Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection

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Executive Summary: The risk of cervical cancer (CC) among women immunosuppressed for a variety of reasons is well documented in the literature. Although there is improved organ function, quality of life and life expectancy gained through use of immunosuppressant therapy, there may be increased long-term risk of cervical neoplasia and cancer and the need for more intense screening, surveillance, and management. Although guidance for CC screening among HIV-infected women (see Table 1) has been supported by evidence from retrospective and prospective studies, recommendations for CC screening among non-HIV immunosuppressed women remains limited because quality evidence is lacking. Moreover, CC screening guidelines for HIV-infected women have changed because better treatments evolved and resulted in longer life expectancy.

The objective of this report was to summarize current knowledge of CC, squamous intraepithelial lesions, and human papillomavirus (HPV) infection in non-HIV immunocompromised women to determine best practices for CC surveillance in this population and provide recommendations for screening. We evaluated those with solid organ transplant, hematopoietic stem cell transplant, and a number of autoimmune diseases.

A panel of health care professionals involved in CC research and care was assembled to review and discuss existing literature on the subject and come to conclusions about screening based on available evidence and expert opinion. Literature searches were performed using key words such as CC, cervical dysplasia/squamous intraepithelial lesion, HPV, and type of immunosuppression resulting in an initial group of 346 articles. Additional publications were identified from review of citations in these articles. All generated abstracts were reviewed to identify relevant articles. Articles published within 10 years were considered priority for review. Reviews of the literature were summarized with relevant statistical comparisons. Recommendations for screening generated from each group were largely based on expert opinion. Adherence to screening, health benefits and risks, and available clinical expertise were all considered in formulating the recommendations to the degree that information was available.

Results: Solid Organ Transplant: Evidence specific for renal, heart/lung, liver, and pancreas transplants show a consistent increase in risk of cervical neoplasia and invasive CC, demonstrating the importance of long-term surveillance and treatment. Reports demonstrate continued risk long after transplantation, emphasizing the need for screening throughout a woman's lifetime.

Hematopoietic Stem Cell Transplant: Although there is some evidence for an increase in CC in large cohort studies of these patients, conflicting results may reflect that many patients did not survive long enough to evaluate the incidence of slow-growing or delayed-onset cancers. Furthermore, history of cervical screening or previous hysterectomy was not included in registry study analysis, possibly leading to underestimation of CC incidence rates.

Genital or chronic graft versus host disease is associated with an increase in high-grade cervical neoplasia and posttransplant HPV positivity.

Inflammatory Bowel Disease: There is no strong evidence to support that inflammatory bowel disease alone increases cervical neoplasia or cancer risk. In contrast, immunosuppressant therapy does seem to increase the risk, although results of observational studies are conflicting regarding which type of immunosuppressant medication increases risk. Moreover, misclassification of cases may underestimate CC risk in this population. Recently published preventive care guidelines for women with inflammatory bowel disease taking immunosuppressive therapy recommend a need for continued long-term CC screening.

Systemic Lupus Erythematosus and Rheumatoid Arthritis: The risk of cervical high-grade neoplasia and cancer was higher among women with systemic lupus erythematosus than those with rheumatoid arthritis (RA), although studies were limited by size, inclusion of women with low-grade neoplasia in main outcomes, and variability of disease severity or exposure to immunosuppressants. In studies designed to look specifically at immunosuppressant use, however, there did seem to be an increase in risk, identified mostly in women with RA. Although the strength of the evidence is limited, the increase in risk is consistent across studies.

Type 1 DM: There is a paucity of evidence-based reports associating type 1 DM with an increased risk of cervical neoplasia and cancer.

Recommendations: The panel proposed that CC screening guidelines for non-HIV immunocompromised women follow either the (1) guidelines for the general population or (2) current center for disease control guidelines for HIV-infected women. The following are the summaries for each group reviewed, and more details are noted in accompanying table:

Solid Organ Transplant: The transplant population reflects a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening and surveillance.

Hematopoietic Stem Cell Transplant: These women have a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening. A new diagnosis of genital or chronic graft versus host disease in a woman post–stem cell transplant results in a greater risk of CC than in the general population and should result in more intensive screening and surveillance.

Inflammatory Bowel Disease: Women with inflammatory bowel disease being treated with immunosuppressive drugs are at greater risk of cervical neoplasia and cancer than the general population and guidelines for HIV-infected women are a reasonable approach for screening and surveillance. Those women with inflammatory bowel disease not on immunosuppressive therapy are not at an increased risk and should follow screening guidelines for the general population.

Systemic Lupus Erythematosus and Rheumatoid Arthritis: All women with systemic lupus erythematosus, whether on immunosuppressant therapy or not and those women with RA on immunosuppressant therapy have a greater risk of cervical neoplasia and cancer than the general population and should follow CC screening guidelines for HIV-infected women. Women with RA not on immunosuppressant therapy should follow CC screening guidelines for the general population.

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L.B.S. is the Editor-in-Chief of the *Journal of Clinical Gynecology and Obstetrics*. The other authors have declared they have no conflicts interests.

DOI: 10.1097/LGT.0000000000000468

Type 1 Diabetes Mellitus: Because of a lack of evidence of increased risk of cervical neoplasia and cancer among women with type 1 DM, these women should follow the screening guidelines for the general population.

Key Words: guidelines, cervical cancer, immunosuppressed

(*J Low Genit Tract Dis* 2019;23: 87–101)

BACKGROUND

The overall objective of this report was to summarize current knowledge of cervical cancer (CC), squamous intraepithelial lesions (SILs), and human papillomavirus (HPV) infection in immunocompromised, non–HIV-infected women. Specifically, we evaluated those with solid organ transplant (SOT), hematopoietic stem cell transplant, and autoimmune diseases and provide recommendations for CC screening in these women based on literature review and expert opinion. For example, SOT and hematopoietic stem cell transplant recipients gain increased life expectancy and quality of life but at the cost of an increased risk of a spectrum of malignancies, mainly attributed to ongoing and long-term use of immunosuppressive medication, graft versus host disease (GvHD), and infections with oncogenic viruses. The risk of malignancy among women with autoimmune disease is also of interest, both because of the disease pathogenesis and the increasing use of immunomodulatory therapy that may alter immunosurveillance. The increased life expectancy gained through use of these therapeutics may confer increased risk for long-term sequelae of CC and interventions for prevention and treatment.

Recommendations for CC screening in immunosuppressed women without HIV remain vague and uncertain. The guidelines for HIV-infected women (see Table 1) have been supported by an increasing number of publications, including prospective studies. Unfortunately, the literature for other immunosuppressed populations remains limited. In addition, guidelines for HIV-infected women have changed with the adoption of better treatments and resultant longer life expectancy. Currently, the immune health of treated HIV-infected women is likely more robust than that of women with iatrogenic immunosuppression.[1] The American College of Obstetrics and Gynecology guidelines note that immunocompromised women "may require more frequent CC screening than is recommended in the routine screening guidelines." This has been translated into annual screening with cytology as standard clinical practice in many institutions.

In this article, we review the role of the immune response in the natural history of HPV, current recommendations for CC screening in the general population, and describe recommendations for HIV-infected women as an example of risk-based alterations in screening algorithms for immunocompromised women. We review the literature for the risks of CC, SIL, and HPV among 3 major groups of immunocompromised women: those with (*a*) SOTs, (*b*) hematopoietic stem cell transplants (HSCT), and (*c*) autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and type 1 DM. We then recommend screening for each of these groups based on this review and expert opinion.

