REVIEW

HPV related diseases in males: a heavy vaccine-preventable burden

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Key words

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Summary

Human Papillomavirus (HPV) has a significant impact in male's health, as cause of clinical manifestations ranging from genital warts to several cancers of the anogenital and aero-digestive tract. HPV types which most frequently affect men are 6,11,16 and 18, included in the HPV quadrivalent vaccine, recently approved for use in males by Food and Drug Administration (FDA) and European Medicines Agency (EMA). Although several data about the safety and efficacy of quadrivalent vaccine are available, the implementation of proper immunization plans dedicate to male's population cannot ignore the knowledge of the characteristics of the disease in men, which in some aspects should be clarify, in particular clearance of type-specific HPV infections and transmission dynamics. Purpose of this review is to summarise the main information about the burden and the natural history of the HPV related disease in males.

Introduction

The human papillomavirus also known as HPV is a ubiquitous virus causative agent of proliferative lesions of the skin and mucous membranes and represents one of the most frequent sexually transmitted infection in both men and women [1].
The demonstration of a causal link between some high-risk HPV sub-types and cervical cancer has focused the attention of scientific community on HPV infections in female leading to the development of highly effective prophylactic HPV vaccines [2-4].
The earlier studies on HPV in males were conducted on Man having sex with Man (MSM) and HIV+ to determine cancer risk associated to HPV infections [5, 6], subsequently the interest has shifted on HPV infections in heterosexual males, especially to clarify their role in the transmission of infection to woman [7, 8].
Several studies demonstrated the significant impact of HPV in males as cause of important disease ranging from genital warts to several cancers of anogenital and aerodigestive tracts [9].
The International Agency for Research on Cancer (IARC) in 2009 revised the carcinogenic role of HPV in human pathology reporting an association with penile and anal cancers and with cancers of oral cavity, oropharynx, larynx and esophagus [10].
Based on data derived from several studies of vaccine efficacy conducted on males, in 2009 Food and Drug Administration (FDA) licensed the use of the HPV quadrivalent vaccine for the prevention of genital warts in males aged 9-26 years and in 2010 the use of quadrivalent vaccine was also extended for the prevention of anal cancer and associated precancerous lesions for males and females aged 9-26 years [11, 12].
The use of quadrivalent vaccine against HPV has been extended for the prevention of genital warts in males 9 to 26 years also by the European Commission, which endorsed the opinion of the Committee for Medicine Products for Human Use (CHMP) European Medicines Agency (EMA) [13].
Despite the availability of the HPV vaccine for use in males, only few countries in the world have developed vaccine programs dedicated to this susceptible population, due to the lack of knowledge of some aspects of the natural history of the disease in men, in particular, the duration and the clearance of type-specific HPV infections together with transmission dynamics.
The explanation of such data is essentials for the implementation of extended screening programs and for the definition of appropriate vaccination plans directed to male's population.
The aim of this review is to summarize the latest knowledge about HPV epidemiology in males, which can provide a starting point for the implementation of cost effective preventive strategies.

Human papillomavirus

HPV, currently classified within papillomavirus family, is a naked icosahedral virus with a diameter varying between 45 and 55 nm containing a double-stranded circular DNA genome of 8000 bp [14].

HPV genome includes 8 "early genes" E1-E8, which encodes for proteins facilitating viral replication and stimulating cell proliferations, 2 " late genes" L1 and L2, encoding for structural proteins and an upstream regulatory region (URR) or long control region (LCR) including sequences for the control of transcription and the origin site for DNA replication.
Based on DNA sequence homology of the E6, E7 and L1 open reading frames (ORFs) more than 100 HPV types were identified, of which approximately 40 types are known to infect the genital epithelia.
Genital HPV types depending on their oncogenic propensity were classified at "low" risk, which usually give rise to a productive infection in permissive cells remaining episomial, and at "high/intermediate" risk, which in non-permissive cells integrates into genome inducing transformation.
A regulatory pathway involving E2, E6 and E7 genes has been shown to be at the origin of carcinogenesis.
In particular, the integration of HPV carcinogenetic type into cellular genome, lead to the inactivation of E2 viral protein which usually inhibits E6 and E7 genes expression [15-17].
E6 and E7 early genes play a key role in carcinogenesis acting as oncogenes by binding and deactivating p53 and p150rb tumor suppressor proteins respectively [18].
A set of about 40 types were frequently associated with sexually transmitted infections and with pathogenesis of the ano-genital tract cancer, among them HPV types 6, 11, 40, 42, 43, 44, 53, 54, 61, 68, 70, 72, 81, frequently associated to genital warts and low-grade squamous intraepithelial cervix lesions, are classified as low-risk, conversely, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and 82 are referred to as high-risk and are related with malignant lesions of cervix, vulva, penis and anus [19].

