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Screening for Anal Cancer in Women

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Abstract

Objective—The incidence of anal cancer is higher in women than men in the general population and has been increasing for several decades. Similar to cervical cancer, most anal cancers are associated with human papillomavirus (HPV) and it is believed that anal cancers are preceded by anal high-grade squamous intraepithelial lesions (HSIL). Our goal was to summarize the literature on anal cancer, HSIL and HPV infection in women, and provide screening recommendations in women.

Methods—A group of experts convened by the ASCCP and the International Anal Neoplasia Society reviewed the literature on anal HPV infection, anal SIL and anal cancer in women.

Results—Anal HPV infection is common in women but is relatively transient in most. The risk of anal HSIL and cancer varies considerably by risk group, with HIV-infected women and those with a history of lower genital tract neoplasia (LGTN) at highest risk compared with the general population.

Conclusions—While there are no data yet to demonstrate that identification and treatment of anal HSIL leads to reduced risk of anal cancer, women in groups at the highest risk should be queried for anal cancer symptoms and have digital anorectal examinations to detect anal cancers. HIV-infected women and women with LGTN, may be considered for screening with anal cytology with triage to treatment if HSIL is diagnosed. Healthy women with no known risk factors or anal cancer symptoms do not need to be routinely screened for anal cancer or anal HSIL.

Keywords

Anal cancer; HIV infection; women; lower genital tract neoplasia

Introduction

The overall objective of this report is to summarize current knowledge of anal cancer, anal squamous intraepithelial lesions (ASIL) and anal HPV infection in different risk groups of women, and provide recommendations for screening women for anal disease, based on expert opinion.

The incidence of anal cancer has been increasing in the general population of women for the last few decades, but the risk of anal cancer varies considerably by risk group. Although not yet proven in formal randomized controlled trials, like cervical cancer, anal cancer may be potentially preventable through screening to detect and treat anal precancerous lesions. Given the variation in risk for anal cancer, ASIL and anal HPV infection, it is likely that an anal screening program would benefit some groups of women more than others.

The expert panel consisted of a group of medical professionals with diverse clinical backgrounds including Adolescent Medicine, Infectious Disease, Epidemiology, Surgery, Pathology, Oncology, Obstetrics and Gynecology, and Nursing--all of whom have been active in the field of anal cancer research and/or care.

Three groups for investigation were created based on consensus discussions: general populations, immunosuppression and lower genital tract neoplasia. Literature search were performed using 5-10 key words (ie. anal cancer, anal SIL, type of disease, type of immunosuppression, etc) for each group. Each group also identified important articles that were missing from the searches. Each group initially reviewed all the abstracts generated by the search and if any appeared relevant, articles were then reviewed in detail. More recent articles (within 10 years) were considered priority for review although it was recognized several articles were seminal and worthy reference. Reviews of the literature were summarized with relevant statistical comparisons.

Recommendations from each group were based on the available evidence wherever possible, and on expert opinion. Health benefits, side effects, adverse effects, risks and available clinical expertise were all considered in formulating the recommendations to the degree that this information was available. No literature was available on patient views or preferences. A formal cost-benefit analysis was not possible and was not done. Final recommendations were reviewed by all authors and agreed upon.

The sponsoring organizations, the ASCCP and the International Anal Neoplasia Society did not influence the content of the review or the recommendations, nor did any commercial entity.

Anal HPV Infection and Disease in Women

Anal cancer is a rare disease comprising only 0.4% of all new cancer cases in the United States.^{1,2} Recent data show an incidence rate of 1.8 per 100,000 persons overall with 1.5 per 100,000 in men and 2.0 per 100,000 in women. In 2015 there will be estimated 7270 new anal cancer cases and 1010 deaths.^{1,2} Worldwide, approximately 27,000 cases of anal cancer were diagnosed in 2008.³ The vast majority of anal cancers are squamous cell carcinomas. Non-squamous anal cancers include adenocarcinomas (some of which may be misclassified rectal adenocarcinomas extending into the anal canal) and melanomas. It is estimated that 90% of anal squamous cancers are caused by oncogenic types of HPV. HPV 16 predominates and is associated with over 75% of these cancers³⁻⁵.

In the US, the incidence of anal cancer has been increasing steadily over the last decade, rising approximately 2.2% each year in men and in women.² Certain populations are at higher risk for anal cancer, notably men who have sex with men (MSM) and individuals who are immunosuppressed. Although HIV is known to contribute to the rising incidence in males, the reasons for these increases in the general population of women is less clear. Death rates have also been rising on average 1.7% each year over 2001-2010 with only 65.5% of patients surviving five years or more.²

Overall, anal cancer is diagnosed in slightly more women than men. An estimated 4630 women in the US will be diagnosed with anal cancer in 2015 and 610 will die of their disease.¹ Racial differences also exist; the incidence of anal cancer is highest in white and lowest in Asian/Pacific Islander women. Anal cancer is also a cancer of older individuals with a peak in those aged 55-64 years and a median age for diagnosis of 60 years. Only 1.1% of anal cancers are diagnosed before age 35.

Assumptions for Anal cancer

Persistent infection with the same HPV type is a necessary intermediate step between infection and cancer.^{6,7} In the cervix, the time from HPV infection to development of high-grade cervical lesions and progression to cancer may be up to 1-3 decades.⁸ A similar natural history is assumed for anal cancer; persistence of anal HPV infection leads to high-grade squamous intraepithelial anal lesions and ultimately, anal cancer. However, several differences are worth noting. Despite similar high HPV infection rates in the cervix and anal canal in young sexually active women (see below for further discussion), cervical cancer is 4 times more common than anal cancer with an incident rate of 7.8 per 100,000 women. Prior to cervical cancer screening, cervical cancer had an incidence of 35 per 100,000. In addition, cervical cancer affects younger women—the mean age of cervical cancer diagnosis is 49 years of age and 14% occur in women under 35 years of age.

Without prospective longitudinal data regarding the incidence and duration of anal HPV, including regression and transience of infection, establishing temporal causality has not been possible. Establishing HPV as the causative agent for cancer using criteria proposed by Hill⁹ is not as strong for anal cancer and other anogenital carcinomas as it is for cervical cancer. The Hill criteria include defining a temporal relationship between infection and disease, biologic gradient, plausibility, coherence and experimental evidence. Additionally, there are no large prospective pathologic repositories from which to define the natural history of progression of anal precancers to invasive anal cancers. Fifty percent of anal cancers are diagnosed at Stage III or worse² underscoring the “lost opportunity” to identify early anal cancer. Limitations in current statistics include misclassifications—cancer registries often combine cases of anal “carcinoma in situ” with invasive cancer or combine rectal and anal cancer diagnoses (particularly in locally advanced cancers). As rectal and anal cancers likely have different etiologies, these limitations result in inaccurate estimates of HPV-associated anal cancers. For purposes of this review, cytology results are reported as anal squamous intraepithelial lesions (SIL) and histopathologic diagnoses are reported as anal intraepithelial neoplasia (AIN).

HPV in women in the general population

Although anal cancer is rare in the general population, there is growing literature examining anal HPV infections in healthy women. No large scale studies have been performed to date, so much of the literature is based upon selected cohort studies. These provide useful information but may not be representative of or generalizable to the wider community.

Several cross-sectional studies have reported high rates of anal HPV infection in young women. In one of the largest studies of healthy women, the Hawaiian cohort study, 1363

ethnically diverse healthy women over 18 years (mean 38 years) were recruited from clinics and provided cervical and anal specimens for HPV detection.¹⁰ At baseline, 29% had cervical HPV detected and 27% had anal HPV detected. Women with a cervical infection had a greater than 3 fold increase risk of anal infection. Approximately 80% of women with both anal and cervical infections shared at least one HPV type, suggesting that these anatomical areas served as potential reservoirs of infection for each other. Anal intercourse (AI) was associated with anal infections but only for those without a concomitant cervical infection. In contrast, in those with anal and cervical co-infections, AI was not associated with anal HPV. The distribution of HPV genotypes in the anus was more heterogeneous than in the cervix and there was a greater proportion of low risk HPV types.

Another recent study of 645 adolescent women (mean age 18 years), a proportion of whom had been fully or partially vaccinated with the quadrivalent vaccine, found anal HPV in 42% and cervical HPV in 54%.¹¹ The most common types detected (including cervical and anal) were HPV 51 and 58. In contrast, infections with HPV 16 were rare—found in less than 2% of anal samples—and concomitant infections widely varied depending on the HPV type detected. Detection of anal HPV was also associated with higher lifetime and recent numbers of anal and vaginal sex partners, younger age at first anal intercourse, and history of Chlamydia and anogenital warts. Odds ratios varied according to whether the factor was associated with HPV vaccine types, vaccine dose, HR types or any HPV type. When modeled by vaccine dose, the odds of detecting anal HPV was significantly reduced for HPV 6/11 (OR per dose = 0.61, 95% CI 0.43–0.86), as well as for HPV18 (OR per dose = 0.46, 95% CI 0.23–0.93). Although the reduced risk for HPV16 was not statistically significant (OR=0.63, 95% CI 0.18–2.20), the low prevalence of HPV 16 precludes any conclusions.

