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The Impact of Human Papillomavirus on Cancer Risk in Penile Cancer

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1. Introduction

Infection with human papillomavirus (HPV) is necessary for the development of the cervical cancer. Although, the relationship between HPV and cervical cancer is well documented and well established in the literature, the relationship between men and HPV-associated cancers is just emerging (Palefsky,2010).

The HPV has been shown to play a causative role in anal, head, neck, oral and penile carcinomas. The latter is a rare tumor accounting of a 1 per 100.000 incidence rate in Western countries, including Europe and North America, and representing less than 1% of all male cancers. On the contrary, the incidence in some emerging countries is much higher, reaching 18% to 20% of all male tumors (Salvioni et al., 2009). General socioeconomic factors and access to health-care systems might contribute to the discrepancies in this incidence.

The incidence rate increases with age, although the disease has also been reported in young men. Early diagnosis may be not only lifesaving but also essential to functionally and esthetically acceptable treatment. Many patients still seek medical attention at a late stage, when a conservative therapeutic approach is no longer feasible. Awareness of penile cancer and its prevention are at the heart of the recent controversies about circumcision and about the necessity to treat HPV infections (Micali et al., 2006).

There has been little progress in managing penile cancer during the past decade. The overall survival figures remain unchanged and its etiopathogenesis is still not fully understood (Chaturvedi, 2010; Dillner et al., 2000). Researchers have focused their investigation on a potential association between HPV infection and penile cancer development. However, this association is not absolute and other factors are implicated in the initiation and progression of the disease. The following chapter focuses on the natural history of penile cancer, addressing the probable mechanism by which HPV leads to malignant transformation of the penile epithelium, the relationship of genital HPV for risk penile cancer, and the preventive strategies to reduce HPV infection in men.

2. The role of human papillomavirus infection in etiology of penile cancer

Among men and women, cancers of the anogenital tract and their precursor lesions have been strongly linked to infection with sexually transmitted HPV (Wilkin & Chiasson, 2004). HPV causes virtually all cervical cancers and the virus is found in association with at least 90% of cervical carcinomas (de Sanjosé et al., 2007; Moscicki et al., 2006). The variability in HPV-attributable proportions for non cervical cancers arises partially from differences in HPV detection methods across studies as well as from true geographic differences in HPV distribution world-wide (Chaturvedi, 2010). Despite the reported variability, 90%–93% of anal cancers, 12%–63% of oropharyngeal cancers, 36%–46.9% of penile cancers, 40%–64% of vaginal cancers, and 40%–51% of vulvar cancers are potentially attributable to HPV infection (Caltellsagué et al., 2002; Chaturvedi 2010; Gillison, 2008; Giuliano et al., 2008; Giuliano et al., 2010; Miralles-Guri et al., 2009). See fig. 1 to identify average prevalence of HPV infection associated with anatomical cancer sites.

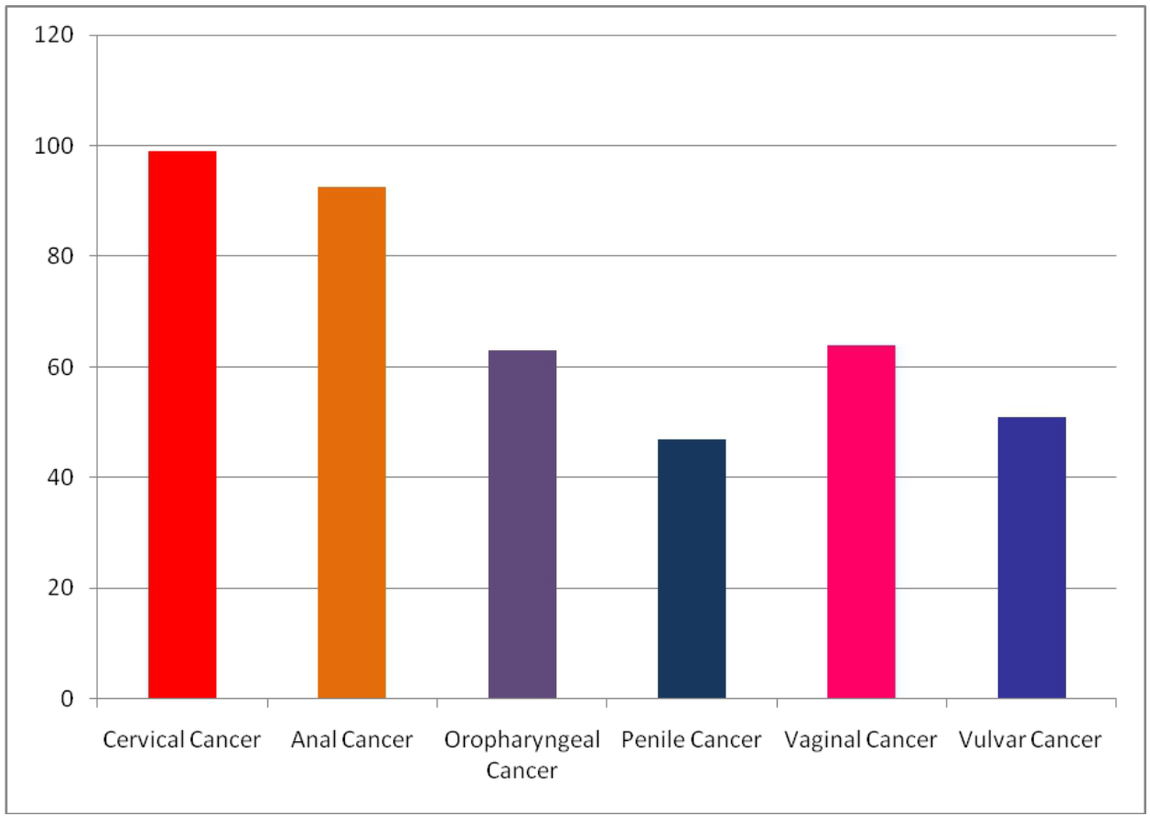


Fig. 1. HPV DNA prevalence among cases of cancer

Acquisition of HPV is very common, particularly among sexually active young adults, and incidence of infection with oncogenic HPV types appears to be higher than the incidence of infection with non-oncogenic types (Baseman & Koutskyl, 2005). Oncogenic HPV types 16 and 18 and history of other concurrent sexually transmitted diseases were found to be significantly associated with progression to cervical cancer (Cavalcanti et al., 2000). Carcinoma of the uterine cervix is the sixth most common cancer among women worldwide, with very high mortality rates in developing countries. It was observed more than 20 years

ago that some types of HPV were more frequent in malignant than in benign lesions, and infection with high-risk types of HPV is now considered the major risk factor for the development of cancer of the uterine cervix (Villa, 2006).

The advent of screening to identify and treat cervical cancer precursor lesions and cervical intraepithelial neoplasia (CIN) has led to a substantial reduction in the incidence of cervical cancer in those countries where routine screening is in place. Conversely, most cervical cancer-related mortality occurs in countries where there is no routine cervical screening. On the other hand, it is clear that HPV infection in men is a serious clinical issue (Palefsky, 2010). The role of men in HPV infection of women was investigated in early epidemiological studies using questionnaires that addressed the sexual behavior of the husbands or sexual partners of women with and without cervical cancer. More recent studies had, in addition, been able to detect the presence of HPV DNA in exfoliated cells from the penile shaft, the coronal sulcus, and the distal urethra (Bosch et al., 2006). Squamous Cell Cancers (SCC) of the penis have a low association with HPV, whereas warty/basaloid cancers are strongly associated with HPV. Depending on the proportion of samples that are squamous vs warty/basaloid in any given report, the proportion of penile cancers associated with HPV varies considerably (Palefsky, 2010).

HPV positivity is higher in penile intraepithelial neoplasias (PIN1/2/3) and in the basaloid histological type, ranging from 75 to 80% and decreasing to a range between 30 to 60% in invasive SCC. Cancers of the penis are largely SCC (IARC 2007; Rubin et al., 2001). Provide that identification of HPV implies a casual role of the virus with the carcinogenic process, the attributable fraction of penile cancer related to HPV could estimated to be 40%-50% of penile cancer and molecular studies have confirmed the role of the HPV 16 and 18 (Miralles-Guri, 2009). On the other hand, the majority of studies included at least one case of cancer with HPV 6 or 11, which in several studies were more common than HPV 18 (Levi et al., 1998; Miralles-Guri et al., 2009; Rubin et al., 2001). HPV 31 and 33 were detected only rarely (IARC 2007).