Natural history of HPV infection in males

Little is known about HPV infection in men especially in terms of duration and transmission dynamics although such information are essential for the adoption of appropriate preventive interventions and are the subject of several investigations.
The first studies about HPV disease in males focused on small groups of men, especially homosexuals and HIV positive who were not representative of the general population. Therefore, data derived from such works have been of little use to the understanding of the natural history of the disease in male population.
Recently, the focus of research has shifted to heterosexual men, being heterosexual transmission the major route of spread of infection and the males seems to exert a key role acting as an asymptomatic reservoir of HPV [20].
Data derived from a cross-sectional study of HPV infection conducted in 463 men from 2003 to 2006 reported an overall prevalence of HPV infection of 65.4% with penile shaft, gland penis/coronal sulcus and scrotum sites presenting the highest positivity for HPV DNA among asymptomatic heterosexual men [21].
Results from a cohort study of HPV infections conducted on 240 heterosexually active male university student ages 18-20 years in United States showed a prevalence of any genital HPV type of 25.8% and a cumulative incidence of new infection of any genital HPV type of 62.4% (95% confidence interval [CI], 52.6%-72.2%). Cumulative incidence of high-risk HPV types was 47.9% (95% [CI], 38.6%–58.0%) [22].
The large continuous prospective HPV in Men study (HIM) whose aim was to study natural history of HPV disease in males aged 18-70 years in three countries (Brazil, Mexico and United States) reported an incidence of new genital HPV infection of 38,4/1000 months person for any HPV type. Concerning the incidence of HPV oncogenic type was estimated to be 22.2 / 1000 (95% [CI], 19.8%-24.9%) month's person, with types 16,51,52 and 59 showing the highest incidences.
The median time to clearance of HPV infection was 7.52 months for any HPV type, with the longest clearance observed in males aged 18-30 years, and 12.19 months for HPV oncogenic type 16, whose clearance was not age dependent. Moreover, clearance of oncogenic HPV types in males appeared inversely related to the number of lifetime female partners and has shown to be more rapid with increasing age. In this study also emerged a decreased clearance of oncogenic HPV types infection in men in Brazil and Mexico compared with the United States [23].
A recent study highlighted that prevalence of HPV in men varies according to different geographical areas and by race with the lowest prevalence among Asian/Pacific islanders (42.2%) compared to Blacks (66.2%) and Whites (71.5%). Further studies will be necessary to clarify the low prevalence of HPV in Asian populations, it has been suggested that sexual behavior and race-specific differences such as variations in the genes involved in immunomodulation can explain these data [24].
Giuliano et al. examined data about the incidence and clearance of HPV infection emerged from two studies conducted on women of 18-35 years and males 18-44 years, respectively. The comparison revealed similar period prevalences for any HPV infection (52.8% in men and 53.8% in women), and similar HPV incidence rates (29.4 per 1000 person-months in both men and women). Moreover males also showed a similar probability of acquiring infection with oncogenic and non-oncogenic types against a significantly higher probability of acquiring oncogenic types in females. The clearance of the infection was similar in males for all HPV types, while in females the clearance of oncogenic types was slowe [25].
About the transmission dynamics several studies of heterosexual partners have been performed to understand the role that partners may have in the spread of HPV infection.
Burchell et al. demonstrated a 64% concordance for at least one HPV type among partners of recently formed heterosexual couples [26].