Natural History of HPV and Immune Control

Ninety-nine to one hundred percent of CCs have been attributed to high-risk HPV (hrHPV) infection.[2,3] Although well more than 400 HPV types have been identified, 12 are considered oncogenic or high risk (hr) (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and another 8 are considered probably or possibly oncogenic (68, 26, 53, 66, 67, 70, 73, 82).[4–7] Human papillomavirus

TABLE 1. Recommendations for Cervical Cancer Screening for Women With HIV

Women with HIV aged <30 y
- If younger than 21 y, known to have HIV or been newly diagnosed with HIV, and sexually active, screen within 1 y of onset of sexual activity regardless of mode of HIV infection.
- Women with HIV aged 21–29 y should have a Pap test after initial diagnosis.
- Pap test should be performed at baseline and every 12 mo (BII).
- Some experts recommend a Pap test at 6 mo after the baseline test (CIII)
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 y (BII)
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30 y.

Women with HIV aged ≥30 y pap testing only:
- Pap test should be performed at baseline and every 12 mo (BII).
- Some experts recommend a Pap test at 6 mo after the baseline test (CIII).
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 y (BII).

Or

Pap test and HPV co-testing:
- Pap test and HPV co-testing should be performed at baseline (BII).
- If result of the Pap test is normal and HPV co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 y (BII).
- If the result of the Pap test is normal but HPV co-testing is positive:

Either
- Follow-up test with Pap test and HPV co-testing should be performed in 1 year.
- If the 1-year follow-up Pap test is abnormal or HPV co-testing is positive, referral to colposcopy is recommended.

Or
- Perform HPV genotyping.
- If positive for HPV 16 or HPV 18, colposcopy is recommended
- If negative for HPV 16 and HPV 18, repeat co-test in 1 y is recommended. If the follow-up HPV test is positive or Pap test is abnormal, colposcopy is recommended.

Or

Pap test and HPV 16 or HPV 16/18 specified in co-testing:
- Pap test and HPV 16 or 16/18 co-testing should be performed at baseline (BII).
- If result of the Pap test is normal and HPV 16 or 16/18 co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 y (BII).
- If initial test or follow-up test is positive for HPV 16 or 16/18, referral to colposcopy is recommended (BII).

16, responsible for 50% of CCs, has been the best studied. Limited information is available for other types, which may negatively impact immunosuppressed individuals. An estimated 80% of women acquire an oncogenic HPV[8] with most (~90%) of cervical oncogenic infections "clearing."[9,10] Although persistent infection is essential in carcinogenesis,[11,12] the definition of "clearance" remains controversial. Some scientists believe that HPV is never cleared but rather goes into a latent state with extremely low viral replication resulting in sequential negative tests for HPV DNA.[13] Although recurrence after clearance of a single type has been demonstrated,[14] it remains unclear whether this represents recurrence or a new infection.

The natural history of HPV is strongly linked to CC risk associated with immunosuppression. Steps including viral entry into the basal epithelial cells, expression of oncogenes E6 and E7 resulting in abnormal basal cell proliferation [referred to pathologically as low-grade SILs (LSIL)] and progression of cell abnormalities to higher epithelial layers [referred to as high-grade (HSIL)] due to persistent HPV infection.[11,15] Further events thought to lead to carcinogenesis include activation of telomerase, blockage of apoptosis, and viral integration.[11] Medications to treat immunosuppression may be involved in interference or enhancement in the cascade of these events.

High levels of antibodies, as generated by the HPV vaccine, protect against infection but have no influence on clearance of persistent infection.[16] Both clinical and in vitro evidence show that cell-mediated immunity is critical to HPV control.[17–19] Dysfunction may be inherited (e.g., epidermodysplasia verricuformis),[20] infection induced (e.g., HIV),[21] or iatrogenic (e.g., SOT). Age-related immune dysfunction has also been hypothesized. Prevalence rates of HPV are highest in young women younger than 25 years. A second peak seen in some studies after the age of 65 years may be due to senescence in immune control allowing latent infections to reactivate[21] or new acquisition.[14,22–24] Both mechanisms leading to positive HPV results may be greater with iatrogenic immune dysfunction.

Current Recommended Screening Strategies in Healthy Women

Cervical cancer screening in the United States primarily focuses on identifying patients with HSIL in order that treatment may prevent CC. This strategy has successfully driven CC rates down dramatically.[25,26] Although CC rates are expected to drop in the general healthy population as vaccinated cohorts age, several studies have documented lower HPV antibodies induced by the HPV vaccine in immunosuppressed patients including those with SLE and transplants.[27,28] The efficacy of the vaccine in these immunosuppressed individuals—whether the vaccine was given before or after diagnosis—is unknown.

Current screening approaches for the general population rely on the sensitivity and specificity of the following 3 strategies: cytology alone, co-testing (HPV plus cytology), and HPV primary screening with reflex cytology.[29,30] All 3 strategies take into account risks of overscreening, which include unnecessary procedures (i.e., colposcopy, biopsy, and excisional therapy) for lesions that would regress spontaneously as well as complication of therapy including infection, bleeding, and preterm birth.[31] The new guidelines recommend screening with cytology every 3 years starting the age of 21 years or with co-testing every 5 years for women 30 years and older.[32] Primary HPV screening starting at the age of 30 years with reflex cytology and/or genotyping every 5 years has been recently introduced as an alternative by the US Preventive Services Task Force.[30] Interim guidance from the ASCCP in 2015 allows primary HPV screening starting at the age of 25 years, as approved by the Food and Drug Administration, with recommended 3-year intervals.[33]

Using Guidelines for CC Screening in HIV Infection as a Model for Screening Other High-Risk Women

Much of the data guiding recommendations for CC screening in immunosuppressed populations in the United States have been driven by the HIV scientific community. Before antiretroviral therapy (ART), CC rates were higher in women with AIDS with the diagnosis becoming one of the AIDS defining illnesses.[1,34–38] One study in North America[39] found a more normalized standardized incident ratio (SIR) of 1.3 among women who were screened and managed closely. With the advent of ART, the risk of CC seems to have remained unchanged, unlike the dramatic decrease seen with Kaposi's sarcoma.[40] Women with low CD4 T-lymphocyte (CD4) cell counts continue to show increased risk of CC[41] and precancerous lesions.[42–46] Recent data suggest that with ART and good viral control, SIL is more likely to regress.[47,48] Adolescents with HIV have particularly high rates of HPV, LSIL, and HSIL, even among perinatally HIV-infected persons[43,49,50] leading to recommended screening shortly after the onset of sexual activity.[42] Although other HPV-associated cancers are also increased in HIV-infected patients, universal routine screening is not recommended.[34,38,51]

Recent data suggest that once an HIV-infected woman is intensely screened with annual cytology (which increases the sensitivity by relying on repetition), screening intervals can be widened. Furthermore, the negative predictive value of co-testing in HIV-infected women equals that in the general population.[52,53] The overall increased risk in HIV-infected women has been used to justify screening throughout their lifetime. Current CC screening recommendations for HIV-infected women are summarized in Table 1.[54]

METHODS

The expert panel conducting this review consisted of a group of medical professionals with diverse clinical backgrounds including adolescent and young adult medicine, infectious disease, epidemiology, family medicine, surgery, gynecologic oncology, nursing, and obstetrics and gynecology—all of whom have been active in the field of CC research, care, or both. Literature searches were performed using 5 to 10 key words (i.e., CC, cervical dysplasia/neoplasia/squamous intraepithelial lesion, human papillomavirus, and type of immunosuppression), resulting in an initial group of 346 articles. Additional publications were identified from review of citations in these articles. All of the abstracts generated by the search were then reviewed to identify relevant articles. More recent articles (within 10 years) were considered priority for review, although several older articles were seminal and worthy of inclusion. Review articles and articles with incomplete data for CC and SIL were excluded. Reviews of the literature were summarized with relevant statistical comparisons. Confidence intervals are given if available.

