GYNECOLOGY

Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review

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The aim of this study was to systematically review the findings of publications addressing the epidemiology of anal human papillomavirus (HPV) infection, anal intraepithelial neoplasia, and anal cancer in women. We conducted a systematic review among publications published from Jan. 1, 1997, to Sept. 30, 2013, to limit to publications from the combined antiretroviral therapy era. Three searches were performed of the National Library of Medicine PubMed database using the following search terms: women and anal HPV, women anal intraepithelial neoplasia, and women and anal cancer. Publications were included in the review if they addressed any of the following outcomes: (1) prevalence, incidence, or clearance of anal HPV infection, (2) prevalence of anal cytological or histological neoplastic abnormalities, or (3) incidence or risk of anal cancer. Thirty-seven publications addressing anal HPV infection and anal cytology remained after applying selection criteria, and 23 anal cancer publications met the selection criteria. Among HIV-positive women, the prevalence of high-risk (HR)—HPV in the anus was 16—85%. Among HIV-negative women, the prevalence of anal HR-HPV infection ranged from 4% to 86%. The prevalence of anal HR-HPV in HIV-negative women with HPV-related pathology of the vulva, vagina, and cervix compared with women with no known HPV-related pathology, varied from 23% to 86% and from 5% to 22%, respectively. Histological anal high-grade squamous intraepithelial lesions (anal intraepithelial neoplasia 2 or greater) was found in 3—26% of the women living with HIV, 0—9% among women with lower genital tract pathology, and 0—3% for women who are HIV negative without known lower genital tract pathology. The incidence of anal cancer among HIV-infected women ranged from 3.9 to 30 per 100,000. Among women with a history of cervical cancer or cervical intraepithelial neoplasia 3, the incidence rates of anal cancer ranged from 0.8 to 63.8 per 100,000 person-years, and in the general population, the incidence rates ranged from 0.55 to 2.4 per 100,000 person-years. This review provides evidence that anal HPV infection and dysplasia are common in women, especially in those who are HIV positive or have a history of HPV-related lower genital tract pathology. The incidence of anal cancer continues to grow in all women, especially those living with HIV, despite the widespread use of combined antiretroviral therapy.

Key words: anal cancer, anal intraepithelial neoplasia, epidemiology, human papillomavirus, systematic review

Squamous cell cancer of the anus (SCCA) incidence has been increasing over the past several decades among women and men. Historically women have had a higher incidence of anal cancer than men, and recent publications have shown that the incidence rate for cancers of the anus, anal canal, and anorectum in all ages and races of women has more than doubled, with an increase from 0.946 per 100,000 in 1975 to 1.827 per 100,000 in 2008.[1] It is estimated that 3000 cases of anal cancer related to human papillomavirus (HPV) occur in women in the United States each year.

Recently many epidemiological studies have highlighted the increase in anal cancer of certain subpopulations of men; specifically, men who have sex with men and HIV-positive individuals have a significantly higher incidence of cancer compared with the general population.[2] There have been fewer publications addressing the changing epidemiology of anal cancer among women, and these publications have demonstrated that the risk of anal cancer has significantly increased among HIV-positive women,[3] with the incidence of anal cancer in HIV-positive women increasing from 0 between 1980 and 1989 to approximately 11 per 100,000 in the years between 1996 and 2004.[4] Thus, SCCA is a growing problem for women in the

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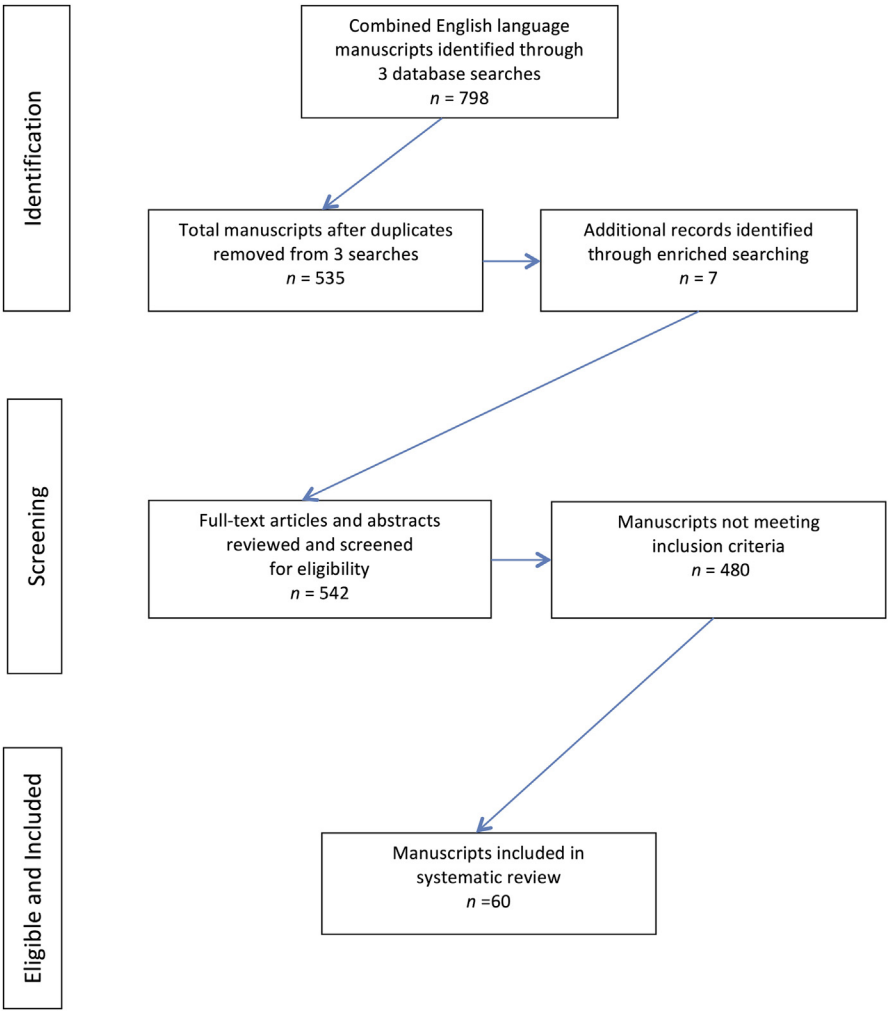
United States, especially those who are HIV positive.

SCCA shares biological similarities with cervical cancer, including detectable precancerous lesions and high-risk (HR) HPV infection. HPV has been detected in 99% of cervical cancers and 80–90% of anal cancers, with HR HPV types 16 or 18 detected in about 70% of cervical and 80% of anal cancers.[5] Thus, anal HPV infection, in conjunction with other yet-to-be determined factors, leads to the development of high-grade squamous anal intraepithelial lesion (anal intraepithelial neoplasia [AIN] 2 or greater), a likely precursor to anal cancer.[6,7]

Because programmatic screening for cervical cancer with cytology has been associated with markedly decreased incidence and mortality of cervical cancer, anal cytology (from a Dacron swab inserted into the anal canal) has been evaluated as a screening method for anal neoplasia. Individuals with abnormal anal screening cytology are referred for a colposcopic evaluation of the anus called high-resolution anoscopy (HRA) in which the anal canal is examined with a colposcope after the application of 5% acetic acid and/or lugol solution and lesions are biopsied for histological diagnosis.

A growing body of literature has utilized screening of the anal canal using HRA and anal detection of HPV. However, the majority of literature evaluating the epidemiology of anal HPV infection, anal neoplasia, and anal cancer has focused on HIV-positive men who have sex with men.

FIGURE
Systematic review process for searching published literature



Defined search terms from Jan. 1, 1997, through Sept. 30, 2013.

Stier. Systematic review of anal HPV infection in women. Am J Obstet Gynecol 2015.

Materials and methods

Objective

The aim of this paper is to systematically review and to summarize the findings of publications addressing the epidemiology of anal HPV infection, anal neoplasia, and anal cancer in women.

Methods

We performed a systematic review for publications of anal HPV infection, anal histological and cytological abnormalities in women, and anal cancer in women published from January 1997 to Sept. 30, 2013. Because the publications evaluating HPV-related disease were so heterogeneous (different methodologies for HPV testing, different types of publications, different types of cohorts) and because we wanted to include as many publications as possible to get a full perspective of the research that has been done to date, we conducted a systematic review rather than a metaanalysis. We confined the search to publications published after Jan. 1, 1997, to limit the publications to the combined antiretroviral therapy (cART) era.

Information sources and search strategy. We performed 3 searches of the National Library of Medicine PubMed database using the following search terms: women and anal HPV, women and anal intraepithelial neoplasia, and women and anal cancer. The searches were limited to humans, published in the English language with full text available during the time period specified.

The searches produced a total of 798 manuscripts. After duplicate papers, review papers, and other nonrelevant papers were removed, a total of 535 papers remained for screening. We also enriched the search by examining germane journals and reviewed reference lists from retrieved publications to identify additional manuscripts not captured by the searches. Seven additional

manuscripts were identified as meeting inclusion criteria through this method.