The same authors in a more recent study have examined 179 newly formed heterosexual couples experiencing a transmission male-to-female rate of 3.5 per 100 person-months (95% [CI], 2.7-4.5) versus a female-to-male rate of 4.0 per 100 person-months (95% [CI], 3.0-5.5). Moreover, no change in the transmission rate across HPV genotypes and no changes in the rate in dependence on the lifetime number of partners reported by the initially uninfected partner were observed [27].
Nytray et al in examining 88 heterosexual couples demonstrated a 59% type-specific positive concordance and that the latter was associated with an increasing difference in partners' lifetime number of sex partners and inversely related to the increasing difference in age [28].
Several studies conducted on females partners of males with HPV lesions highlighted in these an increased risk of developing cervical carcinoma on the contrary, studies conducted on male partners of women suffering of cervical intraepithelial neoplasia (CIN I) showed HPV lesions detectable only in 50% of the cases, according to the hypothesis of a lesser receptivity to or a more effective clearance of HPV infection in men than in women [29, 30].
Martin-Ezquerra et al reported an overall 41% of HPV diagnosed infections among male partners of women with CIN II and III [31].
Recent evidence suggested that HPV infection in males, also with high-risk serotypes, is not always associated with the development of cervical lesions in female's sexual partners [30].
Centers for Disease Control and Prevention (CDCs) recommend the screening of male's sexual partners of women suffering from HPV infection in order to highlight and possibly treat any exophytic lesion [32] even if the treatment does not appear related to a reduction in the risks of development of precancerous cervical lesions.
Although sexual contact represents the major route of transmission, HPV can be transferred on genital organs indirectly due to its ubiquity and environmental resistance. In particular, skin contact would be the main route of indirect transmission (90% of cases); also transfer of infection by inanimate objects was demonstrated between sexual partners [33].

Clinical manifestation associated with HPV infections in males

HPV replicates in differentiated squamous epithelial cells of the skin and mucous membranes causing proliferative lesions ranging from asymptomatic infections to malignant lesions.
The healthy carrier state is the more common conditions for males so that several studies have focused on their role in the transmission of oncogenic HPV types to women [20].
The most frequent HPV clinical manifestations in males are condylomata acuminata (genital warts), wart-like lesions of oropharyngeal tract and less commonly cancers of the penis, anus and oral cavity cancer.

Genital warts

Genital warts, one of the most frequently diagnosed sexually transmitted infections, are benign genital lesions with symptoms such as local pain and bleeding without serious consequence, but frequently associated with psychosocial distress and significant medical costs [34-36].
HPV lesions are very infectious with a transmission rate of > 60% within sexual partnerships from an infected to a susceptible sexual partner. Most of genital warts develop 2-3 months after infection, with an incubation period ranging from 2-8 months [37].
Several studies reported a spontaneous regression rate up to 40% even if in some cases genital warts may recur [38-40].
The most common genotypes detected from condylomata acuminata are non-oncogenic 6 and 11 HPV types with a frequency of 70–100% of exophytic genital wart tissue containing one of these types, while one-third of lesions have multiple HPV types including co-infection with oncogenic types [41, 42].
It has been estimated that about 1% of sexually active men in the United States have genital warts at any one time with an incidence peak of 5.01 per 1000 person-years in the age group 25-29 years. [34, 43]
In Europe, data from two recent studies reported an incidence of genital warts in males ranging from 147.95 per 100,000 men-years in Germany (95% [CI], 144.48 to 151.48) to 168 per 100,000 men years in United Kingdom [44, 45].
Based on these studies Hartwig et al. estimated an expected number of new genital warts cases ranging from 335.301 to 380.961 [46].
Recent data about the trend in genital warts infections in UK based on Genitourinary Medicine (GUM) clinics attendances during the period 2006-2010 show a marked increase of diagnosed cases from 148.5 per 100,000 to 160.5 per 100,000 [47].
A study conducted to determine the incidence of genital warts before and after the introduction in female population of the quadrivalent human papillomavirus vaccine in Sweden, reported 1137 cases/100,000 among males aged > 24 years during 2006-2007; a further increase in incidence of genital warts among males together with a decrease in females was observed between 2008 and 2010 (Tab. I) [48].
The Italian Sentinel Surveillance of sexually transmitted infections (STIs) reported that between 1991 and 2007, the genital warts were the most common diagnosed sexually transmitted diseases with 73% of cases in males and a prevalence peak in the age group 14-25 years [49].
It has been assessed that in Italy, 89% of genital warts were diagnosed from heterosexual patients while 10,1% were from homosexual/bisexual. Among males, an association between number of sex partners (> 2) and concomitant STDs was demonstrated in 50% and 17.1% of genital warts cases, respectively. Moreover 6.9% of males presenting genital warts were also HIV+ [49].