Another cross-sectional study reported on the control arm of the Costa Rica HPV vaccine trial¹² in which 2107 women aged 22–29 years provided a single anal swab sample at year 4 for HPV analysis. All had been sexually active. Overall anal and cervical HPV prevalence were high, 31.6% and 36.5%, respectively. Anal hrHPV prevalence was 22.0% (30.1% in women with AI history and 19.8% in women with no AI history). HPV 51 and 52 were the most common HR types. HPV 16 was found in 4% (6.4% for AI history vs 3.4% for no AI history). Multiple infections were common. Concurrent cervical HPV infections were present in 19.7%. Among women who reported AI, presence of cervical HPV (adjusted odds ratio [aOR], 5.3 [95% CI, 3.4–8.2]), the number of sex partners (aOR, 2.2 [95% CI 1.1–4.6] for 4 partners), and the number of AI partners (aOR, 1.9 [95% CI 1.1–3.3] for 2 partners) were independent risk factors for anal HPV detection. Among women reporting no AI, presence of cervical HPV (aOR, 4.7 [95% CI 3.7–5.9]), number of sex partners (aOR, 2.4 [95% CI 1.7–3.4] for 4 partners), and report of anal fissures (aOR, 2.3 [95% CI 1.1–4.8]) were associated with anal HPV detection.

One of the first prospective studies of anal HPV infections published was by Goodman et al.¹³ These investigators followed 650 women from the Hawaii cohort described above. This group had an enrolment anal HPV prevalence of 42% and a period prevalence of 70% over an average 1.3 year follow-up. The incidence of hrHPV infection was 19.5 (95% confidence interval [CI], 16.0–23.6) per 1000 woman-months. For HPV 16, enrolment prevalence was

4.4% and period prevalence was 7.7%. Adjusting for age, risk factors for acquisition of a hrHPV type included cervical HPV at baseline (odds ratio (OR)= 1.81 [95% CI 1.09-3.02]). In addition, the presence of anal hrHPV infection at baseline increased the risk of acquisition of any HPV type by 65% (95% CI 1%–170%), and the presence of anal low risk HPV infection increased the risk of acquisition of another HPV type by 80% (95% CI 8%–200%). Non-viral risk factors included younger age, white ethnicity, lower socio-economic status, greater number of lifetime sexual partners, past use of noncontraceptive estrogens and condom use. Actual risk varied whether acquisition was high risk, low risk or any HPV type. Further analysis¹⁴ showed a relative risk of 20.5 (95% CI 16.3-25.7) for acquiring an anal HPV infection after a cervical infection with the same genotype (compared with women without a cervical infection), suggesting that the cervix may serve as a reservoir for anal HPV infection. They also found an increased risk of 8.8 (95% CI 6.4-12.2) of acquiring a cervical HPV infection after an anal infection with HPV of the same genotype. A total of 69% of hrHPV infections and 81% of low risk infections cleared within one year. In addition, risk of anal infection was enhanced by the presence of multiple HPV types in the cervix.¹⁵

Few studies have examined clearance of HPV. Shvetsov et al¹⁶ evaluated clearance patterns of anal HPV infection for 215 of these same Hawaiian women. Median duration of anal hrHPV infection was 150 days (compared with 240 days for cervical hrHPV); median duration for HPV 16 was 132 days and for HPV 18, 212 days. Vaginal douching, smoking and AI delayed HPV clearance. Relative Hazards varied by HPV type.

In contrast, Moscicki et al¹⁷ found anal HPV 16 slower to clear than other hrHPV infections in their study of 75 young women (mean age 23.5 years). This slower clearance was likely due to the longer observation period (mean follow up was 85 months) and the stricter definition of clearance (i.e., two consecutive negative visits vs. only one required in the Shvetsov study). At 3 years, 76% of HPV 16 infections had cleared (compared with 83% of non-16 anal hrHPV infections). By 3 years only 36% became negative for all HPV types, underscoring the frequency of new acquisitions. Persistence of anal HPV 16 and other hrHPV was associated with concurrent cervical HPV 16, alcohol use, anal touching, recent AI and no condom use during AI. Relative hazard varied by HPV type. A change in sexual partner was associated with HPV 16 clearance, probably reflecting cessation of re-exposure and infection by the previous partner.

Anal squamous intraepithelial lesions in women in the general population

Compared with studies of anal HPV detection, data on the prevalence, incidence and risk factors for anal squamous intraepithelial lesions (SIL) in healthy women are extremely limited. No studies have been performed in a truly population-based sample of U.S. women.

As with anal HPV infection, most studies of anal SIL have been done in groups of women known to be at increased risk of anal cancer, including those with HIV infection, other forms of immunosuppression, and presence of cervical or vulvar HPV-associated lesions (see Sections on Immunosuppression and Lower Genital Lesions). In several of the studies focusing on anal SIL in HIV infected women, control groups were used for comparison. Most of the control groups were considered to be at high risk of HIV infection since they

often had histories of drug abuse or numerous sexual partners. One such study of HIV-infected and uninfected adolescents and young women found a prevalence of abnormal anal cytology of 5.7%.¹⁸ Risk factors for abnormal anal cytology in the entire group (HIV status was treated as a risk factor) included anal hrHPV infection (OR= 16.5 [95% CI 5.6-48.1]) and greater than one recent sex partner (OR= 4.2 [95% CI 1.5-11.8]). In a population of slightly older, high-risk, HIV-uninfected women, the rate of abnormal anal cytology was only 1%.¹⁹ Moscicki et al.²⁰ examined the rate of abnormal anal cytology among a young healthy cohort who were participating in a natural history study of cervical HPV infection—although most women did not have cervical HPV at the time of anal testing. Women who agreed to anal testing had annual anal cytology. Of the 397 women (mean age was 23 ± 2.5 years) who agreed to anal testing, 684 anal cytologic samples were available for analysis. Eighteen women (4%) had abnormal anal cytology results. Risks for abnormal anal cytology included, history of ever anal sex (OR= 4.45 [95% CI 1.21-16.43]), history of vulvar warts (OR= 4.25 [95% CI 1.48-12.25]), history of abnormal cervical cytology (OR=3.05 [95% CI 1.01-11.55]) and anal HPV infection (OR=6.48 [95% CI 2.22-19.91]). In all the studies above, high resolution anoscopy (HRA) was not performed routinely and the majority of abnormalities were ASC-US and LSIL. Two studies that focused on women with lower genital tract neoplasia (LGTN) (described below) also included a control group of healthy women. Koppe *et al*²¹ performed screening high resolution anoscopy (HRA) and HRA-guided biopsy, if applicable, on 74 healthy women with negative cervical cytology and no history of genital warts recruited from a gynecologic practice. Only 1.4% (95% CI 0.1–6.5%) were found to have AIN on biopsy and none had AIN 2/3. Jacyntho *et al*.²² evaluated 76 healthy women recruited from a clinic in Brazil who presented for cervical cancer screening. Healthy controls had at least 2 recent normal cervical cytology tests (interval not described) and normal genitoscopy. All women had colposcopy and HRA. Only 2 (2.6%) had AIN on biopsy, and both were AIN1. Since neither of these studies performed anal cytology nor random biopsies, the prevalence of AIN may have been underestimated (see below for discussion of HRA).

In summary, although anal cancers are rare in healthy women, the prevalence of anal HPV of one or more genotypes is common in healthy young sexually active women and is comparable to the prevalence of cervical HPV, if not greater. Risk factors for acquisition of hrHPV include any sexual activity, AI, cervical HPV infection, and presence of anal fissures. Genotype concordance with the cervix is common; therefore, the cervix may act as a reservoir for anal infection or vice versa. Most anal HPV infections are transient, consistent with the low rate of anal cancers in healthy women. Persistence of anal HPV is influenced by co-existing cervical infections, alcohol use, and lack of condom use. Investigation of the natural history of anal HPV infections in healthy women is hampered by patient selection biases, frequent incident infections, and multi-type infections. Compared with anal HPV detection, AIN in healthy women is rare. The rate of progression of untreated high-grade AIN in healthy women is not known. Data from the New Zealand experience indicate that approximately 30% of cervical intra-epithelial neoplasia 3 (CIN3) will progress to invasive cancer in 30 years⁸ if left untreated. Since anal cancer rates are much lower than cervical cancer, it is not clear if the same rates can be applied to high-grade AIN. However,

the increasing rates of anal cancer among women underscores the importance of identifying women with high-grade AIN and studying factors associated with progression.

The high prevalence of anal HPV infection and low incidence of anal precancer and cancer in healthy women, coupled with the apparent transient character of many anal HPV infections, indicate that screening for AIN2/3 is unlikely to be a cost-effective strategy for preventing anal cancer among a population of healthy women with no additional risk factors.

Women at high risk of anal cancer

Anal cancer in immunocompromised women—Host immune response is critical in containing almost all viral infections and HPV is no exception. Although the immune response is complex, the predominant immune arm important in clearance of established HPV infections is thought to be the cell-mediated pathway primarily involving T-cells.²³ Hence, conditions that deplete T cells or otherwise interfere with T cell function may render women vulnerable to HPV infections and their sequelae. The association between HPV and immune dysfunction was first noted in immunosuppressed patients including transplant patients noted to have an increased risk of developing warts.²⁴

Anal cancer in HIV infected women—The best studied of the immunosuppressed groups are persons with HIV infection. Numerous studies now demonstrate a strong association between HIV infection and anal cancer. The strongest association is seen in MSM with HIV but strong associations are also seen in heterosexual men and women with HIV.²⁵ A recent large study examined data from 13 North American cohorts followed during 1996-2007.²⁶ Anal cancer incidence rates were examined among 34,189 HIV-infected (55% MSM, 19% heterosexual men, and 26% women) and 114,260 uninfected persons (90% men). Incident anal cancer was ascertained from medical records, patient interviews or linkage with cancer registries. Unadjusted anal cancer incidence rates were 131 per 100,000 person years for HIV-infected MSM, 46 for heterosexual HIV-infected men, 30 for HIV-infected women, 2 for HIV-uninfected men and 0 for HIV-uninfected women. They also compared time periods before and after the availability of highly active anti-retroviral therapy (HAART). The adjusted rate ratio (RR) for anal cancer among HIV-infected persons was 0.5 in 1996-99 compared with 2000-2003 and 0.9 in 2004-2007 compared with 2000-2003. The authors concluded that the increase in anal cancer after HAART initiation (2000-2003) may have been related to increased survival but that this effect leveled off.

