HPV in genital cancers (at the exception of cervical cancer) and anal cancers

Silvia de Sanjosé1,2, Laia Bruni1, Laia Alemany1,2

1. Unit of infections and cancer, Cancer epidemiology research program, Catalan institute of oncology, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
2. CIBER en epidemiología y salud pública (CIBERESP), Barcelona, Spain

Correspondence:
Silvia de Sanjosé,
Unit of infections and cancer, Cancer epidemiology research program IDIBELL, Catalan institute of oncology, Gran Via de l’Hospitalet, 199-203, 08907 L’Hospitalet de Llobregat, Barcelona, Spain.
s.sanjose@iconcologia.net

Available online:
HPV and anogenital cancers
Persistent infection of certain types of human papillomavirus (HPV) are linked to anogenital cancers including cervix, vagina, vulva, anal canal, penis, and head and neck cancers, particularly oropharyngeal. The HPV aetiological contribution differs in each location reflecting different natural history and different tropism. Cancer incidence rates at anogenital anatomical sites other than cervical cancer are much lower than that observed for cervical cancer. The analysis of time trends of incidence rates of these sites is hampered by random fluctuations inherent to the small numbers involved and possible underreporting of anogenital cancer in less developed countries. However, some countries have reported an increase in anal or vulvar cancers.

HPV and anogenital cancers

Summary

Human papillomavirus (HPV) infection has been firmly established as a central and necessary cause of invasive cervical cancer and it has been etiologically linked to other anogenital (vulva, vagina, anus and penis) and head and neck cancers, particularly oropharyngeal. Although being rare, the incidence of some of these cancers in some countries has increased in the last decades. HPV-related anogenital tumors share many risk factors with cervical cancer. The HPV aetiological contribution differs in each anatomical location reflecting differences in the natural history and viral tissue tropism. The highest prevalence of HPV DNA in cancers other than cervix has been described for anal, followed by vagina, penile and vulvar cancers. HPV16 has been described as the most common type detected in all cancer sites with different contributions being the highest in anal carcinoma (around 80% of HPV DNA positive anal cancers) and the lowest in vaginal cancers with a contribution similar to that found in cervical cancers (around 60%). Current HPV vaccines have already demonstrated their efficacy in preventing anogenital pre-neoplastic lesions caused by vaccine HPV types. HPV-based prevention tools like HPV vaccination and to a lesser extend screening (e.g. for anal cancer) can be useful measures for reducing the burden of these anogenital cancers.
In this paper we will review the burden of the vagina, vulva, anal and penile cancers, their associations with HPV infection and potential interventions leading to prevention.

**Cancer of the vulva and the vagina**

Vulvar cancer is a rare entity with age-adjusted incidence rates ranging from 0 to 4.6 per 100,000 women-year, representing about 4% of all gynecological malignancies (figure 1) [1]. It is estimated that each year about 27,000 new cases are being diagnosed worldwide [2]. Lower rates are observed in Asia and Africa than in other parts of the world. Over the past few decades, the incidence rates of invasive vulvar cancer (IVC) and vulvar intraepithelial neoplasia (VIN) have both been reported to increase, particularly among younger women [3,4]. However, in the United States (US) the increase is limited to pre-neoplastic lesions [5] and in the United Kingdom trends are stable [6].

Squamous cell carcinoma (SCC) accounts for more than 90% of the malignant tumours of the vulva and several morphological variants have been described including keratinizing, basaloid, warty and verrucous carcinoma. Basaloid and warty variants representing about 1/3 of cases, are commoner in younger women, and are often associated with HPV DNA detection. These tumors share many risk factors with cervical cancer. By contrast, keratinizing variants arise from chronic vulvar dermatosis, such as lichen sclerosus, are most commonly not associated with HPV and tend to occur in older women. HPV associated vulvar cancers do not seem to differ in prognosis from HPV negative cases although data are scanty and based on few observations [7].