Tab. I. Studies reporting incidence of HPV-related non-malignant diseases in different populations.

Country, year, Author	Disease	Population	Design	Incidence (95%CI)
United States, 2000 Insinga, 2003[34]	Genital Warts	Privately insured populations	Retrospective (medical records)	5.01/ 1000 man-years
Germany, 2006 Kraut 2010 [44]	Genital Warts	General population (10-79 years)	Retrospective cohort	147.95/100,000 man-years (144.48-151.48)
United Kingdom, 2009 Desai, 2011[45]	Genital Warts	General practice + GUM clinic attendees	Retrospective cohort	166/100,000 man-years
United Kingdom, 2006-2011 HPA, 2012[47]	Genital Warts	GUM clinic attendees	Survey	148.5/100,000 man-years (2006) 160.5/100,000 man-years (2011)
Sweden, 2006-2007 Leval, 2012 [48]	Genital Warts	General populations (10-44 years)	Retrospective (medical records)	1137/100,000 man-years
United States, 1993-1994 Derkay, 1995[51]	Recurrent Respiratory Papillomatosis	Children and Adults both sexes	Survey	4.3/100,000 children-years 1.8/100,000 adults-years
Denmark, 1965-1984 Denmark, 1974-1999 Hartwig, 2012[46]	Recurrent Respiratory Papillomatosis	Children and Adults both sexes	Review	0,35-0,38/100,000 person-years

Recurrent respiratory papillomatosis

Recurrent Respiratory Papillomatosis (RRP) is a rare and highly morbid pathological condition caused by HPV types 6 and 11 and characterized by the recurrent appearance of warts like lesions in the respiratory tract, particularly at the larynx and vocal cords [50].

The disease is particularly severe among children who require frequent surgeries to remove recurrent obstructive lesions.

RRP is most commonly diagnosed among children without distinction between genders while it is rarely diagnosed in adults in which affects more males between ages 20 and 30 years [51].

Data from a national survey of practicing otorynolaryngologists in the United States in 1993-1994 provided an incidence of 4.3 per 100,000 in children and of 1.8 per 100,000 in adults [51].

Data derived from two European studies reported an RRP incidence of 0.35-0.38 per 100,000 person-years with a sex ratio for juvenile onset of 1:1; a different distribution of the disease were observed in adults, with a higher frequency in males (Tab. I) [46].

About transmission dynamics several studies demonstrated a vertical HPV transmission from mother to child during birth, while RRP cases among adults may develop as the results of oro-genital sexually transmitted HPV infections [52].

Anal cancer

The incidence of anal cancer is increasing worldwide in men and women with 99.000 new cases estimated in 2002, 40% of cases in men and 60% in women [53].

HPV infections are well known as the main cause of squamous cell carcinoma of the anus (anal SCC) and has been identified in more than 80% of anal canal cancer cases with HPV 16 and 18 oncogenic types responsible of 87% and 9% of intraepithelial lesions, respectively. HPV DNA detection in anal intraepithelial neoplasia (AIN) correlates with their cytological and histological severity: 75% in AIN 1 (mild), 86% in AIN 2 (moderate), and 94% in AIN 3 (severe) [54].

In Europe anal cancer cases among men generally first occurs in the age group 30-35 years, with an estimated value of 1821 new yearly-diagnosed cases due to HPV of which 1699 were attributable to HPV 16 and 18 types (Tab. II) [46].

A twofold increase in the anal cancer incidence was reported in United States after the advent of the HIV period during which was reached an estimated value of 35 per 100 000 among MSM (Tab. II) [5, 20].

Relative risk of developing anal cancer was highest among HIV infected man and among man who were HIV infected through homosexual contact with reported values of 37.9% (95% CI = 33.0-43.4) and 59.5% (95% CI = 51.5-68.4) respectively; consequently the majority of studies on prevalence of anal HPV infection has focused on these susceptible populations [55].