Chiao et al²⁷ also examined temporal trends in the incidence of anal canal cancer in the U.S. using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) reports in 3 time periods: pre-HIV era (1973-81), HIV era (1982 -1995) and HAART era (1995-2001). They identified 43,855 invasive anal cancers. Disease rates in females for the 3 time periods increased over time and were 0.8, 0.9 and 1.1 per 100,000 persons, respectively. Age of anal cancer diagnosis fell for women over this time period from a mean of age 64 years during the pre-HIV period to 61 years for the HAART period. Five-year survival increased from 63% during the pre-HIV era to 72% during HAART.

Yanik et al²⁸ examined more recent trends linking the University of North Carolina (NC) Center for AIDS Research HIV Clinical Cohort, an observational clinical cohort of 3141 HIV-infected patients 30% of whom were female, with the NC Cancer registry data between 2000 and 2011. Across 15,022 person-years of follow-up, 202 cancers were identified with most being virus-related (incidence rate (IR) per 100,000 person-years was 1345; 95% CI: 1166-1544). Anal cancer showed no change in incidence over time with 16 anal cancers identified (IR was 107; 95% CI: 61-173). Of the other virus-related cancers including Kaposi sarcoma and non-Hodgkin's lymphoma, only the latter showed a decrease.

Simard et al²⁹ conducted a similar population-based, record-linkage study using the HIV/AIDS Cancer Match database. From 1980 to 2006, 472378 individuals with AIDS, predominantly men, were identified and linked to cancer registries. The cumulative incidence of cancer in someone living with AIDS was estimated across 3 calendar periods (AIDS onset in 1980-1989, 1990-1995, and 1996-2006). The cumulative incidence of AIDS-defining cancers (ADC) declined sharply across the 3 AIDS calendar periods from 18% to 11% to 4.2%. More specifically, Kaposi Sarcoma and non-Hodgkin's lymphoma (NHL) showed dramatic declines whereas the percentage of cervical cancers among women remained stable at 0.63% during 1980-1989 to 0.64% by 2006. In contrast, the cumulative incidence of anal cancer increased steadily from 0.02% in 1980-1989 to 0.09% by 2006. An increase was also observed for Hodgkin lymphoma and liver cancer. Except for cervical cancer, data were not analyzed specifically for women.

A recent study from Kaiser Permanente California³⁰ specifically examined the incidence rates of non-AIDS defining cancers in HIV-infected and uninfected individuals accounting for CD4 and HIV RNA levels. They followed 20775 HIV-infected and 215158 HIV-uninfected individuals enrolled in Kaiser Permanente (KP) California from 1996-2008. Rate ratios (RR) were calculated adjusting for age, sex, race/ethnicity, calendar period, KP region, smoking, alcohol/drug abuse, and overweight/obesity. Anal cancer as well as Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and colorectal cancer had significant trends for increasing RRs with decreasing recent CD4 counts. Specifically for anal cancer the RR (compared with HIV-uninfected) was elevated among all CD4 counts categories. The RR was 91.5 (48.0-174.5) for CD4 count <200; 63.4 (36.4-100.3) for CD4 200-499 and 33.8 (17.8-64.3) for CD4 >499.

These high rates of anal cancer have also been observed in non-US populations. Several studies noted here have been published from the French hospital database (FHDH-ANRS) and an ongoing cancer surveillance study among HIV-infected persons (OCOVIH) regarding HIV and cancer associations. In a recent publication, the overall incidence of cancer in HIV-infected patients was 14 per 1000 person-years. Most of the men were MSM and the women were predominantly from sub-Saharan Africa. Compared with the general population, the estimated RR for cancer in HIV-infected persons was 3.5 (3.3-3.8) in men and 3.6 (3.2-4.0) in women.³¹ AIDS-associated malignancies made up only 39% of the cancer cases. The most common cancers in men in order of prevalence were lymphomas, Kaposi sarcoma, anal and lung. For women, lymphomas, breast, Kaposi sarcoma and lung were the 4 most common; cervical was 6th and anal was 7th. Of the anal cancers, 11% were in females and the median age was 45 years. Most patients were on HAART therapy. Also

from the same French hospital database, data were available for 263 anal cancer cases from a population of 109,771 HIV-infected persons.³² Women represented 9% of the anal cancer cases with a median age of 42 years compared with 72 years for women with anal cancer in the general population. From 2005-2008, compared with the general population, HIV-infected patients had an increased risk of anal cancer with age standardized incidence ratios (SIRs) of 109.8 (95% CI 84.6-140.3), 49.2 (95% CI 33.2-70.3) and 13.1 (95% CI 6.8-22.8) for MSM, other HIV-infected men, and HIV-infected women, respectively. Risk increased with low CD4 nadir. The rate during the HAART period was greater than pre-HAART (hazard ratio (HR) = 2.5 (95% CI 1.28-4.98)).

Also from the French group, current CD4 cell count was found to be the most predictive risk factor for all malignancies except for anal cancer.³³ For cervical cancer, there was a strong effect of current CD4 (RR = 0.7 per log (2), 95% CI 0.6-0.8; p=0.0002). Although current CD4 count was not associated with anal cancer, the duration of CD4 being <200 was statistically significant. The risk of anal cancer increased with the duration of CD4 counts<200 cells per microL (1.3 per year, CI 1.2-1.5; p=0.0001), and viral load was greater than 100 000 copies per mL (1.2 per year, 1.1-1.4, p=0.005). Use of HAART for at least 6 months was not associated with risk for anal cancer whereas cervical cancer had lower rates. The RR of cervical cancer for those receiving HAART was 0.5 (CI 0.3-0.9; p=0.03).

Although a retrospective review, a report from Italy³⁴ examined a hospital clinic database for non-AIDS defining malignancy from 1985 to 2011 of which a quarter of the almost 6000 patients were women. Comparing the pre-HAART era (1985-1996) to the HAART era (1997-2011), 144 non-AIDS defining malignancies were identified of which 31 were in women--3 pre HAART and 28 post-HAART, reflecting an incidence rate of 0.4 per 1000 person years and 3.6 per 1000 person years, respectively. The SIR for anal cancer in women from 1985-2011 comparing post HAART to pre HAART was 41.2 (95% CI 4.6-148.8) and in comparison, for vulvar cancer was 69.2 (22.3-61.4). Risk factors were a nadir CD4 count of <200 [HR=1.58 (95% CI 1.1-2.3)] and older age [HR =1.35 (95% CI 1.2-1.5)] per every 5 years).

Another clinic-based study in Bonn, Germany compared their HIV group to a reference population from 1996 to 2009.³⁵ Of the 1476 patients entered into their study, they identified 114 patients with invasive cancers. As in other studies, malignancies associated with infectious agents [e.g. HPV, Human Herpes Virus (HHV)-8, Epstein Barr Virus (EBV)] were substantially more frequent in HIV-infected patients than in the general population. In this study, the SIR for anal cancer was relatively equal among HIV infected men and women: the SIR in men was 88 (95% CI 31.6-172.1) and for women was 115 (95% CI 10.0- 330.1). In comparison, the SIR for cervical cancer was 4 (95% CI 1.5-7.9). In this study, use of HAART and high CD4 cell count preferentially reduced the risk of infection-associated cancers, however, these data were only provided in aggregate— infection-specific cancer data were not available.

Anal squamous intraepithelial lesions in HIV-infected women—Numerous studies have reported that HIV-infected women have higher rates of abnormal anal cytology and histopathology than HIV-uninfected women. Unfortunately, most of these studies are cross-

sectional and health status varied quite widely between studies. In this review, retrospective studies were not included.

Rates of abnormal anal cytology in HIV-infected women have ranged from 9% to over 40%, several fold higher than those reported in HIV uninfected women.^{19,36-40,18-20}

In one of the first studies to report on anal cytology in HIV-infected women, anal cytologic abnormalities were found more often than cervical cytologic abnormalities.⁴¹ Rates of AIN2/3 have been more difficult to define since most studies only perform HRA on women with abnormal cytology resulting in gross underestimates.^{19,36,39,40,42}

Durante et al.⁴² reported on a prospective study of women with HIV from New Haven. There was a high incidence of abnormal baseline cytology reports (14 of 100). Of those with normal baseline cytology, the incidence of developing abnormal cytology in later screening rounds was 22 per 100 person years. Most abnormalities were ASC-US. Incidence of SIL by cytology alone was 9 per 100 person years. Risks associated with abnormal cytology were a CD4+ T-cell count of <500 cells/mm³ (3) [relative hazard (RH) = 4.11; 95% CI 1.18-14.25], anal hr HPV infection (RH = 2.54; 95% CI 0.91-7.14) or cigarette smoking (RH = 3.88; 95% CI 1.12-13.42). In this study, HAART had no effect; no HRA was performed.

