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Gender differences in the epidemiology and prevention of human papillomavirus (HPV) and HPV-related diseases

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Summary. Human papilloma virus infection is frequent in both sexes. It can be latent, subclinical or clinically apparent and can cause precancerous and cancerous lesions (HPV-related diseases) in cases of persistence. It has a particular tropism for the ano-genital area and for the epithelium of the head and neck, but it has been recently detected in other cutaneous and mucosal sites. HPV studies have mainly focused on women, due to the high spread of cervical cancer, especially in developing countries, and to the fact that the metaplastic cervical transformation zone is the ideal ground for virus replication. However, men are also infected, and scientific findings have clearly shown gender-specific disparities in human susceptibility to viral infection, in the incidence and the evolution of chronic viral diseases and in the prevalence of HPV-related cancers throughout the world. Many biological factors can affect the dimorphic host-virus relationship in both men and women, but cultural factors, lifestyles, social and relational behaviours create a variegated epidemiological tissue-specific profile, with some interesting sex-gender peculiarities. Much is yet to be discovered but the gender perspective should be a strategic goal for medical research, education and for social and health policies. It could lead to the formulation of more adequate prevention programmes, and the ability to treat patients fairly and appropriately with more targeted plans.

Key words: human papillomavirus, epidemiology, natural history, HPV-related diseases, gender differences, anti-HPV vaccine.

Differenze di genere nell'epidemiologia e nella prevenzione del papilloma virus umano (HPV) e nelle malattie HPV-correlate

Riassunto. L'infezione virale da papilloma virus umano è frequente in entrambi i sessi. Può essere latente, subclinica o clinicamente manifesta. Il virus ha un particolare tropismo per l'area genitale, anale e in alcuni epiteli dell'area testa-collo. Nelle stesse sedi, in diversa proporzione nei due sessi, determina lesioni pretumorali e tumorali (malattie HPV-correlate) in caso di persistenza di ceppi virali ad alto rischio. Studi recenti dimostrano la presenza di HPV anche in altri organi, ma al momento non esistono dimostrazioni conclusive sul nesso causale tra virus e carcinomi in queste sedi. Le evidenze epidemiologiche ed eziopatogenetiche derivano principalmente da studi su popolazione femminile, data la vasta diffusione del cancro della cervice, specialmente nei paesi in via di sviluppo, e per la zona di trasformazione della cervice uterina, sede di metaplasia, che ha permesso di mettere a punto i modelli di replicazione e cancerogenesi virale. Tuttavia l'infezione colpisce anche gli uomini. Differenze di genere sono documentate nella suscettibilità all'infezione virale, nell'incidenza, nella clearance, e, nei casi persistenti di HPV ad alto rischio, nella prevalenza dei tumori HPV-correlati relativi a ogni organo, e nelle varie aree del mondo. Fattori culturali, stili di vita, comportamenti sociali e relazionali rivestono un ruolo importante nella diversa esposizione e trasmissione dei virus tra uomini e donne. Inoltre peculiari fattori biologici dell'ospite (steroidi sessuali, tipo di risposta immunitaria, meccanismi molecolari genetici ed epigenetici) condizionano a livello molecolare l'infezione virale e le patologie HPV-correlate. Sono necessari ancora studi per comprendere tutti gli aspetti, ma la prospettiva di genere dovrebbe rappresentare un obiettivo nella ricerca clinica, nella formazione medica e nelle politiche socio-sanitarie anche per l'infezione HPV. Ne potrebbero derivare programmi preventivi più adeguati, e la capacità di curare le/i pazienti in modo ottimale e più appropriato, grazie a piani terapeutici mirati.

Parole chiave: papilloma virus umano, epidemiologia, storia naturale, malattie HPV-correlate, differenze di genere, vaccino anti-HPV.

Introduction

Human papilloma viruses (HPVs) are a heterogeneous group from the *Papillomaviridae* family, formed by a non-enveloped icosahedral capsid with circular double-stranded DNA (dsDNA), have a tropism for squamous epithelium and mucous tissues, mainly for the metaplastic transformation zone. More rarely, these viruses infect the glandular cells and probably epithelial stem cells[1].

About 40 types infect humans in the anogenital area and non-genital area.

About 90% of infections are transient, asymptomatic and can be cleared in a few months through the host immune response, especially in some types of viruses, like those not at risk of HPV.