The epidemiologic association of HPV with penile cancer fulfills the criteria for causality: strength and consistency of the association, with increased risk of these cancers among HPV-infected individuals; specificity of the association; temporality of the association, with HPV infection preceding the development of cancer by several years; biologic gradient of increasing risk with increasing exposure to HPV infection; coherence, plausibility, and experimental evidence of oncogenic potential of HPVs; analogy of the association of HPV with increased risk of penile cancer; and experimental evidence through the necessity for consistent expression of HPV oncogenes for maintenance of the malignant phenotype (Chatuverti, 2010).

2.1 Epidemiology and natural history of penile cancer

Penile cancer prevalence varies according to geographic region, socioeconomic status and ethnic origin. Penile squamous cell carcinoma (SCC) is a relatively rare disease and accounts for less than 0.5% of all cancers in men worldwide (Backes et al., 2009). In Europe and United States penile cancer incidence rates vary from 0.1 to 1.5 per 100,000 men (Backes et al., 2009; Bigot, 2011; Curado et al., 2007; Reis et al., 2010a). In 2010, there were about 1,250 new cases of penile cancer in the United States, resulting in 310 deaths, with an incidence

rate of 0.3 to 1.8 per 100,000 men (Lawindy et al., 2011). The estimated lifetime direct medical cost for incident penile cancer was $ 4.4 million in 2003 and an estimated 240 associated deaths occurred in 2005 (Smith et al., 2010).

The wide variation of penile SCC prevalence is likely explained by the large variance in risk factors, in particular, the practice of neonatal circumcision (Minhas et al., 2010). The incidence is very low among Jewish populations that commonly practice neonatal circumcision (0.1 per 100,000) [Morris et al., 2011; Pow-Sang et al., 2010]. Typical SCC is the most frequent type of invasive penile cancer, representing about 95% of all cases (Hernandez et al., 2008; Pizzocaro et al., 2010). Penile cancer is much more common in African, Asian, and South American countries, constituting about 10% of the malignant diseases in those countries and thus posing a considerable public health concern (Lawindy et al., 2011). Penile SCC is a common male cancer with an incidence of 2–5 per 100,000 men, constituting up to 10–22% of all male cancers in some regions in Central and South America (Goiania, Brazil), Asia (Chiang Mai, Thailand) and Africa (Kyadondo, Uganda) than in other parts of the world (Parkin et al., 2003; Tornesello et al., 2008). Higher incidence rates are found in some countries such as Uganda (4.4/100,000) and Paraguay (4.2/100,00) [Lawindy et al., 2011; Pow-Sang & Astigueta, 2009].

Brazil has one of the highest rates of penile cancer in the world, 6-14 per 100,000 males per year, comprising 2-6% of all males malignancies with 7% of cases occurring in men aged under 35 y.o. and 39% in men older than 66 y.o. Among cases, 87% are uncircumcised. All tumors seen in men circumcised in childhood were of low grade, whereas 12% of those circumcised in adulthood had high-grade tumors (Favorito et al., 2008). At least in two Brazilian States (Maranhão and Pernambuco), penile cancer is reportedly the 2nd highest cause of carcinoma death in men, second only to lung cancer. At the main oncology hospital in Recife-Pernambuco, in the Northeast region of Brazil, on average one or two men each week need to undergo penile amputation due to cancer, with very poor prognosis (Morris et al.,2011).

Despite the large Brazilian migration from the Northeast to the Southeast, motived mainly by the population seeking for life opportunities in the most developed economic region in the country. Koifman (2011) reported that penile cancer was more prevalent in patients born in the state of Rio de Janeiro. According to the data from the Brazilian Ministry of Health, there is an estimated 850 partial or complete penile surgical procedures performed in the context of malignancy yearly within Brazil, with approximately 50% of these procedures being performed in the North and Northeast regions of the country (Favorito et al., 2008).

The presence of an intact foreskin has been identified as an important risk factor for developing penile cancer (Lawindy et al., 2011). Circumsicion protects against HPV infection, in a cohort study involving men in the USA, Mexico and Brazil, both low-risk and high-risk HPV types were less frequent in circumcised men (Giulliano et al., 2011). Male circumcision is the commonly performed surgical procedure in the world. The surgical technique is determined by social circumstances, together with the indication for the operation and the patient's age. There is no therapeutic male circumcision, which by definition does not treat an underlying pathological process. The motivations underling the procedure may be religious, cultural, social or prophylactic (Perera et al., 2010).

In most cases, the reason for circumcision is of religious or cultural origin. Both Jewish and Islamic laws promote male circumcision. Jewish male infants are circumcised on the eighth day, according to Biblical teaching, whereas among Muslims variations in the timing of circumcision do exist, with some communities delaying the procedure until the age of 10 years. Ritual circumcision is also performed in several African tribes as a ceremony of passage into adulthood (Micali et al., 2006).

Circumcision is the most common operation performed in males in the United States, where approximately 60% of male infants are routinely circumcised in the neonatal nursery, in most cases due to parental choice and nonreligious reasons. In Canada, approximately 48% of males are circumcised (Micali et al., 2006). In Australia the annual incidence of penile cancer was 0.8 per 100,000 men, which is similar to the US figure. As in the USA, over two-thirds of older men in Australia are circumcised. However, since the 1970s, Australia experienced a decline on the number of infant male circumcision. Thus, an increase on penile cancer has been expected in that population (Morris et al., 2011).

In most of Europe, in South and Central America, and in most Asian countries, including the People's Republic of China, Taiwan, Japan, and North Korea, male circumcision is uncommon. In a medical setting, postnatal circumcision is regarded as both a treatment for phimosis and a possible prophylactic measure for the prevention of penile cancer and other infectious or inflammatory conditions (Micali et al., 2006). In countries where circumcision is not practiced routinely, such as those in South America and parts of Africa, penile cancer can be ten times more common than in high-income countries, representing 10-22% of all male cancer (Morris et al., 2011).

The first suggestion linking circumcision and penile cancer was reported in 1932, when, among, 1.103 penile cancer cases in USA, none where Jewish despite 3% of the population being Jewish (Wolbarst, 1932). Circumcision as a measure to prevent penile cancer has been repeatedly related by different investigators. Maden et al. (1993) found that the risk of penile cancer was 3.2 times larger among men who had never been circumcised in comparison to men circumcised at birth and 3.0 times higher among men circumcised after the neonatal period. Schoen et al. (2000) reported that of 89 men with invasive penile cancer whose circumcision status was known, 2 (2.3%) had been circumcised as newborns and 87 had not been circumcised. The relative risk of invasive penile cancer for uncircumcised to circumcised men was 22:1. In a population-based case-control study in western Washington state carried by Daling et al. (2005), men who had not been circumcised in childhood had a 1.5 fold increased risk of developing penile cancer. Morris & Rose (2007) reported circumcision as a biomedical imperative for the 21st century, not only for the reduction of penile cancer, but also for a decrease in urinary tract infections, inflammatory dermatoses, and sexually transmitted diseases.

Studies have consistently reported neonatal or childhood circumcision to be associated with reduced risk of penile cancer, which geographically corresponds to reduced rates of penile SCC in populations that culturally practice neonatal circumcision (Maden et al., 1993; Micali et al., 2006; Morris et al., 2011; Perera et al., 2010; Tseng et al., 2001). The protective effect of childhood circumcision, but not of adulthood circumcision, seems to be attributable to the elimination of inflammatory conditions related to poor genital hygiene, such as phimosis and balanitis (Pizzacaro et al., 2009). On the other hand, the preventive effect of newborn

circumcision on SCC development is still unclear. It occurs only if circumcision is performed at birth or early in life, whereas late or adult circumcision seems to be ineffective in risk reduction.

