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Updated Review for Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection

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Objective: The purpose of this review was to examine new evidence since our 2019 guidelines for cervical cancer (CC) screening in non-HIV immunocompromised persons and to provide updated recommendations based on literature review and expert opinion. In addition, human papillomavirus (HPV) vaccine efficacy in these populations was reviewed.

Methods: A literature search was performed similar to our previous publication but was conducted through March 2023. Risk of CC, squamous intraepithelial lesions, and HPV infection in those living with solid organ transplant (SOT), end-stage renal disease (ESRD), hematopoietic stem cell transplant (HSCT), and autoimmune diseases (AID), specifically systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) with addition of multiple sclerosis (MS) were researched. This update also summarizes data available on newer disease-modifying therapies (DMTs) including monoclonal antibodies (MABs). We then made recommendations for HPV vaccine administration, and screening using either general population guidelines or increased surveillance, the latter based on following current recommendations for women living with HIV. Additionally, the literature search included antibody response to HPV vaccines and recommendations for their administration for these same conditions.

Results: Based on the reviewed risks, evidence continued to support those persons living with SOT, ESRD, HSCT, and SLE, whether on immunosuppressant therapy or not, had an increased risk of HPV, squamous intraepithelial lesions, and CC whereas there was weak evidence that those persons with IBD, RA, and MS not on immunosuppressants were at risk. Data on persons using DMT/MAB were conflicting. Data showed that patients on certain immunosuppressants had lower antibody titers following HPV vaccination. There were no studies on HPV vaccine efficacy.

Conclusions: Following US Center for Disease Control and Prevention HIV Cervical cancer screening (CCS) guidelines is recommended for the following: SOT, ESRD, HSCT, and SLE whether on immunosuppressants or not, and IBD, RA, and MS on immunosuppressants. Shared decision-making about increased surveillance for IBD and RA not on immunosuppressants and persons on any DMT or MAB is reasonable based on conflicting data. Human papillomavirus vaccination should not change the recommendations for increased CC surveillance. A 3-dose series of the HPV vaccine is recommended for all age-eligible patients starting at 9 years of age, with catch-up to 26 years of age. Vaccination from age 27 up to age 45 years per Advisory Committee on Immunization Practices guidelines should be considered in shared decision-making. When possible, HPV vaccine series should be initiated and completed before SOT or initiation of DMT/MAB. For HSCT, the vaccine series should be readministered along with other childhood vaccines.

Key Words: adult, female, humans, immunocompromised host, mass screening/methods*, middle aged, papillomavirus infections/diagnosis*, practice guidelines as topic, squamous intraepithelial lesions of the cervix/diagnosis*, uterine cervical neoplasms/diagnosis*, young adult

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BACKGROUND

In 2019, we published American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for cervical cancer (CC) screening in immunocompromised women not infected with HIV.[1] Specifically, we evaluated those with solid organ transplant (SOT), hematopoietic stem cell transplant (HSCT), and autoimmune diseases and provided recommendations for CC screening based on literature review and expert opinion. The rationale for the initial manuscript was to fill a gap in guidelines for these women as the US Center for Disease Control and Prevention's (CDC) guideline for CC screening for immunosuppressed women is specific to those living with HIV (see q4)—no other immunosuppressed group is included. As well, there is no international or national consensus on CC screening guidelines for non–HIV-immunosuppressed women.

Immunosuppression increases cervical and other HPV disease though impact varies with type and degree of immunosuppression. For example, SOT and HSCT 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 patients with autoimmune disease is also of interest, both because of the disease pathogenesis and the increasing use of immunomodulatory therapy that may alter immunosurveillance. Based on the initial literature review, the authors concluded whether the risk of CC in the specific population of interest was greater or equal to the general population and if the risk was deemed greater, the recommendations were to follow the current US CDC guidelines for women living with HIV.[2] This existing pattern of increased surveillance/increased screening/enhanced screening was chosen if the condition indicated increased CC risk; there was no numerical risk-based evidence for other intervals and also effort to manage complexity of CC screening recommendations. The objective of this report is to update the review of the literature and to modify our original 2019 guidelines[1] if needed.

In this article, we review additional literature that was either not included or published after the 2019 ASCCP guidelines for

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the risks of CC, squamous intraepithelial lesions (SIL), and human papillomavirus (HPV) among 4 major groups of immunocompromised patients: those with (a) SOTs, (b) HSCT, (c) autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), and new to this review (d) multiple sclerosis (MS). We also discuss the role of newer disease-modifying therapies (DMTs) including monoclonal antibodies (MABs). We then recommend CC screening for each of these groups based on this updated review and expert opinion and we underscore those populations who would or would not benefit from more frequent screening than the general population. Please refer to the original guidelines[1] for the previous literature review. Lastly, we review HPV vaccine immunogenicity in each of these groups.