In the host cell, DNA, mainly of the high-risk HPV subtypes, can persist in the episomal form and can reactivate many years later. This persistence is the expression of the altered balance between the viruses and host, in-

fluenced by the cellular microenvironment, the microbioma, the ability of HPV to evade the immune system[2].

All the stages concerning HPV infection and the dialogue between the host and virus are deeply influenced by biological sex and by gender, creating a variegate epidemiological tissue-specific profile, which is peculiar for men and women[3].

Carcinogenesis is the crucial point of HPV infection. Only few infected cases show the way toward cancer, but it is interesting to know in both sexes how it happens, which organs are affected, how often it occurs and how much a prevention is possible[4].

Epidemiology of the infection: gender differences

Genital infection

The incidence and the prevalence of genital infection are different in men and women, this means a differing behaviour of HPV between the two genders (Table 1). The epidemiological data in women are related to the cervical transformation zone, the "weak point" of women, an area with metaplasia and cellular replication, an ideal tissue for the virus lifecycle.

This infection is frequent in both sexes and about 50-80% of sexually active men and women will acquire a genital HPV infection in their lifetime[3-7].

However, studies on incidence have shown a different trend of acquisition and clearance of the infection in both sexes.

The acquisition pattern of HPV in women is inversely proportional to age. In men, the cumulative probability of infection increases progressively over the years, regardless of age and is overall higher than in women[8].

Unlike in women, HPV prevalence is steady across all ages, suggesting that men do not develop protection against reinfection[3].

Table 1. HPV prevalence in different areas: gender differences.

	Females	Males	Note
Genital	22-35%	20% (2-35%)	Acquisition: grater in the younger age in women. Progressive pattern in men independent of age. Clearance: faster clearance in males
Anal	30%	15%	60% in homosexual males
Oral	3.2-3.6%	10.1-11.5%	More frequent in homosexual males than in homosexual women HPV 16 six times more frequent in men

Viral clearance is high in both sexes, but seems faster in men with an average time of 7.5 months (one year for HPV 16), while in women 90% of clearance appears within two years[3-9].

A meta-analysis of 23 studies shows that uncircumcised men have slower rates of clearance than circumcised men. Moreover, viral transmission is higher from woman to man than the opposite: men are more often contaminated than infected[10-11].

Indeed, the rate of positivity in men seems to depend on the timing in which the sampling is done: some studies have shown that tests are already negative after a few days. This evidence shows the greater resistance of the penile epithelial cells compared to the cervical epithelium, thus explaining the shortness of the infection in men[5].

Data in the literature show that the prevalence of male infection is greater than female infection[8].

The overall prevalence of HPV infection is around 11-12% in women with normal cytology, with a peak in Sub-Saharan Africa (24%), Eastern Europe (21%), and Latin America (16%). This prevalence increases in women with cervical disease directly proportional to the severity of the lesion, reaching about 90% in women with cervical intra-epithelial neoplasia (CIN) grade 3 and almost 100% with invasive cervical cancer[3]. In women, the prevalence peak of infection occurs typically within the first decade, after the onset of sexual activity, between 15 and 25 years. On the contrary, prevalence decreases between 35 and 54 years, probably because of the development of specific acquired immunity against HPV or because of a different lifestyle during these ages. A second prevalence peak is evident in menopausal or perimenopausal women, but for all ethnic groups[12]. Three possible causes have been hypothesized: the reactivation of latent infections, the acquisition of new infections from new partners or a cohort effect due to recent changing sexual behaviour among women in this range of age[13].

In men, it is difficult to estimate HPV prevalence because studies are fewer and more recent than for women. There is a wide variability in the prevalence range (1.3% -72.9%, average 20%) in relation to different methods of sampling, to geographical area, to heterogeneity of the anatomical site in which the virus is searched (penile shaft, balanopreputial sulcus, glans, etc.), to number of sites considered in the study and also to difficulty in having a sample representative of the general population. Therefore, most data available for men belong to populations at risk, like homosexuals and immunosuppressed individuals[14].

The higher prevalence of HPV in men is associated with several factors: sexual activity at an early onset and its longer duration, sexual behaviours (a high number of sexual partners, whether female or male), smoking,

genital chlamydial infection, congenital or acquired immunodeficiency and absence of circumcision.

