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REVIEW ARTICLE

Role of HPV in anal squamous cell carcinoma: a narrative review with systematized search

Papel do HPV no carcinoma anal de células escamosas: uma revisão narrativa com busca sistematizada

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ABSTRACT

Introduction: The incidence and mortality of anal squamous cell carcinoma (SCC) has been increasing in recent decades. An association between anogenital infection by human papillomavirus (HPV) and the development of related neoplasms has been described. **Objectives:** To review epidemiological aspects of HPV anal infection and its association with anal intraepithelial neoplasia (AIN) and anal cancer. **Methods:** Systematic review, through the search for articles published between July/2012 and July/2022, in journals indexed in PubMed, using the combination of the following descriptors: "anal neoplasms", "human papillomavirus", "intraepithelial neoplasia" and "risk", written in English and Portuguese. Of the 182 publications identified, 29 were selected for analysis, in addition to three other relevant publications, totaling 32 studies included in the review. **Results and Discussion:** Persistent anal infection by HPV high-risk serotypes (HPV-HR) is the main risk factor for AIN and responsible for almost all cases of anal SCC. The incidence of high-grade AIN and anal cancer in people with HIV is high, especially when associated with risky sexual behaviors. In men who have sex with men (MSM) with the immunodeficiency, the highest incidences of anal cancer are reported. History of HPV associated gynecological neoplasms in women increases the likelihood of anal contamination. **Conclusion:** We report the role of HPV in the possible genesis of AIN and progression to anal SCC, especially in risk groups, in which we found high prevalence of HPV-HR and potentially malignant lesions, in addition to higher incidences of anal cancer. Research is needed to better understand the natural history of anal SCC and the role of HPV in its behavior.

Keywords: HPV; Anal intraepithelial neoplasia; Anal cancer; SCC, risk.

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RESUMO

Introdução: A incidência e mortalidade do carcinoma de células escamosas (CCE) anal vem aumentando nas últimas décadas. É descrita associação entre a infecção anogenital pelo papilomavirus humano (HPV) e o desenvolvimento de neoplasias relacionadas. **Objetivos**: Revisar aspectos epidemiológicos da infecção anal pelo HPV e sua associação com neoplasia intraepitelial anal (NIA) e câncer anal. **Métodos**: Revisão narrativa da literatura, através da busca sistematizada de artigos publicados entre julho/2012 e julho/2022, em periódicos indexados no PubMed, utilizando a combinação dos seguintes descritores: "*anal neoplams*", "*human papilloma virus*","*intraepithelial neoplasia*" e "*risk*", escritos em inglês e português. Das 182 publicações identificadas, 29 foram selecionados para análise, além de outras três publicações de relevância, totalizando 32 estudos incluídos na revisão. **Resultados e Discussão**: A infecção anal persistente por sorotipos de alto risco do HPV (HPV-AR), principalmente o HPV16, é o principal fator de risco para NIA, responsáveis por quase a totalidade dos casos de CCE anal. A incidência de NIA de alto grau e câncer anal em portadores de HIV é alta, principalmente quando associado a comportamentos sexuais de risco. Em homens que fazem sexo com homens (HSH) com a imunodeficiência são reportadas as maiores incidências de câncer anal. História prévia de neoplasias ginecológicas associadas ao HPV em mulheres aumenta a probabilidade de contaminação anal e o risco para neoplasias anais. **Conclusão***:* Reportamos o papel do HPV na possível gênese da NIA e progressão para CCE anal, principalmente em grupos de risco, nos quais encontramos altas prevalências de HPV-AR e de lesões potencialmente malignas, além das maiores incidências do câncer anal. Pesquisas são necessárias para melhor compreender a história natural do CCE anal e do papel do HPV no seu comportamento.

Palavras-chave: HPV; Neoplasia intraepitelial anal; Câncer anal; CCE; Risco.

Introduction

Anal squamous cell carcinoma (SCC), although it remains a rare type of cancer, has been increasing its incidence and mortality globally in recent decades, regardless of the gender or immunological status of the people affected[1-6]. It is commonly diagnosed in individuals between the fifth and sixth decades of life and, in contrast to its historical predominance in females, incidence rates have been comparable in both sexes in recent years, affecting women in high-income countries more frequently, and with a slight predominance in males in low-income countries[2,4-7].

The anal canal – an anatomical region approximately four centimeters long and comprising the anal transition zone (ATZ) of the squamous and glandular epithelium – is the most common site for the occurrence of anal SCC in females, while perianal carcinomas are more frequent in males[1,8]. The general term *anal cancer* is often used in the literature to describe SCC, due to the wide predominance of this histological type (up to 85%) in the anus and anal canal[1,3,6,8,9]. In this review, both terms (anal cancer and anal SCC) will be used to refer to anal carcinoma.

In the United States (US), the incidence of anal SCC rose from 0.8 cases per 100,000 people in 1975 to 1.8 per 100,000 in 2016[2-4]. There was an 18% increase in the number of new cases in that country, between 2015 and 2018[5]. The mortality rate grew, on average, by 3% per year, revealing a 15% increase in deaths from this malignancy between 2010 and 2015[3,5]. According to the American Cancer Society, for the year 2022, there is an estimated 9,440 new cases in the US (66% in females) and approximately 1,670 deaths from anal cancer[10]. European data also reveal an increase in the incidence of anal SCC in that continent, from 0.8-1 case per 100,000 people/year between 2000 and 2007, to almost 4 new cases per 100,000 in 2016[6].

In Brazil, although the estimates for anal SCC are not clearly known in the population, 1,040 deaths from cancer in the anus and anal canal (56% in females) were registered by the National Cancer Institute (INCA) in 2020, a number 14 times higher than those registered in 1990 (74 deaths)[11]. Between 2015 and 2020, there was an almost threefold increase in the number of deaths (406 in 2015), having more than doubled in males between 2018 and 2020[11]. Still according to INCA, in the last 30 years, the country followed the same worldwide trend of increase in mortality from anal cancer, with clear expression in recent years (Figure 1)[12].

A close relationship is described between anogenital infection by human papillomavirus (HPV) and the development of associated neoplasms, including anal intraepithelial neoplasia (AIN) and anal cancer[1-9,13-15]. AIN is defined by the dysplastic growth of squamous epithelial cells in the ATZ of the anal canal and can progress to invasive SCC of the anus if left untreated[1-3,6,9,13-15]. Although not very prevalent in the general population, anal neoplasms are considerably more frequent in certain risk groups, the most studied being: people living with HIV (PLWH) or with another type of immunosuppression, men who have sex with men (MSM) and women with previous gynecological HPV-related neoplasia, in addition to sexual behaviors that are considered risky, mainly receptive anal intercourse and multiple partnerships[1-6,9,13-18].