In a study about the incidence and the risk factors of anal cancer between 1992 and 2004 based on the French Hospital Database on HIV, Piketty et al reported that the majority of cases occurred among males (94%) of which 75% was homosexual. Moreover the incidence of anal cancers was higher in the years 1999-2004 (40/100,000; 95% [CI], 32 to 47) after the introduction of the highly effective antiretroviral Highly Active Antiretroviral Therapy (HAART) therapy [56].

Data derived from a study conducted in United States on 4.506 HIV infected males showed a continuous increase

in cancer rates reaching a value of 128/100.000 (95% [CI], 16 to 1042.2) in 2006-2008. In particular, cancer risk was higher among the patients who had acquired infection by more than 15 years and HAART therapy length did not seem to confer protection against anal cancer (Tab. II) [57].
This observation was confirmed in a recent work conducted to evaluate the trends in the incidence of anal cancers between HIV infected patients receiving long-term combined antiretroviral treatment (cART) between 1992 and 2008. In this study, standardized incidence ratios (SIRs) of anal cancer in HIV-infected patients proved to be high among MSM 109.8 (95% [CI], 84.6 to 140.3) and others HIV infected males 49.2 (95% [CI], 33.2 to 70.3) and no differences were observed between pre and post cART periods, consequently combined antiretroviral treatment appears to have no preventive effect on anal cancer [58].
Although little is known about immunomodulation mechanisms versus HPV infections, it is reasonable that immunosuppressive state could favor HPV infection at the early stage of transformation of precancerous lesions while the subsequent progression of the persistent lesions to invasive cancer could be induced by genetic mutations accumulated over time. The increased life expectancy of HIV infected patients favored by combined antiretroviral treatment may extend time to progression of lesions to cancer.
Specimens from anal cancers in MSM are almost always HPV DNA positive; suggesting that epithelial site of infection and frequency of exposure are factors that may affect the risk of infection [59].
It was postulated that the increased risk of developing anal cancer in MSM could be attributed to the presence of a HPV, susceptible transformation zone similar to that of the cervix [60].
Recent studies focused on HPV infections in traditionally non-high-risk groups, i.e. heterosexual men and HIV negative subjects, reported that anal and perianal HPV infections are very common.
Nyitray et al in a cross-sectional study conducted in United States to assess the prevalence of and risk factors for anal HPV infection in asymptomatic heterosexual men stated an overall prevalence of anal HPV infection of 24.8% in 222 men among which 33.3% had an oncogenic high-risk HPV type [61].
Data derived from the recent HIM study conducted on men residing in Brazil, Mexico, and the United States reported that the prevalence of anal canal HPV was 12,2% and 47,2% in both HIV negative heterosexual and homosexual men respectively [62].
The lifetime number of sexual partners is the main risk factor associated with anal HPV infections as emerged in both the cited studies.
Other reported risk factors for anal cancer common in men and women are history of genital warts, anal intercourse, and cigarette smoking [63].
Of particular interest are the findings from a study about the persistence and clearance of anal infection with HPV oncogenic types among men, showing a 6 month anal persistence of HPV 16 in 5.1% of MSM while no persistence was observed in heterosexual men [64].
The more rapid clearance of infection may partially explain the lower incidence of anal cancer than that of cervical, whereas the persistence of lesions could lead to neoplastic transformation and to the development of invasive cancer.