Study selection criteria. All potentially relevant publications were then evaluated by 4 individuals and were included in this review if they addressed any of the following outcomes: (1) prevalence, incidence, or clearance of anal HPV infection; (2) prevalence of anal cytological or histological neoplastic abnormalities; or (3) incidence or risk of anal cancer. Publications were excluded if they were case reports, did not include original data, did not include women, or did not stratify data by sex or did not report results related to the aforementioned outcomes. Initial search terms yielded 244 publications for anal HPV infection and cytological and histological pathology; 37 publications addressing anal HPV infection and anal cytology remained after applying selection criteria, with 23 publications that presented findings on both outcomes. Two hundred ninety-one publications were identified for the anal cancer search terms, of which 23 met selection criteria (Figure).

Data extraction

For all publications, we recorded the following variables: study location, years of study, methodology, number of participants, and a description of the study population including HIV status. We grouped together publications from the same cohort or population in our tables when appropriate and included the most recent and complete prevalence data presented. The final column in each table allowed us to present the unique findings from each publication.

For publications evaluating HIV-positive women, we recorded the effect of HIV viral load on HPV detection, cytological or histological outcomes based on whichever the primary outcome was reported in the paper. For the anal HPV publications, we recorded the method of HPV testing, incidence/prevalence findings, and concurrent cervical HPV testing findings, if available.

Methods of HPV testing included polymer chain reaction (PCR) and hybrid capture 2 (HC2). The publications varied by overall HPV types detected (high risk or oncogenic HPV genotypes only or high risk combined with low risk) as well as which specific HPV genotypes were included. Of note, there is lack of standardization of HPV testing in the anus (as in the cervix). HPV testing by PCR allows for the identification of specific high- and low-risk HPV genotypes, but HC2 testing does not allow for HPV genotyping; only aggregate data for high-risk genotypes or low-risk genotypes are available through HC2 tests. In addition, PCR has been shown to have a higher sensitivity for detecting low-level HPV infection compared with HC2.[8,9]

For the anal cytology publication, we recorded prevalence of abnormal anal cytology findings, criteria for undergoing HRA, number of individuals who received HRA, and prevalence of abnormal histological findings. Several publications evaluated both anal HPV prevalence and prevalence of abnormal anal cytology. For those publications that presented both outcomes, we divided the outcomes and presented the HPV findings with all the other HPV publications and the cytology findings with the other cytology publications. For the anal cancer publications, we recorded the anal cancer incidence described in each publication and included the standardized incidence ratio if available and other factors associated with increased incidence of anal cancer identified by the publication.

Results

Study characteristics

A total of 60 publications were included in the review. Many of the publications were conducted in women with specific risk factors for anal cancer. Of the anal HPV prevalence publications, 10 publications specified that the population included only HIV-positive women.

Among the publications that did not specify HIV infection, 6 publications were conducted in women with a history of abnormal cervical cytology or intraepithelial neoplasia (IN) 1 or greater of the lower genital tract, 1 publication was conducted among women with non-HIV related immune suppression, and 9 publications were conducted in the general female population.

Among the publications evaluating anal cytological findings, 14 publications evaluated study cohorts of HIV-positive women, 12 publications evaluated study cohorts of women with abnormal cervical cytology or IN1+ of the lower genital tract; and 7 publications assessed anal cytology among the general population. Among the anal cancer publications, there were 7 publications among HIV-positive women, 7 publications evaluated women with a history of HPV-related disease of the vulva or cervix, and 9 publications included women from the general population.

Synthesis of results

Anal HPV infection in HIV-positive women. There were 10 publications, utilizing 7 different study cohorts, that specifically evaluated the prevalence and/or incidence of anal HPV infection in HIV-positive women (Table 1). With the exception of 2 papers,[8,10] all publications reported data on HR HPV.

The prevalence of anal HR HPV was calculated from baseline, point prevalence, or cross-sectional data from the 7 study cohorts.[8,11-16] Two publications calculated incidence of new anal HPV infections from cohort studies.[15,17] Six of the 7 study cohorts were from the United States.[8,11-15]

Most publications used PCR to test for HPV, although the publications differed in HPV types detected (Table 1 footnotes). Three publications utilizing PCR combined low-risk (LR) and HR HPV for their prevalence data.[8,10,17] One publication used both PCR and a HC2 test,[8] and 1 cohort used HC2 only.[11,15]

Prevalence of HPV in the anus (16−85%) was higher than that of the cervix (17−70%) in the majority of publications. Concordant HPV genotypes between the anus and cervix were found in 9−16% of HIV-positive women (compared with only 2% having concordant HPV genotypes in the HIV-matched cohorts).

TABLE 1
HR HPV anal infection in HIV-positive women

Study	Location	Years of study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)	Cervical HR HPV prevalence, n (%)	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Durante et al[12]	United States	1995–1998	Baseline data from cohort study	86	HIV positive with negative anal cytology (mean, 38)	PCR[b]	38 (44)	27 (31)	11 (13%) had concordance of at least 1 HPV genotype in both the anus and cervix
Goncalves et al[16]	Brazil	1996–1997	Cross-sectional	102	HIV positive	PCR[c]	44 (43)	51 (37)	70% had overall HR HPV concordance in the anus and cervix HPV genotype and number of women with concordance in both the anus and cervix: HPV53 (n = 13), HPV18 (n = 12), and HPV16 (n = 9)
Hessol et al 2009[13] Hessol et al 2013[29]	United States	2001–2003	Point prevalence data within a cohort study	470	HIV positive/WIHS	PCR[d]	188 (40)	81 (17)	42% had overall HPV (HR or LR) concordance in the anus and cervix HIV-positive women, compared with the HIV-negative women, were significantly more likely to have overall HPV concordance in the cervix and anus: oncogenic HPV: aOR, 4.6; 95% CI, 1.4–15.5 Non-oncogenic HPV: aOR, 16.9; 95% CI, 2.3–125

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(continued)

TABLE 1
HR HPV anal infection in HIV-positive women *(continued)*

Study	Location	Years of study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)	Cervical HR HPV prevalence, n (%)	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Kojic et al[14]	United States	2004–2006	Baseline data from cohort study	120	HIV positive/SUN (median, 38)	PCR[e]	102 (85)	84 (70)	75 (63%) had overall HR HPV concordance in the anus and cervix Most common HR HPV types: anal HPV: 53 (28%), 16 (24%), 45 (23%), 52 (22%), and 18 and 35 (19% each); cervical HPV: 16 (19%), 58 (15%), 52 (12%), 53 (11%), and 31 (10%) Univariate risk factors for anal HPV infection: CD4 $\geq$500 c/μL: OR, 0.24; 95% CI, 0.06–0.81 Tobacco use: OR, 6.84; 95% CI, 1.61–43.5
Tandon et al[11] Baranoski et al[15]	United States	2006–2010	Baseline prevalence and incidence data from cohort study	100	HIV positive (mean, 40)	HC2	16 (16)[f]	24 (24)	Incidence of new overall anal HR HPV infection: 74.1 per 1000 person-years

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(continued)

TABLE 1
HR HPV anal infection in HIV-positive women *(continued)*

Study	Location	Years of study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)	Cervical HR HPV prevalence, n (%)	HPV concordance between the anus and cervix, principal HPV types, and notable findings
The following publications did not separate the findings based on LR vs HR HPV									
Mullins et al[17] Moscicki et al, 2003[10]	United States	1996–2001	Cohort study	183	HIV positive adolescent (REACH) (mean, 17)	PCR (HR and LR)	59 (32)[g]	—	Incidence of new anal HR HPV infection was 12 per 100 person-years; 95% CI, 8.4–16 Multivariate risk factors for HR anal HPV: Smoking: HR, 3.46; 95% CI, 1.21–9.89 Late CDC AIDS definition: HR, 4.28; 95% CI, 1.29–14.19
Palefsky et al[8]	United States	1995–1997	Point prevalence data within a cohort study	PCR: 223 HC2: 242	HIV positive/WIHS (mean, 40)	PCR (HR and LR) HC2 (HR and LR)	170 (76)[g] 182 (75)[g]	106 (53)	36 (16%) had concordant HPV genotypes in both the anus and cervix Most common concordant HPV types: HPV 16 (15%), 58, 53 Multivariate risk factors for anal HPV (by HC2) CD4 <200: aRR, 1.4; 95% CI, 1.1–1.5 Age ≥45 y: aRR, 0.80; 95% CI, 0.50–0.99 Cervical HPV: aRR 1.3; 95% CI, 1.1–1.4

AIDS, acquired immune deficiency syndrome; *aOR*, adjusted odds ratio; *aRR*, adjusted relative risk; *CDC*, Centers for Disease Control and Prevention; *CI*, confidence interval; *HC2*, hybrid capture 2; *HPV*, human papillomavirus; *HR*, high risk; *LR*, low risk; *OR*, odds ratio; *PCR*, polymerase chain reaction; *REACH*, Reaching for Excellence in Adolescent Care and Health; *SUN*, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; *WIHS*, Women's Interagency HIV Study.