In a study of 251 women participating in the Women Interagency HIV Study (WIHS), 26% of HIV-infected women had abnormal anal cytology. The risk of abnormal cytology increased with lower CD4 level (test for trend $p < .0001$) and higher plasma HIV RNA viral load (test for trend $p = .02$). In the multivariate analysis, history of anal intercourse (RR 2.3, 95% CI 1.2-3.6) and concurrent abnormal cervical cytology (RR 2.1, 95% CI 1.0-3.6) were significantly associated with abnormal anal cytology.⁴³ However, in a more recent study reported from the WIHS, there was little correlation between the severity of anal and cervical disease.⁴⁴ Severity was defined by the highest grade of abnormality found by histology or cytology.

Tandon, et al., and Baranoski, et al.,^{39,45} also reported on a clinic population of 100 HIV-infected women. At study entry, 17 women had abnormal anal cytology. Risks for abnormal baseline anal cytology included CD4 <200, history of a sexually transmitted infection (STI) and concurrent CIN. Thirty-three women had at least one abnormal anal cytology report over the three years of study; the incidence of abnormal anal cytology was 13.1 per 100 person-years. Anal cytologic abnormality was associated with current CD4 count <200 cells/mm³ (OR 12.8, 95% CI 2.0–82.0), anal HPV infection (OR 6.2 95% CI 2.2–16.9) and history of STI other than cervical/anal HPV infection (OR 3.6, 95% CI 1.1–11.5). Anal intercourse was not a risk factor in this population. Over the duration of the study, 12 of the 36 women who had HRA post-abnormal cytology were diagnosed with AIN2/3 (overall prevalence of 12%).

Chaves et al.³⁸ found a prevalence of abnormal anal cytology of 14% in 184 HIV-infected women in Brazil. Independent risk factors for abnormal cytology included smoking (adjusted relative risk (aRR) = 2.51 (95% CI 1.16, 5.39)) and CD4 < 200 count (aRR = 4.38 (95% CI 1.54, 12.48)). From a study in New York, Hou et al.³⁶ reported data from 715 HIV-infected women with no gross evidence of HPV-associated disease and found that 11% had

abnormal anal cytology and 4% of these women had AIN2/3 (overall AIN2/3 rate of 0.56%). Poorly controlled HIV-infection (current CD4 < 250/detectable viral load (VL) was the major risk factor compared with well-controlled HIV (CD4 > 500/undetectable VL (61% vs 5%; p=0.03). Another study based in a New York infectious disease clinic found a much higher prevalence rate than most other studies: 42% (233/556) of women screened had abnormal anal cytology including 29/556 (5%) with ASC-H or HSIL cytology.⁴⁰ Of the women with abnormal anal cytology, 73% underwent HRA and 45 (overall prevalence of 8%) of all women screened were diagnosed with AIN2/3. This study noted that once an HIV-infected patient had an abnormal cytology, the likelihood of having high-grade AIN was similar regardless of whether the person was a MSM or a heterosexual man or a woman.⁴⁰ Similar high rates of abnormal anal cytology were found in a smaller study in Texas: 31% of 204 HIV-infected women had abnormal cytology and 18% had biopsy-proven AIN2/3.⁴⁶ As other studies, the greatest risk factor for high-grade AIN was low CD4 count. Anal intercourse was also a risk as 26% of women who reported anal intercourse had AIN 2/3 versus 13% in those who reported no anal intercourse.

HIV-infected persons are also at risk for multi-focal HPV-associated disease of the genital tract.^{39,47-49} A small study compared 33 immunocompromised (included 16 women with HIV and 7 women with a transplant, lupus, or diabetes) and 304 immunocompetent women referred for colposcopic evaluation because of an abnormal cervical cytology or a genital lesion.⁴⁷ The evaluation included a concurrent HRA. Immunocompromised women had greater rates of vulvar intraepithelial neoplasia (VIN)2/3 (55% vs 23%), vaginal (VA)IN 2/3 (9% vs 6%) compared with immunocompetent women but had similar rates of CIN2/3 and AIN2/3. Multifocal disease involving at least 2 anogenital sites was more common among the immunocompromised patients (61% vs 30%). A retrospective chart review of HIV-infected patients all of whom had anal cytology testing and HRA and immediate biopsy of HRA-visualized abnormalities reported that 72.4% (21/29) of women with CIN and/or genital warts had biopsy proven AIN of which 34.5% (10/29) were AIN2/3.⁴⁸ In comparison, 25% (3/12) of HIV-infected women without a history of CIN or genital warts had AIN and 17% (2/12) were AIN2/3.

Virtually all the studies that included cytology and HRA found poor agreement between the two with concordance rates ranging from as low as 0.11 to 0.40. The role of cytology and HRA is discussed below. No studies to date have examined the natural history of AIN in HIV-infected women. Machalek⁵⁰ estimated that anal high-grade AIN would progress to squamous cell cancer in 1 of 377 HIV-infected MSM per year.

Anal HPV in HIV-infected women—The findings associated with anal cancer and abnormal anal cytology and HIV are not too surprising since numerous studies have documented the high rates of anal HPV in HIV-infected women with most reporting prevalence rates over 70%.⁵¹ As among HIV-uninfected women, the prevalence of anal HPV is higher than cervical HPV.^{41,52} A recent analysis in the WIHS cohort showed that low CD4 cell counts (< 200 cells/mm³), compared with >500 cells/mm³ (RR, 1.4; 95% CI 1.1-1.5), and cervical HPV infection (RR, 1.3; 95% CI 1.1-1.4) were associated with anal HPV infection, similar to abnormal anal cytology.⁴⁴

Unfortunately, few studies report rates of anal HPV persistence in this group. Beachler et al.⁵³ reported on 153 women, 168 heterosexual men and 69 MSM—all HIV infected. With a mean follow-up of 24 months, 31% of persons with a prevalent anal HPV infection and 55% of persons with an incident infection showed clearance. Women were less likely to clear than heterosexual men but similar to MSM. No other risk factors were associated with anal HPV clearance.

In summary, HIV-infected women are at higher risk for anal HPV infection, anal high-grade AIN and cancers than HIV-uninfected women. Based on the data reviewed, the true risk of anal high-grade AIN in HIV-infected women is unknown and argues for more inclusion in prospective studies. This risk appears lower than MSM, but equal to or higher than that of heterosexual HIV-infected men. Although low CD4 counts are a primary risk associated with abnormal anal cytology, some studies found that HIV-infected women with normal CD4 counts are still at higher risk than HIV-uninfected women. The role of HAART remains controversial in affecting anal precancer and cancer rates. HIV-infected women are also at higher risk for multi-focal HPV-associated disease.

All HIV-infected women are a reasonable population to perform some type of anal cancer screening --minimally with digital rectal examinations and screening for anal cancer symptoms (pain and bleeding) with referral for additional diagnostic testing if positive. There are data to support screening with anal cytology particularly those with low CD4 counts or history of CIN or VAIN. There are no data on screening for anal cancers with anal HPV testing, but the high rates of positivity in this group make this approach not likely to be cost-effective. Many studies found anal intercourse as a risk for abnormal anal cytology and histology in women, however, HIV control was a stronger predictor. Most researchers agree that screening should be not guided by a history of anal intercourse.

Anal cancer in women with solid organ transplantation—The increased risk of pathogen-associated cancers including those associated with HPV has long been described for organ transplant patients. This association is thought to be primarily due to the immunosuppressive drugs used to prevent transplant rejection. The level of immune suppression is related to type of organ transplanted and drug regimen. One of the more comprehensive looks at HPV-associated cancer risks in organ transplant patients examined the incidence of HPV-associated cancers among 187, 649 U.S. recipients of organ transplants.⁵⁴ Data were obtained from the US Transplant Cancer Match (TCM) study, an ongoing linkage between the nationwide U.S. organ transplant registry and 15 state and local cancer registries.⁵⁴ Overall, there was an elevated incidence of 4 of the HPV-associated cancers among transplant patients compared with the general population. Vulvar cancers had the highest SIR of 7.3 (95% CI 5.6-9.2) and anal cancer was second highest with an SIR of 5.4 (95% CI 4.4-6.6). Penile and oropharyngeal cancers were also elevated with SIRs of 3.9 (95% CI 2.5-5.7) and 2.2 (95% CI 1.8-2.5), respectively. No increase was found for cervical cancers. Median time from transplantation to all cancer diagnosis was 4-5 years however, the risk for both anal and vulvar cancers began to increase 2 years post transplantation. SIR for in situ cancer (i.e. IN3) was elevated for all anogenital lesions including cervical. The increased risk for cervical in situ cancers but lack of risk of cervical cancer underscores the success of cervical cytology screening and management of precancer to prevent invasive

cervical cancers. The authors note, that even though the risks were elevated, anal cancer had an incidence rate of 12.3 per 100,000, similar to that of the current cervical cancer rates—a rate that may justify implementing anal cancer screening in this population. Of note, vulvar cancer had the highest incidence rate of 20.1 per 100,000. This study also examined types of immunosuppressive drug regimens. Older regimens using cyclosporine and azathioprine were associated with the highest risk of anal cancer whereas newer regimens using tacrolimus and mycophenolate appeared to be protective against anal cancer. Another new agent often used is sirolimus—a known inhibitor of mammalian target of rapamycin (mTOR) pathway which regulates growth factors, nutrients, and energy that promote cellular growth under certain conditions such as stress. Recent data suggest that activation of this pathway is linked with the development of anal squamous cell cancer; hence inhibitors may be protective.⁵⁵ This group suggested that screening organ recipients for anal cancer with cytology beginning at least 2 years post-transplant might be reasonable.

