and cutaneous surfaces, the other affecting moist squamous internal mucosae.

Once viral agents make their way into mitotically active epithelial basal stratus through microlesions or facilitated accesses (i.e. the basis of a pilifer follicle) their vital cycle starts^[1]. Proliferation happening in the lower epithelial stratus and migration to surface are mainly regulated by viral proteins E7 and E6 (Early Proteins), which are also involved in the carcinogenesis of HPV, by interacting with host genes Rb and p53, respectively. Viral proteins L1 and L2 (Late Proteins) regulate encapsidation of the genome.

HPV transmission can be either horizontal, meaning the virus is transmitted through contact (genital-genital, hand-genital, oral-genital), or vertical (mother-to-child). Risk factors in favour of HPV infection are sexual intercourse in youth, multiple sexual partners, prolonged use of oral contraceptives, high parity, no circumcision, tabagism, immunodepression/immunosuppression, HIV or other sexually transmitted diseases co-infection, and no use of condom^[2-5].

Diagnosing HPV infection may be difficult, as the minority of patients presents with clinical manifestations such as genital warts, condylomas or squamous-cell neoplasia, while in most patients the infection is transitory and asymptomatic. Many studies investigated the correlation between HPV and cervix cancer; the prevalence of Papillomaviruses has been found to be as high as 100%. HPVs types more commonly associated with cervix cancer are 16, 18, 45, 31, 33, 52, 58. Women infected with HPV are most commonly found with HPV 16 (2.25%), while HPV 31 (0.81%), 18 (0.76%), 58 (0.73%) and 52 (0.56%) are less common^[6]. The prevalence of HPV is higher in the second and third decade (24.9%<30 years vs 10.2% between 40 and 45 years and 7.5% between 80 and 85 years), probably reflecting sexual habits^[5-7].

Although some authors suggested that uro-genital HPV may

be found in men in percentage similar to that of women, literature concerning infection in male patients is poor. An infected male represents a carrier as well as an infected woman, and it can similarly cause neoplasia. In a survey on 463 asymptomatic men between 18 and 40 years of age, Nielson *et al*^[4] reported that 303 subjects were found with HPV (65.4%). Moreover, 135 (29.2%) had an high-risk HPV. A similar incidence was reported by Partridge *et al*^[3] in a group of 240 healthy young men monitored for 2 years (62.4%). Several studies reported a prevalence of HPV infection in young men ranging between 48%^[8] (in 44 patients of a Sexually Transmitted Disease Clinic, 18-44 year-of-age) and 9%^[9] (in 381 students, median age 22 year-old). More than 2 out of 3 patients affected with cancer of the penis are found with HPV infection, more commonly consisting of HPV 16 or 18 (>90%). These data confirm that the prevalence of HPV in men cannot be ignored.

HPV can affect several sites in men, varying between subjects. A research on 436 men affected with venereal diseases (28% HPV) reported that HPV infection was found in 44% of affected patients on the internal surface of the foreskin, in 30% in the distal urethra, 24% on the internal surface of the foreskin, 24% on the glans, 12% on the scrotum, and 8% in the anus^[10].

Penile brushing (PB) is considered the diagnostic tool with higher sensitivity. A research on 50 partners of HPV positive women reported a sensitivity of PB as high as 88.9%, higher than urethral brushing (UB, 50%) and seminal retrieval (SE, 33.3%); however, when PB was associated with UB or SE, sensitivity reached 100% and 97.2% respectively^[11].

Clinical features of penis HPV infections commonly consist of acuminate condylomata, warts, papulae, intraepithelial neoplasias, and carcinoma in situ. Neoplasia clinically manifests as hyperpigmented papulae, often flat. Typical histological features include epithelial proliferation, hyperkeratosis, and parakeratosis. Cell nuclei are clustered and hyperchromic, they lose organization, maturation and cohesion.

Evolution of such disease still remains unclear, but prevalence of HPV DNA in carcinomas and neoplasias is relevant. Palefsky^[10] found that the prevalence of HPV DNA in series of patients diagnosed with penis cancer ranged between 26.7% and 100%. Several reports highlighted the association between HPV infection and anal cancer; Papillomavirus infection is considered the main risk factor for intraepithelial anal neoplasia and is also associated with other lesions such as condylomas.

Abramowitz *et al*^[12] examined 473 HIV positive patients, finding 108 (23%) of them had HPV-related anal lesions: 47 had condylomata and 61 dysplasia.

Anal cancer accounts for 1.5% of all the malignancies of the gastrointestinal tract, with 4660 newly diagnosed cases and 660 deceases in the USA in 2006, and an increasing trend in the last years^[13]. In Italy the incidence of anal cancer in women and men is 2.1 per 100 000 and increases greatly in homosexual men (30 per 100 000) and HIV positive homosexual men (70 per 100 000). HPV-related oral disease are to be considered too, particularly in men, in whom a higher prevalence of oropharyngeal carcinoma has been reported. A study on 5 000 patients suffering from oropharyngeal cancer found that HPV-DNA was present in 36% of cancers of the oropharynx, 24% of cancers of the oral cavity and in 24% of cancers of the larynx; HPV 16 was the predominant type, with a prevalence of 82%^[14]. HPV-positive cancers have better prognosis than HPV-negative ones, because the cancer-related risk of death is lower in the former.