[a] Mean or median age reported when available; [b] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73; [c] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; [d] HR types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, and 66; [e] HR types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, and IS39; [f] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; [g] HPV prevalence reported only as combined LR and HR types.

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TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Park et al[21]	United States	2006–2007	Cross-sectional	92	IN2+ lower genital tract (including Ca) (HIV positive: n = 1) (mean, 32)	PCR	33 (36)[c]	—	Site of IN2 or greater with anal HPV cervical, 52%; vaginal, 75%; vulvar, 33%; multifocal, 57% (cervix and vagina, vulva, or both) No statistical differences among anal HPV prevalence
Valari et al[22]	Greece	2009–2011	Cross-sectional	235	IN1 or greater (including cervical Ca, n =20, and vulva Ca, n =1) (mean, 34)	PCR mRNA (flow)	72 (31)[d] 19 (8)[e]	91 (39) 60 (26)	HPV type-specific genotype concordance between cervix and anus Total: 24.6%, Partial: 49.0% None: 26.4% Most common HR HPV types: Anal HPV, 18 Cervical HPV, 16 Only statistically significant risk factor for anal HPV is cervical HPV (OR, 3.25, 95% CI, 1.67–6.33)
Véo et al[23]	Brazil	—	Cross-sectional	40	CIN3 (mean, 33)	HC2	9 (23)[f]	39 (98)	Women with CIN3, compared with the women in the gynecology clinic with no CIN3 were significantly more likely to have a higher prevalence of HPV in their anal canal ($P = .014$)
				40	Gynecology clinic (no CIN 3) (mean, 40)	HC2	2 (5)[f]	3 (8)	

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(continued)

TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Goodman et al, 2008[25]; Shvetsov[28]	United States	1998–2003	Cohort study	431	Subset of Hernandez (2005)[24g] (mean, 39)	PCR	96 (22)[h]	143 (33)	Incident rate of anal HR HPV: 19.5 per 1000 woman-months, 95% CI, 16.0–23.6 Clearance rate: 9.16 per 100 woman-months, 95% CI, 6.94–11.87 Median duration of HR HPV infection: Anal HPV, 5 mo Cervical HPV, 8 mo Risk factors for incident anal HR HPV: Cervix HR HPV: OR, 1.81; 95% CI, 1.09–3.02 Lifetime sex partners more than 6: OR, 3.64; 95% CI, 1.25–10.66 Age >45 y (protective): OR, 0.43; 95% CI, 0.23–0.81
Goodman et al, 2010[26]	United States	1998–2008	Cohort study	751	Subset of Hernandez (2005)[24g] (mean, 34)	PCR	—	—	Risk of sequential concordant HPV genotype: Cervix, then anus: OR, 20.5; 95% CI, 16.3–25.7 Anus, then cervix: OR, 8.8; 95% CI, 6.4–12.2

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(continued)

TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Hernandez et al, 2013[27]	United States	2008–2009	Cross-sectional	211	Women, community (mean, 40)	PCR	8 (4)[i]	11 (5)	Multivariate analysis: age <30 y only significant factor for prevalent anal (OR, 2.42; 95% CI, 1.08–5.44) and cervical (OR, 7.87; 95% CI, 2.89–21.74) HPV infections Anal HPV prevalence higher than cervical HPV prevalence at all ages 4% of women had concurrent anal and cervical HPV infections
Pierangeli et al[30]	Italy	2005–2011	Cross-sectional	134	HIV negative, proctology clinic[j] (mean, 42)	PCR	18 (13)[k]	13/108 (12)	Anal HPV 16 detected in 7 women (5%) 12 (9.0%) women had concordant HPV genotypes in both the anus and cervix
Hessol et al, 2009[13] Hessol et al, 2013[29]	United States	2001–2003	Point prevalence within a cohort study	185	HIV negative (WIHS) (mean, 29)	PCR	28 (15)	13 (1)	3 (2%) women had concordant type-specific HR HPV genotypes in the anus and cervix

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TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
The following publications did not separate the findings based on LR vs HR HPV									
D'Hauwers et al[18]	Belgium	2007–2008	Cross-sectional	96	Colposcopy clinic (n = 61) Gynecology clinic (n = 35) (mean, 30)	PCR (HR and LR)	HR and LR 54 (56)[b,l]	HR and LR 59 (61)[b]	40 (42%) at least partial type-specific HPV genotype concordance between anus and cervix
Crawford et al[19]	United Kingdom	2009–2010	Cross-sectional	100	Colposcopy clinic (mean, 34)	PCR (HR and LR) HPV16 HPV31	84 (90)[b,m,n] 52/93 (56) 20/93 (22)	96 (96)[b] 55 (53) 24 (24)	80/93 (86%) had overall HR HPV concordance in the cervix and anus HPV 16 was 2 times greater compared with the next most common genotype, HPV 31, (paired *t* test, two tailed, 95% CI, 10.7–19.59)
Heraclio et al[20]	Brazil	2008–2009	Cross-sectional	303	CIN1 or greater (including cervical Ca, n = 26) (HIV positive, n = 8)	PCR (LR and HR)	255 (84)[b,o]	—	—
Castro et al[31]	Costa Rica	2004–2005	Cross-sectional	2107	Women, community (22–29 y)	PCR HR and LR PCR HR only	666 (32)[b] 464 (22)[p]	768 (36)[b] n/a	Risk factors for anal HPV: Cervical HPV: aOR, 4.8; 95% CI, 3.9–5.9 H/o anal intercourse: aOR, 2.8; 95% CI, 1.7–4.5 Number of lifetime sex partners ≥4: aOR, 2.3; 95% CI, 1.7–3.1

Stier. Systematic review of anal HPV infection in women. Am J Obstet Gynecol 2015. *(continued)*

TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Hernandez et al, 2005[24]	United States	1998–2004	Baseline data from cohort study	1378	Women, community	PCR (LR and HR)	368 (27)[b,q]	368 (27)[b]	Cervical HPV, anal HPV (% cohort) mean age ++ 29.2 (13%) +− 34.9 (14%) −+ 38.7 (14%) −− 40.9 (59%) There were significant age differences among women with anal HPV compared with women with cervical HPV (race adjusted): <30 Reference 30–39: OR, 0.4; 95% CI, 0.3–0.6 40–49: OR, 0.1; 95% CI, 0.1–0.2 ≥50: OR, 0.1; 95% CI, 0.04–0.2 Risk of concurrent anal HPV infection given cervical HPV infection: OR, 3.3; 95% CI, 2.5–4.4, adjusted for age and race/ethnicity

Stier. Systematic review of anal HPV infection in women. Am J Obstet Gynecol 2015. *(continued)*

TABLE 2
HR HPV anal infection in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of Study	Study design	Subjects, n	Population (age)[a]	Methodology for HPV testing	Anal HR HPV prevalence, n (%)[b]	Cervical HR HPV prevalence, n (%)[b]	HPV concordance between the anus and cervix, principal HPV types, and notable findings
Mullins et al[17] Moscicki et al, 2003[10]	United States	1996–2001	Cohort study	82	HIV negative adolescent (REACH) (mean, 17)	PCR (HR and LR)	11 (13)[b]	—	Incidence new anal HR HPV infections: 5.3 per 100 person-years, 95% CI, 2.6–11 Risk factors for anal HPV OR (95% CI) Perianal condyloma 9.9 (1.9–51.30) Vulvar condyloma 3.9 (1.5–10.0) Cervical HPV infection 2.2 (1.1–4.5) HIV status was a significant risk factor only when girls with condyloma were excluded: OR, 2.3;95% CI, 1.1–4.9
Palefsky et al[8]	United States	1995–1997	Point prevalence within a cohort study	PCR: 57 HC2: 67	HIV-negative subset of WIHS (mean, 40)	PCR (HR and LR) HC2 (HR and LR)	24 (42)[b,r] HC2: 20 (30)	12 (24)	—

aOR, adjusted odds ratio; *CI*, confidence interval; *CIN*, cervical intraepithelial neoplasia; *HC2*, hybrid capture 2; H/o, history of; *HPV*, human papillomavirus; *HR*, high risk; *IN1* or greater, intraepithelial neoplasia of the lower genital tract (cervical, vaginal, or vulvar) grade 1 or higher; *LR*, low risk; *OR*, odds ratio; *PCR*, polymerase chain reaction; *REACH*, Reaching for Excellence in Adolescent Care and Health; *WIHS*, Women's Interagency HIV Study.