Male prevalence of the virus is higher in the penile shaft, and lower in the urethra and in sperm. The infection sites in females are chiefly in the cervix and in the vagina and less in the vulvar epithelium[15].

Also, the proportion of high-risk (HR) and low-risk (LR) HPV infections varies by sex: whereas in women it is equivalent, (HR 14-15%; LR 18%), the prevalence of HR HPV in men (30%) is lower than LR HPV (39%)[16].

Anal infection

The anal transformation zone helps viral replication, like the cervix. The prevalence of HPV is gender-specific too in the anus: is about 30% in women, 15% in heterosexual men and reaches 60% in homosexual men[5] (Table 1).

Several risk factors are linked to anal infection. Homosexuality, immunosuppression, oral-anal sexual practices, and sexual promiscuity are the most important risk factors in men; instead, in women, long-lasting smoking and auto-inoculation, as well as the excessive use of douches that could carry the virus outside of vagina seem to play a role[8].

Oral infection

Knowledge about the oral area is still incomplete because only recent studies have focused on it, looking for possible correlation with head-neck tumours.

As in genitals, oral HPV infection is strongly associated with sexual behaviour and its prevalence increases with the number of oral sex partners, but it is also associated with tobacco smoking and marijuana, in both sexes[17]. The mechanism of this association is unknown, but it is hypothesized that smoking, inducing an immunosuppressive and pro-inflammatory effect, increases the risk of incidence and persistence of HPV infection in the oropharynx.

The oral-genital pathway seems to be the most frequent factor, since the prevalence of oral HPV infection is higher in the group with a contemporary genital infection (19.3% vs 4.4% in men and 5.1% vs 2.1% in women); the infection can also be acquired through auto-inoculation with the fingers from the genital infection, or vice versa, in the same individual and maybe through saliva[17-18].

The prevalence of oral HPV infection is generally lower than the ano-genital one[19] (Table 1).

The absolute prevalence of HPV is two to three times higher in men than in women (10.1%-11.5% vs 3.2%-3.6%, respectively); the prevalence of HR HPV is 5 times more frequent in men (7.3% vs 1.4%) and HPV 16 is 6 times more frequent.

There are 2 peaks of prevalence (at 30-34 years and 60-64 years) in both sexes[15-18].

The prevalence of HR HPV is very low in both men and women who do not practice oral sex (<2.5%)[20].

Men with many oral sexual partners (>16 in life), homosexual and with contemporary genital infection (29.8%, 18.2% and 19.3% respectively) are more at risk[18].

This male predominance of oral HPV infection does not seem to be easily explained only by differences in sexual behaviour, suggesting gender differences during exposure to cofactors[17].

After genital infections, men develop a weaker immune response than women, thus men are less protected to the next oral infection, also with the same number of oral sexual partners.

Moreover, women with multiple vaginal sexual partners have less risk of oral infections than men, as if the immunity acquired at the vaginal level determines protection against oral infection. Yet, the male prevalence of oral infection is not high enough to justify population screening, due to its high cost/effectiveness ratio[18,20].

HPV-related diseases: gender differences

Papillomavirus causes mostly benign infections; sometimes, the persistence of the high-risk virus in the host cell activates a transforming mechanism that leads to HPV-related diseases, precancerous lesions and cancer.

Benign diseases

Viral infection may be latent, subclinical and clinically manifest (florid vulvar condylomatosis, respiratory papillomatosis).

Warts are one of the most frequent sexually transmitted diseases. HPV 6 and 11 are involved in >90% of condylomatous manifestations. Incubation varies from 3 weeks to 8 months and about 20-30% of the warts spontaneously regress. In women, the most frequent sites are in the lower genital tract (vulva, vagina and cervix), including perianal and perineal sites, while in men the penile, scrotal and perianal areas are the most affected.

Although surveillance data is difficult to obtain, an annual incidence of 0.1%-0.2% is estimated in industrialized countries, with a peak occurring in adolescents and young adults[3]. The prevalence appears to be similar between sexes, but the diagnoses are more frequent in women, probably because they participate in screening and go more often to the doctor for treatment[9,21].

Other HPV types infect skin surface. About 10% of children and 3.5% of adults, especially meat, poultry, and fish handlers, suffer from cutaneous warts.

