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Epidemiology of Anogenital Human Papillomavirus Infections

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1. Introduction

Human papillomaviruses (HPVs) are infectious agents responsible for emergence of anogenital subclinical and clinical infections. HPV infections are the most common sexually transmitted infections worldwide. More than 100 HPV genotypes have been catalogued so far and from these, over 40 genotypes infect mucosa of anogenital tract and other mucosal areas. The epidemiology of anogenital HPV infections has been well described, especially cervical infections in young women and there are also many epidemiologic data among adults of different age and of different regions of the world. HPV is now recognized as a necessary cause for the apparition of cervical cancer in women, and is responsible for a substantial proportion of many other anogenital neoplasms (anal, vaginal, vulvar and penile cancers), and a non-negligible portion of head and neck cancers (oral cavity, pharynx, and larynx). HPV is also responsible for the development of benign lesions such as *condyloma acuminata* (genital warts). Clinical HPV infections are responsible for substantial morbidity and invoke high costs associated with the treatment of clinically relevant lesions. This chapter will review epidemiology of HPV infections affecting the anogenital tract of men and women.

2. Classification and carcinogenicity of HPVs

Papillomaviruses are from the *Papillomaviridae* family and all HPV genotypes share a common structure, L1 protein, that is highly conserved and consequently used for taxonomical purposes[1]. HPVs are classified into 16 genres (Alpha, Beta, etc.), which are also divided into species. Genus of *Papillomaviridae* share less than 60% nucleotide sequence identity in the L1 protein whereas species within a genus share between 60% and 70% nucleotide identity. A

new HPV isolate is recognized as a new genotype when the nucleotide sequence of the L1 gene differs by more than 10% from the genotype with which it has the greatest homology in DNA sequence. More than 100 HPV genotypes have been identified in humans from which over 40 genotypes infect mucosa of anogenital tract and other mucosal areas. As anogenital HPV infections is the interest of this chapter, focus is made on alpha-papillomavirus genus, which include mucosal HPVs (Table 1) [2].

Mucosal HPVs are also classified according to their oncogenic potential: low-oncogenic risk genotypes (LR-HPVs) and high-oncogenic risk genotypes (HR-HPVs). LR-HPVs may cause benign lesions of the anogenital mucosa such as *condylomata acuminata* (genital warts) while HR-HPVs are linked to the development of pre- and malignant lesions. The latest classification published by the World Health Organization's International Agency for Research on Cancer referred genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 as HR-HPVs[3, 4]. This classification also included many other genotypes as possibly carcinogenic, such as genotypes 26, 53, 66, 67, 68, 70, 73 and 82 (Table 2). These genotypes are referred as possibly carcinogenic because the evidence about their carcinogenicity are more limited. Oncogenic potential classification of HPVs is updated frequently with the occurrence of new epidemiologic evidence[5].

Classification of Human Alpha-Papillomavirus

Genus	Species	HPV Genotypes
Alpha-papillomavirus	Alpha-1	32, 42
	Alpha-2	3, 10, 28, 29, 78, 94
	Alpha-3	61, 72, 81, 83, 84, c62, c86, c87, c89
	Alpha-4	2, 27, 57
	Alpha-5	26, 51, 69, 82
	Alpha-6	30, 53, 56, 66
	Alpha-7	18, 39, 45, 59, 68, 70, c85
	Alpha-8	7, 40, 43, c91
	Alpha-9	16, 31, 33, 35, 52, 58, 67
	Alpha-10	6, 11, 13, 44, 55, 74
	Alpha-11	34, 73
	Alpha-12	RhPV1
	Alpha-13	54
	Alpha-14	c90
	Alpha-15	71

*Adapted from De Villiers et al., 2004 [1]

Table 1. Classification of species and genotypes of HPVs among the Alpha genus

Classification of Human Papillomavirus by carcinogenic potential

Oncogenic potential	Genotypes of HPV
High-oncogenic risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Possibly high-oncogenic risk	26, 53, 66, 67, 68, 70, 73, 82,
Low-oncogenic risk	6, 11, 13, 30, 32, 34, 42, 44, 54, 61, 62, 69, 71, 72, 74, 81, 83, 84, 85, 86, 87, 89, 90