Recommendations for screening generated from each group were largely based on expert opinion. Adherence to screening, health benefits and risks, and available clinical expertise were all considered in formulating the recommendations to the degree that this information was available. A formal cost-benefit analysis was not possible. Management of abnormal cytology and treatment strategies were not reviewed.

In this article, we propose that CC screening guidelines for immunocompromised women without HIV infection either follow the (1) guidelines for the general population or (2) the current center for disease control guidelines for HIV-infected women. A more recent approach to guideline development is to assess risks based on current clinical benchmarks.[55] Robbins et al.[56] compared risks of HSIL among women in the Women's Interagency HIV study to risk benchmarks applied to the general population. Using published

studies, they generated risk benchmarks for HSIL biopsy using CD4 counts that allowed a year 3 return (risk of HSIL histology on follow-up similar to negative cytology), needed a 6- to 12-month return (similar to atypical squamous cells of undetermined significance), or required for prompt colposcopy (similar to LSIL cytology). The authors concluded that their analysis supported the center for disease control recommendations listed in Table 1. We propose that women without HIV but with immunosuppression need to engage in CC screening based on available information on their CC and HSIL risk.

RESULTS

Solid Organ Transplant Recipients

We identified 54 articles that examined the relationship between SOT (kidney, liver, pancreas, heart, lung) and HPV, SIL, and CC published between 1990 and 2018, and 25 were included in this review.

Cervical Cancer Risk

Several studies comparing CC rates in women with SOT of any organ to expected rates in the general population show SIRs ranging from 2.0 to 6.6.[57] All of these studies are limited by lack of information on the intensity of CC screening in these populations. Madeleine et al.[58] used the US Scientific Registry of Transplant Recipients from 1987 to 2009 to examine the risk of HPV-associated cancers in 73,035 women with SOT. The authors found no increase in risk of CC in these women compared with the general population with an SIR 1.0 (95% CI = 0.8–1.3) and speculated that this was due to aggressive screening and treatment of preinvasive diseases (see SIL risk). When the data were stratified by age, however, there was a higher than expected rate of CC in women aged 18 to 34 years compared with women 50 years and older, with an incidence rate ratio (IRR) of 2.3 (95% CI = 1.2–4.8). Busnach et al.[59] also showed an increase risk in women with SOT younger than 40 years conferring a 13-fold increased risk of CC over the general population.

The most common SOT in the United States is the kidney and data generated from studies on kidney transplants are often used for benchmarking relative risk (RR) for other organ transplants. Three studies based on large databases are worth discussion.[60–62] Kasiske et al.[62] examined Medicare billing claims in the United States from 1995 to 2001 for recipients of living and deceased donor kidneys. Compared with the general population, they noted no increase in CC rates 1 year after transplant with an age-adjusted rate ratio of 1.28. At 2-and 3-year posttransplant, however, the age-adjusted rate ratios increased to 6.0 and 5.7, respectively. Cervical cancer risk did not change after transplant compared with that while awaiting transplant [RR = 1.28 (0.48–3.36)], with both groups at increased risk compared with the general population. Vajdic et al.[60] evaluated the risk of CC 5 years before transplantation (before dialysis was required), during dialysis, and after transplantation in 28,855 women in a population-based registry in Australia and New Zealand. The rate of CC increased for women both during dialysis and posttransplant with approximately a 3-fold increase compared with the general population contrasting with no increase before renal failure. Kessler et al.[61] similarly found an increase in CC rates with an SIR of 25.28 (95% CI = 9.3–25.8) during 9 years of observation. This study included 163 women in a network of 17 population-based registries in France. All the women had annual CC screening.

A few studies demonstrated similar rates of CC in heart, lung, and liver transplant recipients compared with renal transplant recipients. In the study by Madeleine et al.,[58] the IRR for heart and lung transplant recipients was 1.8 (95% CI = 0.8–3.7) and for liver transplant recipients was 1.2 (95% CI = 0.6–2.3) compared with the risk associated with renal transplant patients. The rates in women with intestinal or multiple organ transplants had higher risks than reported for women with renal transplants with an IRR of 5.1 (95% CI = 1.5–12.9). One study examined rates of CC specific to liver transplant patients by following 160 Italian women after liver transplantation for an average of 7.2 years and reported an overall SIR of 5.7 (95% CI = 0.1–31.9) for CC.[63]

Although length of immunosuppression has been thought to potentially enhance CC risk, few studies have attempted to address this. In the study by Meeuwis et al.,[64] the median (range) time from renal transplant to CC diagnosis was 5.0 (2.2–9.8) years, whereas Vajdic et al.[60] reported a mean (SD) of 8.5 (4.7) years from renal transplant to CC diagnosis. Using UK transplant and cancer registries, Collett et al.[65] noted a different pattern with a peak risk of CC at 2-year post–liver transplant with a declining risk thereafter. Madeliene et al.,[58] however, reported that the rates for CC were roughly consistent over time with an IRR of 1.4 (95% CI = 0.7–2.7) at 5+ years and 0.9 (95% CI = 0.4–1.8) at 2- to 5-years post–transplant compared with less than 2 years. In another large US study, the IRR for CC after renal transplant was not elevated until year 2 after transplant.[54] These patterns are difficult to interpret because CC risk also increases as women age. The increased risk of invasive CC likely begins shortly after transplant and persists throughout the years after transplant.

Squamous Intraepithelial Lesion Risk

Fewer data have been published on cervical SILs in women with SOT. The largest study was performed by Madeleine et al.[58] using the US Scientific Registry of Transplant Recipients discussed previously, which included 17,100 women for this analysis. The SIR for cervical SIL was 3.3 (95% CI = 2.6–4.2). When the data were stratified by age, a higher incidence of HSIL in the 18- to 34-year-old women was present when compared with the women older than 50 years with an IRR of 4.7 (95% CI = 2.5–93). A registry study by Adami et al.[66] compared SIL rates in 2,339 Swedish women with SOTs with rates in their general population and found an elevated risk for carcinoma in situ with an SIR of 1.3 (95% CI = 1.0–1.8). Silverberg et al.[67] in a relatively large nested case-control study noted that the degree and type of immune suppression impacted the risk of cervical intraepithelial neoplasia (CIN) 2 or worse (CIN 2+). The overall risk of CIN 2+ with a previous organ transplant was elevated with an odds ratio (OR) of 3.3 (95% CI = 2.3–4.8). This risk of CIN 2+ was also associated with the degree of immune suppression based on the number of immunosuppressant medication classes with RRs of 2.0 (95% CI = 0.7–5.5), 3.1 (95% CI = 1.6–6.1), and 4.9 (95% CI = 3.0–7.9) for 0, 1 to 2, and 3 or more medication classes, respectively. Only one study examined risk over time. In a longitudinal cohort study of 459 women after SOT, Long et al.[63] detected increasing cumulative incidence of CIN 2+ and CIN 3+ for at least a decade after SOT, demonstrating ongoing risk even after the initial intense posttransplant immunosuppression.

Regarding SIL risks for specific SOT type, only a few relatively small studies evaluated risk of SIL after renal transplant. Most showed that the risk of SIL increased with increasing years of immunosuppression, with rates ranging from a 2 to 6-fold increase for 2 to 5 years after renal transplant affecting 10% to 20% of posttransplant patients.[64,68,69] A study by Meeuwis et al.[64] included 224 women after renal transplant and noted no increase in SIL. Only 3.6% of women in this population had SIL; however, only 63.4% had at least 1 cytology.