[a] Mean or median age reported when available; [b] Publications reporting only combined HR and LR HPV data (and not separating out the HR HPV) are as follows: Castro et al,[31] Crawford et al,[19] D'Hauwers et al,[18] Goodman et al (2010),[26] Heraclio et al,[20] Hernandez et al,[24] and Palefsky et al[8]; [c] HR types 16, 18, 26, 31, 33, 35,39, 45, 51–53, 56, 58, 59, 66, 68, 73, 82, and IS39; [d] HR types not stated; [e] Flow cytometry for E6 and 7 mRNA of 14 high-risk HPV types (not stated); [f] HR types not stated; [g] Note that these publications are a subset of the cohort from Hernandez et al (2005)[24] with sufficient follow-up; [h] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, and 82; [i] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; [j] Cohort has no history of HPV-related pathologies; [k] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possible HR 26, 34, 53, 66, 70, 73, and 82; [l] HR types 6 E6, 11 E6, 16 E7, 18 E7, 31 E6, 33 E6, 35 E6, 39 E7, 45 E7, 51 E6, 52 E7, 53 E6, 56 E7, 58 E6, 59 E7, 66 E6, 67 L1 and 68 E7; [m] Seven anal specimens were unable to be evaluated for HPV; [n] HR types 16, 31, 33, 53, 59, 45, 56, 18, 66; probable HR-HPV types 26, 35, 39, 51, 52, 58, 68, 69, 70, 73, 82, IS39; LR-HPV types ;6, 11, 40, 42, 54, 61, 72, 81, CP6108; undetermined risk types 55, 62, 64, 67, 71, 83 and 84; [o] HR types not stated; [p] HR types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68/73b; [q] HR types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71,72, 73, 81, 82, 83, 84, CP6108, and IS39; [r] HR types 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 69, 70, 73, AE2, Pap 155, Pap 291, 2, 13, 34, 42, 57, 62, 64, 67, 72, W13B.

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The most common prevalent HPV types identified in the anus were 16, 53, 45, 52, 18, and 35 (compared with the concurrent cervical HPV types 16, 52, 53, 58, and 31). Baranoski et al[15] reported the incidence of new anal HR HPV infections was 74 per 1,000 person-years for HIV-positive women over an average follow-up time of 704 days.

Risk factors for prevalent anal HPV included cervical HPV,[8] CD4 less than 200,[8] smoking,[14] and perianal warts.[10,17] CD4 500 or greater[14] was shown to be significantly protective for anal HPV infection. Of note, reported history of anal intercourse was not associated with anal HPV.[8,14] Only 1 publication, by Palefsky et al[8] evaluated the effect of most current HIV viral load on the detection of both high-risk and low-risk HPV types by both hybrid capture and PCR and did not find any differences in the detection of HPV using either method between individuals with high HIV viral load compared with low HIV viral load.

Anal HPV infection in predominantly HIV-negative female cohorts. Eighteen publications (representing 13 different study cohorts) reported data on anal HPV prevalence, incidence, or clearance in women not known to be HIV positive (Table 2). The 13 study cohorts varied widely by age, recruitment criteria, population pool, and other inclusion criteria. Six of the cohorts were recruited from women attending colposcopy clinics[18-23]; however, the inclusion criteria among these cohorts varied from an abnormal referral cervical cytology, to histological cervical intraepithelial neoplasia (CIN) 3+.

The majority of publications were cross-sectional. Study cohort size ranged from 40 to 2107 participants. Eleven of the publications were done in the United States,[8,10,13,17,21,24-29] 4 in Europe,[18,19,22,30] and 3 in Central/South America.[20,23,31] The vast majority of publications used PCR to test for HPV. Eight publications utilized PCR combined LR and HR HPV for their prevalence data.[8,10,17-20,24,31] Two publications used PCR and either HC2 or flow cytometry,[8,22] and 1 publication used only HC2.[23] Ten publications reported the prevalence of anal HR HPV infection in their study cohorts ranging from 4% to 36%.[13,21-23,25-30]

The prevalence of anal HR HPV in women with HPV-related pathology of the vulva, vagina, and cervix compared with women with no known HPV-related pathology varied from 23% to 36%[21-23] compared with 4−22%,[13,23,25,27-30] respectively. Véo et al[23] reported the prevalence of HPV in the anal canal of the women with CIN III was greater than in the women without CIN III ($P = .014$).

Several publications found that detection of cervical HPV was associated with prevalent anal HPV infection.[22-25,27,31] Other risk factors for anal HPV detection among HIV-negative women include a reported history of anal intercourse,[31] the number of lifetime partners,[25,31] and a history of perianal and/or vulvar condyloma.[17] Hernandez et al[27] (2013) found that age younger than 30 years increased the risk for anal HPV, and Goodman et al[25] found that an age older than 45 years decreased the likelihood of anal HPV.

The data regarding incidence and clearance of anal HR HPV infection were reported from the Reaching for Excellence in Adolescent Care and Health Project (REACH) and Hawaii Cohorts. The REACH cohort (mean age 17 years) reported an incident anal HR HPV infection rate of 5.3 per 100 person-years,[17] whereas the Hawaii cohort (mean age 39 years) reported an incident anal HR HPV infection rate of 19.5 per 1000 person-months.[25] In this Hawaii cohort, the mean duration of anal HR HPV infection was 5 months (compared with cervical HR HPV infections that lasted a mean of 8 months), and the clearance rate of anal HPV was 9.16/100 woman-months.[28]

A longitudinal study of cervical and anal HPV infection (Hawaii cohort) found the risk of anal HPV infection after cervical infection with concordant genotype was 20.5 (95% confidence interval [CI], 16.3−25.7) compared with the risk of a cervical HPV infection after an anal HPV infection with a concordant genotype of 8.8 (95% CI, 6.4−12.2).[26]

Results of anal cytology and histology in women

Tables 3 and 4 summarize publications that evaluated abnormal anal cytology and/or histology in women. Ten publications reported results for only women living with HIV,[11,12,14,15,32-37] 3 publications reported comparative results for both HIV-positive and HIV-negative women.[10,13,38] Twelve publications evaluated study cohorts of women with abnormal cervical cytology or IN1+ of the lower genital tract. Six of these 12 publications included a small number of HIV-positive women,[20,21,39,40-42] 1 publication included a cohort of HIV-positive women with IN1−3 (compared with HIV-negative immune compromised and HIV-negative immune competent with IN1-3),[39] and 2 publications included a comparative cohort of women without a history of IN1−3.[43,44] Two publications included only women from the general population.[30,45] The prevalence of cytological high-grade squamous intraepithelial lesions (HSIL) was 0−5% of women living with HIV,[10-12,14,15,33-38] 0−29% among women with lower genital HPV disease,[18,20,21,40,41,46] and 0−0.3% among women who were HIV negative with unspecified or no known genital HPV.[10,13,30,38,45]

Among HIV-positive women, 5 publications evaluated the effect of HIV viral load on abnormal anal cytological findings, and none of the publications found that HIV viral load was associated with the detection of abnormal anal cytology.[11,15,33,35,38]

Twenty publications reported the histology results from HRA (Tables 3 and 4). HRA examination was done on all participants in 7 publications.[20,39-41,43,44,47] In the remaining 10 reports, HRA was performed only on those with abnormal anal cytology[13,21,35-37,45] or as in the publications on those with abnormal anal cytology or anal HPV infection.[11,15,22]

Abramowitz et al[32] reported on biopsies from simple anoscopy. Histological anal HSIL (AIN 2 or greater) was

TABLE 3
Prevalence of abnormal anal cytology and histology in HIV-positive women

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology: All abnormal, n (%)	Subjects with abnormal anal cytology: HSIL or ASC-H, n (%)	Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA): AIN1-3, n (%)	Subjects with AIN (histology) n (% with HRA): AIN2-3, n (%)	Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)
Abramowitz et al[32]	France	2003-2004	150	HIV positive ID clinic	—	—	All 150 women underwent anoscopy	10 (7)[b]	—	Findings based on directed biopsies with simple anoscopy (HRA not performed)
Chaves et al[33]	Brazil	2006–2008	184	HIV positive STD clinic (mean, 36)	26 (14)	0	—	—	—	Abnormal anal cytology associated with CD4 less than 200: RR, 4.87; 95% CI, 1.67–14.17 Abnormal anal cytology not associated with anal intercourse: RR, 1.15; 95% CI, 0.54–2.43
Durante et al[12]	US	1995–1998	100	HIV positive (mean, 35)	14	0	—	—	—	Incident abnormal Pap test: 22 per 100 person-years; 95% CI, 14–33 (There was only 1 incident HSIL anal cytology)
Gaisa et al[34]	United States	2009–2012	556	HIV positive ID clinic (mean, 48)	233 (42%)	29 (5%)	Abnormal anal cytology (170)	115 (68)	45 (26)	8% prevalence of AIN2 or greater in the total female cohort
Gingelmaier et al[35]	Germany	2007–2008	104	HIV positive gynecology clinic (mean, 38)	13 (13)	2 (2)	Abnormal anal cytology (13)	6 (46)	4 (31)	4% prevalence of AIN2 or greater in the total cohort
Hessol et al, 2009[13]	United States	2001–2003	470	HIVpositive (WIHS) (mean, 33)	—	—	Abnormal anal cytology (n/a)	68 (92)[c]	37 (50)[c]	8% prevalence of AIN2 or greater in the total cohort (note that AIN2 or greater is a composite of cytology/histology)
										Risk factor for AIN2 or greater: OR (95% CI)
										Anal HPV: Oncogenic 7.4 (1.3–37)
										Nononcogenic 2.2 (0.42–11)
										Both HPV types 10 (2–50)
										Cervix HPV oncogenic 1.8 (0.57–5.9)
										H/o anal intercourse 1.2 (0.64–2.4)
										Only 50% of women with abnormal anal cytology underwent HRA