The presence of HPV-DNA in the seminal fluid led some

investigators to hypothesize a correlation between HPV infection and infertility, as HPV genetic material has been found in Sertoli cells, Leydig cells and deferent ducts^[10,11].

Taken into account such a wide spectrum of diseases caused by a single pathogenic agent, a careful consideration about the potential prevention of HPV infection in male subjects is compulsory. As now, the prevention vaccine is obtained using L1 and L2 capsid proteins as antigens, and its efficacy has been demonstrated in 25.000 immunized women, who showed a lower incidence or persistence of HPV infection at 4-year follow-up than controls receiving placebo. This vaccine is recombinant, tetravalent, and specific against HPV 6, 11, 16 and 18, in so that several Countries started with vaccination programmes for both sexes (Mexico, Australia). Vaccination limited to female individuals leaves men exposed to the risk of warts and neoplasia, also increasing the probability that sexually active women develop cancer with the male being a carrier of the infection.

In conclusion, the correlation between HPV and several genital diseases in women is obvious, and young, sexually active women are at higher risk; nevertheless, the prevalence of Papillomavirus infections in men is as much high. In men HPV is associated with different anatomical sites, causes different lesions such as warts and condylomata, and also plays a role in cancerogenesis. Given that HPV infection is frequently asymptomatic, often of uncertain diagnosis, and considered that man is not only a target but also a carrier of the pathogen, prophylactic vaccination^[15] (useless when HPV infection is already present) represents a fascinating perspective. In my opinion more resources should be destined to sensitize men, to intensify HPV screening and to acquire better comprehension of the disease: the hope is to identify the ideal diagnostic tool and to achieve better treatment results both in women and in men.

REFERENCES

- 1 Doorbar J. Papillomavirus life cycle organization and biomarker selection. *Dis Markers* 2007; **23**: 297-313
- 2 Sanclemente G, Herrera S, Tyring SK, Rady PL, Zuleta JJ, Correa LA, He Q, Wolff JC. Human papillomavirus (HPV) viral load and HPV type in the clinical outcome of HIV-positive patients treated with imiquimod for anogenital warts and anal intraepithelial neoplasia. *J Eur Acad Dermatol Venereol* 2007; **21**: 1054-1060
- 3 Partridge JM, Hughes JP, Feng Q, Winer RL, Weaver BA, Xi LF, Stern ME, Lee SK, O'Reilly SF, Hawes SE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. *J Infect Dis* 2007; **196**: 1128-1136
- 4 Nielson CM, Harris RB, Dunne EF, Abrahamsen M, Papenfuss MR, Flores R, Markowitz LE, Giuliano AR. Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis* 2007; **196**: 1137-1145
- 5 Bosch FX, de Sanjosé S. The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers* 2007; **23**: 213-227
- 6 Jenkins D. Histopathology and cytopathology of cervical cancer. *Dis Markers* 2007; **23**: 199-212
- 7 Sheu BC, Chang WC, Lin HH, Chow SN, Huang SC. Immune concept of human papillomaviruses and related antigens in local cancer milieu of human cervical neoplasia. *J Obstet Gynaecol Res* 2007; **33**: 103-113
- 8 Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ, van den Brule AJ. Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. *Sex Transm Infect* 2002; **78**: 215-218
- 9 Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, Oh JK,

- Kong HJ, Rha SH, Jung SI, Kim JI, Jung KY, van Doorn LJ, Quint W. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis* 2004; **190**: 468-476
- 10 Palefsky JM. HPV infection in men. *Dis Markers* 2007; **23**: 261-272
- 11 Giovannelli L, Migliore MC, Capra G, Caleca MP, Bellavia C, Perino A, Viviano E, Matranga D, Ammatuna P. Penile, urethral, and seminal sampling for diagnosis of human papillomavirus infection in men. *J Clin Microbiol* 2007; **45**: 248-251
- 12 Abramowitz L, Benabderrahmane D, Ravaud P, Walker F, Rioux C, Jestin C, Bouvet E, Soulé JC, Lepout C, Duval X. Anal squamous intraepithelial lesions and condyloma in HIV-infected heterosexual men, homosexual men and women: prevalence and associated factors. *AIDS* 2007; **21**: 1457-1465
- 13 Uronis HE, Bendell JC. Anal cancer: an overview. *Oncologist* 2007; **12**: 524-534
- 14 Shah KV, Westra WH. Genital HPVs in the aerodigestive tract: etiologic association with a subset of oropharyngeal/ tonsillar cancers and with recurrent respiratory papillomatosis. *Dis Markers* 2007; **23**: 235-245
- 15 Stanley M. Prophylactic HPV vaccines: prospects for eliminating ano-genital cancer. *Br J Cancer* 2007; **96**: 1320-1323
- Peer reviewer:** Philip H. Gordon, Professor Surgery and Oncology, McGill University and Jewish General Hospital, 3755 Côte St Catherine Road, Montreal Quebec H3T 1E2, Canada.