Penile cancer

Penile cancer is a rare disease accounts for less than 0,5% of cancer cases among males worldwide with an estimated incidence of less than 1/100.000 in developed countries [65].
The age-adjusted incidence rates for penile cancer in the United States during 2004-2008 was about 1.3 per 100.000 among Hispanic men compared to 0.7 per 100.000 in non-Hispanic men; [66] these data confirm the trend observed in Latin American countries (Brazil, Peru, Colombia), where penile cancer incidence is higher and amounts to 1.5-3.7 per 100,000 inhabitants. Incidence of penile cancer is highest in developing countries with a rate of 2,8/100.000 in Uganda and of 1,7/100.000 in Thailand and India (Tab. II) [10].
On the contrary, incidence is particularly low in the Jewish population that commonly practice neonatal circumcision with an estimated rate of 0,04/100.000 [10,66].
In Europe penile cancer tends to increase by age, reaching a peak in the seventh decade of life. Each year were diagnosed 3178 penile cancer cases (95% [CI], 2,623 to 3,751), the half of which, considering an overall HPV prevalence of 46,7%, could be attributed to HPV [46].
Data from the Italian Association of Cancer Registries reported a standardized rate of penile cancer of 1 per 100,000 during the year 2007 (Tab. II) [67].
Detection of HPV DNA in penile cancer has ranged from 40% to 50%, with HPV 16, 18 and 33 identified as the most common types [68].
HPV DNA positivity varies by histological subtype and is higher in basaloid and warty types with an estimated frequency of 80%-100%, while is low (30-60%) in squamous cell carcinoma, which is the most common type of penile cancer accounting for 90% to 95% of cases [69, 70].
Interestingly, incidence of penile cancer remains much lower than that of the cervix; a possible explanation could be the lower susceptibility of the penile tissue to HPV oncogenic types [59].
Among the risk factors associated with penile cancer may be cited: history of anogenital warts, number of multiple female sexual partners, lack of neonatal circumcision, phimosis, early age of first intercourse, cigarette smoking [71, 72].

Head and neck cancers

HPV related head and neck cancers include squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx.

It was estimated that in 2002 405.000 new cases of head and neck cancers occurred worldwide, with a high frequency in South and Central Asia [73].
The expected annual HPV associated oropharyngeal cancer cases based on United States cancer registry data amounted to 9.356 among males [74].
The estimated number of new HPV related head and neck cancers cases among men in Europe accounted to 14,098 (95% [CI], 11,455 to 17,077), including cancers of the oral cavity, oropharyngeal cancers and laryngeal cancers [46].
The Italian Association of Cancer Registries reported an age-adjusted incidence rates in males of 2,5 per 100,000, 1,3 per 100,000 and 2,6 per 100,000 for oropharyngeal, hypo-pharyngeal and oral cancers from all causes respectively, in 2007 (Tab. II) [67].
Although the main risk factors for head and neck squamous cell carcinomas (HNSCCs) are represented by

Tab. II. Studies reporting incidence, prevalence and expected number of cases of HPV related cancers in different populations.

Country, year, Author	Cancer type	Population	Incidence (95%CI)	Prevalence of HPV by cancer site (%) (95%CI)	Expected number of new cases, irrespective of HPV status (bounds)	Expected number of new cases attributable to HPV (bounds)
World WHO, 2012 [53]	Anal	Worldwide populations (both sexes)	ND	ND	99,000 /year	ND
Germany Varnai, 2006 [54]	Anal	Samples from 87 patients with diagnosed AIN (both sexes)	ND	80.9	ND	ND
Europe Hartwig, 2012[46]	Anal	European Populations (males)	ND	84.2 (81.5-86.9)	ND	1,821/year (1,403-2,277)
United States Chin-Hong, 2004 [5]	Anal	MSM	35/100,000 man-years	ND	ND	ND
France Piketty, 2008 [56]	Anal	HIV infected patients (both sexes)	40/100,000 person-years (32-47)	ND	ND	ND
United States Crum-Cianflone, 2010 [57]	Anal	HIV infected patients (both sexes)	128/100.000 man-years (16-1042.2)	ND	ND	ND
United States CDC, 2012 [66]	Penile	General populations	0.7-1.3/100.000	ND	ND	ND
Latin American countries IARC, 2007 [10]	Penile	General populations	1.5-3.7/100,000	ND	ND	ND
Uganda IARC, 2007[10]	Penile	General populations	2.8/100,000	ND	ND	ND
Europe Hartwig, 2012[46]	Penile	General populations	ND	46.7	3178/year (2,623-3,751)	1484/year (1,102-1,925)
Italy AIRTUM, 2007 [67]	Penile	General populations	1/100,000	ND	ND	ND
World Parkin, 2002 [73]	Head and Neck	General populations (both sexes)	ND	ND	405,000/year	ND
United States CDC, 2012 [74]	Head and Neck	General populations males	ND	ND	9,356/year	ND
Europe Hartwig, 2012 [46]	Oral cavity, oropharynx larynx	General populations males	ND	ND	ND	14,098/year (11,455-17,077)
Italy AIRTUM, 2007 [67]	oropharynx hypo-pharynx oral cavity	General populations males	2.5-1.3-2.6/100,000 man-years	ND	ND	ND
World Kreimer, 2005 [77]	Head and Neck	5,046 HNSCC cancer specimens (both sexes)	ND	25,9 (24.7-27.2)	ND	ND