The association between HPV and other more frequent neoplasms, such as those of the cervix, has already been exhaustively studied. Cervical SCC is one of the most frequent cancers in females and its etiopathogenesis is well established in the literature[19,20], accounting for 83% of all cancers attributable to HPV[7]. However, there is a lack of consistent data regarding the epidemiology and behavior of the virus in AIN and anal cancer – despite the growing scientific production in the last decade – limiting the planning of surveillance and control strategies.

The aim of the present work is to review the scientific literature for evidence of the role of HPV in the etiopathogenesis of anal SCC and its precursor lesions, summarizing the findings of publications addressing the epidemiology of anal HPV infection and its association with AIN and anal cancer, focusing on the main populations at risk.

Methods

A narrative review was carried out through a systematic search and selection of papers published between July 2012 and July 2022, in journals indexed in PubMed, using the combination of the following keywords: "anal neoplasms" AND "human papillomavirus" AND "intraepithelial neoplasia" AND "risk". A language filter was applied to articles published in English and Portuguese.

Of the 182 publications identified by the search strategy, 29 were considered eligible based on the interpretation of titles and abstracts. These were then analyzed by the authors in full and organized into the following categories: observational studies (23 studies) and systematic review articles (six studies, of which five with meta-analysis). Eligibility criteria included addressing one or more of the following outcomes: anal HPV prevalence; prevalence of anal abnormalities (cytological and/or histological); incidence and/or risk of both AIN and anal SCC.

Publications published in journals with a Qualis lower than B2 (determined in 2019-2021), studies strictly addressing other HPV-related neoplasia or another histological type in addition to anal SCC, intervention trials focused on the prevention and/or treatment of anal cancer (including HPV vaccination), diagnostic accuracy studies or screening methods for anal neoplastic lesions, guidelines, non-systematic review papers, qualitative studies, case reports and editorials were excluded from the analysis.

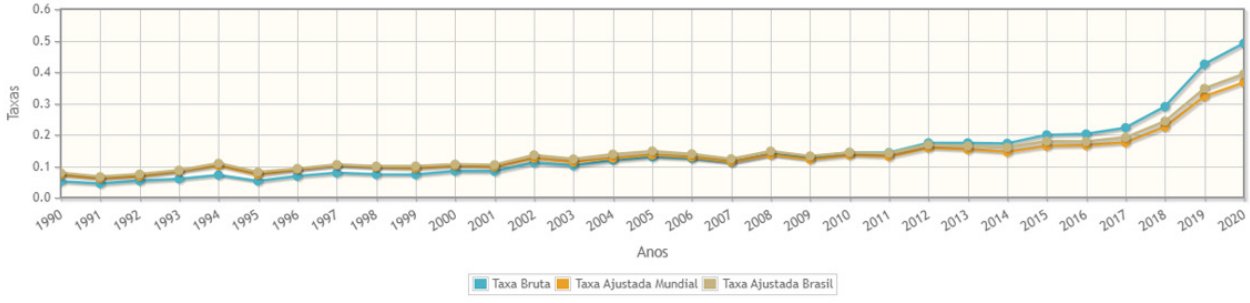

Figure 1. Graph with ANUS AND ANAL CANAL cancer mortality rates, crude and age-adjusted, by world and Brazilian populations in 2010, per 100,000 men and women, between 1990 and 2020[12].

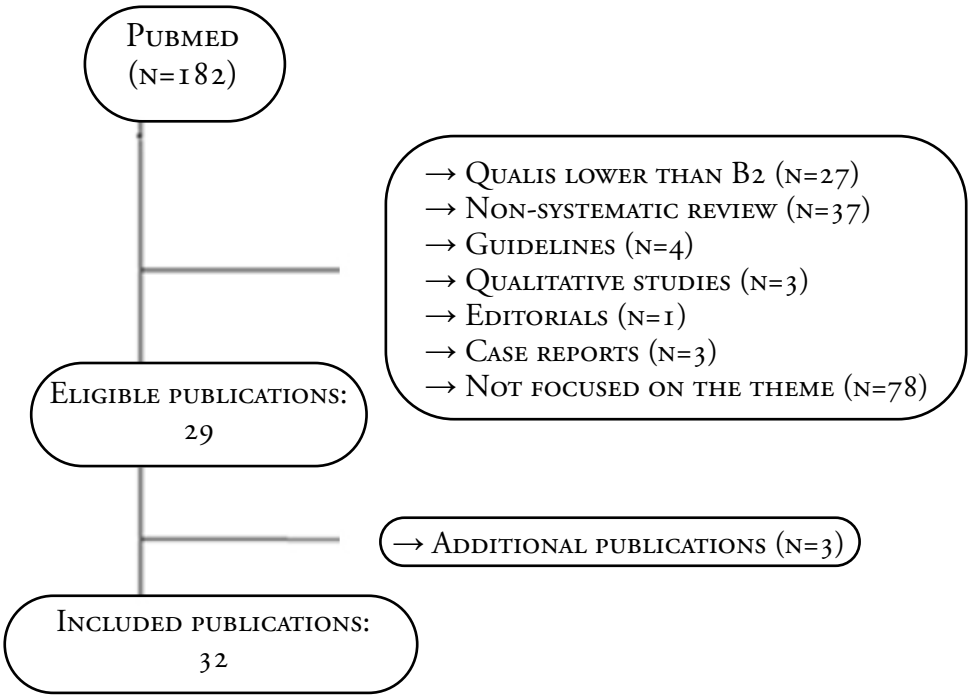

Figure 2. Detailed search methodology.

Three other studies considered relevant for analysis were also selected (one systematic review with meta-analysis and two observational studies) cited in previously selected articles, with a total of 32 publications included in this review (Figure 2). The main characteristics of the studies (authorship, year of publication, type of study/objectives and Qualis) are summarized in Chart 1.

RESULTS

Data extracted from the included publications were presented throughout the narrative, in order to contemplate the following themes proposed for this review: (1) anal HPV infection and associated neoplasms; (2) HIV-HPV co-infection and other associated factors; (3) anogenital HPV infection in females. Casuistic and main results found in the studies are summarized in Chart 2.

1. Anal HPV infection and associated neoplasms

HPV is a small non-enveloped virus, containing a double-stranded DNA genome, belonging to the *Papillomaviridae* family[21]. It presents more than 200 serotypes that infect humans, of which approximately 40 can be transmitted by sexual contact, affecting the anogenital tract in both genders[21-23]. They infect squamous epithelia and can induce various proliferative cutaneous and mucosal lesions, including condylomata, intraepithelial neoplasms and eventually SCC, in regions such as the vulva, vagina, cervix, perineum, anus, penis and oropharynx[2-4,21-23].

The HPV serotypes that affect the anogenital tract can be classified as low- vs. high-risk, according to the oncogenic potential and the lesions to which they are usually associated. Most infections are caused by low-risk serotypes (HPV-LR), the most common being HPV6 and HPV11, usually associated with the development of condyloma and other lesions with low oncogenic potential[2,4,14,22]. Approximately 90% of anogenital warts are caused by HPV6 and HPV11[14,22]. The most studied high-risk serotypes (HPV-HR) are HPV16 and HPV18, which are correlated with potentially malignant lesions and SCC itself, and co-infection between different serotypes may occur[2,4,15,21].