*Adapted from Bouvard et al, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group 2009 [3]

Table 2. Classification of HPV genotypes based on carcinogenic potential

3. Routes of transmission

3.1. Primary route of transmission: Sexual contact with an infected partner

Epidemiologic data supports that the primary route of HPVs transmission is via sexual contacts. The most important risk factors for prevalent infection as well as for acquisition or incidence in adults, are related to sexual behaviour variables: age at sexual debut and number of sexual partners, new, recent or lifetime for example [5-7]. Transmission may occur through peno-vaginal intercourse, but also via other sexual practices. Anal intercourse is also associated with HPV infection. History of receptive anal sex has been identified as an important risk factor for anal HPV infection among men [8-12]. Oral sex is also a possible route of HPV transmission as it has been associated with HPV oral infection [13-15]. Furthermore, digital-genital transmission is possible, as genital HPV genotypes have been found on fingers[16]. Insertive sex toys are also a possible of route of transmission[17]. Studies on genital HPV infection between women who have sex with women also suggest that HPV transmission is possible among lesbian partners[18].

3.2. Non-sexual routes of transmission

HPV genital infections can also origin from non-sexual route of transmission. For example, HPV DNA can be detected in genital or oral tract of newborns and children through perinatal/vertical transmission [19-23]. Vertical transmission of HPV from mother to child (perinatal infection) was first reported in 1956 in a case of juvenile laryngeal papillomatosis[24]. Confirmation of the perinatal transmission of HPV in different mucosa (genital, oral) was subsequently supported by several studies although the route of transmission is not well understood[19-23, 25]. Direct maternal transmission during vaginal delivery or at caesarean section following early membrane rupture is possible as well as in utero through semen or ascending infection from mother's genital tract. Transplacental transmission seems possible since HPV DNA has been detected by PCR in amniotic fluid, placenta and cord blood [25, 26].

It is possible that transmission occurs through semen since it has been demonstrated that HPV DNA is found in sperm in a proportion of 8–64% of asymptomatic men[27]. Studies in vitro shown that HPVs may attach to sperm head, and that infected spermatozoids are able to penetrate oocyte and deliver HPV genome into it. Oocyte can actively transcribed HPV genes, for transmission to occur[28].

Other non-sexual skin contact transmission has been documented such as horizontal transmission via fingers, mouth and fomites[5, 17]. For example, it has been shown that HPV infected individuals may have HPVs in genital sample and in their hands showing that they can not only infect their sexual partners but also themselves somewhere else on their body (hands, conjunctive, etc.) as well as other individuals outside sexual contacts[16, 18].

4. Epidemiology of ANOGenital hpv infections

4.1. Anogenital HPV infections in women

4.1.1. Prevalence

Cervical HPV infections

According to a recent meta-analysis that included data from more than 1 million women with normal cytology in 59 countries, the prevalence of cervical HPV infection ranges from 1.6% to 41.9%, with a global prevalence estimated at 11.7% [29]. Sub-Saharan Africa (24.0%), Eastern Europe (21.4%), and Latin America (16.1%) showed the highest prevalences and the regions with the lowest prevalences are: Northern America with 4.7% and Western Asia with 1.7%. Also, it is important to consider that these percentages are probably underestimated as the laboratory methods used to detect HPV do not necessarily included the detection of all HPV genotypes[30]. The 5 most common genotypes worldwide are HPV-16, 18, 52, 31 and 58. Typically, HPV prevalence increases rapidly in adolescence following sexual debut, followed by an age-related decline, and occasionally a second but more modest peak in prevalence among older women in some regions of the world such as in America (Northern, Central and South) and in Europe[31]. Although the reason for this “menopausal” peak is not clear, it could plausibly be attributed to one or more non-mutually exclusive mechanisms, such as reactivation of latent infections acquired earlier in life due to a gradual loss of immunity, or to acquisition of new infections due to sexual contacts with new partners later in life (cohort effect)[5].