tobacco smoking and alcohol consumption the role of HPV is important with up to 60% of biopsies positive for HPV DNA [75, 76].
Data from a systematic review reported an overall HPV DNA prevalence of 25,9% (95% [CI], 24.7-27.2) among HNSCCs biopsies collected worldwide, with a prevalence peak of 35,6% (95% [CI], 32.6-38.7) in oropharyngeal cancer. HPV 16 was identified in the larger majority of HPV-positive oropharyngeal SCCs (86.7%, 95% [CI], 82.6-90.1) and remains the predominant type (Tab. II). [77]
D'Souza G. et al. in a case-control study demonstrated a significant association between oropharyngeal cancer and oral HPV type 16 infections (odds ratio 14.6%; 95% [CI], 6.3 to 36.6) both revealing a relationship between oral HPV infection and oral intercourse [78].

HPV and male fertility

Some studies have shown how HPV DNA is present in sperm cells both in infected and healthy individuals and although no direct relationship between HPV infection and male fertility has been demonstrated, preliminary data indicate that the presence of HPV can affect sperm function.
In particular it has been shown that HPV can bind to sperm cells surface reducing their motility revealing a possible cause of infertility [79].
A study by Foresta et al conducted to evaluate a possible association between HPV sperm infection and reduction of sperm cell function in infertile patients showed a significantly higher percentage of HPV infection on sperm of infertile patients [80].
Recent evidence on animal models suggested that HPV infected spermatozoa are able to penetrate the oocyte transferring the viral DNA within it acting as vectors for HPV transfer.
HPV genome within the oocyte is activated and transcribed and may interfere with embryo development reducing its ability to survive [81].
A prospective study performed on 199 infertile couples undergoing assisted reproductive technologies (ARTs) showed a highly statistically significant correlation between pregnancy loss rate (66,7%) and positive HPV DNA testing in the male partner. In the light of these findings HPV could be a causal factor both of infertility in man and of ARTs failure [82].

Vaccination

Currently, two HPV vaccines are available: a bivalent vaccine (Cervarix) targeted the oncogenic HPV16 and HPV18 types, recommended for the prevention of cervical cancer in women aged 10-25 years, and a quadrivalent vaccine (Gardasil) directed against the HPV types 6,11,16 and 18, recommended for the prevention of precancerous lesions of cervix, vulva and vagina and of genital warts in women aged 10-45 years and in men aged 9-15 years [83, 84].
Many data are currently available regarding the efficacy of quadrivalent vaccine, the only HPV vaccine approved for use in men, in the prevention of genital and anal lesions among males population.
Giuliano et al. in a double-blind, randomized, placebo-controlled trial evaluated the efficacy of the quadrivalent vaccine (Gardasil) in young men (4065 subjects) between 16 and 26 years of age. The results at a median follow-up of 2.9 years showed an effectiveness of 84% in preventing external genital lesions caused by all HPV types (warts, penile intraepithelial neoplasia, perianal and perineal neoplasia) caused by all HPV types. Vaccine efficacy was 90% against genital lesions related to the types 6,11,16 and 18 included in the vaccine [85].
Palefsky et al. in a double-blind trial conducted on 602 healthy homosexual men aged 16-26 years have evaluated the efficacy of the quadrivalent vaccine for prevention of anal intraepithelial neoplasia. Data from this study demonstrated a high reduction of anal precancerous lesions in the per protocol population (HPV negative subjects from 1 day to 7 month after the first vaccine administration receiving three doses of vaccine) with an efficacy up to 90% against anal intraepithelial neoplasia (AIN and AIN2+) lesions which are direct precursor of anal cancer [86].
A recent cohort study conducted on 202 MSM patients with a history of previously treated high-grade anal intraepithelial neoplasia (HGAIN) showed a significant HGAIN recurrence reduction among patients vaccinated with HPV quadrivalent vaccine. These data suggest the possible use of the vaccine as an effective post-treatment adjuvant form of therapy in MSM patients with previous diagnosis of HGAIN [87].