Laryngeal papillomatosis is another form of clinical infection (prevalence of 1.8/100,000 adults) and is

caused by HPV 6 and 11. It is also present in children (about 4.3/100,000 births) in whom it often occurs between two and five years of age, after acquiring the infection during the passage in the birth canal from an infected mother. The virus induces the proliferation of benign squamous epithelium, most commonly around the larynx, but can also involve the trachea and lungs, and this can have profound functional consequences for breathing and speech[16].

Precancerous diseases and HPV-related cancers

At present, precancerous lesions and invasive tumours attributed to HPV are:

1. cervical intraepithelial squamous lesion (SIL) or cervical squamous dysplasia or cervical intraepithelial neoplasia (CIN), cervical adenocarcinoma in situ (AIS), vaginal SIL or vaginal intraepithelial neoplasia (VAIN), vulvar SIL or vulvar intraepithelial neoplasia (VIN), anal SIL or anal intraepithelial neoplasia (AIN), intraepithelial neoplasia of the penis (PeIN);
2. invasive cancer of the cervix, vagina, vulva, anus, and penis and tumours of the head and neck (tonsils, base of the tongue, other oropharynx sites and Waldeyer's tonsillar ring) are attributed to HPV, in varying proportions: 100% cervix, 88% anus, 78% vagina, 51% penis, 25-40% vulva, 15-69% oropharynx, and 4% oral and larynx[22].

Harald zur Hausen, almost forty years ago, first suggested the concept of viral oncogenesis, indicating the role of HPV infection in the development of squamous cell carcinoma of the uterine cervix. Thanks to this discovery, he won the Nobel Prize for Medicine in 2008[23].

In 1995, cervical cancer was the first cancer to be recognized by the World Health Organization (WHO) as totally due to a viral infection. In 2007, the WHO recognized that HPV 16 is responsible for several other types of cancers in both women (cervical, vaginal, vulvar, anal and oropharyngeal) and men (penile, anal and oropharyngeal)[8].

In 2011, the International Agency for Research on Cancer (IARC) published a classification of carcinogens in humans and recognised that there is sufficient evidence to link HPV with the following cancers: cervix (12 genotypes), vulva, vagina, anus and penis (genotype 16); moreover, the type 16 is also involved in cancers of the oral cavity, tonsils and pharynx[24]. Furthermore, in 2012 the IARC definitively divided the HPV genotypes into 4 groups, according to their risk of carcinogenesis[25]:

- group 1: high risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59);
- group 2A: probably at risk (HPV 68);
- group 2B: possibly at risk (HPV 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 87);
- group 3: non-carcinogenic (HPV 6, 11, 42, 43, 44, 54, 55).

The prevalence in the world of HPV-related tumours also shows gender differences.

Among HPV-related cancers, the female genital organs prevail; in fact, among men, HPV-related cancers are rare (1-6/100,000 in the general population). GLOBOCAN 2012 incidence data show 636,000 new HPV-related tumours: 570,000 in women and 66,000 in men[26] (Table 2).

The proportion of cases attributable to HPV varies in different geographical areas: the highest number of cancers in women compared to men is more evident in developing countries, reflecting the absence of cervical cancer secondary prevention in countries with scarce socio-economic resources (Figure 1). In developed countries the cases of female genital area tumours are decreasing due to screening at least, while penile carcinoma is a rare cancer with an increasing trend worldwide. The glans is the most affected site and HPV 16 causes 50% of HPV-related penile tumours[27]. In recent years, a causal relationship was discovered between HPV and non-genital carcinomas, especially anal and head-neck, and also gender differences were found, probably related to different behaviours and immune defences.

The incidence of anal cancer is increasing by 2% a year in the total population with a ratio of 1.5:1 for women compared to men: this increase is related to changing sexual habits and especially to the increase in anal intercourse[8]. This tumour correlates with the number of partners, the history of previous condyloma and the presence of sexually transmitted genital infections[29].

In particular, the incidence of cancer is up to 80 times higher among homosexual males and among HIV-positive individuals for both sexes (5-131/100,000). About 50% of homosexual men with anal cancer have a his-

Table 2. HPV related cancer prevalence in the world: gender differences (De Martel et al[26]).