One of the largest studies to examine solid organ transplant and risk of malignancies was by Sunesen et al⁵⁶ using linkage data from the Danish National Patient Registry (NPR) and Danish Cancer Registry (DCR). Patients from the NPR were identified with a surgical procedure related to transplantation (41,443 person-years) during the period 1978-2005. Anal cancer definition included those of the rectum, anal canal or anal rectum. Solid organ transplantation was associated with an anal cancer SIR of 14.4 (C.I. 7-26.4). Risk of anal cancer in solid organ transplantation increased with time with a SIR of 4.5 at 1-4 years post-transplant and a SIR of 20 at 5 years or more. This study was limited in that diagnoses were not verified and some of the anal cancer identified in the rectum could have been adenocarcinoma for which the pathogenesis is substantially different from that of anal cancer.

Another study examined risk of cancers among 2878 Italian recipients of solid organ transplants.⁵⁷ The SIR for risk of all cancers among transplant recipients was 2.2 (1.9-2.5). Most excess risk was attributable to virus-associated cancers including Kaposi's sarcoma, non-Hodgkin's lymphoma and liver cancer. Although no increased risk was found for anal cancer, women younger than 40 years of age had a 10-fold increase risk of cervical cancer.

Anal squamous intra-epithelial lesions in women with solid organ transplants

—Few studies have examined associations with abnormal anal cytology and organ transplants. A small prospective study of kidney transplant recipients⁵⁸ performed anal cytology and HRA on 15 women and 25 men. The mean age of this group was 61 years and few ever reported anal intercourse. Biopsies were performed on 11 who had abnormal HRA findings, and of these 4 had AIN1 and 2 high-grade AIN. No gender distribution was reported. Another study reported anal cytology in 108 patients (40 women and 68 men) with a mean age of 52 at time of transplant⁵⁹. On cytology, 4 had ASC, 2 had LSIL, 4 (3.7%) had HSIL. Independent risks for abnormal cytology included receptive anal intercourse (OR=56.36 (95% CI 2.35-1348.91) and genital warts (OR=19.96 (95% CI 1.67, 239,16). Major limitations here were lack of HRA and HRA guided biopsy hence the prevalence of AIN was likely underestimated.

In summary, the data are limited and conflicting regarding solid organ transplant and anal cancer risk. Data from several large transplant and cancer registries demonstrate an increased risk for vulvar and anal cancer but not cervical cancer. These observations suggest that screening for cervical cancer is effective in this population and that screening for the other HPV-associated cancers may be effective as well. With admittedly shorter follow-up, newer immunosuppressive agents appear to result in lower cancer risk than the older regimens. There are no data examining the performance of anal cancer screening using either anal cytology or HRA further limiting any recommendations using these modalities.

Women who received transplants and were exposed to older regimens warrant a minimum of digital rectal screening and screening for anal cancer symptoms (pain and bleeding) with referral for additional diagnostic testing if positive. Further research is needed in this group.

Anal cancer in women with autoimmune disease—Immunosuppressive treatments are also common in patients with autoimmune diseases. With better treatments, patients with severe autoimmune diseases are living longer with the development of long-term sequelae of their disease and treatment including malignancies. The data remain conflicting and vary by the type of autoimmune disease. In addition, cancer risk may not necessarily be related to immunosuppressive treatment, but to the disease itself.

Of all the autoimmune diseases, systemic lupus erythematosus (SLE) has received the most attention.⁶⁰⁻⁶² A group of investigators from the University College London Hospitals Lupus Clinic performed a nested case control analysis from retrospective chart reviews of 595 patients with SLE followed for up to 32 years⁶³. Thirty-three patients were diagnosed with cancer after their SLE diagnosis. Controls were matched for age, sex, ethnicity and disease duration. Increased risks of HPV-associated cancers were found for both cervical (SIR =4.0 (95% CI 3.5-4.5) and anal cancer (SIR=1.8 (95% CI 1.48-2.12)). Other cancers with increased risk included prostate, and pancreatic. No drug dose or duration effect was seen, however, hematologic abnormalities (particularly cytopenia), and anticardiolipin and antithyroid globulin antibodies were associated with overall cancer risk. Risk for individual cancers was not described.

Sunesen and colleagues⁵⁶ examined risks of anal cancer among individuals with autoimmune diseases as well as solid organ transplantations. Using linkage data between the Danish NPR and DCR, they identified first time hospital diagnosis of any one of 24 selected autoimmune disorders (2,127,325 person years) during 1978-2005. When all autoimmune diseases were considered, the risk of anal cancer was increased (SIR=1.3 (95% CI 1.0-1.6)). When diseases were examined separately, highest risks for anal cancer were seen for Crohn's disease, dermatitis herpetiformis, polyarthritis nodosa, and Wegner's granulomatosis with SIRs ranging from 3.1 to 12.4. Marginal effects were found for SLE, polymyositis, and Sjogren's syndrome and no association was seen for ulcerative colitis. As seen for solid organ transplantation, risk for anal cancer increased with time after diagnosis.

In a hospital based Danish cohort (n=576) diagnosed with SLE, Dreyer et al⁶⁴ linked medical records to the DCR from start of diagnosis. Patients with SLE (of whom the majority were women), had an overall increased risk of cancer (SIR 1.6 (95% CI 1.2, 2.0)).

Risk was even higher among virus-associated cancers (SIR = 2.9 (95% CI 2.0, 4.1) with the highest risk being anal cancer (SIR = 26.9 (95% CI 8.7, 83.4). Other HPV associated cancers were also elevated including vulvar cancer [SIR = 9.1 (95% CI 2.3, 36.5)]. Cervical CIN3 was found to have an increased risk (SIR=1.8 (95% CI 1.2, 2.7)—no risk was seen for invasive cervical cancer. Similar to what was seen in solid transplant patients, cervical cancer screening programs are likely responsible for these associations. Other virus-associated cancers also had increased risk including liver cancer, bladder cancer and non-Hodgkin's lymphoma. This report concluded that virus-associated cancers particularly anal and vulvar cancers are increased in patients with SLE.

Anal cancer in women with inflammatory bowel disease—Although inflammatory bowel disease (IBD) reflects autoimmune processes and therefore exposure to immunosuppressive agents is common, both Crohn's disease and ulcerative colitis (UC), are of particular interest because of the involvement of the anus in disease expression. UC by definition starts at the dentate line affecting only columnar epithelium involving the distal rectum and not the anus. Crohn's disease may involve the anus and/or the distal rectum. Loss of mucosal integrity and chronic inflammation associated with either disease is believed to further potentiate the likelihood of anal canal HPV infection.

Studies on anal cancer in patients with IBD often include case reports or are limited to small sample sizes that result in contradictory findings.^{65,66} Slesser, et al.,⁶⁷ recently performed a systematic review of the literature to try and determine the incidence of anal cancer and AIN in this patient population. Basing their analysis on 11 peer-reviewed reports published between 1980-2010, they identified 33 cases of invasive squamous cell carcinoma in patients with IBD. The majority of cancer cases were in patients with Crohn's disease most of whom were women (17 cases women vs. 3 cases in men). The women were also found to be younger at diagnosis than the men (median age of 41 for women, 79 for men). The annual incidence of anal cancer in patients with Crohn's disease was 0.002% per year and for UC, 0.0009% per year. Several studies found that risks of anal cancer increased with >10 years disease duration and perianal involvement (including those with Crohn's related anal fistula formation). Among 17 of the anal cancer patients with IBD the 5-year survival rate was 37%. This is less than half the overall US anal cancer survival rate (SEER data). Survival rates may be lower due to a delay in diagnosis in patients accustomed to chronic anal and perianal symptoms erroneously attributed to Crohn's disease. On the other hand, these anal cancers may not be HPV associated. None of the studies examined the cancers for the presence of HPV DNA.

Sunesen et al.⁵⁶ looked at anal cancer rates in persons with a multitude of immunosuppressive disorders between 1978-2005 living in Denmark. This study found an increased risk of anal cancer in the over 11,000 patients identified with Crohn's disease [SIR= 3.5 (95% CI 1.4, 7.2)], but no increased risk was seen in the over 25000 patients identified with UC [SIR = 0.9; 95% CI, 0.3, 2.3). This study pointed out that although risk among Crohn's disease was higher than the general population, it still remained quite rare with only 1 anal SCC case per 25,000 person years.

The difference in risks for anal cancer associated with ulcerative colitis and Crohn's disease is likely multifactorial. The two diseases have different cytokine profiles, involve different anatomic locations and involve the tissues with different depths of inflammation. Crohn's disease has been historically associated with T-helper (Th) type 1 responses with more recent data finding a role for Th 17 cells in tissue destruction. In UC, Th2 type immune responses cytokines are thought to contribute to disease development.⁶⁸ The effect of imbalances in these systems on the infectivity and persistence of HPV have not been clarified. Crohn's disease is a full thickness disease that may involve the anus and rectum while UC involves just the mucosa of the rectum and colon and by definition does not involve the anus or perianal area. Thus the involvement of the anus and/or the depth of the inflammation of the anus, may increase susceptibility to HPV infection in patients with Crohn's disease but not those with UC. The lack of association with UC may change as systemic immunosuppressive therapy becomes more of a mainstay of therapy.⁶⁷

In summary, reports about autoimmune diseases are limited and conflicting. Some data support an increased risk of SLE and Crohn's Disease. The age of anal cancer presentation may be younger than what is often seen with anal cancer in the general population. There appears to be an increased risk of developing anal cancer with Crohn's-associated perianal disease and of greater than 10 years disease-duration. Little can be concluded about rarer autoimmune diseases because of sparse data. Most of the studies are limited since type of immunosuppressive agent used and degree of immunosuppression were never adequately defined.