Beyond lack of circumcision there are others factors related with penile cancer such as phimosis. A history of phimosis also imposes a significant risk for the development of penile cancer, which is. Approximately 25% - 60% of patients with penile cancer have phimosis (Lawindy et al., 2011). Precancerous lesions are found in an additional 15% to 20% of patients with phimosis (Pow Sang et al., 2002). Thus, phimosis is considered one of the strongest risk factors for penile cancer. The relative risk of penile cancer among men with phimosis was 64.6. The frequency of phimosis in men with penile carcinoma is high, ranging from 44% to 85%. Phimosis leads invariably to retention of the normally desquamated epidermal cells and urinary products (smegma) resulting in conditions of chronic irritation with or without bacterial inflammation of the prepuce and the glans. However, there is no supporting evidence of the role of smegma as a carcinogen. Therefore, much debate still exist regarding this risk factor, as smegma is not yet believed to contribute to the development of penile cancer (Lawindy et al., 2011).

In a meta-analysis reported by Larke et al. (2011), four studies evaluated the association between phimosis and penile cancer (OR range 4.9-37.2). The effect of childhood/adolescent circumcision on invasive penile cancer may be largely mediated through elimination of phimosis, since there was no evidence of an association of circumcision with invasive disease when analyses were restricted to individuals with no history of phimosis. Morris et al., (2011) related that 45-85% of men with penile cancer have a history of phimosis and causes dysplastic (pre-cancerous) changes in the skin of the preputial sac. The authors demonstrated 52% of penile cancer with a long foreskin had phimosis. These findings have led to conclusion that circumcision in early childhood by elimination phimosis may help prevent penile cancer. Thus, the phimosis is a stronger risk factor for invasive disease compared to *in situ* cancer which further supports the argument that circumcision acts through prevention of phimosis and that some *in situ* cancers develop through a different pathway to invasive cancer (Daling et al., 2005; Larke et al., 2011).

Poor genital hygiene in uncircumcised men, even in the absence of phimosis, may also lead to the retention of microorganisms and secretions, including smegma. Whether good standards of genital personal hygiene in uncircumcised males may provide the same level of protection of circumcision against penile SCC has been questioned. Although a lower incidence of penile SCC, even among uncircumcised individuals, is noted in countries and communities with a high standard of genital hygiene and widespread diffusion of private bathing facilities (Micali et al., 2006).

Smith et al. (2010) reported that flat penile lesions are much more frequent in uncircumcised men and associated with higher prevalence of HPV and higher viral loads. The authors suggest that circumcision reduces the prevalence of HPV associated flat lesions and may ultimately reduce male to female HPV transmission. The increased risk of HPV infection among uncircumcised men observed and has important implications regarding HPV associated malignancies in men and their female partners. However, despite some favorable medical evidence, the promotion of circumcision as a mean of controlling HPV and other sexually transmitted infections remains controversial (Hernandez et al., 2008; Van Howe, 2007).

HPV infection alone is insufficient to cause epithelial malignancy in men. Unlike cervical cancer, evidences suggest that HPV infection is not a necessary cause of penile cancer with HPV prevalence ranging between 15 and 71% among penile cancer tissues (Rubin et al., 2001). Daling et al., (2005) measured the percentage of HPV DNA-positive tumors in their study and concluded that there was a consistent association between HPV infection and the development of most penile cancers.

The role of circumcision in penile cancer prevention is unclear: it could possibly be ascribed to a lower baseline risk of disease due to a decrease in the amount of susceptible tissue, prevention of potential cofactors with HPV (such as phimosis) from promoting disease or another mechanism.

However, male circumcision has been widely debated as a preventive measure for sexually transmitted infection human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), urinary tract infection and penile cancer (Gray et al., 2010; Perera et al., 2010). Individuals with HIV/AIDS are at increased risk of HPV-associated cancers. This increased risk among persons with HIV or AIDS is consistent with a high incidence and persistence of HPV infections (Chaturvedi et al., 2009). On the other hand, circumcision can be considered an important cofactor in the natural history of HPV infection, since it may influence the risks of the acquisition and transmission of HPV as well as of cervical cancer. Castellsague et al., (2002) has provided epidemiologic evidence that male circumcision is associated with a reduced risk of genital HPV infection in men and with a reduced risk of cervical cancer in women with high-risk sexual partners. Thus, male circumcision may potentially reduce exposure of female partners to HPV infection.

Early age at first sexual intercourse, high lifetime number of female sexual partners, smoking, and lack of condom use are identified risk factors for penile SCC (Maden et al., 1993; Reis et al., 2010a). Some studies have also identified chronic smoking as an associated risk factor for the development of penile cancer (Pow-Sang et al., 2010). Tseng et al. (2001) found that the incidence of penile cancer among men who had ever smoked cigarettes was 2.4 times that of men who had never smoked. Harish & Ravi (1995) found a significant association between smoking or chewing tobacco and the development of penile carcinoma. In 503 men and age-matched controls, a multivariate analysis demonstrated a significant association and dose-dependent relationship. Maden et al. (1993) found that the risk of penile cancer among men who smoked at diagnosis was 2.8 times that of men who had never smoked, and lifetime smoking of >45 pack-years of cigarettes elevated the risk to 3.2 times that of men who had never smoked.

The efficacy of latex condoms for reducing risk of contracting sexually acquired HPV infection is not well established, although some degree of protection is likely provided. *In vitro* studies demonstrated the impermeability of latex condoms to HPV during conditions simulating sexual intercourse. Thus, condom use could be effective in reducing HPV-associated outcomes such as genital warts, cervical, anal and penile cancers (Shew & Fortenberry, 2005).

The incidence of penile cancer is lower compared to that of cervical cancer (Curado et al., 2007), likely due to the lower susceptibility of the penis to the malignant transformation virus-induced as compared to the cervix. Additionally, penile cancer, like cervical cancer,

is caused by high-risk HPV, but penile cancer is 10 times less common than cervical cancer (Morris et al., 2007). In a large case series, HPV DNA was positive in invasive penile cancer in 40% to 50% of cases. Thus, many studies have shown a strong correlation of the presence of HPV types 16 and 18 with penile carcinoma (Daling et al., 2005; Gentile et al., 2006; Pascual et al., 2007; Senba et al., 2006; Tornesello et al., 2008; Villa & Lopes., 1986).

2.1.1 Human papillomavirus infection in men who have sex with men

HPV infection is considered to be a sexually transmitted disease, and the risk of HPV infection is increased by certain sexual behaviours (Sirera et al., 2006). HPV associated malignancies have been reported to occur in excess among patients with HIV or AIDS (Frisch et al.,2000). Co-infection with HIV and HPV has been investigated in studies due to the increased risks of warts and malignant neoplasias in the anal and genital tracts. Several studies conducted in men infected with HIV focus on the anal canal due to the high rates of HPV infection, anal intraepithelial neoplasia (AIN) and anal cancer. On the other hand, few studies have examined the penile region for HPV infections in men infected with HIV (Silva et al., 2011).

HPV infection is an independent risk factor for acquiring human immunodeficiency virus (HIV) infection and some forms of cancer. Men who have sex with men (MSM) may be difficult to identify in general practice because many of them do not self identify as homosexuals or bisexuals or are still having sex with women as they develop their sexual identity. The incidence of anal cancer among MSM is higher than cervical cancer rates among women. HPV has been definitively associated with more than 85% of all cancerous or precancerous anal lesions worldwide (Dietz & Nyberg, 2011).

The vast majority of HPV infections in immunocompetent individuals is transient, and the amount of persistent infections is rather low. This contrasts to immunosuppressed individuals, as patients with HIV infection exhibits high rates of persistent HPV infection. Consequently, these individuals have a high risk for HPV-associated malignant disease. Within the last decade, sufficient data were published to conclude that AIN and anal cancer continuously increase in HIV-positive MSM despite the use of highly active antiretroviral therapy. In contrast, only limited data are currently available on HPV-associated diseases at other anatomical sites of HIV-positive MSM, for example, oral cavity or penis (Kreuter &Wieland, 2009).