	Females	Males
Total HPV related cancer	***570,000***	***66,000***
Cervix Vagina Vulva	530,000 12,000 8,500	–
Penis	–	13,000
Anus	18,000	17,000
Oropharynx	5,300	24,000
Oral	3,000	5,600
Larynx	860	6,400

tory of anogenital condylomas, whereas among heterosexual men and women only 20% have a history of warts[21]. The number of HPV-related anal cancer cases is similar in the two genders[8,30].

The epidemiology of head-neck tumours has changed in the last 40 years: the incidence of tumours associated with tobacco is decreasing, while the incidence and prevalence of HPV-related tumours is increasing. Most HPV-related cancers originate in the oropharynx, less in the larynx and oral cavity.

The incidence of oropharyngeal squamous cell carcinoma is increasing and for some years now has been correlated with an increase in oral exposure to HPV[31]. HPV is found in 45-90% of oropharyngeal tumours, more frequently in palatine tonsils and at the base of the tongue; the most frequent type of HPV is 16 (68-87% of cases). Positivity to HPV gives a better prognosis[28]. The correlation to HPV is similar for both genders (58% male-52% females), but men have a worse prognosis[31].

In the United States, since 2002 there has been a progressive increase in HPV-related oropharyngeal squamous tumours in men such that the incidence of this tumour (7.8/100,000) is now comparable with the incidence of cervical carcinoma (7.4/100,000). In 2030, the number of oropharyngeal tumours is expected to be three times higher than the number of cases of cervical cancer[28]. The increased incidence in men probably correlates with enhancing risk factors (smoking, alcohol, earliness of first-time intercourse and increase in the number of sexual partners). In women, the incidence of squamous oropharyngeal carcinoma is decreasing, like that of cervical cancer. Seroconversion rates after genital HPV infection are lower in men than women and that association between HPV infections at oral and genital sites might be contributing to this heterogeneity between sexes[18].

In Italy, 3,984 cases of HPV-related cancers (14.1% of all head and neck cancers) were diagnosed between 1988 and 2012 (81.6% in males). In men, incidence trends were stable over the observation period, because of increasing HPV infection rates, counterbalanced by the reduction in tobacco and alcohol consumption. Instead, in Italian women the annual incidence of squamous cell carcinomas, at potentially HPV-related sites, increased during the observation period, mainly in women over 60 years of age. This trend has been attributed to changing sexual behaviours following the sexual revolution of the 1960s, but, compared to other Western countries, in Italy the first signs of a more liberal attitude were noted in the 1970s[32].

The persistence of oral infection seems to be related to the role of tonsillar crypts as a reservoir in which the virus immersed in the tonsil biofilm escapes the immune response[33]. Currently, there are no adequate tests to identify those who are most at risk of HPV-related oropharyngeal carcinoma in the general population and oral HPV positivity cannot be used as screening test[34]. Moreover, when compared with cervical female cancer, precancerous lesions are not known in squamous oropharyngeal carcinoma and therefore real secondary prevention is not available.

Non-oropharyngeal head and neck squamous cell cancer are less related to HPV infection (2% oral cavity,