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(continued)

TABLE 3
Prevalence of abnormal anal cytology and histology in HIV-positive women *(continued)*

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology		Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA)		Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)		
					All abnormal, n (%)	HSIL or ASC-H, n (%)		AIN1-3, n (%)	AIN2-3, n (%)			
Holly et al[38]	United States	1995–1997	235	HIV positive (WIHS)	61 (26)	2 (1)	Abnormal anal cytology (46)	33 (72)	14 (30)	8% prevalence of AIN2 or greater in the total cohort		
										Risk factor for abnormal anal cytology	RR	(95% CI)
										HIV infection	3.2	(1.3–7.5)
										H/o anal intercourse	2	(1.3–3.1)
										CD4 <200	5.5	(2.2–16)
Hou et al[36]	United States	2008–2010	715	HIV positive[d] (mean, 49)	75 (10)	4 (0.6)	Abnormal anal cytology (75)	54 (72)	29 (29)	4% prevalence of AIN2 or greater in the total cohort $P = .03$		
										Risk factor for AIN2 or greater	Number with abnormal anal cytology	AIN2, %
										CD4 <250	18	61
										CD4 >500	20	5
Kojic et al[14]	United States	2004–2006	120	HIV positive (SUN) (mean, 38)	46 (38)	4 (3)	—	—	—	—		
Moscicki et al, 2003[10]	United States	1996–2001	162	HIV-positive adolescents (REACH) (mean, 17)	34 (21)	4	—	—	—	—		
Tandon et al[11]	United States	2006–2007	100	HIV positive ID clinic (mean, 40)	17 (17)	0	Abnormal anal cytology or HR HPV infection (HC2) (14)	10 (10)	3 (3)	3% prevalence of AIN2+ in the total cohort 74% of women referred underwent HRA		
										Risk factor for AIN2 or greater	OR	(95% CI)
										CD4 <200	14.62	(2.48–86.11)
										Abnormal cervical cytology	3.79	(1.05–13.72)

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(continued)

TABLE 3
Prevalence of abnormal anal cytology and histology in HIV-positive women *(continued)*

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology: All abnormal, n (%)	Subjects with abnormal anal cytology: HSIL or ASC-H, n (%)	Criteria for HRA (n)	Subjects with AIN (histology) n (% with HRA): AIN1-3, n (%)	Subjects with AIN (histology) n (% with HRA): AIN2-3, n (%)	Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)
Baranoski et al[15]		2006–2010			33	0	Abnormal anal cytology or HR HPV infection (HC2) (36)	—	12 (12)	12% period prevalence (up to 3 visits over 4 y) of AIN2 or greater for the entire cohort 33% period prevalence of abnormal anal cytology for the entire cohort 77% of women referred underwent at least 1 HRA
Tatti et al[39]	Argentina	2005–2011	31	HIV positive IN1-3 (mean, 37)	—	—	All participants (31)	16 (52)	8 (26)	26% prevalence of AIN2 or greater in the total cohort HIV+ women had higher prevalence of AIN2 or greater compared with immune-competent and other immunosuppressed women ($P < .001$) (Table 4)
Weis et al[37]	United States	2006–2008	204	HIV positive ID clinic (mean, 40)	64 (31)	1 (0.5)	Abnormal anal cytology (51)	50 (98)	35 (69)	18% prevalence of AIN2 or greater in the total cohort Note that 60% of women AIN2 or greater did not report anal intercourse 80% of women referred underwent HRA

	H/o anal intercourse	No H/o anal intercourse	
Abnormal anal cytology	39%	27%	$P = .004$
AIN2 or greater	26%	13%	$P = .03$

AIN, anal intraepithelial neoplasia; *ASC-H*, atypical squamous cells, cannot rule out high grade; *CI*, confidence interval; *CIN*, cervical intraepithelial neoplasia; *h/o*, history of; *HRA*, high-resolution anoscopy; *HSIL*, high-grade squamous intraepithelial lesion; *ID*, infectious disease; *IN1* or greater, intraepithelial neoplasia of the lower genital tract (cervical, vaginal, or vulvar), grade 1 or higher; *OR*, odds ratio; *PAIN*, perianal intraepithelial neoplasia; *Pap*, Papanicolaou; *REACH*, Reaching for Excellence in Adolescent Care and Health; *RR*, risk ratio; *STD*, sexually transmitted disease; *SUN*, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; *VaIN*, vaginal intraepithelial neoplasia; *VIN*, vulvar intraepithelial neoplasia; *WIHS*, Women's Interagency HIV Study.

[a] Mean age reported when available; [b] Combined AIN1-3 as "dysplasia"; [c] Numbers don't add because grade of the lesion was defined as the more advanced diagnosis on cytology or histology. If no histological data was available, grade based only on cytology; [d] No gross anal disease on physical examination.

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found in 3−26% of the women living with HIV,[11-15,32-39] 0−9% among women with lower genital tract pathology,[20-22,39-44,47] and 0−3% for women who are HIV negative without known lower genital tract pathology.[13,43-45]

In a publication of women with IN1 or greater who were HIV positive, immunosuppressed, and HIV negative, or immunocompetent, the prevalence of AIN2/3 was 26%, 9%, and 4%, respectively ($P < .001$).[39] Among HIV-positive women, 4 publications reported on the effect of HIV viral load on histological diagnosis of histological anal HSIL (AIN 2 or greater).[13,17,32,36] Hou et al[36] found that poor HIV control was associated with a higher percentage of histological anal HSIL detection in a univariate analysis of 75 women. Mullins et al[17] found that poor HIV control was associated with a higher risk of anal condyloma (hazard risk, 1.55; 95% CI, 1.12−2.17) in a multivariable analysis, but there was no effect of HIV viral load control on anal dysplasia risk in 278 HIV-infected adolescent women. The other 2 publications did not find an association between HIV virologic control and histologically defined anal dysplasia.

Anal cancer in women

Twenty-three publications describing the IRs or standardized incidence ratio (SIRs) of anal cancer involving women were included in this review (Table 5). Of these publications, 11 included women in North America[48-58] and the majority of the other publications were from Europe (United Kingdom and Scandinavia).[59-71] Seven publications identified women living with HIV.[50-53,64-66] Four publications evaluated the IR or SIR in women with CIN3, cervical cancers, or other HPV-related genital cancers,[48,49,61,62] and 3 other publications evaluated the SIR of anal cancer in women with genital warts.[59,60,63] Nine publications reported IRs and risk factors of anal cancer within the general population.[54-58,68-71]

The incidence of anal cancer among HIV-positive women ranged from 3.9 to 30 per 100,000 among the 4 publications that reported incidence rates.[52,53,64,66] The SIR ranged from 3.2 to 41.2 compared with the general population.[50,51,64,66] There was only 1 publication that compared HIV-positive and HIV-negative women and found that the SIR for HIV-positive women was 18.5, and the SIR for HIV-negative women studied was 0.[50]

In addition, other publications demonstrated that the SIR was higher among subsets of HIV-positive women. For example, Picketty et al[66] and Silverberg et al[53] found that the SIR among women diagnosed more recently (2005−2008 for Picketty et al[66] and 2004−2007 for Silverberg et al[53]) were both higher than the SIRs in earlier years. Other publications also found that the SIR and relative risk (RR) among younger women was higher than among older women.[52,66] Of note, the lowest SIR (3.23) included only women through 1994 and therefore did not include women diagnosed during the era of cART.[51]

Among women with a history of cervical cancer or CIN 3, the IR of anal cancer ranged from 0.8 to 63.8 per 100,000 person-years[48,49,61,62]; however, it should be noted that the 63.8 per 100,000 IRs reported by Chaturvedi et al[48] included rectal cancers as well as anal cancers. The SIRs ranged from 1.8[48] (including women with rectal cancer) to 13.6.[49] The SIRs for anal cancer in those women with genital warts ranged from 7.8[59] to 9.0.[63]

In the general female population, the IRs ranged from 0.55 per 100,000 person-years to 2.4 per 100,000 person-years.[54-58,68-71] Nelson et al[58] reported the highest incidence rate (2.4; 95% CI, 2.3−2.5) and included cases through 2009, which is the most up-to-date publication. Multiple publications from different countries found that the incidence of anal cancer has been increasing over the past several decades.[56-58,69-71] In addition, several publications also reported that individuals with a lower median household income had significantly higher rates of anal cancer.[54,68]

Comment

Main findings

Our systematic review of the literature revealed that anal HPV infection in women is prevalent in general and comparable with rates of cervical HPV infection. In particular, HIV-positive women and women with HPV-related pathology of the lower genital tract were found to have high rates of HR HPV infection, high rates of high-grade AIN 2 or greater on biopsy, and elevated rates of anal cancer. Of note, few longitudinal publications evaluating anal HR HPV infection and AIN 2 or greater on women have been conducted; thus, there are few publications describing the natural history of HR HPV infection in HIV-positive or HIV negative women. In addition, for all populations, the retrospective publications evaluating anal cancer incidence in women demonstrate a significant increase in anal cancer incidence during the last several decades.