Giuliano et al. (2011) designed a cohort study to estimate the incidence and clearance of type-specific genital HPV in men and to assess associated factors. The incidence of a new genital HPV infection was 38.4 per 1000 person in 1159 men studied (95% CI 34.3–43.0). Oncogenic HPV infection was significantly associated with having a high number of lifetime female sexual partners (hazard ratio 2.40, 1.38–4.18, for at least 50 partners *vs* not more than one partner), and number of male partners who carried out anal intercourse (2.57, 1.46–4.49, for at least three male partners *vs* no recent partners). The median duration of HPV infection was 7.52 months (6.80–8.61) for any HPV and 12.19 months (7.16–18.17) for HPV 16. Clearance of oncogenic HPV infection decreased in men with a high number of lifetime female partners (0.49, 0.31–0.76, for at least 50 female partners *vs* not more than one partner), and in men in Brazil (0.71, 0.56–0.91) and Mexico (0.73, 0.57–0.94) compared with the USA.

Clearance of oncogenic HPV was more rapid with increasing age (1.02, 1.01–1.03). The results from that study provided much needed data about the incidence and clearance of HPV infection in men. These data are essential for the development of realistic cost-effectiveness models for male HPV vaccination internationally.

Current data on the spread of HPV infection to the different body parts implicated in sexual practices in both MSM and heterosexual men are limited. A cross-sectional study was carried out to evaluate the prevalence of HPV infection in the anus, mouth and penis in this specific population. The authors found the prevalence of penile HPV infection in HIV-positive men was 36% (95% CI, 26–48%), with a prevalence of 38% (95% CI, 25–53%) in MSM and 32% (95% CI, 14–55%) in heterosexual men, p= 0.43. (Sirera et al., 2006). The first study to address HPV DNA persistence and clearance in the genital area among men infected and non-infected with HIV. The authors observed that more men infected with HIV presented with multiple HPV types compared to the men seronegative to HIV. This finding may be attributed to the two groups' different immunodeficiency levels. Multiple infections with different types of HPV including high-risk HPVs are more frequent in men who are infected with HIV (Silva et al., 2011). However, there are few available studies on the persistence and elimination of HPV infection in men, such as HPV associated with penile carcinoma.

2.2 Mechanism of neoplastic transformation in cells

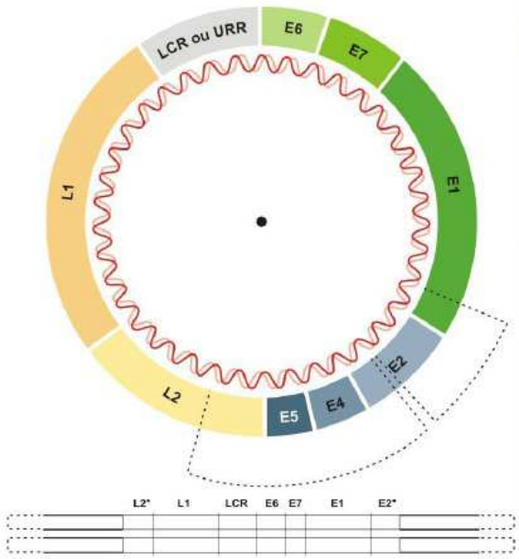
Papillomaviruses (PV) are small, non-enveloped, double-stranded DNA viruses that infect mucosal and cutaneous epithelia in a wide variety of higher vertebrates in a species-specific manner and induce cellular proliferation. PV isolates are traditionally described as ''types''. PV types have been detected in all carefully examined mammals and birds, with the possible exception of laboratory mice. In the only extensively studied host, humans, more than 100 human PV (HPV) types have been described based on the isolation of complete genomes, but independent studies indicate that many more exist, with a yet larger number presumed to exist based on the detection of subgenomic amplicons (Bernard et al., 2010, de Villiers et al., 2004). From the HPV types identified, approximately half of them infect the genital tract (Bosch et al., 2008). Many of these HPV types have been shown to be ubiquitous and globally distributed (de Villiers et al., 2004).

HPV are small DNA viruses that infect epithelial tissues. Whether cutaneous or mucosal, the more than 100 types of HPV described have in common a circular DNA genome of about 8.000 base pairs. A double-stranded circular DNA genome encodes approximately eight open-reading frames (ORFs). These small genomes are organized into an early, a late, and a long control region. The products of 3 genes from the early control region, genes *E6, E5* and *E7*, are essential in the HPV-induced processes of cellular transformation and immortalization (Moddy & Laimins, 2010), and 2 genes from the late control region, genes *L1* and *L2*, encode the viral capsid proteins (Villa, 2006). The figure 1 shows the general organization of the HPV genome (Ghittoni et al., 2010; Villa, 2006).

The process by which HPV facilitates tumor initiation and fosters tumor progression is an exceptional model to understand the development of many human cancers and also allows identification of additional signaling pathways targeted in malignant progression (Moddy & Laimins, 2010). An explanation for this is that the expression of viral genes *E6* and *E7* is

increased in cells with integrated high risk HPV genome, and these genes products, the oncoproteins E6 and E7, respectively bind and inactivate cell tumor suppressor proteins p53 and pRb (Ghittoni et al., 2010).

The association between HPV and human cancer was first proposed more than three decades ago by Harald zur Hausen (2002). Subsequently, his group isolated several mucosal HPV types from cervical lesions, including the high-risk HPV16 (Bosch et al., 2008). Additionally, several studies have demonstrated the direct role of HPV infection in the development of several human cancers (Bosch et al., 2008; Caltellsagué et al., 2002; Gillison et al., 2008; Giuliano et al., 2008; Giuliano et al., 2010). HPV 16 and HPV 18 are the most frequently found HPV types in cervical cancers worldwide (Bosch et al., 2008; Munoz et al., 2003).



Function of viral proteins
E1: viral replication
E2: viral replication and transcription
E4: destabilization of cytokeratin network
E5: mediates mitogenic signal of growth factors
E6: major oncoprotein
E7: major oncoprotein
L1: major viral coat protein
L2: minor viral coat protein

Fig. 1. The genome of the HPV. The diagram indicates the ORFs of the early (E) and Late (L) genes, and the long control region (LCR). Functional of viral proteins.

For this reason, the majority of the biological studies were focused on these two HPV types (Moddy & Laimins, 2010; Villa, 2006). High-risk HPVs are also associated with many vulvar, anal, and penile carcinomas and contribute to oral cancer (Parkin & Bray, 2006). On the other hand, carcinomas from different anatomical sites, in contrast to cervical cancer, appear to be preferentially associated with HPV 16 (Chaturvedi, 2010; Gillison, 2008; Miralles-Guri et al., 2009). For instance, in the subset of penile cancer attributed to HPV infection, HPV 16 was found in 60,23% of cases (Miralles-Guri et al., 2009).

HPV-associated cancers are intimately linked to HPV persistence and the accumulation of chromosomal rearrangements in the infected tissue (Moody & Laimins, 2010). Studies suggest an association between HPV infection and penile cancer. The mechanism by which HPV leads to malignant transformation is likely mediated through two viral genes *E6* and *E7*, which are actively transcribed in HPV infected cells (Pow-Sang & Astigueta, 2009). The products of the early genes, *E6* and *E7*, of the high-risk HPV types play a key role in both events. Indeed, these proteins have developed a number of strategies to evade host immune

surveillance allowing viral persistence, and to alter cell cycle and apoptosis control, facilitating the accumulation of DNA damage and mutations. Often, the oncoproteins target the same cellular pathways with different mechanisms, showing a strong synergism in promoting cellular transformation and neutralizing the immune response (Ghittoni et al., 2010).

In cervical carcinogenesis, recombination between HPV and chromossomal DNA is frequent and likely necessary for cancer progression. Moreover, DNA methylation, specifically on the *L1* gene, has been accepted as an important biomarker for cancerous progression in the cervix. The term DNA methylation refers to the transfer of a methyl group to cytosines that are part of CpG dinucleotides (meCpGs), which results in the binding of meCpG specific transcriptional repressors, for example MeCP2. In undifferentiated cervical cells, HPV-16 acquires a low and sporadically distributed CpG methylation, which disappears completely upon differentiation. During carcinogenesis, upon integration of HPV-16 and 18 into cellular DNA, the *L1* gene, and to a lower extent adjacent long control region (LCR) sequences, become hypermethylated, a fate of HPV DNA shared with most unrelated external DNA sequences that enter mammalian cells. The same mechanisms apparently occur during penile carcinogenesis, according with the study of Kalantari et al. (2008), which investigated the properties of HPV genomes in penile carcinomas from Brazilian patients. Their observations of frequent viral DNA methylation, chromosomal integration, and the prevalence of high-risk variants suggest that HPV dependent carcinogenesis of the penis and cervix follow similar etiological and epidemiological parameters.