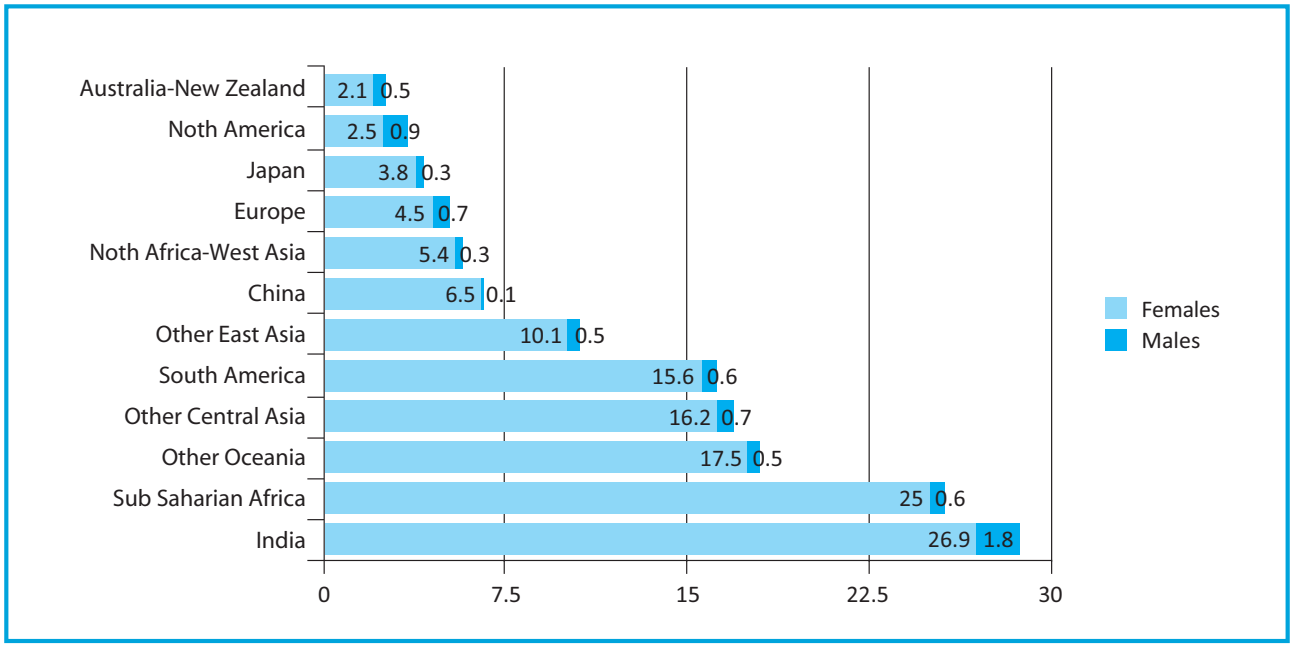

Figure 1. Proportion of total cancer cases attributable to HPV (population-attributable fractions %) in females and males by geographical region/country. Modified from Giuliano et al 2015[8].

5% nasopharynx, 10% larynx) and HPV status is not a prognostic factor[31]. The role of HPV in squamous laryngeal carcinomas remains controversial: the prevalence of related HPV is positive in 3.5% to 28% of cases; the range is so wide because of differences between geographical areas. HPV positive laryngeal tumours are prevalent in the supraglottis, in non-smokers and non-alcoholics, with a higher prevalence in women[35].

Recent studies are also reported finding a correlation of HPV with skin, lung, oesophagus, prostate, bladder and breast cancers. However, additional studies are necessary to clarify whether the association between these cancers and HPV is clinically relevant.

Human papillomavirus infection can cause cutaneous squamous cancer in rare genetically predisposed individuals (epidermodysplasia verruciformis) and verrucous carcinoma of the penis (Buschke-Lowenstein tumour). A 2015 meta-analysis found a positive overall association between HPV types 5, 8, 15, 17, 20, 24, 36, and 38 and cutaneous squamous cancer. However, HPV skin infections are common and the relationship between HPV and cutaneous squamous cell carcinoma in the general population is unclear[36].

For lung cancer, the increasing trend of carcinomas in non-smokers (15-20% in men and 50% in women) has driven the search for other causes beyond smoking. In the last 20 years, the ratio of females to males has increased rapidly from 1:3,3 to 1:2. A study has found that the carcinomas were positive for HPV 16-18 in 55% vs 27% of cases in healthy controls and were much more common in non-smoker women aged > 60 years[28]. Another recent study pointed out that about 80% of women infected with HPV and lung cancer have had a CIN, with the same type of HPV, hypothesizing the cervical origin of the virus. A systematic review has shown a significant association ($p < 0.001$) between HPV and squamous cell carcinoma, adenocarcinoma and small cell carcinoma, and not for other histological types[37]. HPV transmission at the pulmonary level could also occur by contiguity from the oral cavity or by inhalation[38].

For the oesophagus, there are data of association with HPV in 17% of the carcinomas and in 7% of the lymph nodes and there is 40% positivity for types 6, 11, 16, 18 and 30 (among which 27% HPV 16-18)[28].

The association between HPV infection and prostate cancer is also debated: there are no studies defining its type-specific prevalence. The prevalence of HPV is 17-18% in prostate cancer, lower than that found for cancer of the penis and anus; HPV is more frequent in high-grade tumours (Gleason score >7). The carcinogenic mechanism of HPV would start from inflammation with prostatitis which is associated with the development of cancer[39].

Condyloma acuminate has also been found in the bladder. HPV 16 is the predominant viral type in the urothelial epithelium and has been correlated with an increased risk of cancer. Most bladder tumours affect men, who also appear to have the highest infection rate[40].