Very few studies of SIL risk for nonrenal transplants exist. Only one published study prospectively examined rates of cervical

SIL in lung transplant patients,[70] following 166 Australian women with annual cervical cytology screening after transplantation. Ten percent developed cervical abnormalities (7 had LSILs and 6 had HSILs). For LSIL, the incidence was 42.2 per 1,000 women screened after transplant compared with 8.3 per 1,000 in the general population registry, and for HSIL, the incidence was 30 per 1,000 women screened posttransplant compared with 6.2 per 1,000 in the general population.

Human Papillomavirus Risk

Two studies examined the frequency of HPV infection, HPV type, and rate of HPV clearance in the SOT population. One case matched control study compared 60 kidney transplant recipients and 60 healthy controls and found that rates of hrHPV were no different between the 2 groups.[71] Clearance in the transplant group was slightly, but not statistically, less than that in the control group (82% vs 93%, respectively; $p = .37$).

In a prospective study of 35 Italian women after kidney transplant, 13 (50%) tested positive for hrHPV—all with normal cytology.[72] These same women had all tested negative for hrHPV every 6 months while on dialysis before transplant, suggesting that reactivation of a latent HPV or new infection occurred after transplantation.

Recommendations for CC Screening in Solid Organ Transplant Recipients

Studies analyzing all type of SOT together had conflicting data for risk of CC except for women transplanted at a younger age. In contrast, the data specific for renal, heart/lung, liver, and pancreas transplants show a more consistent increase in risk. Increased risk for HSIL was also consistent across studies demonstrating the importance of surveillance and treatment. We concluded that the transplant population reflects a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening frequency. The data demonstrate continued risk long after transplantation, endorsing the recommendation for screening throughout a woman's lifetime.

For solid organ transplant patients:

- Cytology is recommended if younger than 30 years
- Co-testing is preferred, but cytology is acceptable if 30 years or older
- If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 years
- If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 years
- If transplant before the age of 21 years, begin screening within 1 year of sexual debut
- Continue screening throughout lifetime (older than 65 years). Discontinue screening based on shared discussion regarding quality and duration of life rather than age

Allogeneic Hematopoietic Stem Cell Transplantation

We identified 27 articles that examined the relationship between hematopoietic stem cell transplant and HPV, SIL, and CC published between 1990 and 2018, and 10 were included in this review.

Cervical Cancer Risk

In contrast to SOT, less has been published for allogeneic hematopoietic stem cell transplant. An early registry study by Curtis et al.[73] showed no increase in the incidence of CC in a study of 7,851 women from the International Bone Marrow Transplant Registry and the Fred Hutchinson Cancer Center after more than 10 years of follow-up: [SIR = 0.70 (95% CI = 0.0–3.9)].

In 2001, Bhatia et al.[74] conducted a retrospective cohort and nested a case-control study of hematopoietic stem cell transplant patients at the City of Hope Cancer Center. Four of 919 women developed CC after transplant, at a median age of 41.3 years, with age-standardized incidence rate of 13.3 (95% CI = 3.5–29.6) compared with a normalized population sample. Rizzo et al.[75] reported on the risk of secondary solid cancers in an international cohort of 11,752 female patients who received allogeneic hematopoietic stem cell transplant between 1964 and 1994 and who survived for at least 1 year after transplant. Incidence rates were compared with standardized local population incidence rates. The median age of hematopoietic stem cell transplant was 27 years; 58% of the patients were younger than 30 years; and 31% had chronic GvHD at 3-year posttransplantation. The SIR for CC was 1.65 (95% CI = 0.54–3.85) with excess absolute risk of CC of 0.54 per 10,000 person-years at risk. The CC SIR increased from 2.16 at 1- to 4-year posttransplantation (with 15,170 surviving patients) to 18.9 at 15-year posttransplantation (with only 378 surviving patients), suggesting that the risk of CC increased with survival time, although this did not reach statistical significance, likely because of low numbers of long-term survivors. In a similar pattern, Atsuta et al.[76] found no overall increase in CC in a retrospective cohort study of 7,149 female hematopoietic stem cell transplant patients [SIR = 1.4 (95% CI = 0.6–3.0)] but showed an SIR of 1.6 for survivors for 10 years.

Majhail et al.[77] conducted a cohort study of 4,318 patients to investigate solid cancer risk for allogeneic HSCT patients using high-dose busulfan and cyclophosphamide conditioning instead of total body irradiation. Their results found no increase in SIR of CC [SIR = 2.32 (95% CI = 0.48–6.77)] when compared with standardized population incidence rates from cancer registries in the regions where patients were treated. Investigators reported that the relative lack of long-term survivors, with only 774 of the original 4,318 patients surviving to 10 years, limited their ability to detect differences. A recent systematic review by Chang et al.[78] also reported no overall increased risk of invasive CC in women after HSCT in large studies ($n > 1,000$).

Squamous Intraepithelial Lesion Risk

Sasadeusz et al.[79] conducted a retrospective cohort study of cervical cytology in 64 women receiving allogeneic or autologous bone marrow transplant at a single center in Melbourne, Australia, from 1989 to 1998. Pretransplantation as well as posttransplantation abnormal cytology rates were increased over the general Australian population. In age-adjusted analyses, pretransplantation and posttransplantation odds of abnormal cytology were elevated [aOR = 2.1 (95% CI = 1.1–4.0) and aOR = 6.6 (95% CI = 4.5–9.6), respectively]. Considering only allogeneic HSCT recipients, these women had a higher rate of cervical cytological abnormality posttransplantation compared with pretransplantation [aOR = 6.8 (95% CI = 1.8–25.2)]. There was no molecular testing for HPV nor assessment of grade of abnormality in this study.

Wang et al.[80] conducted a retrospective case series of cervical SIL and genital HPV infection in 89 long-term survivors of allogeneic HSCT in Norway. In histologically confirmed cases, only chronic GvHD was associated with HSIL [aOR = 47.7 (95% CI = 1.83–1234.65)]. Savani et al.[81] completed a 2-year prospective cohort study of cervical HPV infection, cervical cytology, and

observation for genital GvHD in 38 women who had received allogeneic HSCT at least 3 years before study entry. With a median of 85 months since transplantation, posttransplant HSIL was associated with chronic genital GvHD requiring systemic therapy [aOR = 4.6 (95% CI = 1.1–16.4)]. More recently, Shanis et al.[82] described a retrospective cohort study of 82 allogeneic HSCT patients showing an increased risk of HSIL in women with genital GvHD or extensive GvHD [aOR = 13.1 (95% CI = 1.6–108.3)].

Human Papillomavirus Risk

Only one study examined HPV risk. Shanis et al.[82] observed that pretransplant HPV was associated with posttransplant HPV positivity [aOR = 6.5 (95% CI = 1.65–25.9)] and persistent HPV [aOR = 25.2 (95% CI = 5.0–108.4)]. As with HSIL, genital or extensive GvHD was associated with posttransplant HPV positivity [aOR = 5.7 (95% CI = 1.9–17.2)].

Recommendations for CC Screening in Hematopoietic Stem Cell Transplant Patients

Although there is some evidence for an increase in CC in large cohort studies of HSCT patients, the conflicting data may reflect that many patients did not survive long enough to evaluate the incidence of slow-growing CCs. Furthermore, history of cervical screening or previous hysterectomy was not included in registry study analysis, possibly leading to underestimation of CC incidence rates. We concluded that the HSCT population reflects a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening frequency. Furthermore, we conclude that a new diagnosis of genital GvHD or chronic GvHD[83] in a patient with a previous HSCT again results in a greater risk of CC than the general population and should result in resumption of the more intensive screening guidelines.