Anal HPV infections

Less research has been conducted to determine the prevalence of HPV in anal tract of women. A prevalence of 42% has been observed in healthy women [32] and by contrast to cervical prevalence that shows an age-related decline, the prevalence of anal infection seems relatively steady in all age groups[33]. Some studies also shown that women with cervical HPV infection had more than three fold increased risk of concurrent anal-cervical infection with a high correlation between the concordance of HPV genotypes, indicating a common source of infection[33]. As anal intercourse is not strongly associated with anal HPV infection in women,

other important route of transmission have been suggested such as no penetrative sexual contact (for example, involving the fingers or mouth of partner), non-sexual contact, or HPV shedding from the vagina to the anus given the close proximity of these two areas[33, 34].

Vaginal and vulvar HPV infections

It has been suggested that vaginal and vulvar HPV infections are also very common in healthy women although much less data is available for these site specific areas. Some studies have detected HPVs in cervicovaginal samples compare to cervical samples and showed positivity for HPV in cervicovaginal swabs are higher compared to cervical specimens suggesting a higher prevalence HPV in the vagina or vulva than in the cervix only[35]. For example, a prevalence of 42.5% has been observed among females in United States using self-collected cervicovaginal specimen[36].

4.1.2. Incidence

Cervical HPV infections

High rates of incidence of HPV cervical infection are observed especially in young women. Cumulative incidence of more than 40% after 3 years of follow-up has been demonstrated among university students [5, 6, 37]. The highest incidence rates of cervical HPV infection are observed in young women corresponding to age of sexual intercourse debut. Thereafter, incidence in women tends to decline with age, although second peaks are sometimes observed in older women (such as for prevalence data)[5]. For example, in a cohort of women between 13 and 65 years of age in Bogota in Colombia[37], the cumulative incidence of any HPV after five years of follow-up among women aged 15-19, 20-24, 25-29, 30-44 and more than 45 years were 42.5%, 36.9%, 30.0%, 21.9%, and 12.4%, respectively. The cumulative incidence after 5 years of follow-up in all age groups was 26.3% and infections rate with HR-HPVs were more frequent than infections with LR genotypes (5.0 cases and 2.0 cases/100 woman-years, respectively). Although some studies observed higher incidence of HR-HPV than LR-HPV, these comparisons depend on the assays used. More recent assays detect more types, many of which fall into the LR category.

Anal HPV infections

Cumulative incidence of anal HPV infection in a cohort of women of Hawaii (median age: 40 years old) has been evaluated at almost 70% in an average period of 1.3 years of follow-up. The rate of acquisition of anal HPV infection with any genotype was observed at 46.9 cases per 1000 woman-month. The incidence rate of anal HPV infections with HR-HPVs is also higher than with LR-HPV (such as for cervical infection) with estimates reported by Goodman et al (2008) at 19.5 and 8.2/1000 woman-months for an incident anal HR-HPV and LR-HPV, respectively[32]. Lower risk of acquisition of anal HR-HPV in women over 45 years of age have also been observed compared to women under 25 years of age.

Vaginal and vulvar HPV infections

To our knowledge, there are no estimates on the incidence of vagina and vulvar HPV infection in healthy women.

4.1.3. *Special population: HIV-positive women and sex workers*

HIV and HPV infection status has been under the projectors during the last years. In a systematic review of HIV-positive women with no cytological abnormalities, prevalence of HPV has been evaluated at 36.3% [38], higher than in worldwide estimated prevalence (11.7%)[29].

More attention was also paid to sex workers in the last years. For example, in a study made in China, prevalence of any HPV genotype was estimated at 38.9% in this population[39]. A recent study in Spain also demonstrated a higher incidence and a higher risk of persistence of HR-HPV infection in sex workers compared to the general population (incidence of 3.98 per 100 women-years relatively to 26.81 per 100 women-years)[40].