Of note, the "2019 ASCCP Risk-Based Management Consensus Guidelines,[3]" published 1 year after our 2019 "Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection[1]" aligned with our recommendation to screen all immunosuppressed patients according to the CDC guidelines for opportunistic infections that were published in 2018. In 2023, the original 2019 ASCCP Risk-Based Management Guidelines Committee, representing 19 national organizations, formally voted to endorse the updated 2021 CDC Opportunistic infection guidelines as the screening pattern for immunosuppressed individuals.[3,4] As the CDC document only refers to people living with HIV, this review will add to the evidence related to risks of CC among those living with other immunosuppressive conditions.

Current Recommended Screening Strategies in Healthy Patients

Since the last guidelines, American Cancer Society (ACS) in 2020 updated their recommendations for CC screening in the general population.[5] Primary HPV screening is recommended starting at age 25 years. If negative, 5-year screening intervals are recommended. Alternatively, cotesting or cytology alone can be used with intervals of 5 and 3 years, respectively, also starting at 25 years of age. At the time this manuscript was written, ASCCP, American College of Obstetricians and Gynecologists (ACOG), and US Preventive Services Task Force (USPTF) continued to endorse the previous recommendations starting with cytology at 21 years of age and cotesting and primary HPV at 30 years of age. In part, ACS referenced several publications demonstrating the decrease in HPV vaccine types and abnormal cytology in the United States after the introduction of the HPV vaccine, and rates of girls receiving at least 1 vaccine dose are now above 50% for most states. In addition, ASCCP updated their management of abnormal CC screening tests based on a calculated risk of cervical intraepithelial neoplasia (CIN) 3+ from known databases and prespecified cut-offs for management (ie, close monitoring vs referral to colposcopy vs immediate treatment).[3] Management is also based on knowledge of previous HPV test result when available. Screening intervals and management of abnormal CC screening tests are referred to the 2019 ASCCP guidelines which is a live, working document updated on regular intervals. Both the ACS and ASCCP emphasize that their guidelines are for the general population and not special populations such as the immunocompromised since there are no large databases that allow for risk-based screening or management in these populations. This is also true for the immunocompromised who have received the HPV vaccine since several studies have documented lower antibody titers in this populations.[6,7] The efficacy of the vaccine in these immunosuppressed individuals—whether the vaccine was given before or after diagnosis—remains unknown.

METHODS

The expert panel conducting this updated review consisted of those initially involved in the creation of the 2019 guidelines[1] with the addition of a medical oncologist with knowledge of the new immunosuppressant agents commonly used. Literature searches were performed using 7–10 key words (ie, CC, cervical dysplasia/neoplasia/squamous intraepithelial lesion, human papillomavirus, HPV vaccine, and type of immunosuppression). 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. 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 given limited available data. Consistent with the 2019 guidelines,[1] 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 patients without HIV infection either follow the (1) guidelines for the general population (ie, no strong evidence of increased risk of CIN 3 and CC) or (2) increase the frequency of screening based on the previous guidelines using the CDC guidelines for patients living with HIV (ie, evidence of increased risk of CIN 3 and CC). The latter will be referred to as "following the CDC HIV guidelines.[2]"

We also recognize that the guidelines for patients living with HIV are likely to change based on their increasing healthier status due to advancing therapies. In contrast, the immunosuppression of the non-HIV groups discussed here are primarily immunosuppressed therapeutically or iatrogenically. Consequently, we chose to endorse the current 2024 CDC guidelines even in the case that the HIV guidelines change to less frequent screening.

RESULTS

Solid Organ Transplant Recipients

Fourteen new articles fulfilled the criteria for full review. We also reviewed the literature from 2013 to 2021 to address three new areas: SOT in pediatric patients (2 articles), CC/SIL risk in those with End-Stage Renal Disease (ESRD)/Dialysis (4 articles), and HPV vaccination in female (assigned at birth) SOT patients (5 articles).