Finally, there are inconclusive results on the association between HPV infection and breast carcinoma. HPV-DNA (types 33, 18, and16) was found in 22% of tissues of mammary tumours, with differences by geographical area (13% in Europe, 42% in Oceania and 32% in Asia). Positivity for HPV would increase the risk of breast cancer by 3-6 times[41].

Anti HPV-vaccine: gender differences

The vaccine is based on humoral immunity. The protective role of natural immunity is uncertain in the natural history of infection, because the detection methods of antibodies are not applicable on the market and are not standardized.

The presence of anti-HPV antibodies is a sign of a previous infection and is associated with a reduced risk of reinfection from the same virus, in particular for type 16. This suggests the possibility of protective immunity after natural infection.

However, the extent and duration of this protection is not known yet, and many women do not develop antibodies as a result of infection, making reinfection with the same genotype possible[2,6]. Therefore, the vaccine's action appears much more rapid and effective than natural immunity.

Types of vaccine

The era of prevention began with first-generation vaccines, bivalent (against HPV 16-18) and quadrivalent (against HPV 16-18 and 6-11), first introduced for females (9-26 years old) after studies of immunogenicity and efficacy for the prevention of carcinoma of the cervix, of genital warts and of persistent genital infections[42].

In 2014, the Food and Drug Administration (FDA) and in 2015 the European Committee for Medicinal Products for Human Use approved the nonavalent vaccine which induces antibodies against types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Initially, it was studied and indicated for the prevention of cervical, vaginal, vulvar and anal carcinomas and in the prevention of condylomas and preneoplastic lesions in females, between 9 and 26 years old, and for prevention condyloma (HPV 6-11), anal intraepithelial neoplasia (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) and anal cancer (HPV 16, 18, 31, 33, 45, 52, and 58) in males, between 9 and 26 years old[43].

The upper age limit has now been removed from the nonavalent package insert and in first generation vaccines.

It should be noted that the first-generation vaccines are being taken off the market in the US to be replaced by the nonavalent and the same phenomenon is also happening in Europe and Italy.

Evidence of efficacy

The substantial evidence of efficacy comes partly from real epidemiological data and partly from simulation models, mainly female-based.

A recent systematic review assessed that the efficacy showed until now by first-generation vaccines in randomized controlled trials with a follow-up of 1.3 to 8 years differs greatly based on the age of administration and initial HPV status of women[44] (Table 3).

Nonavalent vaccine efficacy is estimated at 99% in HPV 6, 11, 16 and 18 related diseases and 96.7% in diseases related to the other five viruses (31, 33, 45, 52, and 58)[45]. The added value of the nonavalent vaccine seems to be equal to +20% for prevention of cervical cancer, +30% for CIN2-3, +20% for CIN1 compared to first-generation vaccines[46].

The potential impact on tumours of the anus and of the oropharynx in both sexes has also been estimated to increase prevention by +8.5-10.4% and + 0.0-1.6% respectively, compared to first-generation vaccination[47].

Spread of vaccination

Since 2007 vaccines have been on the market and the expanded vaccination programmes were initially prepared for the female population only.

In 2008, the WHO recommended vaccination with three doses in girls between 9 and 13 years and from 2014 vaccination with two doses between 9 and 14 years.

Furthermore, it has been shown by real data that a strategy of recruitment to more extensive vaccination (e.g., women over 26 years and men) yielded a relative reduction in HPV prevalence of 49.4% and 55.6%, respectively, as compared to a more restrictive strategy (38.6% decrease in women)[48].

The extension to males has been the subject of discussion, because the cost-effectiveness studies were aimed so far at the prevention of female HPV-related genital diseases, but there are no studies focused on the prevention of other HPV-related male and female tumours. Since 2009, the FDA has approved the use of the quadrivalent vaccine for the prevention of warts in males between 9 and 26 years.

It has been calculated that male vaccination for cervical carcinoma prevention is cost-effective only if the rate of vaccinated women is less than 75%, otherwise the benefit for women is minimal while the costs increase greatly[49].

Male vaccination would find theoretical justification for eliminating the male reservoir of infection, for preventing diseases related to homosexuality if the treatment occurs in adolescence and to reduce the share of anal and oropharyngeal HPV tumours even if they are not very frequent[27].