For all HSCT patients:

- Cytology is recommended if younger than 30 years
- Co-testing is preferred, but cytology is acceptable if 30 years or older
- If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 years
- If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 years
- If transplant before the age of 21 years, begin screening within 1 year of sexual debut
- Continue screening throughout lifetime (older than 65 years). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
- For HSCT patients who develop a new diagnosis of genital GvHD or chronic GvHD, resume annual cervical cytology until 3 consecutive normal results at which time perform cytology every 3 years, or perform an initial baseline co-test, and, if cytology is normal and HPV is negative, perform co-testing every 3 years.

Autoimmune Diseases

Inflammatory Bowel Disease. We identified and reviewed 19 articles evaluating the association between IBD and HPV, SIL, and CC published between 1994 and 2017, and 15 articles were included in this review.

Cervical Cancer Risk

An early single-center cohort study assessed malignancy risk associated with azathioprine treatment for IBD. Among the 366 women with Crohn disease and ulcerative colitis enrolled and treated between 1962 and 1991 (median treatment duration of 12.5 months), 2 cases of CC in the Crohn disease population compared with 0.5 expected ($p = .09$).[84] Hutfless et al.[85] described a nested case-control study of women aged 15 to 68 years enrolled in Kaiser Permanente of Northern California between 1996–2006 in which 1,165 women with IBD (427 with Crohn disease and 738 with ulcerative colitis) were compared with 12,124 age-matched controls without IBD. No statistically significant difference in CC was noted between the IBD and control groups [aOR = 1.45 (95% CI = 0.74–2.84)] overall, nor with use of aminosalicylates, corticosteroids, or immunomodulators (all $p > .05$).[85] Comparable results were noted in a retrospective analysis of combined Swedish national data sets that identified 199,466 women with 1 or more of 33 autoimmune diseases. The incidence of CC was not increased for the 12,886 women with Crohn disease [SIR = 0.89 (95% CI = 0.58–1.31)] nor the 14,272 women with ulcerative colitis [SIR = 0.98 (95% CI = 0.67–1.40)].[86] In 3,611 women with Crohn disease followed for an average of 5 years as part of a prospective population-based cohort study, there were no significant differences in CC rates between patients with Crohn disease who received infliximab [SIR = 1.07 (95% CI = 0.03–5.94)], other treatments (defined as corticosteroids and/or immunosuppressant medications including azathioprine, 6-MP, or methotrexate) [SIR = 1.26 (95% CI = 0.03–7.02)], immunosuppressant use only [SIR = 1.77 (95% CI = 0.21–6.40)], or no immunosuppressant use [SIR = 0.00 (95% CI = 0.00–5.04)] and women in the general US population based on the SEER database.[87]

A large Danish population-based cohort study[88] included 18,691 women with ulcerative colitis and 8,717 women with Crohn disease diagnosed between 1979 and 2011 who were each age matched to 50 control patients. In the presence of slightly higher screening rates, women with ulcerative colitis had similar CC risk as controls [IRR = 0.78 (95% CI = 0.53–1.13)]. In contrast, among women with Crohn disease, CC risk was increased [IRR = 1.53 (95% CI = 1.04–2.27)] with a similar screening rate as controls. In women with Crohn disease or ulcerative colitis, a history of tumor necrosis factor α (TNF-α) antagonists, corticosteroids, mesalamine, or azathioprine use was not associated with increased risk. The risk of CC in the IBD population 1 to 9 years before being diagnosed with IBD was increased in both ulcerative colitis [OR = 2.78 (95% CI = 2.12–3.64)] and Crohn disease [OR = 1.85 (95% CI = 1.08–3.15)] groups compared with controls. The study authors acknowledged this as an unexpected observation without a clear explanation and suggested the need for additional research to corroborate.[88]

Another population-based cohort study used the Danish National Patient Register from 1977 to 2010 and identified 341,758 women with 1 of 39 autoimmune diseases to compare their risk of CC with the general Danish population.[89] This included 15,951 women with Crohn disease and 29,215 women with ulcerative colitis. Patients with Crohn disease had a nonsignificant increase in risk [SIR = 1.3 (95% CI = 0.9–1.7)] and the ulcerative colitis group had no increase in risk [SIR = 0.9 (95% CI = 0.7–1.1)]. In the autoimmune population as a whole, systemic corticosteroid or antimetabolite use was not associated with a higher risk of CC compared with no immunosuppressant use [hazard ratio [HR] = 1.0 (95% CI = 0.8–1.2)]. Azathioprine use, however, was associated with increased CC risk specifically in women with autoimmune disease who had received more than 300 doses [HR = 2.2 (95% CI = 1.2–3.9)]. The authors suggest that women with IBD

with higher total dosing of azathioprine be considered for high-risk CC screening intervals.

Squamous Intraepithelial Lesion Risk

Using 2 U.S. commercial insurance databases from 2001 to 2012, Kim et al.[90] assessed the combination of HSIL and CC rates (with a relative larger representation of HSIL) among women 18 years and older in this large population-based cohort study. Comparison was made between 133,333 women with systemic inflammatory diseases including IBD, psoriasis, RA, and SLE and 533,332 age-matched women without inflammatory disease but with a diagnosis of hypertension. The incidence rate of HSIL/CC among those with IBD was 110.3 (95% CI = 85.4–412) and 73 (95% CI = 68.5–78.6) among those with hypertension. When adjusting for age, comorbidities, number of prescription drugs, sexual and substance use behavior, contraception, and HPV vaccine status, the HR for HSIL/CC was 1.22 (95% CI = 0.93–1.6). The HR for HSIL/CC was lower when adjusting for immunosuppressive drug use [HR = 1.07 (95% CI = 0.79–1.45)], suggesting that the risk of HSIL/CC is associated with level of immunosuppression.[90]

Lees et al.[91] reported rates of SIL in 362 women with IBD (184 with Crohn disease and 178 with ulcerative colitis) compared with 1,448 healthy controls using a retrospective case-control method. Rates of abnormal cervical cytology were similar in the IBD (14.6%) and control (17.3%) populations [OR = 0.82 (95% CI = 0.59–1.13)]. Among women with abnormal results, no difference existed in the proportion of LSIL or HSIL results between the IBD and control groups (p = .37). Immunosuppressant use was documented in 29% of the IBD population with no effect on the incidence of SIL [OR = 0.72 (95% CI = 0.37–1.43)].

Singh et al.[92] reported on a population-based, nested case-control study in which cases were defined as those with a history of any abnormal cervical cytology, cervical biopsy, or diagnosis of CC for a 4-year window of time using a national CC screening database and cancer registry from Manitoba. All identified cases (19,692 women) were matched to 3 controls with normal cervical cytology tests (57,898) and the association between IBD (ulcerative colitis and Crohn disease), history of immunosuppressant medication, or systemic corticosteroids and cervical abnormality were assessed. Overall ulcerative colitis and SIL were not associated with SIL. The only association with SIL in the Crohn disease population was in women with more than 10 oral contraceptive prescriptions filled during the study period [OR = 1.66 (95% CI = 1.08–2.54)]. Use of both immunosuppressant and corticosteroid medication was associated with an increased risk of any cervical abnormality in the IBD population compared with not using either medication [OR = 1.41 (95% CI = 1.09–1.81)]. High-risk lesions, defined as HSIL*, atypical squamous cells, cannot rule out high grade disease, CIN 2 or 3, and invasive CC, however, were not increased [OR = 1.28 (95% CI = 0.77–2.12)].