Currently, non-invasive squamous lesions suggestive of HPV infection are classified into two cytomorphological diagnoses, as described in The Lower Anogenital Squamous Terminology Standardization (LAST) project[24], providing guidelines for unification of nomenclature: low- or high-grade squamous intraepithelial lesion (LSIL and HSIL, respectively). They are associated with the degree of dysplasia and the probability of malignant transformation to SCC, following the same terminology for all anogenital sites[24].

In the anus, HSIL correlates with the histological diagnosis of high-grade AIN – grades II and III – which present, respectively, moderate and severe dysplasia, the latter equivalent to carcinoma *in situ*[21-24]. It is associated with HPV-HR, which express oncoproteins capable of interfering with the cell cycle, favoring persistent viral infection and are therefore considered pre-malignant[2,4,9,14,15,21-24]. LSIL is associated with HPV-LR, correlates with condylomata

Chart 1. Characterization of the studies.

Authorship	Pub. Year	Type of Study/Objectives	*Qualis*
De Vuyst H *et al.*	*2009*	Systematic Review + Meta-analysis: HPV prevalence in different anogenital neoplasms.	A1
Lin C *et al.*	2017	Systematic Review + Meta-analysis: anal canal HPV prevalence (sex and HIV).	A1
Medina-Laabes DT *et al.*	2018	Cross-sectional study: HPV-HR association with AIN in HIV+ individuals.	B2
Hildebrand JA *et al.*	2019	Retrospective cohort: HPV-HR association with AIN.	A1
Silverberg MJ *et al.*	2012	Multicohort: anal SCC incidences in HIV+ and - individuals.	A1
Machalek DA *et al.*	2012	Systematic Review + Meta-analysis: anal HPV and AIN prevalence, anal SCC incidence, in HIV+ and - MSM.	A1
Sendagorta E *et al.*	2014	Cross-sectional/prospective cohort: HPV-HR association with AIN in HIV+ MSM.	B1
Schofield AM *et al.*	2016	Prospective cohort: anal HPV and AIN prevalence in HIV+ and - MSM.	A1
Boldrini NAT *et al.*	2018	Cross-sectional study: anal HPV prevalence in HIV+ individuals; risk factors.	B1
Faber MT *et al.*	2020	Prospective cohort: risk of anal SCC from previous precursor lesions.	A1
Donà MG *et al.*	2018	Cross-sectional study: prevalence of changes in anal cytology in HIV+ and - MSM; HSIL peak age.	A2
Stier EA *et al.*	2015	Systematic Review: epidemiology of anal HPV infection, AIN and anal SCC in females.	A1
Heard I *et al.*	2015	Cross-sectional/prospective cohort: anal HPV prevalence in HIV+ women; risk factors for high-grade AIN and anal SCC.	A1
Stier EA *et al.*	2019	Prospective cohort: anal HPV and AIN prevalence in HIV+ women; risk factors for high-grade AIN.	A1
Duan R *et al.*	2022	Cross-sectional study: anal HPV prevalence in HIV+ women; risk factors.	A2
Gandra S *et al.*	2015	Retrospective cohort: HPV-HR association with AIN in HIV+ individuals.	A1
Larsen HK *et al.*	2020	Cross-sectional study: high-grade AIN prevalence in kidney transplant recipients vs. immunocompetent controls; risk factors.	A1
Chinyowa S *et al.*	2018	Cross-sectional study: anal HPV prevalence in HIV+ individuals; risk factors.	B2
Machalek DA *et al.*	2016	Prospective cohort: AIN prevalence in MSM; risk factors.	B1
Melo VH *et al.*	2014	Multicenter cross-sectional study: prevalence of anal cytology abnormalities in HIV+ men; risk factors.	B2
Lammé J *et al.*	2014	Prospective cohort: HPV-HR and anal dysplasia in immunocompetent women with HPV+ cervical abnormality.	A1
Donaire C *et al.*	2017	Prospective cohort: HPV-HR and anal dysplasia in immunocompetent women with HPV+ cervical abnormality.	B2
Eráclio SA *et al.*	2019	Cross-sectional study: anal HPV prevalence in women with HPV+ premalignant cervical lesions or cervical SCC; risk factors.	B1
Wohlmuth C *et al.*	2020	Prospective cohort: prevalence of anal HPV, AIN and anal cytology abnormalities in women with high-grade cervical dysplasia/SCC.	A1
Lopez-Cavanillas B *et al.*	2021	Cross-sectional study: prevalence of anal HPV and anal cytology abnormalities in women with high-grade cervical neoplasia; risk factors.	B2
Eleutério Jr *et al.*	2022	Case-control study: frequency of anal HPV-HR and anal cytology abnormalities in women with cervical SCC.	B2
Lin C *et al.*	2019	Systematic Review + Meta-analysis: cervical determinants in the prevalence of anal HPV, high-grade AIN and anal SCC in women, according to HIV status.	A1
Ebisch RMF *et al.*	2017	Prospective cohort: incidence and risk of neoplasms and HPV+ anogenital SCC in women with grade III cervical intraepithelial neoplasia (CIN III).	A1
Loopik DL *et al.*	2019	Prospective cohort: incidence and risk of neoplasms and HPV+ anogenital SCC in women with CIN III recurrence.	B1
Bertoli HK *et al.*	2020	Prospective cohort: incidence and risk of high-grade vulvar/vaginal/anal intraepithelial neoplasia or SCC, according to cervical HPV-HR.	A1
Gilbert DC *et al.*	2018	Systematic Review + Meta-analysis: incidence and risk of a 2nd HPV+ SCC after a previous diagnosis.	A1
Kalliala I *et al.*	2020	Systematic Review + Meta-analysis: incidence and risk of new HPV+ SCC after a previous diagnosis of neoplasia/cervical SCC in women.	A1

Chart 2. Casuistry and main results.