The lack of any studies examining anal cytology in these groups precludes any recommendation for anal cancer screening with cytology, specifically in Crohn's where the inflammatory changes associated with the disease itself may lead to misinterpretation of cytology. Digital anorectal exams may be of value in patients with SLE and Crohn's. In addition, patients should be asked about development of or change in anal symptoms (bleeding, pain) on a regular basis with referral for additional diagnostic testing if positive.

Anal cancer in women with hematologic malignancies—There are few studies available for risk of anal cancer among those with hematologic malignancies. In the study by Susensen et al⁵⁶, women with hematologic malignancies (163,458 person years) were also examined for anal cancer risk. The SIR for anal cancer among all hematologic malignancies was 2.3 (95% CI 1.1, 4.2) compared with the general population. When examined by specific diagnosis, marginal increased risks for anal cancer were found for non-Hodgkin's lymphoma or chronic lymphocytic leukemia [SIR =2.1 (95% CI 0.9, 4.4)] and multiple myeloma or other plasma cell malignancies [SIR = 5.3 (95% CI 0.9, 17.6)]. One study also found that HIV-seronegative chronic lymphocytic leukemia and small lymphocytic lymphoma survivors had an increased risk for anal cancer (SIR = 2.44 (95% CI 1.05, 4.80)).⁶⁹ The increased risk was magnified 60-fold if the survivor was HIV-infected.

The limited data available for hematologic malignancies do not support anal cancer screening in this population if HIV uninfected.

Prior lower genital tract neoplasia

Anal Cancer in Women with Lower Genital Tract Neoplasia—Since HPV infection is necessary for anal cancer and often considered a field infection of the anogenital tract, it is quite plausible that women with a history of prior HPV-associated lower genital tract neoplasia (LGTN) may be at increased risk for anal cancer. Several large-scale cancer registry studies provide strong evidence of associations between a history of CIN (especially CIN3), cervical cancer, VIN, vulvar cancer, vaginal cancer and cancers of the anus.⁷⁰⁻⁷⁴

Based on a population-based cohort study, Edgren & Sparén (2007)⁷⁰ assessed the risks of anal and other cancers in women with previous history of CIN3 by linking Swedish national registries with cancer registries between 1918-1986. Of the 3,747,698 eligible women followed for 27 years, 125,292 women received diagnosis of CIN3. For anal cancer the incident rate ratio (IRR) was 4.68 (95% CI 3.87,-5.62) for women with prior CIN3 compared with those with no CIN3 history. The risk was highest for women ages 18-29 years at time of CIN3 diagnosis (IRR=31.09 (95% CI 3.74-258.44) and the risk increased substantially after 5 years beyond diagnosis for all ages.

Evans et al. 2003⁷¹ analyzed data from the Thames Cancer Registry (TCR) in England. Based on 14 million people in the registry, two cohorts were formed: one of women with CIN3 (59,586) and one of women with invasive cervical cancer (21,703). Following a diagnosis of CIN3, women had a statistically significant higher risk of developing anal cancer than those without [SIR= 5.9 (95% CI 3.7,-8.8)]. With a diagnosis of cervical cancer, anal cancer risk also increased [SIR = 6.3 (95% CI 3.7-10.0)], however, the increase in anal cancer was only significant 10 or more years after initial cervical cancer diagnosis, indicating a long latency period. In another study based on SEER data, similar high risks were found for anal cancer among women with a prior history of cervical or vulvar cancers.⁷⁵

Using population based sample data from the SEER program from 1973 through 2007, Saleem, et al⁷² examined 189,206 women with either high-grade disease (defined as “in situ”) or invasive cervical, vulvar, or vaginal cancer. The group then followed these women for 139-million person-years to examine the incidence of a subsequent primary anal cancer. The authors identified a significant association between gynecologic neoplasia and anal cancer for both “in situ” (high-grade precancer) and invasive cancers of the cervix, vulva and vagina. The highest risk for anal cancer was in those women with either “in situ” or invasive vulvar squamous cell cancer. SIRs were calculated from the observed number of subsequent anal cancers compared with those expected based on age, race, and calendar year-specific rates in the non-affected population. For women with an “in situ” or gynecologic cancer, the SIR for developing anal cancer was 13.6 (95% CI 11.9-15.3). The SIR for anal cancer incidence among women with “in situ” vulvar cancer was 22.2 (95% CI 16.7-28.4) and for those with invasive vulvar cancer was 17.4 (95% CI 11.5–24.4). The SIR for anal cancer for women with “in situ” cervical cancer was 16.4 (95% CI 13.7–19.2) and for invasive cervical cancer was 6.2 (95% CI 4.1– 8.7). For “in situ” vaginal carcinoma the SIR was 7.6 (95% CI 2.4 –15.6) and for invasive vaginal cancer the SIR was 1.8 (95% CI

0.2–5.3). In this study, the median time to diagnosis of anal cancer from lower genital tract cancer ranged from 4.5 years for vaginal and vulvar cancer to 16.0 years for cervical cancer.

Chaturvedi et al. (2007)⁷³ similarly examined the long-term trends in second cancer risk among 104,760 women with cervical cancer. Using 13 population-based cancer registries with a total of 104,760 women (Denmark, Finland, Norway, Sweden, and the United States), the authors calculated SIRs for second cancers including information on whether cervical cancer patients were or were not treated with radiation. The authors found that women with diagnosed cervical cancer had a higher risk of developing anal/rectal cancers than women in the general population, regardless of radiation therapy status (SIR = 1.84 (95% CI 1.72-1.98). When cancers of the anus and rectum were evaluated separately in a subset of SEER data (N=27466), statistically significant rates were observed for both the anus (SIR =3.12, 95% CI 1.88-4.88) and rectum (SIR =1.43, 95% CI 1.14-1.76). Edgren & Sparén⁷⁰ reported similar findings.

Jiménez et al.⁷⁴ conducted a population based, case-control study in Ontario, Canada, using a database of 12.4 million residences and three cancer registries to locate cancer diagnoses. The goal was to examine women diagnosed with squamous cell cancer of the anus to compare those with a previous HPV-related gynecological cancer (cervical, vaginal and vulvar) to a control group of women with no prior history, matched for age, socioeconomic status and place of residence. Researchers selected 674 women diagnosed with anal cancer from 1992-2005 and selected 5 matched controls per case. Seven women with a history of cervical cancer, 3 with vulvar cancer and one with vaginal cancer were diagnosed with anal cancer. Women who developed anal cancer were 10 times more likely to have had a history of a lower genital tract cancer [OR=10.5, 95% CI 3.6-30.3]. This study did not examine past history of high-grade precancers.

Anal squamous intra-epithelial lesions in women with lower genital tract neoplasia—As for many of the groups discussed earlier, limited data are available for rates of abnormal anal cytology among women with lower genital tract neoplasia (LGTN).⁷⁵ Most studies are limited because of the small sample sizes. In the Park, et al. study⁷⁶ which evaluated 102 women with LGTN, abnormal anal cytology was found in 9 women—ASC-US in 5, ASC-H in 2, and LSIL in 2. Women with vulvar lesions had highest prevalence of abnormal anal cytology (21%). HRA with biopsy was performed in 7 of these women and all showed low grade AIN.

In a study led by Santoso et al⁷⁷, 205 women with cervical/vulvar/vaginal biopsy proven intraepithelial neoplasia, ten of whom were HIV positive, had anal cytology sampling. Twelve women (5.9%, 95% CI 3-10%) had anal cytology reports of ASC-US or LSIL; none had reports of HSIL. Anal cytology did not correlate well with histologic results (see next section). Data were not stratified by genital site (i.e. cervical, vaginal or vulvar). In another study of 196 women with SIL cervical cytology reports, the prevalence of abnormal anal cytology was 17.6%.⁷⁸ Cervical hrHPV infection was associated with anal hrHPV infection [OR= 3.6, 95% CI 1.19-10.77]) and anal hrHPV was associated with having abnormal anal cytology [OR =6.5, 95% CI 2.74-15.6]

As discussed above and later, the low sensitivity of anal cytology is a limitation of all of these studies. Most studies performed HRA as part of triage for abnormal anal cytology. Scholefield et al.⁷⁹ performed HRA on 152 women with CIN3 and found 11 with high-grade AIN (defined as AIN3) and nine who also had vulvar/vaginal lesions. Two women progressed to anal cancer. An additional 18 had AIN1 and AIN2. They further stratified the 152 women with CIN3, and found that 115 had CIN3 alone and 37 had multi-centric LGTN. The rate of AIN differed between these 2 groups, with 8/115 (7%) of women with CIN3 alone having AIN compared with 21/37 (57%) of women with CIN3 and concomitant VaIN or VIN. They compared the women with CIN3 to a control group of women with normal cervical cytology reports who were undergoing sterilization and had colposcopy and anoscopy under anesthesia. No cases of AIN were found in the control group.

Jacyntho, et al.²² evaluated 260 immuno-competent women: 184 with known LGTN, and 76 controls without LGTN (described above). HRA was performed on all women with HRA-directed biopsy, if lesions were seen. AIN was found in 32 of 184 (17.4%) women with LGTN including 6 (2.3%) with high-grade AIN, compared with 2 of 76 (2.6%) controls without LGTN. In this study, the risk of AIN increased significantly in the presence of multicentric LGTN. When 3 or 4 sites were involved, the prevalence ratio (PR) for anal canal lesions was 13.1 (95% CI 2.7-63.3). The PR was also higher for perianal AIN (PR=21.4, 95% CI 4.6-100) than for the other genital sites, although all LGTN sites were associated with significantly increased risk of AIN when compared with women without LGTN. Adjusting for presence of LGTN, risks for AIN included anal intercourse (PR = 2.5 (95% CI 1.3-5.1), no condom use (PR=2.6, 95% CI 1.3-5.3)] and history of Herpes simplex virus (PR=1.8 (95% CI 1.0-3.4).