HPV DNA prevalence in vulvar cancer varies greatly by histology. A 40% positivity has been referred when pooling published studies [8,9]; however a recent large scale worldwide analysis using an homogeneous protocol for HPV testing reported a lower HPV DNA detection in vulvar carcinoma. Among 1571 invasive vulvar cancers and 524 high-grade preinvasive intraepithelial lesions, HPV DNA was detected in 28.6% and 86.7%, respectively. Interestingly, when p16INK4a overexpression was considered, 25% of the vulvar carcinomas were both HPV DNA positive and p16INK4a positive. HPV16 was the commonest type identified representing over 75% of all positive cases [10]. Further work is ongoing exploring the role of other markers evaluating viral activity.

Vaginal cancer is also a rare malignancy, with an estimated of 13,000 new cases diagnosed worldwide in 2008 and accounting for about 2% of all gynecologic cancers [2,11]. The age-adjusted incidence rates range from 0.5 to 1.7 per 100,000 women per year (figure 1) [1]. Most vaginal invasive cancer cases occur in patients older than 60 years, except for adenocarcinomas, which occur in younger ages [11,12]. Like in vulvar cancers the SCC is the most frequently diagnosed histological type (80–90%), followed by adenocarcinomas [11]. As for cervical cancer, squamous cell vaginal cancer is preceded by premalignant lesions or vaginal intraepithelial neoplasia (VAIN).

Several risk factors have been described for vaginal cancer and in particular for the SCC type which resemble those of cervical cancer like smoking, immunosuppression, high number of sexual partners, and also history of cervical precancerous and cancerous lesions [13–15]. In contrast, the vaginal...
HPV in genital cancers (at the exception of cervical cancer) and anal cancers

VIRUSES ASSOCIATED WITH SKIN AND MUCOSAL CANCERS

Adenocarcinoma type, particularly the clear cell adenocarcinoma, has been largely related in the past to in utero exposure to diethylstilbestrol (DES), which was prescribed as an abortifacient until the early 1970s [16-18]. HPVs have been causally linked to vaginal cancers in the few case-control studies that have been conducted [15]. The viral DNA has been identified in a large proportion of vaginal SCC and, as in other anogenital cancers, HPV16 has been shown to be the predominant HPV type [8]. A meta-analysis on HPV prevalence and type distribution in different anogenital cancer sites included only 191 cases for VAIN 2/3 and 136 invasive vaginal cancer cases [8]. Furthermore, due to the diversity of the study protocols and of the techniques used for HPV DNA detection in the studies, HPV prevalence varied from 50 to 100%, with an average of 90% in VAIN 2/3 and from 25 to 89%, with an average of 70% in invasive cancers of the vagina [8]. Sinno et al. [19] in a series of 60 cases of invasive vaginal cancer from US detected HPV DNA in 75% of them. Although there is still a small proportion of adenocarcinomas that are related to DES which are expected to be HPV negative tumors, the majority of the remaining cases are consistently HPV related.