The prevalence of HR HPV anal infection appears to be higher among women who are HIV positive and women with HPV-related lower genital tract disease compared with that in the general population. Publications with both HIV-positive and HIV-negative cohorts found that HIV infection was associated with an increased prevalence of anal HPV,[8,13] consistent with the findings of a metaanalysis on anal HPV infection in men who have sex with men (MSM), which reported a greater pooled prevalence of anal HR HPV in HIV-positive men than in HIV-negative men ($P = .010$).[72]

Interestingly, all of the reporting simultaneously collected specimens for HPV from the cervix and the anus found comparable or higher detection rates of HR HPV in the anus compared with the cervix. Most publications found that HPV infection of the cervix was a significant risk factor for anal HPV. In addition, there was significant concordance of HR HPV genotypes between the cervix and anus.

A reported history of prior anal intercourse was not a consistent risk factor for anal HPV. These data support the likelihood that HPV has a field effect on the lower genital tract, that anal HPV is often found in women who have no history of anal receptive intercourse, and that anal HR HPV infection is as

TABLE 4
Prevalence of abnormal anal cytology and histology in predominantly HIV-negative female cohorts

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology: Any, n (%)	Subjects with abnormal anal cytology: HSIL or ASC-H, n (%)	Criteria for HRA (n)	Subjects with AIN (histology), n (%) with HRA: AIN1-3, n (%)	Subjects with AIN (histology), n (%) with HRA: AIN2-3, n (%)	Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)		
Calore et al[46]	Brazil	Not stated	49	CIN1 or greater by cytology (no gross anal lesions) (mean, 32)	29 (59)	14 (29)	—	—	—	—		
D'Hauwers et al[18]	Belgium	2007–2008	93	H/o abnormal cervical cytology (n = 58) Normal screening (n = 35) (mean, 30)	10 (11)	0	—	—	—	—		
ElNaggar et al, 2013[41] ElNaggar et al, 2012[42]	United States	2006–2010	324	IN1+ (including cervical Ca, n = 4) (HIV+ positive, n = 16) (other immunosuppression, n = 12) (mean, 39)	18 (6)	1 (0.3)	All participants (324)	64 (20)	28 (9)	9% prevalence of AIN2+, in the total cohort		
										Risk factor for AIN1-3	OR	(95% CI)
										Immunosuppression	5.75	(2.58–12.8)
										H/o VIN	3.81	(1.84–7.87)
										H/o anal sex	1.85	(1.06–3.23)
										Probability of AIN1-3 among women who are not immunosuppressed, have no h/o VIN, or h/o anal sex is 9% Probability of AIN-3 among women who are immunosuppressed, have a h/o VIN, and h/o anal sex is 72% Performance of anal cytology to detect AIN1-3:		
												(95% CI)
										Sensitivity	9.4%	(0.039–0.199)
										Specificity	88.6%	(0.78–0.95)
										agreement of anal cytology to histology (κ)	−.0213	(−0.128 to 0.086)
Heraclio et al[20]	Brazil	2008–2009	324	CIN1+ (Including cervical Ca: n = 26) (HIV+: n = 8)	102 (31)	10 (3)	All participants (324)	13 (4)	8 (2)	2% prevalence of AIN2+, in the total cohort		

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(continued)

TABLE 4
Prevalence of abnormal anal cytology and histology in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology: Any, n (%)	Subjects with abnormal anal cytology: HSIL or ASC-H, n (%)	Criteria for HRA (n)	Subjects with AIN (histology), n (%) with HRA: AIN1-3, n (%)	Subjects with AIN (histology), n (%) with HRA: AIN2-3, n (%)	Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)		
Jacyntho et al[43]	Brazil	2003–2004	184	IN1-3 (72% <40 y)	—	—	All participants (184)	32 (17)	6 (3)	3% prevalence of AIN2 or greater, in the total cohort Risk for AIN 1-3 by site of IN1-3 (compared with no IN1 or greater)		
			74	No h/o IN1–3 (72% <40 y)			All participants (74)	2 (3)	0	Presence of:	PR for AIN1-3	(95% CI)
										PAIN1-3	21.4	(4.6–100)
										VIN1-3	9.4	(2–44.6)
										ValN1-3	7.8	(1.6–36.7)
										CIN1-3	7.0	(1.5–32.5)
Koppe et al[44]	Brazil	2008–2010	106	IN1-3 (38)	—	—	All participants (106)	11 (10)	5 (5)	5% prevalence of AIN2+, in the total cohort		
			74	HIV-(no IN1-3) (M = 50)			All participants (74)	1 (1)	0			
Park et al[21]	US	2006–2007	102	IN2+ lower genital tract (including Ca) (HIV+: n = 1) (M = 32)	9 (9)	2 (2)	Abnormal anal cytology (7)	7 (100)	0	—		
Santoso et al[40]	United States	2006–2009	205	Women with genital intraepithelial neoplasia (HIV positive, n = 10)	12 (6)	0	All participants (205)	25 (12)	17 (8)	Performance for detection of AIN1-3	Anal cytology, % (95% CI)	HRA, % (95% CI)
										Sensitivity	8% (2–24%)	100% (87–100%)
										Specificity	94% (89–97%)	71% (64–77%)
										PPV	15% (4–42%)	37% (24–44%)
										NPV	88% (82–91%)	100% (97–100%)
										5% prevalence of AIN2 or greater, in total cohort		
Likes et al[47]	United States	2006–2009	310	Abnormal cervical cytology or vulvar lesion (mean, 40) immune-competent	—	—	All participants (310)	61 (19)	26 (8)	Rates of AIN2 or greater comparable in immune compromised vs immune competent (9% vs 8%, respectively) (P = .4543) Rates of VIN2 or greater higher in immune compromised vs immune competent (55% vs 23%, respectively) (P < . 0001)		
			33	Immune compromised[b]			All participants (33)	3 (9)	3 (9)			

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(continued)

TABLE 4
Prevalence of abnormal anal cytology and histology in predominantly HIV-negative female cohorts *(continued)*

Study	Location	Years of study	Sample size	Population (age)[a]	Subjects with abnormal anal cytology: Any, n (%)	Subjects with abnormal anal cytology: HSIL or ASC-H, n (%)	Criteria for HRA (n)	Subjects with AIN (histology), n (%) with HRA: AIN1-3, n (%)	Subjects with AIN (histology), n (%) with HRA: AIN2-3, n (%)	Prevalence AIN2 or greater for cohort (if available) and notable findings (including statistically significant independent risk factors for AIN2 or greater)
Tatti et al[39]	Argentina	2005–2011	404	Immune competent IN1-3 (mean, 30)	—	—	—	104 (26)	16 (4)	CIN2,3 increased the risk of AIN1-3, regardless of immune status: OR, 1.91; 95% CI, 1.1–3.6
			46	Immune compromised IN1-3 (HIV negative)[c] (mean, 40)			All participants (46)	15 (33)	4 (9)	
Valari et al[22]	Greece	2009–2011	235	IN1 or greater (including Ca, n = 21) (mean, 34)	—	—	Abnormal anal cytology or positive HPV DNA or mRNA (25)	8 (32)	0	AIN2 or greater was not detected. Prevalence of AIN1/condyloma was 3% in the total cohort. Low rate of women referred underwent HRA[d]
Hessol et al, 2009[13]	US	2001–2003	185	HIV- (WIHS) (M=29)	–	–	Abnormal anal cytology	7 (9)	2 (3)	1% prevalence of AIN2+, in total population Hessol et al[13] in Table 3
Holly et al[38]	US	1995–1997	61	HIV- (WIHS)	5 (8)	0	–	–	–	–
Moscicki et al, 2003[10]	United States	1996–2001	67	HIV-negative adolescents (REACH) (mean, 17)	4 (6)	—	—	—	—	—
Pierangeli et al[30]	Italy	2005–2011	109	HIV-negative proctology clinic[e] (mean, 42)	38 (35)	0	—	—	—	—
Moscicki et al, 1999[45]	United States	1994	410	HIV negative family planning clinics (mean, 23)	16 (4)	0	Abnormal anal cytology (9)	5 (56)	2 (22)	0.5% prevalence of AIN2 or greater, in total cohort Multivariate analysis, risk factors for abnormal anal cytology
										Risk factor — Adjusted OR — (95% CI)
										Anal HR HPV — 12.28 — (3.91–43.53)
										H/o cervical SIL — 4.13 — (1.29–4.85)
										H/o anal intercourse — 6.90 — (1.71–47.15)

AIN, anal intraepithelial neoplasia; *ASC-H*, Atypical squamous cells, cannot rule out high grade; *Ca*, cancer; *CI*, confidence interval; *CIN*, cervical intraepithelial neoplasia; *h/o*, history of; *HRA*, high resolution anoscopy; *HSIL*, high-grade squamous intraepithelial lesion; *IN1 or greater*, intraepithelial neoplasia of the lower genital tract (cervical, vaginal, or vulvar), grade 1 or higher; *NPV*, negative predictive value; *OR*, odds ratio; *PAIN*, perianal intraepithelial neoplasia; *PPV*, positive predictive value; *PR*, prevalence ratio; *REACH*, Reaching for Excellence in Adolescent Care and Health; *SIL*, squamous intraepithelial lesion; *VaIN*, vaginal intraepithelial neoplasia; *VIN*, vulvar intraepithelial neoplasia; *WIHS*, Women's Interagency HIV Study.