4.2. Anogenital HPV infections in men

4.2.1. *Prevalence*

Depending of the anatomic sites (coronal sulcus, glans, prepuce, shaft, urethra, scrotum, perianal area, anus, semen or urine) that is analysed, HPV prevalence (any genotypes) can vary from 1% to 84% among the general population of men and from 2% to 93% in high-risk men (such as STI clinic attendees, HIV-positive males, and male partners of women with HPV infection or abnormal cytology)[41]. For example, the site specific prevalences of HPV infection in male were estimated between 6.5%-50% in corona and/or glans, 5.6%-51.5% in penile shaft, 24%-50% in prepuce, 7.1%-46.2% in scrotum, and 8.7%-50% in urethra [27]. Contrarily to what is reported in women, HPV prevalence is relatively stable across age groups in men [41, 42]. Prevalence of anal HPV infection in men who have sex with women has been reported to range between 0% and 32.8% [27]. It is important to consider, however, that a high variability in the prevalence estimates may occurred in man due to the variability of sites tested or to the type of specimen used for which the detection method is not completely optimized (such as urine).

4.2.2. *Incidence*

Few studies have reported HPV infections incidence in men. Cumulative incidence calculated with penile and scrotal sampling, in a cohort of USA men aged between 18-44 years old (mean age: 29.7 years) was 29.3% after a follow-up of 12 months[42]. Incidence rate in this cohort for any HPV genotype infection was 29.4 per 1000 men-months. Incidence rates of HPV-6, 11, 16, and 18 infections were 2.8, 0.5, 4.8, and 0.8 per 1000 men-months, respectively.

4.2.3. *Special population: Men who have Sex with Men (MSM) and HIV-positive men*

HPV infection is strongly associated with the number of lifetime female sexual partners in men who have sex with women (MSW) and also with the number of male anal-sexual partners in men who have sex with men (MSM) [43]. For MSM, prevalence of any HPV genotype was estimated at 18.5% on the penis, 17.1% on the scrotum, 33.0% on the perineal/perianal region, 42.4% in the anal canal, and 48.0% at any site. The prevalence of HPV infection is high among young sexually active MSM, with the anal canal being the most common site of infection[44]. A study comparing the anal canal HPV prevalence in MSW (12.2%) to MSM (47.2%), confirmed

the higher prevalence in MSM[45]. Another example from a cohort of Italy have settled prevalence of anal HPV infection to 74.8% in MSM[8]. As for the general population of men, the incidence of HPV infection does not seem to drop with age in MSM as the prevalence remains high in all age groups[46].

Also, it appears that HIV status increases the risk of HPV infection in MSM. For example, a recent systematic review that compared HPV prevalence in MSM according to HIV status has shown that the anal canal prevalence was higher in HIV-positive individuals: (92.6% for HIV-positive compared to 63.9% for HIV negative men) [47]. HR-HPVs were detected in 73.5% of HIV-positive men whereas it was 37.2% in HIV-negative men. The prevalences of HPV-16 and 18 were also higher in HIV-positive men (35.4% compared to 12.5% for HPV-16 and 18.6% compared to 4.9% for HPV-18).

4.2.4. Circumcision and genital HPV infections

Circumcision has been described to reduce the risk of HPV infections in men. The most recent published meta-analysis shown an inverse association between circumcision and genital HPV prevalence in men with an estimated pooled odds ratio of 0.57 (95% confidence interval: 0.54-0.82)[48]. However, as not many studies have been published on the role of circumcision and HPV infection and as most of them are from observational design, more studies are needed to confirm the protective role of circumcision with HPV anogenital infections in men.

5. Natural history

5.1. Clearance and persistence of HPV infection

5.1.1. Clearance

Although high prevalence of HPV is found in both males and females, most of the HPV infections will be cleared spontaneously. Literature has consistently shown that at least 80 to 90% of cervical HPV infections are transient and are no longer detectable within 1-2 years[49]. HR-HPV infections seem to persist longer than LR-HPV[5]. For example, in cervical swabs of female university students, LR-HPV and HR-HPV infections typically last (in average) 13.4 and 16.3 months, respectively[50]. In a review paper, the median duration (time for 50% of infections to be cleared) of cervical infection reported from published studies ranged from 4 to 20 months, with a tendency for HPV-16 infections to last a little longer[5].