A single nucleotide polymorphism (SNP) in codon 72 of *TP53* has attracted wide attention over the past decade. The most common polymorphism at codon 72 results in a non-conservative change of arginine to proline within a proline-rich region of p53, in a domain known to be important for growth suppression and apoptotic functions (Tornesello et al., 2008), may be involved in multiple steps of carcinogenesis and may also account for genetic differences in susceptibility to cancer (Reis et al., 2010b; Tornesello et al., 2008, Almeida et al., 2008). It has been demonstrated that the *TP53* polymorphism distribution varies according to ethnic and geographical backgrounds, like most human genetic polymorphisms (Reis et al., 2010b).

Storey et al. (1998) found that women who are homozygous for *TP53*Arg are seven times more susceptible to HPV-associated squamous carcinoma of the cervix than are heterozygous women. Since then, many groups have reported an effect of the *TP53* codon 72 polymorphism on cervical cancer and others carcinomas. A meta-analysis of several studies on *TP53* polymorphism at codon 72 confirmed that arginine homozygous genotype is associated with an increased risk of invasive cervical cancers, but not with squamous intraepithelial lesions, supporting the hypothesis that the polymorphism may have a main role in the progression of HPV-related cancers, rather than in the tumor initiation (Koushik et al., 2004). On the other hand, very few studies have been designed to investigate *TP53* polymorphisms in penile carcinomas.

In a case-control study, Tornesello et al. (2008) analyzed the polymorphism of the gene *TP53* at codon 72 and found the polymorphism associated with increased risk for 78 penile SCC biopsies (n = 17 from Uganda and n = 61 from Italy). Despite, significant differences in arginine and proline allele distribution were observed when the cases were stratified by

HPV status. Thus, no evidence of association between homozygosity for p53 arginine and HPV-related or HPV-unrelated penile SCC was observed among Ugandan or Italian populations. In another study, the *TP53* Arg/Arg genotype did not appear to represent a risk factor for the development of genital SCC in men, and no correlation was found between the *TP53* polymorphism at codon 72 and the presence of HPV DNA in the tumour tissue (Humbey et al., 2003).

The role of several tumour suppressor genes and cellular oncoproteins has been characterized by studying HPV E6 and E7 and or other related viral oncoproteins. The knowledge of HPV and cancer association obtained during the past three decades is extremely relevant. Worldwide, this knowledge has led to clinical and scientific achievements such as the generation, commercialization, and distribution of cervical cancer high-risk HPV vaccines. As a consequence of research studies on virus and cancer association, the Nobel Prize in Physiology or Medicine 2008 was awarded to Dr. Harald zur Hausen for his discovery of HPV causing cervical cancer (Ghittoni et al., 2010).

Certainly, the expression of viral oncoproteis is needed to induce and maintain the neoplastic phenotype of cervical cancer cells. The similarity of the tissues leads one to assume that a similar mechanism may play a role in the development of HPV-induced penile cancer (Kayes et al., 2007). Provided that identification of HPV implies a causal role of the virus with the carcinogenic process, the attributable fraction of penile cancer related to HPV has been estimated at 47%. The etiology of penile carcinomas is likely to be heterogeneous, co-existing both HPV related and HPV-independent pathways. Based on cervical cancer studies, penile cancer could also arise from initial HPV infection which persists over time, causing genetics alterations within the infected penile epithelium, leading to the cancer development. However, the molecular mechanisms underneath HPV-induced penile cancer remain to be completely understood (reviewed in Miralles-Guri et al., 2009).

2.3 High risk HPV-associated penile cancer

Molecular biology techniques with different sensitivity and specificity have facilitated the characterization of the entire HPV genome, where different functional regions are identified, as a profile of their gene expression. The techniques of Southern blotting and i*n situ* hybridization have been used extensively in the past to identify viral sequences in tissues. Additionally, polymerase chain reaction (PCR) and its variants have been recognized as the most appropriate method to identify and type HPV genomes because of its higher sensitivity and specificity (Campisi et al., 2007).

The most studies in penile cancer use PCR consensus primers for HPV DNA detection, such GP5+/6 and My9/11. However, a small set of PCR studies included the SPF10 primers to identify HPV genomes. Almost all studies used previously stored formalin-fixed and paraffin-embedded samples (Table 1). However, sample preparation and fixation lead to DNA degradation, decreasing PCR efficiency and reducing the size of amplifiable DNA (Miralles-Guri et al., 2009).

When using PCR as a strategy to identify viral genome, false-negative results may occur due to variations of the primer binding sites on target DNA, which in turn would lead to lower amplification signals of some HPV genotypes. Because of this problem, the PCR method may not detect all HPV genotypes present in the sample. Recently, studies involving

genotyping of HPV with genotype-specific oligonucleotides and DNA microarray analysis have been reported. A novel DNA biochip is described based on a plastic substrate, onto which small polymer droplets and single-stranded DNA are printed in the form of microarrays. After DNA isolation, PCR and biochip read-outs were compared, the chip allowed for genotyping of the most common virus strains, which, according to current prevalence studies, cover 85–95% of all infections. Following the biochip approach, as little as 10 virus copies can be detected within a short exposure time. Even using paraffin-embedded material and 104 copies per PCR are sufficient to allow rapid and reliable HPV genotyping (Brandstetter et al., 2010). The biochip technique has become more successful for early cervical and non-cervical cancer diagnosis and might become the methodology of choice for HPV detection in the near future.

As HPV E6 and E7 expression is necessary for the induction and the maintenance of the transformed phenotype, HPV-associated tumors are valuable tools to investigate important aspects of human carcinogenesis. Molecular evidence for a causal association includes the presence of HPV genomes in tumor cells, integration and specificity of HPV genomes, high HPV viral load in tumors, and elevated and constitutive expression of E6 and E7 oncogenes in tumor cells (Chaturvedi, 2010). Presence of HPV was found to be a risk factor for penile SCCs (Rubin et al., 2001; Gregoire et al., 1995). Several molecular techniques with different sensitivity and specificity have been used for HPV detection and genotyping among the different epidemiological studies. Considering that the incidence of penile and cervical cancers is high in the same geographical areas, it is reasonable to assume that both types of cancer share the same etiological factors. However, less than half of penile cancers are related to HPV infection (Gross & Pfister, 2004; Rubin et al., 2001) whereas the virus is found in almost all cervical SCCs (Chaux et al., 2010).

Additionally, studies have reported a heterogeneous prevalence of high risk HPV types, suggesting that only a subset of cases can be attributed to viral infection (See table 1). In the two recent studies of the HPV type distribution in penile carcinoma, a global HPV prevalence was found to be approximately 46.9% and 47,9%, (Backes et al., 2009; Miralles-Guri et al., 2009). About half of the penile tumors were associated with HPV 16 (64.07%) and 18 (9.70%) with little presence of other genotypes, 45 (1.45%), 33 (0.97%) and 31 (0.36%), respectively. As expected, the literature confirmed a higher prevalence of HPV 16 and 18 in penile tumors (73.78%). This finding was in agreement across of all 36 studies presented in table 1.

Virtually all of the studies in Table 1 used PCR to detect HPV DNA, a method slightly more sensitive than southern blotting and *in situ* hybridization. The higher the sensitivity of the method used, the more likely the prevalence of HPV is closer to the real prevalence associated with penile cancer. The relatively wide range of HPV prevalence in penile tumors in the published literature confirms that in addition to geographic differences. The greatest percentage of studies used PCR consensus primers for HPV DNA detection, such as GP5+/6+ and MY09/11.