[a] Age or mean age reported when available; [b] For immune compromised, 16 were HIV positive, 5 were transplant patients, 7 had lupus, and 1 had diabetes, 1 had celiac Bruce disease, and 1 had Crohn's disease; [c] Immune compromised by other causes, HIV negative but otherwise not specified; [d] Study reports high fallout rate but rate not specified (4 of 19 with HPV positivity and unknown of abnormal cytology); [e] Women seen at a proctology clinic with no history of HPV-related pathologies.

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TABLE 5
Incidence of anal cancer in women

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Blomberg et al[59] Friis et al[60a]	Denmark	1978–2008	Patients with genital warts[c]	Danish National Patient Register	49,088	32,933 (67)	Genital warts	Not reported	SIR 7.8; 95% CI, 5.4–11.0 SIR 21.5; 95% CI, 14.4–30.9 in men
Chaturvedi et al[48]	Denmark, Finland, Norway, Sweden, US	Varies by registry[b]	One year survivors of cervical cancer[c]	13 population-based cancer registries from 5 countries	104,760	104,760 (100)	Cervical cancer	63.8 (no CI reported)	SIR 1.84; 95% CI, 1.72–1.98[d]
Edgren and Sparen[61]	Sweden	1968–2004	Women aged 18–50 y with history of CIN 3	Sweden National Registry	3,747,698	All women	CIN 3	6.0 (no CI reported) for patients with CIN 0.96 (no CI reported) for patients without hx CIN	Adjusted anal IRR 4.68; 95% CI, 3.87–5.62 Risk of anal cancer increases with time since first CIN3 diagnosis, with greatest risk for women with CIN3 diagnosed >10 y Risk of anal cancer increases with younger age at first CIN3 diagnosis
Evans et al[62]	United Kingdom	1960–1999	Women with history of CIN 3[c] Women with history of invasive cervical cancer[c]	Thames Cancer Registry	CIN 3: 59,519; cervical cancer: 21,605	All women	CIN 3 or cervical cancer	4.8 (CIN3) no CI reported 12.4 (cervical cancer); no CI reported	SIR 5.9 (95% CI, 3.7–8.8) for women diagnosed with CIN3 SIR 6.3 (95% CI, 3.7–10) for women diagnosed with cervical cancer
Nordenvall et al[63]	Sweden	1965–1999	Hospitalized patients with condylomata acuminata[c]	Sweden inpatient register and nationwide registers	10,971	9286 (85)	Genital warts	4.8 (no CI reported)	SIR 9.0; 95% CI, 3.6–18.6

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(continued)

TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Saleem et al[49]	United States	1973–2007	Patients with either in situ or invasive cervical, vulvar or vaginal neoplasm[c]	SEER	189,206	All women	HPV-related gynecological neoplasm	0.8 (no CI reported)	Overall SIR 13.6; 95% CI, 11.9–15.3 Anal cancer SIRs highest in African American women with invasive vulvar cancer: SIR 45.5; 95% CI, 14.3–95.0 Anal cancer SIRs lowest in women with invasive vaginal cancer: SIR 1.8; 95% CI, 0.8–5.3
Hessol et al[50]	US	1994–2001	HIV-positive women over the age of 18	Women's Interagency HIV study & SEER	1559 HIV-positive women 391 HIV-negative	All women	HIV	Not reported	HIV-positive: SIR 18.5; 95% CI, 0.5–68 HIV-negative: SIR 0; 95% CI, 0–289
Fordyce et al[51]	United States	1981–1994	Women with AIDS, aged 15–69 y	New York State Cancer Registry and New York City AIDS registry	15,146	All women	HIV	Not reported	Adjusted SIR 3.23; 95% CI, 1.39–6.36[d] Unadjusted SIR 2.68; 95% CI, 1.16–5.29[d] Relative risk increased from 2.35 (early pre-AIDS: 60–25 mo before AIDS diagnosis) to 5.08 (post-AIDS: 4–60 mo after AIDS diagnosis)

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Franzetti et al[64]	Italy	1985–2011	HIV-positive patients[c]	L Sacco Department of Clinical Science at the University of Milan	5924	1542 (26)	HIV	13.8 (no CI reported)	SIR 41.2; 95% CI, 4.6–148.8 Incidence of non-AIDs defining cancers during the HAART period was higher in both women and men Only SIR for vulva was higher in the HAART era for women: SIR 69.2; 95% CI, 22.3–61.4
Frisch et al (JNCI)[52]	United States	1995–1998	Patients with HIV/AIDS[c]	AIDS-cancer registry match in 11 state and metropolitan locations[e]	309,365	51,760 (40)	HIV	3.9 (no CI reported)	RR of invasive anal cancer Overall (all age groups): RR, 6.8; 95% CI, 2.7–14 Age at AIDS onset <30 y was highest: RR, 134.3; 95% CI, 16.3–484.8 RR for anal cancer similar to those of cervical and vulvar/vaginal cancer
Lanoy et al[65]	France	2006	HIV-positive patients with incident cases of cancer[c]	ONCOVIH cohort and FHDH	53,853	Not reported	HIV	Not reported	55 incident cases of anal cancer, 6 in women

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Picketty et al[66,67f]	France	1992–2008	HIV-positive patients	French Hospital Database on HIV	109,771	Not reported	HIV	9.4 (no CI reported)	SIR 13.1; 95% CI, 6.7–22.8[g] In women the incidence rates have increased in recent years: 1992–1996: 0 1997–2000: IR, 6.3; 95% CI, 0–13.4 2001–2004: IR, 12.9; 95% CI, 4.0–22.0 2005–2008: IR, 18.3; 95% CI, 8.0–28.7 In women, SIRs were significantly higher at younger than older ages 25–34 y: IR, 83; 95% CI, 9–300 45–54 y: IR, 8; 95% CI, 2–17
Silverberg et al[53]	US, Canada	1996–2007	HIV-positive and negative women[c]	NA-ACCORD, SEER	8842 HIV-positive women 11,653 HIV-negative women	20,495	HIV	30 (17–50)	No cases were observed for HIV-negative women Incidence rate was lowest in 1996–1999 (early cART) 1996–99: 0 2000–03: IR, 41.5; 95% CI, 16.7–77.4) 2004–07: IR, 24.7; 95% CI, 9.1–48.0

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Benard et al[54]	United States	1998–2003	Incident cases of HPV-associated cancers, women 20 y of age or older	CDC, NPCR, SEER, BRFSS data	138,043	95,961 (70)	General population	2.14 (2.10–2.19)	Lower median household income associated with significantly higher rates of anal cancer (compared with areas with income >$50,000) <$35,000: IR, 2.20; 95% CI, 2.11–2.29 $35,000-49,999: IR, 2.22; 95% CI, 2.17–2.77
Brewster and Bhatti[68]	United Kingdom	1975–2002	Incident cases of squamous cell carcinoma of the anus[c]	Scottish Cancer Registry	Not reported	Not reported	General population	0.55[h]	Significantly higher rates of SCCA in women in economically deprived areas ($P = .027$) Increase in incidence rates 1970s: IR, 0.23–0.27 1998–2002: IR, 0.55[h]
Fisher et al[55]	United States	1985–1992	Incident cancers of the lower anogenital tract in women[c]	Michigan Tumor Registry	Not reported	Not reported	General population	0.7 (no CI reported)	Blacks at a similar risk as whites for anal cancer

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Frisch and Goodman (Cancer)[56]	United States	1973–1996	Incident cases of squamous cell carcinoma of cervix, vulva, vagina, anus, penis, and tonsils[c]	SEER (Hawaii and 8 other locations)[j]	Not reported	Not reported	General population	US whites: 0.9[i] (no CI reported) Hawaii whites: 1 (no CI reported)[i] Hawaii APIs: 0.4 (no CI reported)[i]	SCCA SIR significantly increased over study period only in US whites Estimated annual increase of invasive SCCA, 1.5% ($P < .05$) Estimated annual increase of in situ SCCA, 4.6% ($P < .05$)
Jin et al[69]	Australia	1982–2005	Incident cases of invasive anal cancer[c]	Australian National Cancer Statistics Clearing House database	Not reported	Not reported	General population	1.10 (1.02–1.18)[i,k] Rate adjusted to the 2001 US standard population	Incidence of SCCA in women increased by 1.88% per annum; 95% CI, 1.18–2.58 Annual rate of increase of SCCA was almost 2 times higher in men than in women 5 year survival of invasive anal cancer increased over time, and women had better outcomes than men