The Santoso (2010)⁷⁷ study also included performance of HRA and biopsy as indicated, in addition to the anal cytology, on the women with LGTN. Of 78/205 women (38%) with abnormal HRA findings, 25 patients (12.2%, 95% CI 8-17%) had AIN on biopsy including 17 (8%) that were high-grade AIN. Half of the patients with AIN had normal cytology. They concluded that HRA is a more accurate screening tool than cytology for AIN among high-risk populations such as women with LGTN. Koppe, et al.²¹ performed screening HRA on 106 women with LGTN and 74 women without LGTN (described above). Biopsy proven AIN was higher in the women with LGTN [10.4%, (95%CI 5.6-17.3%)] than in women without LGTN (1.4% (95% CI 0.1-6.5%, p = 0.016). Of the AIN lesions found, 5 were high-grade AIN and all 5 were in the women with LGTN (5/106). The authors calculated a prevalence ratio for AIN of 7.68 (95% CI 1.01-58.21) for women with a history of LGTN compared with women without LGTN.

Heraclio et al (2011)⁸⁰ studied 324 Brazilian women with CIN or cervical cancer. The women had anal cytology, anal hrHPV testing, and HRA with biopsy for suspicious lesions on HRA or for abnormal cytology result. Twenty-eight women with AIN suspected on HRA underwent biopsy (6 refused biopsy) and 19 were found to have AIN. If women had HRA findings consistent with metaplasia or HPV infection (n=169), biopsy was obtained only if the cytology was ASC-US: 70 had abnormal results and of these 14 (20%) had AIN, grade not specified. The overall prevalence of abnormal anal cytology was 31.5% (102/324) including 10 with HSIL (3%), and AIN2/3 was diagnosed in 13/324 (4%). Since this study

did not include biopsies of all abnormal lesions, the rate of high-grade AIN is likely underestimated.

A study of 481 women with LGTN (235 with CIN, 92 with VaIN, and 227 with VIN) was reported by Tattiet al⁴⁹ All women were evaluated by anal cytology, HRA and biopsy of any suspicious lesions. Of the entire study population, 404 (84.0%) were immunocompetent, 31 (6.4%) were HIV-infected, and 46 (9.6%) were immunosuppressed from other causes. They did not report how many women had biopsies. By histology, 28 (5.8%) of the participants had high-grade AIN, and 107 (22.2%) had low grade AIN. There was an association of high-grade AIN with HIV infection, high-grade CIN and VIN and perianal intraepithelial neoplastic lesions.

Anal HPV infection in women with LGTN—Among women with LGTN, anal hrHPV infections are also frequently detected. In a small study of HPV testing among 100 HIV-negative women with abnormal cervical cytology, the prevalence of hrHPV at both cervical and anal sites was 75%.⁸¹ Multiple HPV subtype infections were very common, with HPV 16 the most prevalent type. Park et al⁷⁶ found anal HPV infection in 51% of women with LGTN. Of the 47 women with anal HPV infection in this study, 70% were infected with at least one oncogenic type, most commonly HPV 16. In a study of 235 women with HPV-associated cervical or vulvar disease, anal hrHPV was detected in 31% of anal cytology specimens and 39% of cervical cytology specimens.⁸² Concordance of HPV types between anal and cervical sites was seen in 74% (absolute concordance in 29% and partial in 49%).

In summary, there is strong epidemiological evidence demonstrating an increased risk of anal cancer in women with a prior history of in situ and invasive cancers of the cervix, vagina, and vulva compared with the general population. The greatest risk is for women with vulvar cancers. These data suggest that following these women more closely with anal cancer screening is reasonable, however further studies are needed to define the optimum time to initiate screening and the optimum method.

Current evidence suggests that screening for anal cancer among women with vulvar cancer should begin with the initial diagnosis. In contrast, data for timing in women with cervical or vaginal cancer suggest a wider range (0 to 10 years). Screening should minimally include digital rectal examinations and screening for anal cancer symptoms (pain and bleeding) within 5 years of diagnosis. Screening with anal cytology warrants consideration.

Anal Cancer Screening Methods: Strengths and Limitations

Although this review focused on anal cytology and HRA as potential screening tools for AIN in high risk populations, it is important to understand the limitations of these screening tools, including digital ano-rectal examination (DARE).

Anal cytology

The development of anal and cervical cancers share a number of features. The anus resembles the cervix in that both have a transformation zone that is highly susceptible to HPV infection and prone to neoplastic transformation. Squamous cell cancer of either site is

frequently preceded by a high-grade precursor lesion (AIN3 or CIN3). Given the similarities between anal and cervical neoplasia, an approach similar to that used for the detection of cervical precancers and cancers has been adopted by some for anal precancer and cancer detection and includes cytologic testing using the conventional glass slides or liquid based cytology (LBC).⁸³

Anal cytologic screening is most commonly performed without direct visualization of the canal, utilizing a moistened Dacron swab.⁸³ Other implements (such as cervical brushes and a flocced nylon swab) have been studied^{20,84-88} and self-sampling may also be feasible in some populations.⁸⁹⁻⁹² The swab is gently inserted into the anal canal, stopping when the swab abuts the wall of the distal rectum. This corresponds to a distance of approximately 4cm in women, who have a slightly shorter anal canal than men. The swab is rotated around the full circumference of the canal with firm lateral pressure, while it is slowly withdrawn. The aim is to sample the entire length of the anal canal. LBC is preferred to conventional cytology, to reduce fecal contamination and air-drying.^{93,94} The swab must be vigorously rinsed in the vial of fixative fluid and the LBC specimen is then processed as for cervical cytology samples.

Anal cytology is reported using the terminology and definitions of the Bethesda System (TBS).⁹⁵ Minimum cellularity for anal LBC preparations, according to TBS guidelines, is 2000-3000 nucleated squamous cells.⁹⁶ This definition of a 'satisfactory' sample does not include the presence of a 'transformation zone component', namely rectal glandular cells or squamous metaplastic cells, which indicate that the sampling implement has reached above the original squamocolumnar junction of the anal canal. The presence or absence of this component should be reported, however, and more studies are needed to determine whether this correlates with detection of abnormalities.^{84,97-100} Cytomorphologic criteria for TBS categories of ASC-US, ASC-H, LSIL and HSIL are very similar to those described for cervical cytology, with some subtle differences described.^{83,84,101,102} Nevertheless, specific training and experience in reading anal cytology slides are essential to optimize accuracy of reporting¹⁰³. At least moderate diagnostic reproducibility among cytopathologists can be expected.^{104,105} Organisms that may be seen on anal cytology should be reported. These include Herpes simplex virus, cytomegalovirus, Candida, ameba (both pathogenic and non-pathogenic types), Enterobius and Strongyloides.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), have been reported to vary widely in several recent reviews.¹⁰⁶⁻¹⁰⁸ As for any screening test, these parameters are influenced by the underlying prevalence of AIN in the population being tested. Sensitivity and PPV tend to be higher in populations with high disease prevalence. These characteristics are also affected by the design of the study such as the proportion of participants who undergo HRA and the criteria for biopsy. With these caveats, sensitivity of a single anal cytology test for detection of histological HSIL (AIN2/3) ranges from 55–93% and specificity from 32–81%.¹⁰⁶⁻¹⁰⁸ PPV of an ASC-US+ cytoprediction has ranged from 26-57% and NPV from 82-88%.¹⁰⁶ Cytology performance data for female populations are very limited. The Santoso report referred to previously⁷⁷ studied 205 women with genital intraepithelial neoplasia and a prevalence of AIN2/3 of 8%. The sensitivity and specificity of cytology was 8% and 94%, respectively and the PPV and

NPV was 15% and 88%, respectively. Both PPV and NPV in a population have been reported to increase with repeat testing over a two year period.⁹⁷ Many studies have found poor correlation between grade of the cytology report and grade diagnosed on subsequent biopsy.^{46,84,97,109-111} This may reflect the difficulty of thorough anal canal cytologic sampling, the skill of the anoscopist and the inherent limitations of HRA and HRA-guided biopsy.^{110,112}

For these reasons, anal cytologic screening recommendations emphasize the need for repeat cytology testing at regular intervals, referral to HRA at ASC-US+ cytology threshold and repeat HRA when an HSIL cytology cannot be initially histologically confirmed.^{77,113} Attempts to enhance the suboptimal accuracy of the anal cytology have included the use of immunostaining for p16/Ki67 on the slide and detection of HPV16/18 DNA or HPV E6/E7 mRNA in the residual liquid-based specimen.^{105,114,115} Similar to cervical HSIL, anal HSIL in females is related to hrHPVs, especially HPV16.^{49,116-118} More work in this area is needed.