Marehbian et al.[93] reviewed US-based insurance claims from 2002 to 2005 for 22,130 patients with Crohn disease and 111,550 controls (55% women) in a retrospective cohort study designed to study associations between Crohn disease treatments including corticosteroids (prednisone or budesonide), immunosuppressants (azathioprine, 6-MP, or methotrexate), and anti–TNF-α medications (infliximab or adalimumab), and adverse events, including SIL or HPV. Comparing all patients with Crohn disease regardless of treatment history with control patients, patients with Crohn disease had a higher rate ratio (RR) of SIL or HPV than controls [RR = 1.35 (95% CI = 1.28–1.43)]. An increased risk of SIL or HPV was also observed in patients with Crohn disease treated with an immunosuppressant [HR = 1.81 (95% CI = 1.30–2.51)] or a combination of steroid and immunosuppressant [HR 2.31 (95% CI = 1.19–4.50)] compared with patients with Crohn disease on no medication. Grade of SIL and HPV types were not addressed.[93]

In the large Danish cohort study by Rungoe et al.,[88] discussed previously, risk was slightly increased for both LSIL [incidence rate ratio (IRR) = 1.15 (95% CI = 1.00–1.320)] and HSIL [IRR = 1.12 (95% CI = 1.01–1.25)] in the ulcerative colitis population and for both LSIL [IRR = 1.26 (95% CI = 1.07–1.48)], and HSIL [IRR = 1.28 (95% CI = 1.13–1.45)] in the Crohn disease population. Increased risk of HSIL among women with Crohn disease was associated with past TNF-α antagonist use [IRR = 1.85 (95% CI = 1.12–3.04)] and history of filling an azathioprine prescription [IRR = 1.08 (95% CI = 1.04–1.13)]. Other medications did not increase risk of HSIL in ulcerative colitis or Crohn disease.

An increased risk of SIL (severity not differentiated) was also seen by Jess et al.[94] among 441 women with Crohn disease in a population-based cohort study compared with the general population [SIR = 1.65 (95% CI = 1.10–2.37)]. Cervical cytology abnormalities were highest among smokers [SIR = 2.15 (95% CI = 1.27–3.40)], women diagnosed with IBD before the age of 20 years [SIR = 2.52 (95% CI = 1.26–4.51)] and in those who received 5-aminosalicylic acid [SIR = 1.69 (95% CI = 1.08–2.51)] or thiopurines [SIR = 2.47 (95% CI = 1.54–3.73)]. The risk of SIL for the 707 women with ulcerative colitis was comparable with that for the general population [SIR = 0.7 (95% CI = 0.43–1.11)].

A meta-analysis of 3 case-control and 5 cohort studies by Allegretti et al.,[95] which included 77,116 female IBD patients on immunosuppressive treatments in whom 995 had HSIL or CC, showed an increased risk of HSIL/CC compared with the control population [OR = 1.34 (95% CI = 1.23–1.46)]. Variable approaches to assessing exposure to medications were used across the studies, so secondary analysis by medication class could not be performed. In addition, the authors acknowledged the limitation of not reporting HSIL and CC separately.

Several smaller observational studies have reported a positive association between IBD and SIL. A retrospective cohort study compared cervical cytology results 5 years before enrollment in 116 women with IBD (52 with ulcerative colitis and 64 with Crohn disease) with 116 age-matched healthy controls and found a significant difference with 18.1% of IBD patients versus 5.2% of controls having abnormal cervical cytology, but this included a combination of atypical squamous cells of undetermined significance, LSIL, and HSIL (p = .004).[96] A case-control study[97] of 40 patients (8 with ulcerative colitis and 32 with Crohn disease) and 120 matched controls (by age, parity, and race) observed an increase for both LSIL [OR = 2.2 (95% CI = 1.7–4.4,)] and HSIL [OR = 3.1 (95% CI = 1.3–8.7)] in the IBD group. High-grade lesions were more prevalent in the immunosuppressant exposed IBD group compared with nonexposed IBD patients (p < .05) or with the control group (p < .001).[97]

Human Papillomavirus Risk

Marehbian et al.[93] (described previously) was the only study to include HPV results but only reported rate ratios of combined cervical SIL or HPV in patients with Crohn disease compared with controls.[92]

Recommendations for CC Screening in Patients With Inflammatory Bowel Disease. There is no strong evidence to support that IBD alone increases cervical SIL or CC risk. In contrast, immunosuppressant therapy does seem to increase the risk, although results are conflicting regarding which type of immunosuppressant medication increases risk. Available studies

are limited by their primarily observational nature and lack of distinction of HSIL from all SIL, potentially underestimating CC risk in the IBD population. Similar CC risk may also be due to intense screening, which would have led to enhanced detection and treatment of preinvasive lesions. Recently published preventive care guidelines for IBD patients from the American College of Gastroenterology recommend frequent screening only for women with IBD on immunosuppressive treatment.[98] We concluded that the IBD patients on immunosuppressive treatment reflect a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening frequency. In comparison, IBD patient not on immunosuppressive treatments are not at an increased risk and we recommend screening similar to the general population.

For IBD patients on immunosuppressive treatments:

- Cytology is recommended if younger than 30 years
- Co-testing is preferred, but cytology is acceptable if 30 years or older
- If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 years
- If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 years
- If on immunosuppressant therapy before the age of 21 years, begin screening within 1 year of sexual debut
- Continue screening throughout lifetime (older than 65 years). Discontinue screening based on shared discussion regarding quality and duration of life rather than age

For IBD patients not on immunosuppressive treatments:

- Follow general population screening guidelines

Systemic Lupus Erythematosus and RA. We identified 53 articles that examined the relationship between SLE and RA and HPV, SIL, and CC published between 1981 and 2017, and 29 articles were included in this review.

SYSTEMIC LUPUS ERYTHEMATOSUS

Cervical Cancer Risk

Studies comparing the observed rate of cancer among women with SLE with population registries show SIRs of between 1.1 and 4.0 for any cancer,[99–101] with most increased risk due to CC. Many of these studies were limited by populations too small to detect a statistically significant increase in risk.[99]

A systematic review from 2011 examining the existing literature on SLE and HPV infection, cervical SIL, and CC found 33 relevant articles that met authors' criteria.[102] All studies had relatively small numbers of women with SLE (between 11 and 85, other than 1 retrospective cohort study of 321 women) and were too heterogeneous to allow for a meta-analysis. The authors identified 15 articles evaluating the association between SLE and CC, 14 of which found no increased frequency of CC among women with SLE. A more recent study by Dey et al.[101] showed an SIR of 4.0 (95% CI = 3.5–4.5) for CC in a nested case-control study of 595 patients with SLE followed for 32 years. A study comparing Danish registry data[100] with a cohort of 576 SLE patients showed an overall elevated risk of all HPV-associated cancers [SIR = 2.3 (95% CI = 1.4–3.6)], and SIL [SIR = 1.8 (95% CI = 1.2–2.7)], but not for CC alone [SIR = 0.6 (95% CI = 0.1–4.5)] in the SLE cohort.