Year; Authors	Casuistry	Main results
2009; De Vuyst H *et al.*	29 studies (n: 1280 with AIN and n: 955 with anal Ca). Majority: HIV + and MSM.	HPV preval. + anal Ca: 84.3%; HPV in high-grade AIN: 93.9%. HPV16 more frequent.
2017; Lin C *et al.*	95 studies (n: 2358 anal Ca).	High-risk HPV preval. in anal Ca, regardless of sex or HIV status: 90%. Preval. of high-risk HPV in HIV+ with anal Ca: 98%.
2018; Medina-Laabes DT *et al.*	n: 239 HIV+.	High-risk HPV preval. in high-grade AIN: 95.6%.
2020; Hildebrand JA *et al.*	n: 210, screening for anal neoplasia. Majority of men HIV+; Most women HIV-	High-risk HPV preval. in AIN grade III: 67.5%.
2012; Silverberg MJ *et al.*	13 studies (n: 34,189 HIV+/n: 114,260 HIV-). Most studies in men, regardless of HIV status.	Ca anal incid. in HIV+ men n: 46:100,000; HIV- men: n: 2:100,000; MSM HIV+: 131:100,000; HIV+ women: 30:100,000; HIV- women: 0:100,000.
2012; Machalek DA *et al.*	21 prevalence studies. HPV (n:2718 MSM HIV+, n:3246 MSM HIV-); 07 prevalence studies. NIA (n:1442 MSM HIV+ and n:449 MSM HIV-); 09 studies for anal Ca incid. (n:956,095 HIV+ and n:48,881 HIV-).	Anal Ca incid. in HIV+ MSM: 45,9:100,000; HIV- MSM: 5,1:100,000. HPV preval. in HIV+ MSM: 92.6%. Preval. High-grade AIN in HIV+ MSM: 29.1%; HIV- MSM: 21.5%.
2014; Sendagorta E *et al.*	n:298, screening for HSIL and HPV preval. (MSM and bissexuals; HIV+).	High-risk HPV preval. in HIV+: 80,9%. Abnormal citology: 80,7%; HSIL: 54%. HPV 16 more frequent.
2016; Schofield AM *et al.*	n: 284 MSM; screening for anal Ca (n:203 HIV+ and n:81 HIV-).	HPV preval. in HIV+ MSM: 88%; high-grade AIN preval. in HIV+ MSM: 26.6%; HIV- MSM: 20.9%.
2018; Boldrini NAT *et al.*	n: 223 HIV+ screening for anal Ca (n:80 men and n:143 women).	HPV preval. in HIV+: 68.6% (71% men). Abnormal cytology: 2.2% for LSIL and 0.8% for HSIL; 02 cases with high-grade AIN; HPV 16 more frequent.
2020; Faber MT *et al.*	n:12.6174 (pepole with non-neoplastic anal disease or NIA).	5-year anal Ca risk increases with the severity of the injury Risk incidence ratio of anal canal in non-neoplastic lesions: 2.8%. 5-year risk of anal Ca after AIN III: 14.1% in HIV+ and 3.2% in HIV-.
2018; Donà MG *et al.*	n: 1021 MSM: screening for anal neoplasms (n:388 HIV+ and n:633 HIV-).	HPV preval. in HIV+ MSM: 95% (77.9% for high-risk serotypes); Peak HSIL age (35 – 39 years in HIV+ MSM vs >45 years in HIV-).
2015; Stier EA *et al.*	23 HPV prev. studies (n: 1284 HIV+ women and n: 6202 HIV-); 21 AIN prev. studies (n: 2565 HIV+ women and n:2789 HIV-); 23 studies: anal Ca incid.	Anal Ca incid. in HIV+ women: 3.9-30:100,000; HIV- women: 0.55-2.4:100,000; high-risk HPV preval. in HIV+ women: 15-85%; High-grade AIN preval. in HIV+ women: 3-26%; HIV- women: 0-3%.
2015; Heard I *et al.*	n: 171 HIV+ women: screening for anal neoplasms.	High-risk HPV preval. in HIV+ women: 57.9%. High-grade AIN preval. in HIV+ women: 12% (51.9% HPV16).
2019; Stier EA *et al.*	n: 256 HIV+ women > 18 yr, cervicai/ vaginal/anal citology and e HRA with biopsy.	Anal HSIL preval. in HIV+ women: 27%. HSIL-related anoreceptive sexual intercourse history (OR 2,44).
2022; Duan R *et al.*	n: 409 HIV+ women. Colposcopy and biopsy in cervical HPV+ or abnormal citology.	HPV preval. HPV in HIV+ women: 34,2% (cervical) and 34,7% (anal). High-grade NIA (30,6% and 30,3% respectively). Early initiation of antiretroviral therapy decreases the prevalence of anogenital HPV.
2015; Gandra S *et al.*	n: 221 HIV+: screening for anal neoplasms. Majority MSM (74 women).	High-risk HPV preval.: 40% (27% in women). High-grade AIN preval.: 66% (25% in women).

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Chart 2. Casuistry and main results.

Year; Authors	Casuistry	Main results
2020; Larsen HK *et al.*	n: 250 kidney transplant recipients and n: 250 controls (125 men and 125 women in each group).	Preval. high-grade AIN in kidney transplant recipients with HPV-AR: 3.8%; in immunocompetent controls: 9.5%. Risk factors: anoreceptive sexual intercourse and presence of genital warts.
2018; Chinyowa S *et al.*	n: 152 HIV+ (n: 64 men and n: 88 women) and 1 MSM.	HPV preval. in HIV+ individuals: 44% (60% in women); Risk factors: perianal condyloma, multiple sexual partners and history of CIN.
2016; Machalek DA *et al.*	n: 617 MSM (n: 220 HIV+ and n: 397 HIV-); 95.3% homosexuals.	High-grade AIN preval. in HIV+ MSM: 47%; HIV- MSM: 32%; most frequent HPV16. Risk factors: anoreceptive sexual intercourse, multiple partners, HIV, HPV16.
2014; Melo VH *et al.*	n: 343 HIV+ men.	Cytology abnormalities preval. in HIV+ men (LSIL/ HSIL): 24.8%; High-risk HPV: 36.7%; Risk factors: smoking, MSM, high-risk HPV.
2014; Lammé J *et al.*	n: 196 women with abnormal cervical cytology results who underwent anal cytology.	Anal HPV preval.: 32.5%. Abnormal anal cytology: 17.6%.
2017; Donaire C *et al.*	n: 166 women with cervical changes associated with HPV, undergoing anal cytology.	Anal high-risk HPV preval.: 64.4% (majority HPV 16 and 18). Abnormal anal cytology: 3.61%.
2019; Eráclio SA *et al.*	n: 152 women with cervical histopathological diagnosis of HPV-related lesions, subjected to anal cytology and HRA with biopsy.	Anal high-risk HPV preval.: 66.4% (majority HPV 16 and 18). Risk factors: anoreceptive sexual intercourse, alcohol consumption.
2020; Wohlmuth C *et al.*	n: 317 women with HSIL or cancer, = or > 40 yr, subjected to anal cytology with DNA-HPV test. HRA with biopsy in abnormal cytologies.	Preval. abnormal anal cytology: 30.3% (12.5% HSIL; 19.8% LSIL; 6.3% ASC-H; 61.5% ASC-US). 31.9% HPV+. Risk factors: advanced age and smoking.
2021; Lopez-Cavanillas B *et al.*	n:171 women between 21 and 65 yr with high-grade CIN, subjected to DNA-HPV, anal citology and HRA.	Preval. HSIL: 31% (mostly HPV16). Preval. HPV: 45.8%. Risk factors: immunosuppression, cervical HPV and > 40 years.
2022; Elutério Jr J *et al.*	n:59 women diagnosed with weakly invasive SCC in the cervix and n:60 controls. Subjected to cytology and HPV-DNA in anal samples.	Negative for AIN or malignancy: 64.4% (CCE) and 85% (control). Negative for HPV test: 31.5% (CCE) and 93.3% (control). 67.6% HPV 16.
2019; Lin C *et al.*[40]	36 studies n: 13427 women (n: 3352 HIV+);	Anal high-risk HPV preval. in HIV+ women: 62%; HIV-women: 33%. Cervical determinants: HIV, cervical HPV16 and previous diagnosis of cervical Ca or high-grade cervical lesions.
2017; Ebisch RMF *et al.*	n: 178,036 women (89018 with histopathological diagnosis of CIN III; 89018 controls).	CIN III increases the risk for the development of intraepithelial neoplasms and Ca in the vulva, vagina, anus and oropharynx, compared to the absence of CIN III. Greater strength of association for vaginal Ca (IRR: 86,08).
2019; Loopik DL *et al.*	n: 1797 women with recurrent CIN III compared with n:1797 women with no history or 1 episode of CIN III.	Women with recurrent CIN III were at increased risk of developing high-grade non-cervical HPV-related premalignancies (IRR: 25.96), compared to women with a single episode of CIN III (IRR: 2.48).