Discussion

The HPV infection in males are associated with a significant epidemiologic burden causing disease ranging from non-malignant conditions to malignant disease such as anal, penile and head and neck cancers. HPV related disease in males also have an important economic impact, as demonstrated by a recent study conducted in Italy which shows that the economic burden attributable to HPV 6,11,16 and 18 related disease in males, amount to 38.8 % of the total direct costs of HPV related diseases [88].
Based on epidemiological consideration and on data about HPV vaccine efficacy in male population, FDA and EMA approved the extension of HPV vaccination to boys and men.
Some mathematical models highlighted how the extension of HPV vaccination coverage to males could reflect positively in terms of herd immunity, although suggest that the predicted efficacy of the vaccine strategies depends on the characteristics of the infection in males that remain unclear in some aspects [89].

The herd immunity effects elicited by quadrivalent HPV vaccine between sexual partners has been demonstrated in a study conducted in Australia; in this analysis a decrease of genital wart diagnosed cases among heterosexual men was observed after the introduction of the HPV vaccination program targeting women [90].
Certain economic models concludeed that vaccination of males could be cost effective only in presence of a low vaccination coverage rate among females [91, 92].
These models were supported by the consideration that reaching vaccination coverage up to 50% in women the herd immunity effect could protect heterosexual men, disregarding MSM populations in which HPV infection and associated diseases incidence were significantly higher.
The introduction of the vaccine in MSM could exert a more positive benefit in terms of reduction in the number of anal cancer cases that represent in this population an important cause of health care assistance request with an incidence equivalent to that of cervical cancer in women and even higher in HIV infected MSM.
On the other hand, vaccination of MSM, representing a small portion of the males population could be cost effective but not ethically justified.
Moreover, in many developed countries, it has been observed an upward trend in the burden of HPV-related diseases, especially anal cancer and oropharyngeal squamous cell carcinomas in all men regardless of sexual orientation. In the light of these data, ethical considerations and reasons of social fairness would advise against the choice of protecting males only through herd immunity, effect achievable only after decades.
Nevertheless, the implementation of vaccination programs in males is complicated by the reduced knowledge about several aspects of natural history of the disease with particular regard to the transmission dynamics between sexual partners, concordance data about which are often conflicting. Another point to clarify is the definition of the factors such as immunomodulation pathways and genetic background that could influence the different duration and clearance of the infection in males respect to females. Furthermore an important aspect to consider is the lack of a reference-screening test universally accepted for clinical diagnosis of HPV in males.
Several countries including the United States, Canada and Australia have introduced vaccination programs for boys and men since 2009. Currently, in United States CDC recommends HPV quadrivalent vaccine for all boys aged 11 or 12 years, and for males aged 13 through 21 years, who did not get any or all of the three recommended doses when they were younger. HPV quadrivalent vaccine is also recommended for gay and bisexual men and men with compromised immune systems (including HIV) through age 26.
Given the clinical implications as well as the high economic burden associated to HPV in males, implementation of HPV vaccination strategies dedicated to men requires depth assessment.

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■ **List of abbreviations and acronyms:**
HPV, human papillomavirus
MSM, Man having sex with Man
IARC, International Agency for Research on Cancer
FDA, Food and Drug Administration
CHMP, Committee for Medicine Products for Human Use
EMA, European Medicines Agency
ORFs, open reading frames
HIV, Human immunodeficiency virus
URR, upstream regulatory region
LCR, long control region
HIM, HPV in Men
CIN, cervical intraepithelial neoplasia
CDCs, Centers for Disease Control and Prevention
GUM, Genitourinary Medicine
STIs, sexually transmitted infections
STDs, sexually transmitted diseases
RRP, Recurrent Respiratory Papillomatosis
SCC, squamous cell carcinoma
AIN, anal intraepithelial neoplasia
HAART, Highly Active Antiretroviral Therapy
cART, combined antiretroviral treatment
SIRs, Standardized incidence ratios
HNSCCs, Head and neck squamous cell carcinomas
ARTs, assisted reproductive technologies
HGAIN, high-grade anal intraepithelial neoplasia

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