Squamous Intraepithelial Lesion Risk

Studies have consistently shown that SLE increases the risk of SIL. Although many have been limited by sample size, more recent studies analyzing cancer registry or insurance data have shown a consistent link. The systematic review by Santana[102] identified 18 studies evaluating the association between SLE and SIL, of which 15 showed a higher frequency of premalignant lesions among SLE patients. Only 3 of these studies, however, showed a statistically significant increase in the rate of HSIL (others included LSIL within a composite outcome).[102,103] A case-cohort study from China comparing 85 SLE patients with 2,080 healthy controls showed a more than six-fold increase in rates of cytologic HSIL [3.5% vs 0.5%, OR = 6.6 (95% CI = 3.2–13.9)], with no difference seen by use of immunosuppressive agents.[104]

Two more recently published registry-based studies showed a relationship between SLE or RA and cervical SIL. Wadstrom el al.[105] carried out a nationwide cohort study using Swedish national registry data to quantify the risk for cervical neoplasia and cancer among women with SLE. Compared with the general population, women with SLE had an increased risk of LSIL [HR = 2.33 (95% CI = 1.58–3.44)] and HSIL [HR = 1.95 (95% CI = 1.43–2.65)]. In the Kim et al.[90] US insurance registry study mentioned previously, the authors found that the crude incidence of HSIL or CC was highest in SLE (141 per 100,000 person-years) compared with other systemic inflammatory diseases. The HR was almost twice the general population [HR = 1.90 (95% CI = 1.38–2.61)] and remained significantly elevated across 5 multivariate models that included age, smoking status, immunosuppressant use, and healthcare utilization factors (aHRs range = 1.53–1.66). In this same study, the authors found that the relationship between RA and HSIL or CC was not significant [HR = 1.13 (95% CI = 0.92–1.38)] until adjusted for these covariates (aHR range =1.38–1.49).

Studies have shown an increase in the risk of SIL among women with SLE on common cytotoxic or cytostatic medications, with the strongest risk seen with the use of azathiaprine.[103,106] Dugue et al.[106] showed that across autoimmune disorders, there was a cumulative dose effect of Azathioprine, with an adjusted HR of 2.2 (95% CI = 1.2–3.9) for women who had maximal exposure (cumulative >300 defined daily doses) compared with nonsignificant results when not stratified by dosage level [aOR = 1.3 (95% CI = 0.7–2.3)]. Other studies showing an increased risk of SIL with increasing disease severity or use of immunomodulators have been limited by the small numbers of patients or outcomes, the use of cytologic outcomes, and the inclusion of LSIL in the outcomes.[103,107]

Human Papillomavirus Risk

In the review by Santana,[102] the association between SLE and HPV was mixed, with 3 studies showing a significantly increased risk of HPV infection, whereas 2 studies did not. A case-cohort study by Tam et al.[104] showed an increase in the prevalence of hrHPV [10.6% vs 4.2% with OR = 2.7 (95% CI = 1.3–5.6)] among women with SLE compared with controls, with an even greater risk of infection with multiple high-risk types [4.7% vs 1.1% with OR = 4.6 (95% CI = 1.6–13.7)]. In a prospective follow-up of SLE patients for 3 years, the authors found a high frequency of persistent HPV infection where 86.7% of incident infections lasted greater than 12 months; however, the study was limited by loss to follow-up and a lack of a non-SLE control group.[108]

RHEUMATOID ARTHRITIS

Cervical Cancer Risk

In 2015, Simon et al.[109] published a meta-analysis describing the relationship between RA and cancer. The Simon study

identified 13 publications that compared the rates of CC in patients with RA with population SIRs derived from registry data. Among all articles, there was a range of SIR from 0.43 to 2.15, with a pooled SIR of 0.87 (95% CI = 0.72–1.05).

The relationship between CC and RA among woman on disease-modifying antirheumatic drugs has been examined in several studies. Askling et al.[110] showed no overall increase risk of CC in patients with RA [overall, SIR = 1.03 (95% CI = 0.71–1.45) and for early RA, SIR = 0.8 (95% CI = 0.02–4.3)], with no difference in risk among the 67 women receiving the disease-modifying antirheumatic drugs anti–TNF-α [SIR = 1.0 (95% CI = 0.0–5.8)]. In contrast, in a population of 1,152 women receiving anti–TNF-α or methotrexate, Setoguchi et al.[111] showed a decreased risk of CC [SIR = 0.5 (95% CI = 0.31–0.82)]. This same study compared patients with RA on disease-modifying antirheumatic drugs with patients with RA using methotrexate and showed no increase in the overall risk of cancer with the immune-modulators compared with methotrexate [0.98 (95% CI = 0.73–1.31).]

Wadstrom et al.[112] compared risk versus the general population using Swedish national registry data and found that disease-modifying antirheumatic drug-naive women had no increased risk of invasive CC [HR = 1.09 (95% CI = 0.71–1.65)]. Compared with disease-modifying antirheumatic drug-naive women, however, women on anti–TNF-α therapy had an increased risk [HR = 2.10 (95% CI = 1.04–4.23)].

Squamous Intraepithelial Lesion Risk

In contrast to the lack of association with CC, Wadstrom et al.[112] found that disease-modifying antirheumatic drug-naive women had an increased risk of LSIL [HR = 1.53 (95% CI = 1.23–1.89)] and HSIL [HR = 1.39 (95% CI = 1.16–1.66)]. Compared with disease-modifying antirheumatic drug-naive women, women on anti–TNF-α therapy had an increased risk of HSIL [HR = 1.36 (95% CI = 1.01–1.82)] similar to that found for CC. This difference was not attributable to differences in screening patterns and was attenuated when controlled for time on anti–TNF-α therapy [2–5 years, HR for HSIL = 1.39 (95% CI = 0.92–2.10); 5+ years HR for HSIL = 1.06 (95% CI = 0.63–1.78)]. These results suggest that the risk for cervical neoplasia may be more related to the disease severity necessitating the disease-modifying antirheumatic drugs than the medications themselves.

Recommendations for CC Screening in Patients With SLE and RA. The risk of HSIL and CC was better demonstrated among women with SLE than RA, although studies were limited by size, inclusion of LSIL in main outcomes, and variability of disease severity or exposure to immunosuppressants. In studies designed to look specifically at immunosuppressant use, however, there did seem to be an increase in risk, identified mostly in women with RA on disease-modifying antirheumatic drugs. Although the strength of the evidence is limited, the consistent increase in risk merits a higher intensity screening strategy. We concluded that all women with SLE (with or without immunosuppressant treatments) and those with RA on immunosuppressant treatments reflect a greater risk of CC than the general population and guidelines for HIV-infected women are a reasonable approach for screening frequency. In comparison, patients with RA not on immunosuppressant treatments are not at an increased risk, and we recommend screening similar to the general population.

For all patients with SLE and patients with RA on immunosuppressant treatments:

- Cytology is recommended if younger than 30 years
- Co-testing is preferred, but cytology is acceptable if 30 years or older
- If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 years
- If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 years.
- If on immunosuppressant therapy before the age of 21 years, begin screening within 1 year of sexual debut
- Continue screening throughout lifetime (older than 65 years). Discontinue screening based on shared discussion regarding quality and duration of life rather than age

For patients with RA not on immunosuppressant treatments:

- Follow general population screening guidelines

Diabetes Mellitus. We identified 21 articles that examined the relationship between type 1 diabetes mellitus (DM) and HPV, SIL, and CC, and 9 articles were included in this review.