Continued...

...continued Chart 2

Chart 2. Casuistry and main results.

Year; Authors	Casuistry	Main results
2020; Bertoli HK *et al.*	n: 40399 women; cervical Ca screening.	Cervical HPV16 increases the risk for the development of high-grade intraepithelial neoplasms in the vulva, vagina, and anus, compared to the absence of any high-risk cervical serotypes. Greater strength of association for vaginal intraepithelial neoplasms (HR: 23,5).
2018; Gilbert DC *et al.*	32 studies: incid. of second HPV-related cancer (cervical, anal, vulvovaginal, penile and oropharynx).	Diag/treatment of previous Ca + HPV increases the risk of a second Ca associated with the virus. Stronger strength of association between vulvovaginal cancer and anal Ca.
2020; Kalliala I *et al.*	27 studies reporting incidences of HPV-related cancer or mortality after CIN treatment.	Incidence of cervical Ca after NIC treatment: 39 per 100,000 woman-years. Cervical Ca RR: 3.30 (general population comparison). RR greater for women >50 years, RR Ca vaginal: 10.84; RR Ca vulvar 3.34 and RR Ca anal: 5.11. Elevated cervical/vaginal Ca mortality (RR 5.04).

and grade I AIN – which presents mild dysplasia – and, despite the low risk of malignant transformation, can eventually progress to HSIL[2,4,9,14,21-24]. In anal cytology, two diagnoses can still be described: atypical squamous cells of undetermined significance (ASC-US) – considered LSIL – and atypical squamous cells without excluding high-grade lesion (ASC-H), to distinguish cases that are more likely to exist as a precursor lesion of anal cancer[13,14].

High HPV prevalences are described in patients with AIN and anal SCC, usually associated with persistent anal infection by HPV-HR[1-3,7,14,15,21]. In a broad meta-analysis comparing different anogenital neoplasms, De Vuyst *et al.* (2009)[25] found a high frequency of anal HPV infection (93.9%) in individuals with high-grade AIN and an overall prevalence of nearly 85% in cases of anal SCC. In the study mentioned, HPV16 was the serotype most frequently identified in samples with high-grade lesions and anal cancer (73.4% in the latter). In a more recent meta-analysis including 2,358 people with anal SCC, Lin et al. (2017)[26] described an anal HPV-HR prevalence that reached 90%, regardless of gender or immunological status. HPV16 was identified in 86% of samples with anal cancer and its frequency was directly associated with the severity of the lesion[26].

The magnitude of HPV-AR frequency as anal lesions progress to high-grade can be seen in recent observational studies. In a cross-sectional study investigating 239 PLWH, Medina-Laabes et al. (2018)[27] revealed an anal HPV-HR prevalence of 63.6% in adults without anal diaplasia, rising to 70.5% in those with low-grade histological lesions, and reaching 95.6% in those with high-grade AIN. In a retrospective analysis involving 121 participants of an anal cancer screening program, Hildebrand et al. (2019)[28] demonstrated that the identification of HPV-HR was significantly higher in samples with AIN grade III (67.5%) compared to AIN grades I and II (12.9%) and to condyloma (29.5%).

2. HIV-HPV co-infection and other associated factors

Some population groups are considered at high-risk for persistent anal HPV infection, increasing the probability of developing associated neoplasms and cancer. PLWH represent the most studied population, revealing a strong association between HIV-HPV co-infection and the increase in AIN prevalence and in anal SCC incidence. It is estimated that more than 90% of HIV carriers are infected by HPV and that, in up to 90% of those who develop AIN, some high-risk serotype is identified[2]. Furthermore, the prevalence of the virus in those who developed anal cancer can reach 98%, as reported in a previously described meta-analysis[26].

Compared to the general population, PLWH have a 30–100 times greater risk of developing this malignancy, with incidences varying according to the subpopulation studied[2,4]. When associated with sexual practices that are considered risky – such as receptive anal sex – the incidence is even higher, with approximately 80% of anal SCC in people with this immunodeficiency occurring in MSM[2,4,9,14].

Silverberg et al. (2012)[29], in a classic multicohort, estimated an annual incidence of 46 cases of anal cancer per 100,000 HIV-positive men, compared to 2 cases per 100,000 HIV-negative men, the latter possibly reflecting the general population. In that study, when only MSM with immunodeficiency were analyzed, the incidence reached

131 cases per 100,000 per year. Machalek et al. (2012)[30] also reported estimates in a broad meta-analysis, in which MSM with and without HIV were compared, revealing an annual incidence of 45.9 cases of anal SCC per 100,000 MSM with HIV against 5.1 cases per 100,000 immunocompetent MSM. These authors found an anal HPV-HR prevalence of 79.1% in MSM carrying HIV, identifying high-grade AIN in 29.1% of the analyzed samples, compared to 21.5% in samples of immunocompetent MSM.

Sendagorta et al. (2014)[31] reported 22% of positive histological analyses for high-grade anal lesions in 298 MSM with HIV, identifying HPV-HR in 81% of the samples. Schofield et al. (2016)[32] also reported high anal HPV-HR prevalence (88%) in 284 MSM (most carrying HIV), in addition to high-grade AIN prevalence of 26.6% and 20.9% in HIV-positive and negative MSM, respectively. Boldrini et al. (2018)[33], in turn, documented low prevalences of anal cytological abnormalities (2.2% for LSIL and 0.8% for HSIL) in 223 PLWH (mostly female), and only two cases of high-grade AIN. However, when only samples from MSM were analyzed in this study, the prevalence of abnormal anal cytology reached more than 40%.