In the study of Gregoire et al. (1995), HPV DNA was detected in 26 (22.2%) of 117 specimens. In 23 (88.5%) of the 26 HPV-positive specimens, only HPV type 16 was identified. HPV DNA was frequently associated with SCC in areas showing basaloid and/or warty changes virus DNA was more often associated with high-grade tumors ($p=0.0278$) exhibiting aggressive growth ($p=0.0382$) localized to the penile glans ($p=0.0324$). Stepwise

logistic regression analysis revealed that only tumor histopathology was a significant predictor of an HPV association. Heidman et al. (2007) detecetd HPV DNA in 46 of 83 (55%) and HPV16 was the predominant type, appearing in 24 (52%) of 46 of penile SCCs. In a case control study in Denmark, of the 37 penile SCC patients whose tumor tissues were PCR-examined for the presence of HPV DNA, 24 (65%) were high-risk HPV positive, and 1 (3%) was positive to a low-risk HPV type (HPV 6) [Madsen et al., 2008].

Author	Year	Country	Sample	Method	Cases	HPV	HPV 16	HPV 18	HPV 31	HPV 33	HPV 45
Villa & Lopes	1986	Brazil	Frozen	Southern Blot (SB)	18	8	0	7	0	0	0
Kiyabu et al.	1989	USA	PE	PCR TS	5	2	2	0	0	0	0
Varma et al.	1991	USA	PE	PCR TS 6/11/16	30	23	15	0	0	0	0
Wiener et al.	1992	USA	FFPE	PCR TS 16/18 / SB	29	9	8	1	0	0	0
Sarkar et al.	1992	USA	FFPE	PCR TS 6/11/16/18	12	9	9	0	0	0	0
Iwasawa et al.	1993	Japan	FFPE	PCR TS 16/18	111	70	68	2	0	0	0
Suzuki et al.	1994	Japan	Fresh /PE	PCR TS	13	7	4	0	1	2	0
Chan et al.	1994	China	PWE	PCR TS 16/18	41	6	2	2	0	0	0
Cupp et al.	1995	USA	FFPE	PCR My9/11 TS 16/18	45	23	17	2	0	0	0
Gregoire et al.	1995	USA/ Paraguay	FFPE	PCR TS 6/11/16/18 SB	117	26	23	0	0	0	0
Cubilla et al.	1998	USA /Paraguay	FFPE	PCR TS	11	0	0	0	0	0	0
Nasca et al.	1999	Italy	FFPE	PCR TS	4	3	2	0	0	0	0
Poblet et al.	1999	Spain	FFPE	PCR TS	2	2	2	0	0	0	0
Levi et al.	1998	Brazil	Frozen	PCR My9/11 TS 16/18	50	28	16	3	0	0	0
Picconi et al.	2000	Argentina	FFPE	PCR GP5+/6+	38	27	6	8	0	0	0
Bezzera et al.	2001	Brazil	FFPE	PCR TS	82	25	13	4	0	0	1
Gil et al.	2001	Brazil	FFPE	My9/11 PCR TS	55	17	3	0	0	0	0
Rubin et al.	2001	USA/ Paraguay	FFPE	PCR SPF	142	60	36	2	0	0	4
Perceau et al.	2003	France	FFPE	PCR GP5+/6+ TS	17	6	3	0	0	0	0

Author	Year	Country	Sample	Method	Cases	HPV	HPV 16	HPV 18	HPV 31	HPV 33	HPV 45
Liegl et al.	2004	Austria	FFPE	PCR TS	5	5	5	0	0	0	0
Nascimento et al.	2004	Brazil	Fresh /PE	My9/11 PCR TS	16	10	1	0	0	1	0
Daling et al.	2005	USA	FFPE	My9/11	94	75	65	0	0	0	0
Salazar et al.	2005	Mexico	FFPE	PCR TS 16	46	28	28	0	0	0	0
Gentile et al.	2006	Italy	FFPE	PCR My9/11 GP5+/6+	11	8	5	2	0	0	0
Lont et al.	2006	Nerther-lands	FFPE	PCR GP5+/6+	171	50	38	3	0	2	3
Dorfman et al.	2006	Venezuela	FFPE	My9/11	5	5	0	0	0	0	0
Senba et al.	2006	Thailand	FFPE	PCR SPF	65	53	1	36	0	0	0
Protzel et al.	2007	Germany	FFPE	PCR TS 6/11/16/18	18	4	3	0	0	0	0
Pascual et al.	2007	Spain	FFPE	PCR My9/11 GP5+/6+	49	38	32	4	0	0	0
Heidman et al.	2007	Nerther-lands	FFPE	-	83	46	24	3	0	1	2
Guerrero et al.	2008	Spain	FFPE	PCR GP5+/6+	24	11	11	0	0	0	0
Yanagawa et al.	2008	Japan	FFPE	PCR - RFLP	25	3	3	0	0	0	0
Scheiner et al.	2008	Brazil	frozen	PCR My9/11	80	58	12	1	2	2	2
Madsen et al.	2008	Denmark	-	PCR GP5+/6+ TS	37	25	24	0	0	0	0
Prowse et al.	2008	UK	FFPE	PCR SPF	26	14	11	0	0	0	0
Tornesello et al.	2008	Uganda /Italy	FFPE	PCR My9/11 GP5+/6+	78	40	36	0	0	0	0
Total					1655	824	528	80	3	8	12

PE=paraffin-embedded
FFPE= formalin-fixed paraffin- embedded
PCR TS= polymerase chain reaction type specific
PCR-RFLP= polymerase chain reaction – restriction fragment length polymorphism

Table 1. Prevalence for HPV in 36 studies (n=1.644) Adapted from Backes et al., 2009; Miralles-Guri et al., 2009.

The objective of the Senba et al. (2006) study was to determine the relation between penile cancer and the prevalence of HPV genotypes in northern Thailand. Eighty-eight specimens of penile tissue (65 malignant, 1 pre-malignant, and 22 benign cases) were examined to determine the association of HPV infection. HPV DNA was detected in 81.5% of cases of penile cancer using PCR. The high-risk HPV16, most commonly associated with penile

cancer in previous reports, was found in only one case in this study. The most prevalent genotype was the high-risk HPV-18, found in 55.4% of the cases (32.3% single and 23.1% multiple infection) followed by the low-risk HPV-6, found in 43.1% of the cases (24.6% single and 18.5% multiple infection). In this study, penile cancer was found to be highly correlated with HPV DNA.

Several studies have confirmed a predominance of penile cancer in the North and Northeast of Brazil which are regions with lower human development indexes (Favorito et al., 2008; Koifman et al., 2011; Reis et al., 2010a). Scheiner et al. (2008) in Rio de Janeiro, Brazil found that HPV infection may have contributed to malignant transformation in a large proportion of their penile cancer cases but only inguinal metastasis was a prognostic factor impacting survival of those patients. In another Brazilian study the patients having HPV type-16 in their tumors were submitted to major surgical procedures to remove the primary tumor ($p=0.04$). The relative risk of death for patients with HPV type-16 was 7.59 times greater than that for the virus negative group. Also, patients presenting HPV type 16 in the tumor presented a lower tendency for survival (without statistical significance). Coilocitosis was detected in 12 patients, presenting a significant correlation with the presence of HPV type-16 ($p=0.026$). The authors concluded the infection by HPV was strongly associated with penile epidermoid carcinoma (30.9%). The presence of HPV type-16 in the tumors was associated with increased tumor-related mortality. No HPV 18 was detected in their samples (Gil et al., 2001). The presence of genomic DNA of HPV 16 and 18 in penile cancers identified by Southern blotting (Villa & Lopes, 1986) and polymerase chain reaction (PCR) (Bezerra et al., 2001) assays also in Brazil.

In a case control study to analyze the genetic susceptibility involving *TP53* polymorphism, 78 penile SCC biopsies (n= 17 from Uganda, n= 61 from Italy) and blood samples from 150 healthy controls (n = 57 from Uganda, n = 93 from Italy) were collected. Among Uganda cases the heterozygous, proline homozygous and arginine homozygous genotype frequency was 41.2%, 52.9% and 5.9%, respectively, and among controls was 40.3%, 54.4%, and 5.3%, respectively ($P = 0.9917$). Conversely, among Italian cases genotype distribution was 42.6%, 4.9%, and 52.5%, and among controls was 34.4%, 7.5%, and 58.1%, respectively ($p=0.5343$). No significant differences in arginine and proline allele distribution were observed when the cases were stratified by HPV status. Therefore, no evidence of association between homozygosity for p53 arginine and HPV-related or HPV-unrelated penile squamous cell carcinoma was observed among Ugandan or among Italian populations (Tornesello et al., 2008).