Anal cancer

Globally, there are about 27,000 new diagnosed cases every year with an average worldwide incidence rate of 1 per 100,000 (figure 1) [1,2]. Since the 1970s, the incidence of anal cancer has been increasing in developed countries by about 2% per year in the general population [20]. The median age of diagnosis of anal cancer is 57 years among men and 68 years among women. Anal cancer is more common in certain high-risk groups; these include: MSM (men having sex with men), anyone with a history of anal warts or high-grade CIN/VIN/cervical or vulvovaginal cancer; immunosuppressed populations, including those with human immunodeficiency virus (HIV) infection and graft recipients [21,22]. Anal cancer affects more women than men [1]. Between 1998 and 2003, in the US, the average annual incidence of anal cancer was 1.0/100,000 among men and 1.5/100,000 [23] among women. Between 2003 and 2007, the incidence of anal cancer had risen to 1.4/100,000 among men and 1.8/100,000 among women. The incidence of anal cancer among MSM was estimated to be as high as 37/100,000 prior to the onset of the HIV epidemic [24], and is even higher among HIV-seropositive MSM [25]. The advent of antiretroviral therapy has not led to a reduction in the incidence of anal cancer [26]. The incidence may continue to increase as this population lives longer with HIV disease. Histologically, like in other HPV-related anogenital cancers, these cancers are predominantly squamous cell carcinoma. Few case-control studies have evaluated the association between HPVs and anal cancer reporting odds ratios between 2 and 7 for HPV16 and HPV18 seropositivity for both men and women [27]. In addition, one case-control study that evaluated the presence of the virus in tumor tissue found a higher viral detection among anal carcinomas (88%, 340/388) than rectal adenocarcinomas (0%, 0/20) [28]. Among HPV-related cancers, anal cancer has been linked to HPV with the highest DNA detection rates just after cervical cancer. HPV DNA prevalence has been estimated at 94% in AIN grades 2/3 and 88% in anal cancer, with HPV16 the most frequent HPV type identified [8]. In a recent published data from US, a high HPV DNA prevalence was reported 133/146 (91.1%) in invasive anal cancers, and almost 80% of anal cancers were positive for the vaccine types HPV16 or HPV18 [29].

Penile cancer

Globally, the annual burden for penile cancer has been estimated to be 22,000 cases with incidence rates strongly correlating with those of cervical cancer [1,2]. Invasive penile cancer is rare and most commonly affects men aged 50-70 years. Incidence of penile cancer is higher in less developed countries, where penile cancer accounts for up to 10% of male cancers in some parts of Africa, South America and Asia [30]. Penile pre-neoplastic intraepithelial (PeIN) lesions are rare. Cancers of the penis are primarily SCC (95%) and the most common penile SCC histologic sub-types are in decreasing order, keratinizing, mixed wart-basaloid, verrucous, warty, and basoid. HPV DNA is most commonly detected in basaloid and warty tumours but is less common in keratinizing and verrucous tumours. HPV DNA is detected in approximately half of the penile cancers. Among HPV-related penile tumours, HPV16 is the most common type detected, followed by HPV18 and HPV types 6/11 [2,9,31]. Recently, Hernandez et al. reported even a higher HPV DNA detection (63%) in a series of 79 invasive penile cancers from US, and observed that penile cases diagnosed in more recent years were more likely to be HPV DNA positive [32]. In table I, an estimation of the annual number of anogenital cancer cases diagnosed worldwide, and the number of cases related to HPV and HPV16/18 are summarized.

Primary and secondary prevention

Primary prevention through prophylactic HPV vaccination

Currently there are two HPV vaccines commercialized, Cervarix® (against HPV types 16/18-bivalent) and Gardasil® (against HPV types 6/11/16/18-quadrivalent). Vaccine clinical trials have shown excellent safety and immunogenic profiles for both vaccines. These vaccines have also demonstrated similarly high efficacy against the vaccine targeted HPV types for a range of cervical endpoints from persistent infection to cervical intraepithelial neoplasia grade 3 (CIN) [33].
Regarding protection against infection and lesions in other anatomical sites, Gardasil® also demonstrated high protection against vulvar and vaginal pre-neoplastic lesions. High protection against HPV targeted types-related high grade vulval and vaginal lesions has been shown in a pooled analysis of randomised prophylactic vaccination trials with quadrivalent HPV vaccine, 100% (95% confidence interval [CI], 82.6–100.0) in baseline HPV16/18-negative women, and 79.0% in intention-to-treat population, (95% CI, 56.4–91.0) [34]. Results regarding the protection conferred by Cervarix® vaccine were also presented in a conference abstract [35]. Vaccine efficacy against HPV16/18 associated VIN1+/VAIN1+ was of 75.1% (95% CI, 22.9–94.0) in baseline HPV16/18-negative women [35].