More recently, in a large cohort based on Denmark population registries, comprising more than 126,000 individuals with previous anal lesions, Faber et al. (2020)[34] estimated a 4% increase in the absolute risk for anal SCC five years after the diagnosis of grade III AIN. The 5-year risk rises to 14% in PLWH, against 3% in immunocompetent people. Still, the peak prevalence of high-grade lesions seems to occur at younger ages in HIV carriers, as demonstrated by Donà et al. (2018)[35] with data from 1,021 MSM (35-39 years in HIV-positive MSM vs. > 45 years in immunocompetent ones).

Regarding women living with HIV, studies are sparser, as well as in heterosexual men (HSM). According to Stier et al. (2015)[36], in a systematic review, the annual incidence of anal SCC varies between 3.9-30 cases per 100,000 HIV-positive women and between 0.55-2.4 cases per 100,000 immunocompetent ones, the latter possibly reflecting the general population. Heard et al. (2015)[37] identified anal HPV-HR in 57.9% of 171 women with HIV in a cohort, revealing 12.9% of samples presenting high-grade AIN. In another cohort involving 256 HIV carriers, Stier et al. (2019)[38] reported a prevalence of high-grade anal lesions in 27% of women. Also in this study, a history of anal receptive sexual intercourse was associated with the presence of precursor lesions of anal cancer.

In a recent study also investigating 409 women living with HIV, Duan et al. (2022)[39] estimated an overall anal HPV prevalence of 34.7%, being 30.6% for HPV-HR. In this cross-sectional study, which also analyzed cervical specimens for viral identification, a strong correlation between cervical and anal HPV positivity was found. In a retrospective cohort conducted with 221 PLWH (74 females and 40 HSM), Gandra et al. (2015)[40] reported similar anal HPV-HR prevalences in women and HHS (27% and 28%, respectively), and samples with high-grade AIN in 25% and 13%, respectively.

Other forms of chronic immunosuppression – such as immunosuppressive pharmacotherapy after solid-organ transplantation – are also associated with HPV-related malignancies, including AIN and anal SCC. Anal HPV-HR prevalences ranging from 18-23% in liver transplant patients and up to 50% in kidney transplant patients have been described[2,4,41]. In those carrying HIV, the prevalence is even higher, reaching 67% after 24 months of transplantation[2,4,41].

Studies with transplant patients also reveal the presence of some degree of anal dysplasia in 20-24% of cases, in addition to a 5-fold increase in the anal cancer risk[2,4,41]. In a recent cross-sectional study, Larsen et al. (2020)[42] reported high-grade AIN prevalences reaching 33.8% in renal recipients with anal HPV-AR, compared to 9.5% in immunocompetent controls. Also in this study, the practice of receptive anal sexual intercourse and the presence of genital warts were associated with the development of high-grade lesions.

Finally, other factors associated with both AIN and anal cancer described in the literature, regardless of immunological status or sexual orientation, are: smoking, sexual behaviors considered at risk (receptive anal intercourse, multiple partnerships), history of previous gynecological HPV-related neoplasms in women, presence of genital warts and anal infection by high-risk serotypes (mainly HPV16) or by multiple serotypes[2-4,6,33,37,43-46].

Chart 3 summarizes the main risk factors for HPV-AR infection and/or persistent anal infection:

Chart 3. Risk factors for persistent HPV anal infection. Adapted from Roberts JR et al. (2017), Buzard C et al. (2018), Davis KG et al; (2018).

Behaviors: • MSM; • Multiple sexual partners; • Anoreceptive intercourse; • Smoking.
Co-infections: • HIV; • HPV (mainly high-risk types HPV16 and HPV18); • Multiple HPV subtype infection;
Chronic Immunosupression: • Immunosuppressive therapy in solid organ recipients;
Anogenital Neoplasm: • History of anogenital warts; • Women with a history of cervical, vaginal or vulvar cancers.

3. Anogenital HPV infection in females

There is a growing body of evidence suggesting that women with prior HPV-related gynecological malignancies

may have concurrent anal infection,[36] putting them at risk for AIN and anal SCC. Several studies have evaluated the association between cervical abnormalities suggestive of viral infection and a prevalence of anal HPV and related neoplasms.

Lammé et al. (2014)[47] found this significant association in a cohort involving 196 immunocompetent women who had abnormal results in cervical cytology, revealing an anal HPV-HR prevalence of 32.5% in the analyzed samples, with 17.6% of abnormal anal cytology. These authors already suggested that cervical HPV-HR infection increases the odds for the presence of high-risk serotypes also in the anus, increasing the probability of abnormalities in anal cytology. In Donaire et al. (2017)[48], despite having reported a high anal HPV-HR frequency (64.4%) in a cohort evaluating 166 immunocompetent females with cervical alterations, abnormalities in anal cytology were detected in only 3.61% of the samples.

Eráclio et al. (2019)[49] also reported a higher anal HPV-HR prevalence (66.4%) in 152 women with previous cervical and/or anal neoplasms. In this cross-sectional study, serotypes HPV16 or HPV18 were identified in 52.6% of anal specimens with high-grade AIN, while receptive anal sexual intercourse was reported by 73% of women. Wohlmuth et al. (2020)[50] investigated 317 females with a previous history of high-grade cervical lesions or cervical cancer, 33.4% of whom had abnormal anal cytology, with a lower HPV-HR frequency (31.9%). In this cohort, there was a significant association between abnormal anal cytology results and HPV-HR identification (42% in LSIL samples and 66.7% in both HSIL and ASC-H samples). More recently, Lopez-Cavanillas et al. (2021)[51] identified anal HPV-HR in 45.8% of 171 women with high-grade cervical neoplasia and in 84.2% of abnormal anal cytology specimens. On the other hand, there was no significant difference in anal HPV-HR prevalence between samples with low or high-grade cervical lesions in this study.

Also, in a recent case-control study evaluating 54 Brazilian women diagnosed with cervical SCC, Elutério Jr et al. (2022)[52] observed a higher HPV-HR frequency and abnormal anal cytology compared to 60 controls without cervical neoplasia, with HPV16 being the most frequent serotype (67.6%) in the tested samples. Furthermore, in a broad meta-analysis investigating cervical determinants in the anal HPV prevalence and high-grade AIN – involving 13,427 females – Lin et al. (2019)[53] concluded that cervical HPV16 infection and previous diagnosis of cervical high-grade lesions or cancer are associated with an increased risk of anal dysplasia and cancer. In this study, an increase in the anal prevalence of HPV16 in women with HPV-HR in the cervix was found, regardless of the immunological status.