Clearance has also been studied in men. For example, a study on the clearance of HPV infections in penile and scrotum sampling in a cohort of USA men has shown that the median time to clearance of any HPV infection was 5.9 months and that 75% of HPV infections cleared by 12 months[42]. Contrarily to women, LR-HPV and HR-HPV infections durations were almost the same with a median duration of 5.8 months and 6 months respectively. Recent data from a cohort study regrouping men from Brazil, Mexico and USA also supports that median duration of HPV infection is shorter in men than in women with 7.5 months for any HPVs[43].

5.1.2. Persistence

Persistence with an HR-HPV over long periods is an important risk factor for the development and progression of cervical malignant lesion[51]. Approximately between 10% and 20% of women fail to clear HPV infections, resulting in long-term cervical persistent infection[52]. It is not known, however, why some women will develop cervical cancer following persistent infection whereas others do not. Finally, persistence of HPV is recognised as an important step in the etiologic pathway of cervical cancer but it has not been studied in other anogenital cancers in women (vulva, vagina, anal cancer) and in men (penile and anal cancer).

5.2. Multiple HPV infections and reinfection with same or different HPV genotype

5.2.1. Multiple HPV infections

Individuals infected with multiple HPV genotypes are also a very common finding of many epidemiologic studies. For example, among the cohort of Brazilian women, between 1.9% to 3.2% were co-infected with multiples genotypes at a same visit (concurrently infected) whereas when considering cumulatively (period prevalence) during the first year and the first 4 years of follow-up, 12.3% and 22.3% were infected with multiple genotypes, respectively[53]. Coinfection in men have also been studied. In a healthy mexican military cohort, HPV prevalence was 44.6% at one of these sites (urethra, urethral meatus, scrotum, penile, shaft or coronal sulcus) and 51.1% of them had mutiple HPV genotypes[54]. MSM have been studied and are also at high risk of coinfection. For example, Dona et al (2012) in an Italian cohort demonstrated that 65.3% of the HPV-positive MSM had multiple HPV infections[8].

Consequences of multiple HPV infections are still debated, but multiple infections with HR-HPV as well as infection with other agents, such as HIV, may play a critical role in furthering the progression to cervical intraepithelial neoplasia and cervical cancer in women[55]. Co-infection with multiple HPV genotypes is common in women with premalignant lesion but the prevalence of co-infections decreases with the severity of the lesion. It is well recognized that cervical cancer specimen do not frequently harboured multiple HPV genotypes[56]. Although multiple genotypes infection may increase the risk of pre-malignant lesions[53], it is possible that co-infection with multiple HPV genotypes acts as a biomarker of immune failure to clear HPV (which allow HPV-16 to progress more easily) rather than etiologic factors that act synergistically to cause cancer.

5.2.2. Reinfection with same or different HPV genotype

The risk of HPV reinfection with the same genotype is also well debated. What has been shown is that it is possible to see cervical reinfection with the same genotype[57]. However, the provenance of the virus is not well understood in re-infected women. Two hypotheses have been advanced to explain reinfection. The first is based on the assumption that infections acquired at a young age never completely clear but become latent; infections appearing later in life would mostly represent the reactivation of such latent infections acquired many years earlier. The second hypothesis is that infections do clear following an initial immune response,

which does not completely protect against future infections by the same HPV genotype, following new exposure via sexual activity later in life[58-60]. Recent studies have shown that reinfection with a same genotype is associated with new sexual partners suggesting that infection in adult women may result not only from reactivation of HPV infections acquired at a young age that never completely cleared, but also from new exposure via sexual activity[37, 57]. There is no available study concerning the probability of reinfection with a same or a different genotype in men.

6. HPV related anogenital diseases

6.1. Low-risk HPV genotypes are associated to non-cancerous anogenital lesions

Condylomata acuminata or genital warts (GWs) in anogenital area are usually caused by low-risk HPV genotypes. Recent studies have shown that about 100% of GWs are caused by either HPV-6 or 11 but that 20–50% of lesions also contain co-infections with HR-HPV genotypes. The majority of individuals who develop genital warts do so approximately 2–3 months after infection[61]. Approximately 30% of all warts will regress within the first four months of infection without any treatment, but recurrence will be seen in majority of cases, even if adequate treatments have been done[62]. Long-term remission rates remain largely unknown. GWs cause also significant psychological morbidity and substantial healthcare costs. Occasionally, GWs persist for long periods of time and, rarely, such long-standing lesions may progress to malignancy. GWs are highly infectious and contribute significantly to spread of HPV infections[63].