HPV vaccination also holds promise for the reduction of the incidence of anal cancer in the long term. A recent clinical trial in HIV-negative MSM has shown an efficacy of Gardasil® against AIN 2/3 lesions and persistent anal infection by vaccine targeted types in men of 74.9% (95% CI, 8.8–95.4) and 94.9% (95% CI, 80.4–99.4), respectively [36]. Prevention of AIN and anal cancer was approved by the US Food and Drug Administration (FDA) as an indication for the quadrivalent HPV vaccine in men and women aged 9–26 years. Cervarix® has also shown a protection against vaccine-targeted anal infections in women, particularly in among those most likely to be HPV16/18 naive at entry. Protection against anal infection related to the vaccine targeted types was 83.6% (95% CI, 66.7–92.8) in the analyzed cohort restricted to women who were negative for cervical HPV16/18 DNA and antibodies at enrolment [37].

There is also data on protection of the quadrivalent vaccine in the efficacy against male genitals persistent infection, with figures of efficacy against targeted types persistence infection in the per protocol population being 85.6% (95% CI, 73.4–92.9) [38].

The large contribution of HPV16 and the currently evidence on HPV vaccines efficacy reinforces the potential impact of HPV vaccines in the prevention of the HPV-related lesions in these anogenital sites, with a higher impact in anal and vaginal cancers which are largely related to HPV.

### Anal cancer: screening to prevent anal lesions

Regarding secondary prevention, the only evidence supporting screening at these anatomical sites is for anal lesions. Currently, no evidence is available supporting screening for VIN, VAIN, PeIN, vulvar, vaginal or penile cancers. It is however likely that vulvar and vaginal pre-neoplastic lesions are more likely to be detected among women undergoing cervical cancer screening. For anal cancer and high grade AIN lesions (HGAIN) screening is proposed for high-risk groups but not for the general population. The main argument in favour of screening is the analogy with, and success of screening and treatment for CIN to prevent cervical cancer [39]. The primary argument against anal screening is the absence of studies showing that HGAIN treatment reduces the incidence of anal cancer. It is critical to set up such trials as well as studies on biomarkers to predict progression from HGAIN to cancer.

Currently, the primary screening tool for anal HPV-associated diseases is anal cytology, with referral of screen-positive individuals for high-resolution anoscopy and anal biopsy, with treatment decisions based on the grade of AIN [39]. HGAIN can be treated using a variety of approaches depending on size and location. Some clinicians screen high-risk patients with standard anoscopy.

### Penile cancer: prevention of genital HPV infection and disease through circumcision

Circumcision at young age has long been known to be associated with a decreased risk of penile cancer. Recent clinical trials showed that adult male circumcision resulted in approximately 50% decreased incidence of HIV infection, as well as a significant lower incidence of penile hr-HPV infection in both HIV-negative and -positive men, and in female partners of HIV-negative men but not in the female partners of HIV-positive men.
men [40]. Therefore circumcision of neonatal boys and adult males contributes directly to HPV control, as well as to the control of other sexually transmitted diseases acting as cofactors for HPV transmission.

**Sponsorship**

The work has been partially supported by grants from the Instituto de Salud Carlos III (Spanish Government, RD12/0036/0056, and CIBERESP), from the Agència de Gestió d’Ajuts Universitaris de Recerca (Catalan Government, grants AGAUR 2005SGR 00695, 2009SGR126, and 2014SGR177).

**Disclosure of interest:** SdS has received occasional travel fund to attend scientific meetings from Merck, Sanofi Pasteur MSD and Qiagen; and unrestricted grants through the Institution to conduct epidemiological studies from GlaxoSmithKline, Merck and Qiagen. LB has received occasional travel fund to attend scientific meetings from Sanofi Pasteur MSD. LA has received occasional travel fund to attend scientific meetings from Merck and Sanofi Pasteur MSD.

## References


31. Miralles-Guri C, Bruni L, Cubilla AL et al. Human papillomavirus prevalence and type...