Poblet et al. (1999) described two cases of penile SCC in HIV-positive patients with distinctive clinicopathologic characteristics. The tumors appeared in patients infected with HIV and were located in the glans of the penis. Histologically, the tumors were well-differentiated, infiltrating, penile SCC. The entire spectrum from benign condyloma to infiltrative SCC was present in the two patients. The reported cases suggest a synergic interaction of HPV and HIV in the carcinogenic process of some penile carcinoma. In fact, the immune system efficiency is a key to control HPV replication, which was evident in the increased incidence of lesions caused by HPV and recurrent infections in the group seropositive for HIV. However, the cellular and molecular mechanisms responsible for protection from and elimination of HPV infection are not fully established (Silva et al., 2011). Based on cervical cancer studies, penile cancer could also arise from an initial HPV infection

which persists over time and causes genetic alterations, leading to an interference of the cell division cycle and apoptosis. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence to classify HPV infection as a Group I carcinogen for cancers of the cervix, anus, oropharynx, penis, vagina, and vulva (IARC, 2007). However, epidemiologic and molecular data in support of a causal association are currently sparse and do not extend beyond detection of HPV genomes in tumor cells in these cancers (Chaturvedi et al. 2010).

The most serious consequences of genital HPV infections in women are high-grade squamous intraepithelial lesions, which can progress to invasive cervical cancer (IARC, 2007). Numerous studies have investigated the potential risk factors for HPV among heterosexual men, men who have sex with men (MSM), and men with HIV/AIDS. Universal HPV risk factors described have included the number of lifetime sex partners, frequency of condom use, race/ethnicity, educational level, presence of a concomitant sexually transmitted infections (STIs) [especially HIV/AIDS infection], and a positive history of tobacco use.

High-risk male populations, most notably MSM and HIV/AIDS-infected males, as a community, characteristically have a lifestyle that may incorporate psychosocial, physical, and sexual practices that place them at greater risk for STIs such as HPV infections. This population falls increasingly vulnerable to HPV-associated cancers because of frequent high-risk behaviors, increased likelihood of concomitant infections, and a current lack of male cancer screening guidelines (Kreuter et al., 2009). However, studies have shown that uncircumcised men have an additional anatomical risk factor as there is a lower incidence of HPV infection and HPV-associated penile cancer in circumcised men, especially in those men who were circumcised at a younger age (Castellsague et al.,2002).

Studies have demonstrated that HPV infection in the penis is highly prevalent among heterosexual men who are seronegative for HIV, with rates ranging from 52% to 72% (Giuliano et al., 2008; Silva et al., 2011). In a recent longitudinal study to assess the persistence and clearance of HPV DNA from the penis of men infected and non-infected with HIV, the results demonstrated 66% of men without HIV infection presented with some type of HPV. The vast majority of such infections are transient, and virus elimination occurs rapidly in immunocompetent individuals (Silva et al., 2011)

The quadrivalent HPV vaccine was licensed in 2006 for use in women aged 9 to 26 to prevent infection with HPV serotypes (6, 11, 16 and 18) to prevent HPV related cervical cancer. The immunization protocol covers the most prevalent HPV serotypes (Garland et al., 2007). In 2009, the vaccine approval was extended to boys and men aged 9 to 26 based on prevention of infection with serotypes 6 and 11, and subsequent prevention of genital warts. In 2010, the vaccine received an additional indication for prevention of anal cancer in men and women. However, given multiple etiologies and the low incidence of penile cancer, vaccination also will likely provide marginal benefit on a population level. Nevertheless, the vaccine should decrease penile cancer caused by HPV 16 and 18, which are the most common subtypes associated with penile carcinomas. Vaccination is likely to have a more substantial benefit for benign HPV-related diseases of the penis, such as condyloma acuminata, which are far more common in any population (Barroso et al., 2011).

When considering the impact of a vaccine on cancer incidence, it is useful to consider the past experience with Hepatitis B virus (HBV) (Franceschi et al., 2002). Like HPV, HBV is the cause of cancer, specifically hepatocellular carcinoma – in chronically infected individuals. Unlike HPV, however, HBV is also associated with acute disease at the time of infection and substantial morbidity and mortality from causes other than cancer (Plummer & Franceschi, 2002). In the case of HPV vaccination, it is likely that secular trends in cervical cancer incidence or mortality will provide convincing evidence of its effectiveness. Thus, a decline in the incidence and in the mortality rates from cervical and non-cervical cancers is expected in many populations after the introduction of screening and immunization programs.

2.4 Prevention for penile cancer

Two HPV vaccines were developed, a quadrivalent vaccine that provides protection against HPV types 6, 11, 16, and 18 and a bivalent vaccine that protects against HPV types 16 and 18. The quadrivalent and bivalent vaccine were approved by the U.S. Food and Drug Administration (FDA) for the prevention of HPV associated cervical cancer, adenocarcinoma *in situ*, cervical intraepithelial neoplasia (CIN) grades 1–3, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia grades 2/3, vaginal cancer, vulvar cancer, and genital warts in women aged 9–26 years (Chaturvadi et al., 2010). The quadrivalent Gardasil™ (Merck and Co. Inc - Whitehouse Station, NJ) vaccine is currently approved for sale in 85 countries. Cervarix®, the HPV vaccine produced by GlaxoSmith Kline, has been approved in the European Union, Australia, and Kenya, with applications pending elsewhere (Agosti and Goldie, 2007). According to the researchers, the vaccine was 89% effective in preventing infection with HPV types 16 and 18, and 100% effective in preventing the diseases associated with these types (Chaturvadi et al., 2010).

The L1 virus-like particles (VLP) for specific HPV types is a highly efficacious vaccine antigen in humans. Clinical trials of multivalent L1 VLP vaccines intended to be disseminated in public health programs have shown safety, immunogenicity, and high efficacy (Bosch & Harper, 2006). Studies have shown that serologic diagnosis of HPV infection using genetically engineered HPV capsids (VLPs) correlates well with HPV DNA presence in cervical smears. The L1 VLP vaccines are unlikely to be effective as a treatment of women currently positive for a persistent HPV infection of the same type. Because the vaccines are prophylactic and not therapeutic, vaccination is not effective in clearing either established infections or pre-existing disease. Although the duration of protection is as yet unknown, current data indicated that both vaccines are immunogenic and efficacious for up to 4 years after vaccination (Chaturvadi et al., 2010). The antibodies produced recognized type-specific conformational epitopes present on VLPs, particularly against the viral capsid protein L1 and the humoral response against HPV, i.e., the production of IgG, is stable over time (Chatuverti et al., 2010; Villa, 2006). Both the quadrivalent and the bivalent prophylactic vaccines have demonstrated high efficacy (90%–98%) against persistent HPV infection and vaccine type–related CIN 2 or above (Paavonen et al., 2007). Additionally, both vaccines are safe and immunogenic among adolescent males aged 10–18 years and 9–15 years, respectively. The quadrivalent vaccine has demonstrated high efficacy in preventing persistent HPV infection (85.6%), external genital lesions (90.4%), condyloma (89.4%), and PIN (100%) among adolescent boys and young men aged 16 to 26 years (Chaturvadi et al., 2010).

Some studies have demonstrated a strong association between lifetime number of sexual partners and genital HPV acquisition. The acquisition of new sexual partners continues throughout all age groups. In addition, studies have shown consistently that the risk of cervical cancer can be predicted as much by a woman's own sexual behaviour as by the sexual behaviour of her husband/partner. The presence of HPV DNA in the penis and urethra of her sexual partner(s) is directly related to her HPV carrier status and, therefore, her increased risk of developing cervical cancer (Castellsague et al., 2009).