Studies have also demonstrated associations between different anogenital HPV-related neoplasms in females. Ebisch et al. (2017)[54] revealed an increased risk of new anogenital SCC attributable to HPV in women previously diagnosed with grade III cervical intraepithelial neoplasia (CIN III). In this large cohort, a total of 89,018 participants who had a significantly higher risk of developing other high-grade anogenital neoplasms, as well as anal, vaginal and vulvar cancer, were included, compared to women without a previous cervical diagnosis. The relative risks for high-grade AIN and anal cancer were maintained for up to 20 years after the diagnosis of CIN III, and the strength of association was greater for high-grade vaginal intraepithelial neoplasia and vaginal cancer[54].

In the most recent follow-up of a subset of this cohort, including 1979 women who recurred from a CIN III lesion two years after treatment, Loopik et al. (2020)[55] reported no new cases of anal cancer, despite the increased risk for non-cervical HPV-related premalignant neoplasms. Also, in a recent cohort involving 40,373 women aged 14-95 years, Bertoli et al. (2020)[56] concluded that cervical HPV16 infection increases the risk for the subsequent high-grade intraepithelial neoplasia in the vulva, vagina and anus during a 15-year follow-up, with the strength of the association also greater for vaginal cancer.

Finally, two meta-analyses summarize the risks of subsequent anogenital SCC in females. Gilbert et al. (2018)[57] investigated the development of a second HPV-related cancer in patients with prior anogenital malignancy. This meta-analysis revealed an increased risk for most neoplasms compared to previously healthy patients, with the strongest association between anal and vulvo-vaginal cancer, in which the previous diagnosis of one increases the risk of the other by up to 10 times. More recently, Kalliala et al. (2020)[58] also reported a significant increase in the risk of vulvo-vaginal cancer, followed by anal cancer, in women previously treated for cervical intraepithelial neoplasia, compared to the general population. This meta-analysis, in turn, revealed a 5-fold increase in the risk of anal SCC in a universe of more than 600,000 women, with relative risks remaining high for at least 20 years after treatment.

Discussion

HPV is the most common sexually transmitted etiological agent among those that cause anogenital lesions. It is estimated that almost all sexually active people acquire the infection at some point in their lives, although it has an asymptomatic course with spontaneous resolution in up to 90% of cases[2-4,13,14]. The risk of exposure to HPV can reach 25% with each new sexual partnership, affecting approximately 45% of the general population.[9] Anal infection, in turn, is described in approximately a quarter of the immunocompetent heterosexual male population and in up to a third of healthy women[15].

The incidence of anal SCC has been increasing in both sexes in recent decades, while other gastroenterological cancers have declined in several countries.[59] The evidence considered in this work review supports that AIN is

associated with HPV infection and can progress to anal cancer, regardless of the gender or immune status of the people affected[25-28,30-32]. Due importance is given to HPV-HR, which are attributed to up to 90% of all anal SCCs, and can be identified in more than 90% of high-grade anal lesions in certain risk groups[26-28].

Compared to cervical SCC, where HPV16 and HPV18 are the most frequently encountered serotypes (together they make up approximately 75% of cervical cancers)[7,25,36] a strong HPV16 predominance is described in anal SCC[7]. We noticed the broad protagonism of this serotype in the analyzed studies, with prevalences reaching up to 86% (against 55% in cervical cancer), as reported in a meta-analysis[26]. In the anus, HPV16 seems to have greater carcinogenic potential compared to other HPV-AR, as its prevalence increases with progression to higher-grade lesions and cancer[26]. HPV18, on the other hand, has its prevalence surpassed by other HPV-HR in anal SCC, despite being among the most frequent in high-grade AIN[26].

Most studies investigating the HPV association with anal neoplasms are carried out in Europe and North America, while there is a lack of epidemiological data in Latin America. In a meta-analysis involving 18 observational studies conducted in Brazil, evaluating people with non-cervical genital cancer, Peder et al. (2018)[60] found only one study for anal SCC, whose findings are consistent with those of this review. A high anal prevalence of HPV (81.5%) was reported in this cancer, with an HPV16 predominance identified in 100% of the positive samples for the virus[60].

In certain risk groups we found the highest prevalences of HPV anal infection, reaching up to 98% in PLWH[26,59], in which the highest incidences of anal SCC are also described[29,30,34]. HIV carriers are susceptible to persistent HPV infection, with anal prevalence generally exceeding 80% in the MSM population, to which the highest risk of developing anal cancer is attributed, with incidences ranging from 46 to 131 cases per 100,000 HIV-positive MSM per year in this review[28,29]. These high rates are concerning, as they are comparable to the incidence of cervical SCC before the introduction of screening programs for this cancer[30].

Meta-analysis[30] data also reveal that nearly a third of PLWH presents high-grade AIN, while some observational studies differ in results, with prevalences ranging from 20-30% in HIV-positive MSM[31-33]. Furthermore, the absolute risk of developing anal SCC five years after the diagnosis of the high-grade lesion seems to increase exponentially in HIV patients compared to immunocompetent individuals (14% and 3%, respectively)[34]. We also found studies suggesting a peak prevalence of these lesions at younger ages in this population, in addition to a strong association between sexual initiation before age 15 and HPV-HR infection[32,35].

In female HIV carriers, an increase in both the prevalence of AIN and the incidence of anal SCC is also observed, despite greater inconsistency in epidemiological results, due to the smaller number of studies in this population[33,36-40]. We found anal HPV-HR prevalences ranging from 14-85%[9,14,36-40] and high-grade AIN between 3–27% in women living with HIV, compared with 0-3% in in those who are immunocompetent[4,36-40]. We also showed a concordant prevalence of high-grade anal lesions in both women and HSM with HIV[38,40], but sometimes with lower prevalence in females[37,40].

It is believed that the HIV-related immunosuppression increases the activity and duration of the HPV-HR infection, reducing the viral elimination capacity, reflecting the high prevalence described in the literature regarding this population[4,9,43,61]. However, a meta-analysis[34] has reported a lower anal HPV16 frequency in PLWH with anal SCC, compared to immunocompetent people with this cancer (70% vs 85%) and approximately one third of those immunocompromised had multiple infections with other HPV-HR. It is suggested that HPV16 has a greater ability to escape host immune control than other carcinogenic serotypes and that, in patients with impaired immune function, other HPV-HR may persist longer in the anus and cause lesions more frequently[26,52].

Furthermore, the role of immunosuppression in amplifying exposure to anal HPV-AR appears to be important regardless of etiology, as revealed in patients receiving pharmacological immunosuppression after solid organ transplantation[2,4,41,42]. In this population, both immunosuppression duration and intensity seem to contribute to the increasing risk of HPV infection and development of neoplasms[41,42]. Approximately half of kidney transplant patients may have anal HPV-HR, with high-grade AIN being identified in up to one third of cases in this review[42]. Yet, the risk for anal SCC may increase by up to five times in transplant recipients compared to the general population[41].

In immunocompetent people, in turn, most anogenital HPV infections are transient and only a small proportion of individuals develop anogenital neoplasia, usually due to persistent HPV-HR infections[61]. In this context, we found incidences of anal SCC reaching 2–2.4 cases per 100,000 people without immunodeficiency, in both sexes, suggesting that it remains a rare condition in the general population[29,30,36].