Therefore, the vaccine is now recommended in girls, boys and adults too. The CDC currently ideally suggests vaccination in all people who have had contact with HPV (women with positive Pap tests, HPV positive tests, HPV-related lesions, condylomata, etc.) for the benefits to viral types not yet acquired, but not for therapeutic use: vaccines do not accelerate clearance or treat HPV infections already in place[50].

Vaccines have also been recommended for subgroups of at-risk populations such as men who have sex with men (MSM) and immunocompromised individuals (HIV, transplanted, etc.)[51].

In addition, a study showed that the effects of a vaccination programme are influenced by a population's age-specific sexual behaviour: traditional sexual behaviour (in which genders have different age-specific sexual activity rates and a wide gap in ages of sexual partners, such as India) and gender-similar sexual behaviour (in which genders have similar age-specific sexual activity rates and a narrow gap in ages of sexual partners, like the US, with rapid diffusion of the virus). Vaccination in cultures with traditional sexual behaviours has

Table 3. First generation vaccine efficacy on prevention of all CIN 2+ and CIN 2+ 16/18, at different age (Arbyn et al[44]).

HPV at the beginning	Age	Absolute risk				Quality of the evidence
		CIN2+ 16/18		CIN2+ all		
		Not vaccination	Vaccination	Not vaccination	Vaccination	
HPV negative	15-25	164/10,000	2/10,000	287/10,000	106/10,000	High
HPV 16/18 negative	15-25	113/10,000	6/10,000	231/10,000	95/10,000	High
	>25	43/10,000	14/10,000			Moderate
HPV positive or negative (all)	15-26	341/10,000	157/10,000	559/10,000	391/10,000	High
	25-45	145/10,000	107/10,000	343/10,000	356/10,000	Moderate

been more effective, even in the case of low coverage: these data encourage the rapid launch of vaccination programmes in low-medium growth populations worldwide, before the transition phase to new sexual behaviours[52].

In Italy, the 2017-2019 National Vaccination Plan aims to achieve coverage of up to 95% in both 12-year-old females and males. The administration in other ages is allowed in co-payment, with regional differences. It is also offered to the population at risk of MSM (men that have sex with men) while some regions offer free vaccination to HIV individuals[53].

It is estimated that 71 countries (80 including pilot projects) currently have implemented national vaccination programmes for females (37% of world nations). Unfortunately, only 1-4% of the girls are vaccinated in developing countries, where 85% of the cervical cancer is concentrated[43,54]. In the world, only 6% of countries have implemented programmes for the male population[49].

In summary, it will take at least another 20-30 years for HPV vaccines to demonstrate the true impact on cervical carcinoma. The challenge of the coming years is to focus on the possible benefits in the prevention of other HPV-related non-genital tumours in female and male[55].

Key messages

- HPV is very common, has a high clearance in both sexes, has a tropism for ano-genital and oral sites, as well as skin and mucosa, and has a latent, subclinical and clinical form.
- The persistence of high-risk virus infection may trigger the mechanism of transformation towards carcinogenesis in the host cell.
- Gender differences in the incidence and prevalence of the infection and in the frequency of HPV-related tumours suggest a different behaviour of HPV between the two sexes.
- Cultural factors, lifestyles, specificity of the target organs and biological factors peculiar to the host (sex steroids, immune responses, genetic and epigenetic molecular mechanisms) play an important role in the gender-specific epidemiology of HPV-related diseases.
- The gender perspective should be a strategic goal for researchers and medical education. Social and health policies should be committed to more adequate prevention and vaccination programmes and more targeted plans of treatment.

Conclusions

HPV infection and HPV-related diseases occur with gender differences. The conditioning factors of these differences are at various levels.

At the molecular and biological level, the inflammatory reaction to HPV is different between females and males with inhibition by oestrogen and activation by testosterone making viral clearance faster in men.

The genital organs are differently affected by HPV; in the woman, the cervix is most affected and the male genital area rarely.

Finally, the different behaviours have an effect on epidemiology, for example making some groups of men (homosexuals, HIV, smoking, alcohol abuse) at higher risk of tumours in sites like the oropharynx and anus. Socio-economic conditions influence the distribution of HPV-related diseases worldwide and also highlight gender differences.

A challenge for the future is to understand if the extension of vaccine can prevent all the HPV-related diseases in both sexes, but much more needs to be clarified at a biological, etiopathogenetic and epidemiological level.

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