Cervical Cancer Risk

Diabetes is associated with an increased risk of several cancers; however, the data on CC are unclear.[113] A pooled analysis of 8 cohort studies of more than 300,000 subjects in Japan examined the association between preexisting diabetes and total or site-specific cancer risk. Diabetes was associated with increased risk of CC after adjusting for co-founding factors [HR = 2.63 (1.20–5.80)]. No information on the rates of CC screening or type of DM was available.[114]

Several large population-based retrospective analyses have found no association between type 1 DM and CC risk. Carstensen et al.[115] reported on the incidence of CC among 9,149 cancers found in women with type 1 DM compared with the general population in Australia, Denmark, Finland, Sweden, and Scotland. There was no increase in incident CCs in women with type 1 DM compared with the general population with a HR of 0.92 (95% CI = 0.80–1.06). In a retrospective population-based cohort study conducted in Taiwan, there was no statistically significant increase in CC [SIR = 1.41 (95% CI = 0.93–2.05)] in 7,752 women type 1 DM compared with the general Taiwanese population.[116] Shu et al.[117] reported on the risk of cancer among 24,052 individuals hospitalized for type 1 DM retrieved from the Swedish Hospital Discharge Registry and compared the risk of subsequent cancers with the general population in Sweden. In this cohort of 11,290 females with type 1 DM, no increased risk for CC was seen [SIR = 1.09 (95% CI = 0.56–1.90)].

Squamous Intraepithelial Lesion Risk

No data were available to review.

Human Papillomavirus Risk

No data were available to review.

Recommendations for CC Screening in Patients With Type 1 diabetes mellitus. There is a paucity of evidence-based reports associating type 1 DM with an increased risk of cervical SIL and CC. Therefore, CC screening for women with type 1 DM should follow the screening guidelines for the general population.

For patients with type 1 (DM):

- Follow general population screening guidelines

Adherence to CC screening. Relevant to the previous discussions, 1 mechanism for the increased risk of observed SIL and CC across diseases is underscreening.

It has been reported that in women with a renal transplant, only 41% had adequate screening, 31% had their last screen more than 5 years ago, and 29% had no screening at all.[118] Courtney et al.[119] followed 173 women with a functioning renal transplant for a median time of 121-month posttransplant. The expected number of cervical cytology tests, based on annual screening that was standard during the period, was 1,148, but the actual number of cervical cytology tests performed during this time was only 425. Thirty-two percent had no screening. A large study from the Netherland's national transplant registry had similar findings.[64] Cervical cytology tests were recommended every 6 to 12 months after renal transplantation, but the average number of cervical cytology tests per woman was 0.2 per year, equivalent to 1 cervical cytology every 5 years.[64] HSCT patients demonstrated better adherence to CC screening. A US survey[120] showed that 85% of 753 female HSCT recipients received a cervical cytology test within the previous 3 years, whereas in another study of 191 Australian women, 75% reported cervical cytology testing within the previous 2 years.[121]

Suboptimal screening was demonstrated among women with autoimmune diseases. A cross-sectional study that examined US insurance claim data found suboptimal screening rates in both control and IBD patients (65.2% vs 70.4%).[122] When the IBD patient data were controlled for immunosuppressant use, the women with IBD had lower CC screening rates [OR = 0.81 (95% CI = 0.74–0.88)].[122] Singh et al.[123] reported lower rates of CC screening in women with IBD only when adjusting for past immunosuppressant use [OR = 0.50 (95% CI = 0.29–0.88)]. Similarly, in relatively large studies, women with RA or with SLE did not show any differences in CC cancer screening rates when compared with the general population.[124,125] The Lupus Outcome study showed that similar barriers exist for CC screening compared with the general population including poverty, lack of insurance, and not having a generalist involved in care.[125]

The data on women with DM are not as clear and were conflicting in several large studies. Data extracted from The National Health Interview Survey (17,666 nondiabetic women and 1,448 diabetic women) as well as the population-based study using data from the Swiss Health Survey did not show any significant difference in CC screening between women with and without diabetes after adjusting for sociodemographic factors.[126,127] Contrary to these studies, Zhao et al.[128] reported that diabetic women had a lower adjusted prevalence and aOR for acquiring CC screening than women without diabetes [74% vs 79%; $p < .05$, and aOR = 0.73 (95% CI = 0.66–0.81)]. Martinez-Huedo et al.[129] examined the adherence with cervical cytology screening among women with and without diabetes in women participating in the European Health Interview survey between 2006 and 2010 and reported an aOR of 0.74 (95% CI = 0.60–0.91; $p < .05$) for CC screening.

Limitations of all of these studies include recall bias, nonresponse bias, and lack of consideration for confounding factors in their analysis, with potential to affect the validity of the data. Study findings suggest a variety of reasons including a focus on comorbidities and disparities in care as reasons for lack of screening. Ultimately, it is the provider's responsibility to assure that CC screening proceeds based on current recommendations.

SUMMARY

In review of the literature, there was a mixed picture of CC risk among our 3 groups. Risk groups were identified as women with SOT, HSCT, SLE, and IBD and RA on immunosuppressants

TABLE 2. Immunosuppressants and Immunosuppressive Treatments

Calcineurin inhibitors	Cytotoxic agents	mTOR inhibitors	Steroids	Biologics	Monocolonal antibodies
• Tacrolimus (Crohn; non-FDA) • Cyclosporine (UC; non-FDA)	• Mycophenolate • Azathrioprine (IBD; non-FDA) • Leflunomide (Crohn; non-FDA) • Chlorambucil • Cyclophosphamide • Mercaptopurine (IBD; non-FDA) • Methotrexate (Crohn; non-FDA) • Platinum compounds • Fluorouracil • Dactinomycin	• Sirolimus • Everolimus	• Prednisone (IBD; FDA) • Prednisolone (IBD; FDA) • Budesonide (IBD; FDA) • Dexamethasone (IBD; FDA)	• Abatacept • Adalimumab (IBD; FDA) • Anakinra • Apremilast • Certolizumab (Crohn; FDA) • Etanercept (Crohn; non-FDA) • Golimumab (UC; FDA) • Infliximab (IBD; FDA) • Ixekizumab • Natalizumab (Crohn; FDA; UC; non-FDA) • Rituximab • Secukinumab • Tocilizumab • Ustekinumab (Crohn FDA) • Vedolizumab (IBD; FDA)	• Basiliximab Daclizumab • Muromonab

FDA indicates Food and Drug Administration.

TABLE 3. Summary of Cervical Cancer Screening Recommendations for Non-HIV Immunocompromised Women

Risk group category	Recommendation
Solid organ transplant	-Cytology is recommended if younger than 30 y -Co-testing is preferred, but cytology is acceptable if 30 y or older -If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y -If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y -If transplant before the age of 21 y, begin screening within 1 y of sexual debut -Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age -Screen patients on dialysis and posttransplant similarly
Allogeneic hematopoietic stem cell transplant	-Cytology is recommended if younger than 30 y -Co-testing is preferred, but cytology is acceptable if 30 y or older -If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y -If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y -If transplant before the age of 21 y, begin screening within 1 y of sexual debut -Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age -For HSCT patients who develop a new diagnosis of genital GVHD or chronic GVHD, resume annual cervical cytology until 3 consecutive normal results at which time perform cytology every 3 y, or perform an initial baseline co-test and, if cytology is normal and HPV is negative, perform co-testing every 3 y
Inflammatory bowel disease on immunosuppressant treatments	-Cytology is recommended if younger than 30 y -Co-testing is preferred, but cytology is acceptable if 30 y or older -If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y -If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y -If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut -Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
Inflammatory bowel disease not on immunosuppressant treatments	-Follow general population screening guidelines
Systemic lupus erythematosus and rheumatoid arthritis on immunosuppressant treatments	-Cytology is recommended if younger than 30 y -Co-testing is preferred, but cytology is acceptable if 30 y or older -If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y -If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y -If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut -Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
Rheumatoid arthritis not on immunosuppressive treatments	-Follow general population screening guidelines
Type 1 diabetes mellitus	-Follow general population screening guidelines

(current immunosuppressants are listed in Table 2). Women with RA and IBD not on immunosuppressants and women with DM were considered at no increased risk compared with the general population. Screening recommendations based on these risks are summarized in Table 3.

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