The higher incidence of AIN and anal cancer in certain at-risk populations is due, in part, to the high anal HPV-HR prevalence in these groups, and due to the fact that these are the groups in which most studies are carried out. Nevertheless, knowledge of the impact of behavioral factors – regardless of gender, immunological status or sexual orientation – on the risk of HPV-HR infection and/or persistent anal infection is relevant. The factors most frequently found in this review were anal receptive sexual intercourse, multiple sexual partnerships and smoking[38,39,42-46,49].

The incidence of anal cancer can even double in immunocompetent MSM compared to the general population, as reported in a meta-analysis[30]. Despite a

prevalent practice in this group, we found few studies involving women reporting receptive sexual anal intercourse, proving to be an important factor associated with the anal prevalence of HPV-HR and SCC precursor lesions in these studies[38,49]. There is, therefore, a greater demand for evidence in different behavioral contexts, regardless of gender or sexual orientation. Unfortunately, sociocultural limitations can still make it difficult for study participants to report these practices, making it difficult to obtain epidemiological data.

In this context, preliminary results of the POP-Brasil project (Epidemiological Study on the National Prevalence of HPV Infection) revealed that a large number of young Brazilians (83.4%) exhibit high-risk sexual behavior[62]. In this cross-sectional, multicenter study, involving 5,812 females and 1,774 males (mean age 20.6 years), a considerable overall prevalence of HPV (54.6%) was estimated, with high-risk serotypes identified in 38 .4% of participants. These data point to the possible impact of behavioral factors on the HPV-related neoplasms incidence – including AIN and anal SCC – justifying the need for public health policies focused on prevention and control in the young population.

Anal SCC shares certain aspects with other more frequent HPV-related genital neoplasms such as cervical cancer, which also presents as SCC[4,6,9,36]. It is notable that the histological transition zone of the anal canal as well as the uterine cervix – an area of high cell turnover – is the most common site where HPV changes are found, conferring clinical and histological similarity to these two types of cancer[4,9,13]. The anus and uterine cervix also share common embryological origins and equivalent susceptibilities to viral infection, favoring the presence of the same serotypes in both malignancies[4,9].

Given these similarities, our review suggests that chronic HPV-HR infection at virus-susceptible anatomical sites may increase the risk for anal infection, AIN, and anal SCC, as observed in women with a history of pre-existing HPV-related cervical, vulvar or vaginal neoplasms[47-49,53-57]. We found anal HPV-HR prevalences ranging from 32.5-66.7% in those with cervical abnormalities (including cancer), with a direct association between the degree of severity of both cervical and anal lesions[47-52]. As with other risk groups, HPV16 was the serotype most frequently identified in both high-grade AIN and anal cancer samples in this specific population[49,52,53].

Other studies are consistent with these results. Robinson et al. (2015)[63], evaluating women with and without genital neoplasia history, concluded that the presence of lower genital tract neoplasms increases the chances of positive anal cytology for HPV, of containing high-risk serotypes in the anal canal and of presenting AIN. More recently, Bregar et al. (2018)[64] compared rates of concurrent anus and cervix viral infection, revealing that a positive history for cervical neoplasia also increases the likelihood of anal HPV in women, also suggesting a possible association with AIN and anal SCC.

Despite evidence demonstrating the concurrent HPV-HR presence in both cervical and anal specimens – suggesting the cervix as a "reservoir" for the virus – studies included in this review report higher frequency in colo-vagina co-infection than colo-vulva or colo-anus co-infection, probably due to the anatomical proximity of the uterine cervix to the vagina[53-58]. Even so, there is a considerable risk of women developing a second HPV-related cancer in another susceptible anatomical site from a previous anogenital cancer, as revealed in a meta-analysis[57], in addition to the strong association between anal and vulvo-vaginal cancer[57,58,65]. One of the possible pathophysiological explanations would be the reduction in the viral elimination capacity in the presence of other high-grade anogenital lesions, increasing susceptibility to infection in another anatomical site, which may lead to the development of synchronous lesions[54].

Conclusion

It is known that cervical cancer – the most common HPV-related malignancy in females – remains an important public health problem. However, relatively uncommon cancers, such as those of the anus, have shown an increasing incidence in recent years in both genders. In the present review, we reinforced the role of HPV in the possible etiopathogenesis of AIN and progression to anal SCC, especially in risk groups, in which higher anal HPV-HR prevalences and potentially malignant anal lesions are found, in addition to higher incidences of anal cancer. Furthermore, we believe that the notable increase in its occurrence may be mainly due to the role of viral transmission, in which changes in sexual behavior may be preponderant.

There is a lack of consistent results in the literature with epidemiologic data concerning HPV behavior in anal neoplasms, especially from lower-income countries and less studied risk populations. Putting aside any controversies, it is clear that more research is needed to fill gaps in the natural history of the disease, from anal HPV infection to the development of SCC, in different populations.

A better understanding of HPV prevalence in anal neoplasms, the distribution of viral serotypes and the risk of progression to anal cancer from premalignant lesions, in addition to the investigation of risk factors for persistent HPV-HR infection, may provide relevant epidemiological information towards the elaboration of local or regional public policies.

Finally, taking into account the important HPV association with AIN and anal SCC in individuals at specific risk, it makes sense to evaluate possible benefits of screening for precursor lesions as a preventive and control measure for these groups.

Author's Contribution

The authors' contributions are structured according to the taxonomy (CRediT) described below:

Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data: Fernando Augusto Figueiredo Montandon, Eduardo Ângelo Braga, Iure Kalinine Ferraz de Souza, Anderson Ribeiro Duarte, Sávio Lana Siqueira, Fernanda da Cruz Leão, Claudia Martins Carneiro, Sarhan Sydney Saad; *Preparation of the work´s draft, or its critical review for important intellectual content:*Fernando Augusto Figueiredo Montandon, Eduardo Ângelo Braga, Iure Kalinine Ferraz de Souza, Anderson Ribeiro Duarte, Sávio Lana Siqueira, Fernanda da Cruz Leão, Claudia Martins Carneiro, Sarhan Sydney Saad; *Final approval of the version to be published:* Fernando Augusto Figueiredo Montandon, Eduardo Ângelo Braga, Iure Kalinine Ferraz de Souza, Anderson Ribeiro Duarte, Sávio Lana Siqueira, Fernanda da Cruz Leão, Claudia Martins Carneiro, Sarhan Sydney Saad; *Agreement to be accountable for all aspects of the work, ensuring that issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* Fernando Augusto Figueiredo Montandon, Eduardo Ângelo Braga, Iure Kalinine Ferraz de Souza, Anderson Ribeiro Duarte, Sávio Lana Siqueira, Fernanda da Cruz Leão, Claudia Martins Carneiro, Sarhan Sydney Saad.

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