6.2. High-risk HPV genotypes are associated to cancerous anogenital lesions

The viruses cause approximately 15% of human cancers, and of this proportion, nearly half is attributable to HPVs with cervix, vulva, vagina, penis and anal cancers[64]. According to Centers for Disease Control and Prevention (CDC), it has now been accepted that HPV is a necessary cause of cervical cancer as virtually 100% of specimens presents HPV DNA. It is also now accepted that HPV is responsible for 50% of vulvar cancer, 65% of vaginal cancer 35% of penile cancers and 95% of anal cancers[65].

7. Economic and health care system burden of HPV infections

Clinical HPV infections are responsible for substantial morbidity and invoke high costs associated with the treatment of clinically relevant lesions[66]. Currently, two vaccines are available: a bivalent HPV 16/18 AS04-adjuvanted vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) and a quadrivalent HPV 6/11/16/18 aluminum-adjuvanted vaccine (Merck and Co., West Point, PA, USA). Both vaccines are designed to protect against the two more prevalent HPV genotypes, HPV-16 and 18, that are responsible together for about 70% of all cervical cancer cases worldwide. The quadrivalent vaccine also offers a protection against

HPV-6 and 11, which cause over 90% of genital warts. These vaccines are likely to have a major impact on the incidence and mortality of cervical cancer in the future as well on the burden of other HPV related diseases. Most of developed countries have national recommendations for the use of HPV vaccines in women and many have implemented publicly funded or co-payment routine vaccination programs[67]. These vaccination programs will have a significant impact on the direct and indirect costs related to HPV infections[68].

7.1. Example of economic burden of HPV-related cancers in U.S.A

Direct and indirect costs related to screening and treatment of HPV-related cancer is substantial. Direct costs include usually costs related to medical services such as appointments with physicians and/or gynaecologists, hospital (including inpatient services), nursing and home care and drug prescriptions and time lost for patients or caregivers. However, indirect costs might also be considered in the evaluation of the burden associated to HPV (loss of productivity, psychological, emotional burden on patient)[68].

A recent study in United States evaluated direct medical cost of the prevention and treatment of pathologies associated with HPV[69]. Most of the annual direct medical costs are attributed to cervical screening and follow-up are estimated at 6.6 billions of U.S. dollars: \$5.4 billion for cervical screening routine and \$1.2 billion for follow-up costs. Cervical cancer costs \$441 millions annually, vulvar and vaginal cancer costing for \$37 and \$12 millions respectively. Anal cancer and penile cancer treatment costs has been estimated at \$155 millions and \$7 millions of annual costs respectively.

7.2. Genital warts are also an important economic and health care burden

Direct and indirect costs related to genital warts are also important. Genital warts are known to be resistant to treatment and having high recurrence rates even if the appropriate treatment has been done[62]. This involves repeated physicians visits for treatment and high direct costs. The indirect costs include lower productivity for the patient due to illness as well as psychological and emotional burden such as anger, stress, anxiety, depression, shame, guilt and isolation which are also realities for patients [70, 71]. Chesson et al. evaluated at \$288 millions the direct medical costs related to genital warts in United States [69].

8. Conclusion

Anogenital HPV infections are very common and transmitted principally via sexual contacts. High prevalence has been found in both female and male adults. Even if the majority of anogenital infections will clear spontaneously, a small proportion of infection will progress and cause different anogenital cancers. HPV is a necessary cause of cervical cancer and plays a role in other anogenital cancers in men and women. Some subgroups such as MSM, sex workers and HIV individuals are particularly at risk of HPV infections. Clinical HPV infections are responsible for substantial morbidity and invoke high costs associated with the treatment of clinically relevant lesions. Prevention is always preferable to treatment and in this optic,

HPV vaccination, which is currently implanted all over the world, is expected to prevent a substantial proportion of cervical and other HPV-related cancers in the future.

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