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Joseph et al[57]	United States	1998–2003	Incident cases of all types of anal cancer	NPCR, SEER (83% of US population)	Not reported	Not reported	General population	1.51 (1.48–1.54)[i] rate adjusted to the 2000 US standard population	Women had a higher rate of SCCA than men Black women had a significantly RR of SCCA than did white women Rate was significantly higher in the South (RR, 1.24; 95% CI, 1.66–1.77) and the West (RR, 1.14; 95 % CI, 1.51–1.63) compared with the Northeast Invasive SCCA rates increased significantly from 1992 through 2004, by 2.8% During same period, rate of in situ tumors increased by 4%
Nelson et al[58l]	United States	1973–2009	Incident cases of AAC or anal SCCA	SEER database	Not reported	Not reported	General population	2.4 (2.3–2.5)[l,m] Rate adjusted to the 2000 US standard population	Rates of anal adenocarcinoma remained stable, whereas rates of SCCA were significantly increased in the time period after 1997 1973–1996: SIR, 1.4; 95% CI, 1.4–1.5 1997–2009: SIR, 2.4; 95% CI, 2.3–2.5

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TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Nielsen et al[70]	Denmark	1978–2008	Incident cases of anal cancer	Danish Cancer Registry and Danish Registry of Pathology	5.5 million	Not reported	General population	1.48[i,n] (no CI reported)	66% of incident cases of anal cancers were in women Average annual percentage change over study period: 2.9%; 95% CI, 2.2–3.6 Increase in age-adjusted anal cancer SIR was significantly greater in women <60 y (APC <60 = 5.2%; 95% CI, 4.0–6.3) than in women over 60 y (APC >60 = 1.7%; 95% CI, 0.9–2.5) 80.7% of cases of anal cancer in women were associated with HPV (compared with 67.9% in men)

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(continued)

TABLE 5
Incidence of anal cancer in women *(continued)*

Study	Location	Years of study	Population	Study design	Total number of patients in cohort	Women in cohort, n (%)	Risk factor	Anal cancer incidence (95% CI) in women per 100,000 person-years	SIR for anal cancer and other notable findings
Robinson et al[71]	United Kingdom	1960–2004	Incident cases of anal, vulvar, vaginal, cervical, and penile cancers[c]	Thames Cancer Registry	12 million	Not reported	General population	1.18[i,o] (no CI reported)	2676 cases of anal cancer in women, 1988 cases of anal cancer in men Increase in age-standardized period rates in women was greater than that in men In women: 0.45 (95% CI, 0.36–0.54) in 1960–1964 to 1.18 (95% CI, 1.08–1.29) per 100,000 in 2000–2004 (3-fold increase) In men: 0.79 (95% CI, 0.64–0.93) in 1960–1964 to 1.06, (95% CI, 0.95–1.17) per 100,000 in 2000–2004

AAC, anal adenocarcinoma; *BRFSS*, Behavioral Risk Factor Surveillance System; *CDC*, Centers for Disease Control and Prevention; *CI*, confidence interval; *CIN*, cervical intraepithelial neoplasia; *HPV*, human papillomavirus; *hx*, history; *IR*, incidence rate; *IRR*, incidence rate ratio; *JNCI*, Journal of the National Cancer Institute; *NPCR*, National Program of Cancer Registries; *RR*, relative risk; *SCCA*, anal squamous cell carcinoma; *SEER*, Surveillance, Epidemiology, and End Results; *SIR*, standardized incidence ratio.

[a] Data in the table from elsewhere[59,60] is a previous analysis of the same data; [b] Denmark, 1943–1998; US SEER, 1973–2001; Sweden, 1958–2001; Norway, 1953–1999; Finland, 1953–2001; [c] No age range reported; [d] Cancers of rectum and anus combined; [e] Atlanta, Connecticut, Florida, Illinois, Los Angeles, Massachusetts, New Jersey, New York City/State, San Diego, San Francisco, and Seattle; [f] Data in the table from elsewhere[66,67] is a previous analysis of the same data; [g] For time period 2005–2008; [h] For time period 1998–2002; [i] Age standardized incidence rate; [j] San Francisco–Oakland, Detroit, Atlanta, Seattle, Connecticut, Iowa, New Mexico, and Utah; [k] For the time period 2000–2005; [l] Data in the table from elsewhere[58] is a previous analysis of the same data; [m] For time period 1997–2009; [n] For the time period 2003–2008; [o] For time period 2000–2004.

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prevalent as if not more prevalent than cervical HR HPV infection.

Comparison with existing literature

Although we were unable to conduct a metaanalysis with the publications identified for this review because of the heterogeneity in outcomes and the small numbers of publications per outcome for women, the findings from our systematic review of women can be broadly compared with the metaanalysis and review by Machalek et al.[72] These authors conducted a metaanalysis reviewing publications evaluating the incidence and prevalence of HPV-16, HPV-18, anal squamous intraepithelial lesions (SILs) and anal cancer among MSM. Their review drew upon 31 publications evaluating HPV prevalence and 19 estimates of cytological abnormalities, and 11 publications evaluating the incidence of anal cancer. The authors were able to derive pooled prevalence and incidence estimates of both HPV-16 and HPV-18 infection and HSIL (AIN 2 or greater) lesions. In the review by Machalek et al,[72] the pooled incidence of high-risk HPV was 73.5 (95% CI, 63.9−83.0) and 37.3 (95% CI, 27.4−47.0) for HIV-positive MSM and HIV-negative MSM, respectively. These estimates are generally higher than the incidence and prevalence of high-risk HPV infection among both HIV-positive and HIV-negative women in the publications we reviewed.

The pooled prevalence of histological AIN2 or greater was found to be 29.1% (22.8−35.4) and 12.5% (9.8−15.4) among HIV-positive and HIV-negative MSM, respectively. The publications of anal HPV−related disease in MSM included a concurrent collection of anal HPV, anal cytology and HRA with directed biopsies at a single study visit. In comparison, in the majority of cohort studies conducted among women, the HRA was conducted based on abnormal anal cytology. Using these criteria, the prevalence of AIN 2 or greater among all female cohorts were lower than that that of MSM.

Finally, Machalek et al[72] reported that the pooled incidence of anal cancer was 45.9 per 100,000 (31.2−60.3) in the cART era and 5.1 per 100,000 (0−11.5) among HIV-positive and HIV-negative men, respectively, and these are higher estimates than the majority of anal cancer publications reported in our review. Thus, although the publications in women were too heterogeneous to conduct a metaanalysis, the pooled estimates from the review by Machalek et al[72] for high-risk HPV, AIN 2 or greater, and anal cancer in HIV-positive and HIV-negative MSM all appear higher than those found in the majority of publications among women reviewed in our current review.

Strengths and limitations

Our systematic review of the literature regarding anal HPV infection, neoplasia, and cancer in women revealed significant heterogeneity in both study design and findings, and results should be considered accordingly. The study cohorts included differing combinations of HIV-positive women, HIV-negative women, and women with unknown HIV status. In addition, a number of cohorts included women with HPV-related disease of the lower genital tract; however, the inclusion criteria varied from anogenital condyloma, vulvar lesions, abnormal cervical cytology, and specifically CIN3 or greater. Furthermore, several publications did not separate nononcogenic from oncogenic HPV genotype expression such that the findings cannot be compared with those publications investigating only oncogenic HPV.

There was significant variance in the methodology for HPV testing from HC2 to PCR. Because cervical HPV infection has itself been identified as a risk factor for anal HPV infection,[26] comparing publications that do not use a similar methodology to detect cervical HPV or HPV-related pathology will not represent the true relationship between HIV status, cervical/vaginal/vulvar HPV-related disease, and anal HPV infection. In addition, the publications of HIV-positive cohorts varied in their methods of accounting for immune reconstitution. Thus, the findings vis a vis prevalence and risk factors of HPV anal infection detected in these publications varied dramatically.

Additional limitations should be considered. First, the heterogeneity of sampling methods utilized by the publications in this review may have over- or underestimated the prevalence for each specific population, resulting in the large range of prevalences reported. Second, the majority of reported anal cytology results include publications that performed HRA only on those with abnormal cytology results, which may undercall the true rate of AIN2 or greater. Third, some of the included publications reported composite anal cytological/histological diagnosis based on which was more advanced, which also estimates rates of only true AIN2 or greater. Finally, our exclusion criteria were intentionally less rigorous to get a full perspective of the research that has been done to data; thus, the data reported are extremely heterogeneous in regard to not only sampling method but also study method and outcomes.

Conclusions and implications

Despite the limitations of this review, the results of this review demonstrate the evolving importance of anal HPV-related pathology and cancer among women. To our knowledge, this is the first systematic review of anal HR HPV infection, cytology, histology, and anal cancer in women. Our findings show that anal HPV infection and dysplasia are common in women, especially in those who are living with HIV or have a history of HPV-related lower genital tract pathology. Furthermore, incidence of anal cancer continues to grow in all women and especially those living with HIV, despite the widespread use of cART.

The lack of longitudinal data highlights the absence of conclusive knowledge in the prevention, detection, and management of anal HPV infection, dysplasia, and cancer in women. Further publications are needed to elucidate the natural history of anal HPV infection and HPV-related disorders of the anus in women to accurately and efficiently address this growing problem. ■

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