High resolution anoscopy (HRA)—Similar to the role of colposcopic biopsy in defining CIN3 lesions, HRA guided biopsy is the “gold standard” for determining prevalence of biopsy-proven AIN. Because of its cost and lack of general availability, HRA is currently intended for triage in women with an abnormal screening test or anal cancer symptoms rather than for primary screening. HRA was first developed in the early 1990s and hence there are far fewer experienced and skilled providers compared with the number of colposcopists world-wide. Furthermore, training and certification for HRA are less standardized. In experienced providers clearly find less AIN2/3 than more experienced providers and, similar to colposcopy, the number of biopsies taken increases the chances of finding AIN2/3.^{109,119-121}

The performance characteristics of HRA in general populations and in women with higher risks for anal cancer such as those with HIV or LGTN are not well known. Accurate estimation of test characteristics (sensitivity, specificity, PPV and NPV) of HRA and HRA-guided biopsy requires a comprehensive evaluation of a given population where all women undergo complete ascertainment of disease such as HRA with biopsy of visible lesions and four quadrant biopsies of the anus. The AIDS Malignancy Consortium is currently evaluating HRA using this design as well as comparing cytology and several different types of HPV testing strategies in a group of HIV-infected women. (NCT01946139) Our best estimate of the accuracy of HRA comes from a handful of studies on high risk populations in which all women underwent HRA. However, none of the studies performed random biopsy: only HRA-guided biopsy.^{22,77,79,122} Of these, only Santoso calculated performance statistics. As mentioned previously, Santoso et al⁷⁷ compared anal cytology and HRA to histologic results in women with LGTN. Using anal biopsy as the gold standard for diagnosing AIN, HRA had a sensitivity of 100%, specificity of 71%, PPV of 32%, and NPV of 100%. Since women were biopsied only if they had HRA abnormalities, the sensitivity and NPV are falsely elevated.

Digital ano-rectal examination—Relatively little is known about digital ano-rectal examination (DARE) in the practice of anal cancer screening. No national guidelines exist

for anal cancer screening and no randomized clinical trial has been performed to validate any type of anal cancer screening. The only recommendation currently comes from The New York State Department of Public Health AINS Institute which recommends a digital anal-rectal examination along with anal cytology screening at baseline and annually in HIV-infected people, any patient with a history of anogenitalcondyloma, and HIV-infected women with abnormal cervical and/or vulvar histology.¹²³ However, one study aimed to identify current practices and barriers to using DARE for anal cancer screening.¹²⁴ Although 86% of physicians participating believed anal cancer screening was important, only 22% were currently screening. The primary reason for not screening was the absence of guidelines.¹²⁴

DARE has been considered in the literature as an essential tool for detecting anal cancer¹⁰⁷ since most early invasive anal carcinomas may be palpable. It has been recommended, at minimum to perform a DARE on high-risk individuals since it is a low-cost, low-tech procedure. Evidence regarding the utility of DARE could be derived from a recent study evaluating the progression of AIN2/3 to cancer. Berry et al¹²⁵ reported that a mass, area of in duration, or ulcer were palpable in 23 of the 27 men (85%) diagnosed with anal cancer. Current prospective studies evaluating the epidemiology of low- and high-risk HPV infection utilizing DARE, cytology, and HRA in MSM are underway and are anticipated to be completed in 2018.(NCT02007421)(Australian New Zealand Clinical Trials Registry number is ACTRN12613001335785.)¹²⁶

Future Research—The paucity of data on anal precancer in women argues for innovative research into potential screening strategies that might effectively identify and triage these largely asymptomatic women. Both cytology and HRA have their limitations, hence studies attempting to estimate AIN2/3 prevalence in specific populations should use a combination of cytology and HRA-guided biopsy. Further research is needed to clarify the nature of the relationship between cervical and anal HPV infections and the role of multiple infections (both cervical and anal) in both acquisition and clearance or persistence of anal HPV infection in all populations. In addition, comparison of the HPV genotypes in the cervix and anus, tropism of specific types for specific sites, differentiation between the presence of HPV (deposition) and true infection and the potential role of HPV16 genotyping, measurement of mRNA and other biomarkers for anal cancer screening are important areas for research.

The Anal Cancer/HSIL Outcomes Research (ANCHOR) study (NCT02135419) is designed to determine whether treating anal AIN2/3 in HIV-infected persons over the age of 35 will prevent anal cancer. The study plans to enroll 5,058 persons with AIN2/3 who will be randomized to active monitoring consisting of close follow-up every 6 months with anal cytology, DARE, and HRA versus treatment of their AIN2/3. Participants will be followed for 5 or more years; the incidence of anal cancer in each arm will be compared. If treatment of AIN2/3 effectively prevents anal cancer, this information will be critical in developing guidelines for screening including best methods and optimal intervals for screening both men and women with HIV disease. Hopefully this study will also inform the design of future studies in other populations of high risk women including those with LGTN and other forms of immunosuppression. Studies are desperately needed to determine the true natural history

of anal HPV infection, and anal cytological abnormalities in all populations of women. The majority of invasive anal cancers occur in women without known risk factors.

Conclusions

Healthy women have high rates of anal HPV but relatively low rates of abnormal anal cytology and anal cancer as compared with other high risk populations. Further research is needed to determine if screening this group of healthy women would reduce their risk of anal cancer, and if routine screening would be cost effective since this group of healthy women make up the largest percent of women who develop anal cancer.

Until more data are available, no screening recommendations can be made for healthy women. However, DARE is appropriate when women present with anal cancer symptoms. Any woman diagnosed with AIN either during colonoscopy or surgery for benign anorectal conditions should be referred to specialists for evaluation and possible treatment.

Several high risk groups have been identified including those immunosuppressed and those with LGTN. The lack of association with invasive cervical cancers in immunosuppressed groups is thought to be due to the success of cervical cancer screening programs. This suggests that screening for other HPV associated pre-invasive cancers such as anal cancer may also prevent the development of invasive cancers in high risk populations. Women with organ transplants, SLE and Crohn's disease may benefit from some type of screening but lack of screening trials in these groups make any recommendation difficult.

Because of the possible increase in risk for anal cancer, screening with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might indicate cancer may be the best approach for these groups with prompt referrals if positive for either.

The most compelling data for anal cancer screening using cytology are among those women with HIV infection and history of LGTN. Screening with HRA is likely not cost effective but may play an important role in certain situations such as among those with vulvar cancers. Screening with cytology remains controversial since no trials to date have shown that screening and treating will decrease anal cancer rates in these populations. Critical studies are underway. Although anal cytology is imperfect with varying performance as seen with cervical cytology, screening with cytology may be effective in preventing anal cancer if precancers are detected and treated early.

Providers should screen with cytology only if referrals to HRA and treatment are available. Otherwise, screening can include DARE and review of symptoms with referral for further diagnostic work-up if either is positive. The optimal age to start screening is not known; however, anal cancers rarely occur under the age of 30 years even in HIV infected persons. For those with HIV infection, screening under this age is not recommended. For women with vulvar cancers or high-grade VIN, immediate screening is recommended. For women with cervical or vaginal cancers or high-grade CIN or VaIN, screening with cytology or DARE and symptom review within 5 years of initial diagnosis is suggested. There are no data to guide intervals. Expert opinion by a few suggest annual or biannual.

In summary, the limited data available do not support anal cytology or anal cancer screening in immunocompromised women other than those that are HIV-infected or have undergone solid organ transplantation. However, providers who care for these women should be aware of the possible increase in risk for anal cancer and promptly and appropriately evaluate women who present with anal lumps, pain or bleeding.

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Abbreviations

aOR	Adjusted odds ratio
aSIR	Adjusted standardized incident ratio
AIN	Anal intraepithelial neoplasia
CI	Confidence interval
HAART	Highly active antiretroviral therapy
HSIL	High-grade squamous intraepithelial lesions
HRA	High resolution anoscopy
HR	Hazard Ratio
hrHPV	High risk Human papillomavirus
IBD	Inflammatory bowel disease
HPV	Human papillomavirus
LSIL	Low grade squamous intraepithelial lesions
LR	Low risk
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
RR	Rate ratio
RH	Relative hazard
SIR	Standardized incident ratio

Table
Summary of Recommendations

Risk Group Category	Recommendation*
HIV-infected women	Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Given their high incidence of anal cancer, some experts recommend routine screening for, and treatment of, AIN2/3 in this population in an effort to reduce their risk of anal cancer. Screening may include anal cytology with referral for high resolution anoscopy-guided biopsies, followed by treatment of biopsy-proven AIN2/3. The efficacy of this approach to prevent anal cancer has not yet been studied; a clinical trial is in progress to determine if screening and treatment of anal AIN2/3 in this population should become standard of care.
Women with organ transplant	Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Further research is recommended on screening for, and treating AIN2/3 to reduce the risk of anal cancer in this population
Women with systemic lupus erythematosus and Crohn's disease	Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Further research is recommended on screening for, and treating AIN2/3 to reduce the risk of anal cancer in this population
Women with vulvar cancer or high grade VIN	Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Some experts recommend routine screening for, and treatment of, AIN2/3 in an effort to reduce the risk of anal cancer in this population. The efficacy of doing so has not yet been shown in this population and screening is not yet standard of care.
Women with cervical or vaginal cancer or high grade CIN or VaIN	Screening for anal cancer with DARE and routine assessment for the development or change in anal cancer symptoms such as pain or bleeding that might suggest cancer, with prompt referrals if positive for either. Some experts recommend routine screening for, and treatment of AIN2/3 to reduce the risk of anal cancer in this population. The efficacy of doing so has not yet been shown in this population and screening is not yet standard of care.
Healthy women with none of the risk factors above	No screening for anal cancer or AIN2/3 is recommended at this time. Prompt referral for further diagnostic work-up if symptoms of anal cancer (pain and bleeding) are present.

* Providers should screen with cytology only if referrals to high resolution anoscopy and high resolution anoscopy-guided treatment are available.

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