Jasen & Shaw (2004) presented three major issues to be resolved in order to take full advantage of the promise of HPV vaccines. First, the global infrastructure must be reinforced to accommodate the logistics of delivery of a new vaccine to a, perhaps, non pediatric population. This is a rather tall order, and in practice, this may become a pediatric vaccine in developing countries even if the developed world makes a different choice. There are no adolescent vaccination programs in most parts of the world. The World Health Organization's Expanded Program for Immunization delivers the "basic six" vaccines (diphtheria, tetanus, pertussis, polio, measles and BCG) to a large fraction of the world's birth cohort. If effective immunity could be shown to last into adulthood, then pediatric administration may be the easier solution for developing countries. Second, the capacity for producing HPV vaccines on a global scale must be created. The "chicken-and-egg" aspect of this problem might not be as obvious to those outside the vaccine industry. In order to justify the capital and other ancillary investments necessary to create manufacturing capacity approximately ten times greater than one might normally contemplate, there must be some reasonable assurance of a market for the product. This is tightly linked to the third issue, funding. In most of the world, vaccines are paid for by governmental or international donor agencies. Until recently, the vaccines provided through such funding mechanisms have been "traditional" vaccines such as the "basic six" mentioned above.

To deliver an HPV vaccine for cervical cancer to the women in greatest need, many of whom live in the very poorest countries around the world, one can only hope that industry, governments, and donor organizations will make similar efforts and alliances to guarantee the proper deliver of the vaccines for those who truly need them. Clinical studies to date have focused on women because they suffer most from the pathology of HPV infection. Men, however, are considered important vectors in the chain of HPV infection and dissemination. With the notable exception of penile warts and some cases of penile and anal cancer, there is little obvious pathology associated with HPV in heterosexual males, making HPV very difficult to be detected in that population. This is partly because of the lack (until recently) of an acceptable method of sampling. MSM how practice anal intercourse are subjected to development of anal intraepithelial neoplasia. The anal epithelium has a transition zone similar to that of the cervix, and this is the most frequent site of HPV infection in this group. Since vaccines work best when given to large proportions of the population, vaccination trials to show some efficacy in men are also being considered (Jansen & Shaw, 2004).

As a consequence of the recent licensing of the quadrivalent and the bivalent HPV vaccines, important questions have emerged regarding investment policies for vaccination programs. The decision for an individual country, such as Brazil, over others developing countries, to introduce a new public health intervention must take into consideration multiple factors. These include the disease burden, effectiveness of the intervention, the financial costs

required to initiate and sustain the program, the cost-effectiveness of the intervention, the programmatic capacity and infrastructure necessary to successfully deliver the intervention, and the likelihood of cultural acceptability, political will and public support (Goldie et al., 2007).

The quadrivalent vaccine also dominates the bivalent vaccine as it lacks cross-reactivity against non-16/18 oncogenic HPV types and it also reducces the incidence rates of on genital warts (Dee &Howel, 2010). In a recent study, Malasya (2011) reported for the cost-effectiveness analysis, the cost per life year saved vaccine compared to no vaccine, as $12,866 and $12,827 for the quadrivalent and the bivalent vaccines, respectively. Comparing the bivalent to the quadrivalent vaccine, the cost-effectiveness ratio (ICER) is $12,488, showing that the bivalent vaccine saves more lives per cost. However, the cost per Quality-Adjusted Life Years (QALY) saved for the quadrivalent vaccine compared to no vaccine was estimated as $9,071, while it was $10,392 for the bivalent vaccine, with the quadrivalent vaccine dominating the bivalent vaccine due to the additional QALY effect on the reduction of genital warts (Lee et al., 2011).

A study also investigated the cost-effectiveness of HPV vaccination in France, using a quadrivalent HPV vaccine. This study compared screening plus vaccination at age 14 years with screening alone. The ICER for the addition of vaccination to screening was €13,809/QALY when considering all direct healthcare costs. This is somewhat higher than the finding of €9,706/QALY for the bivalent vaccine,. Although it should be noted that no study undertook a direct head-to-head comparison of the two products and the results may therefore not be directly comparable (Bergeron et al., 2008).

For a country like Brazil, the clinical benefits of an HPV 16/18 vaccine is likely to be substantial. The most influential factor on cost-effectiveness is the vaccine cost. If the cost per vaccinated woman is less than I$ 25,00 implying a per dose cost of approximately I$ 5,00 vaccination is likely to be extremely cost-effective in Brazil. The most effective strategy, within a framework that would still be potentially cost-effective in Brazil, would be vaccination before age 12, followed by screening three times per lifetime between ages 35 and 45. Assuming a coverage rate of 70%, this strategy would be expected to prevent more than 100,000 cases of invasive cervical cancer over a 5-year period. Finally, vaccination strategies we have identified as cost-effective may be unaffordable in low and even middle income countries without international financial aid. The results from the studies carried out in North America and Europe can provide guidance to the global community by helping to identify health investments of highest priority and with the greatest promise and best effectiveness to the population at risk (Goldie et al., 2007).

After a vaccination campaign begun, the population will be a mixture of younger, vaccinated women and older unvaccinated women. The impact of vaccination is not seen in the population as a whole until the vaccinated group dominates in the high-risk age group (Bosch & Harper,2006). Thus, screening programs will be required to complement vaccine programs for many decades, providing the epidemiological means to understand the actual effect of the vaccination on the selected group. On the other hand, educational actions to prevent cervical and non cervical cancers, which are part of basic health actions, should be implemented as a professional commitment to the population's quality of life and a health care quality, emphasizing patients' autonomy in self-care.

Recently, a Brazilian study aimed to evaluate the applicability of an educational booklet that contained information for the general population about promotion and prevention of infections and neoplasic diseases caused by the HPV. The study was arranged in two phases. First, the booklet was given to 2000 volunteers who evaluated the applicability of the booklet without previous education or discussion about the subject. The educational material was published and 2000 copies were distributed during a health social event. In the event, the booklet raised the interest of the general public and gave the volunteers a chance to participate in a study that investigated the presence of the HPV as part of the genital microbiote. In a second phase, a detailed analysis of the data was made and the booklet revealed applicable. The authors concluded that managing and presenting the information beforehand is an important step to promote and improve preventive campaigns and strategies aimed to the population at large regarding HPV infection and its potential role on carcinogenesis (Reis et al., 2010c).

Education should not only be considered an extra activity, but an effective action to redirect health promotion practices as a whole. Reis et al. (2010c) suggested that preventive knowledge about the natural history of cervical and non cervical cancers and, including the feasibility of HPV vaccination programs for both sexes, will decrease the incidence of HPV associated cancers and has the potential to be of great significance to health management of high-risk female and male populations.

Proper condom use as a primary prevention measure for STI should remain a top priority for health official campaigns. The preventive strategies should keep on focusing primarily on the increase of STI. This knowledge is proven powerful to elicit individual awareness responsible for influencing individual risk perception amongst those sexually active. However, the campaigns must understand that modifying individual risk perception does not effectively translate into changes of preventive behaviors. To reach the public health goal of reducing STI prevalence, barriers to engaging in STI prevention need to be addressed, including education strategies.

3. Conclusion

Penile SCC is a severe and uncommon disease with devastating medical psychological consequences for the patients. The disease is mainly related to poor hygiene, sexual history, and smoking. Male circumcision has been used as a preventive measure for sexually transmitted infection with positive impact on the reduction of penile cancer incidence rates when neonatally performed. Penile cancer development is facilitated by phimosis. In general, penile SCC imposes an increase in the relative risk of invasive disease compared to an *in situ* cancer. The understanding of the natural history of penile cancer is fundamental to promote effective preventive strategies. Globalization and promiscuity are expected to be the major causes leading to the increase of penile SCC incidence. The oncoproteins of high risk HPV types target cellular pathways promoting cellular transformation and neutralizing the immune response. FDA recently approved and licensed the first vaccine for HPV-6, -11, -16, and -18 for early prevention in teenagers and young adults. Vaccination is likely to have a more substantial benefit for prevent cervical and non cervical cancers. Novel preventive strategies are important to complement the immunization programs that should always take educational strategy as an important step on primary prevention.

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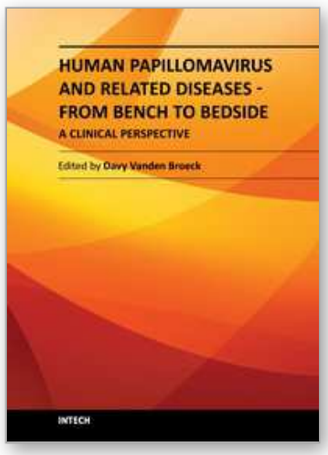

Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective

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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on the clinical aspects of HPV and related disease, highlighting the latest developments in this field.

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