Human Papillomavirus. Since our last review, 2 studies confirmed increased HPV prevalence and acquisition of HPV after SOT.[8,9] The larger of the two was a cross-sectional observational study comparing 125 patients with SOTs (68 kidney, 4 kidney and pancreas, 28 liver, 17 lung, and 8 heart) to 132 immunocompetent controls. There was an increased frequency of cervical hrHPV types seen in the SOT recipients (19.4% vs 7.9%, $p = .014$).[9]

Squamous Intraepithelial Lesions. Since 2019, there were 3 additional studies reaffirming the increased risk of SIL in SOT patients.[10–12] Two studies,[10,11] both of which did not stratify types of SOT, showed increased LSIL and HSIL in SOT recipients. The larger cross-sectional study showed that within 5.5 years of transplant, SOT recipients had higher rate of SIL when compared to controls (15% vs 2.4%, $p = .001$).[11] Although no statistical comparisons were made, HSIL alone was noted to be higher as well (5.3% vs 0.8%, respectively).

Reinholdt et al.,[10] specifically examined the age at time of renal transplant and subsequent development of CIN 2,3 within 20 years of transplant compared to randomly selected, age-matched controls from the Danish registry over the time period 1990–2015: 4,261 renal transplant patients and 212,673 control patients.[10] Renal transplant patients had an increased hazard ratio of 2.1 (95% confidence interval [CI] = 1.7–2.8) for CIN 2,3 as compared to controls. When the cumulative incidence of SIL was examined longitudinally, patients <30 years of age at time of transplant had higher incidence

of CIN within 20 years when compared to those who were aged 30–39 at time of transplant (15% [95% CI = 10%–21%] vs 10% [95% CI = 6%–15%]); both groups had greater than the 4%–8% risk of CIN 2,3 when compared to the control group. Those with a functioning renal graft, implying adherence to immunosuppressive medications, had an increased adjusted hazard ratio for CIN 2,3 of 2.3 (95% CI = 1.8–3.0) compared to the control population.[10] Of note, guidelines from the American Society of Transplantation Infectious Diseases Community of Practice stated that every 6-month cytology for 1 year after management of acute rejection, especially with antilymphocyte agents, might be reasonable; no definitive data regarding risk of SIL after treatment of acute rejection was identified.[12]

Cervical cancer. The one additional publication examining rates of CC after an SOT was a large cohort study utilizing nationwide registry data. Renal transplant patients compared to control patients had an increased CC risk (hazard ratio = 2.8; 95% CI = 1.4–5.4).[10] Overall HPV vaccination rates were low at about 2% in both the renal transplant and control groups. [10]

Childhood and Adolescent SOT and Risk of HPV, SIL, CIN, and CC. There have been limited data published on HPV, SIL, and CC risks following SOT in pediatric and adolescent patients. Given the advances in SOT, many childhood SOT recipients have longer life expectancies allowing them to benefit from health screenings. One retrospective study examined posttransplant malignancies in 884 females (assigned at birth) with a renal transplant that occurred between the ages of 0 and 17 years; three with cervical adenocarcinomas (0.3%) during a median follow-up of 19.6 years (interquartile range [IQR] = 9.3–29.8)[13] were identified, which would be higher than expected based on SEER data for the same time period.[14] The second study, based on registry data, showed the incidence rate for CC was 1.7 per 10,000[15] in females (assigned at birth) younger than 18 years old at transplant with a standardized incidence rate ratio (SIR) of 11 (95% CI = 0.3–61.2).[15]

Risk Factors for Abnormal Cervical Cytology Prior to Transplant in ESRD: Risk of HPV, SIL, CIN, and CC in ESRD. Patients with ESRD on dialysis prerenal transplant are another immunosuppressive group with increased risk of HPV, SIL, and CC.[16–19] End-stage renal disease was associated with an increased risk of CC with an incident rate ratio (IRR) of 1.81 (95% CI = 1.01–3.23) compared to controls in a prospective registry dataset.[19] United States registry data showed an additional increased risk of CC the more years with ESRD on dialysis; specifically, the IR of CC in 6 years went from 48.9/100,000 in ESRD patients (general population IR of 7.9/100,000) to an IR in the ESRD population of 117.7/100,000 (general population IR of 7.0/100,000).[17] Another study showed that the odds ratio (OR) for CC increased by 1.18 (95% CI = 1–1.38) for every 10% decrease in estimated glomerular filtration rate (eGFR).[18]

Several risk factors have been associated with increased abnormal cytology and CC in ESRD/dialysis patients including: autoimmune chronic kidney disease (OR = 2.71), age less than 50 years (OR = 1.68), and history of prior kidney transplant (OR = 2.64).[16,18] Lastly, when comparing patients on dialysis to those with a functioning renal transplant, the incident rates (IR) for CC were 55.9 (95% CI = 28.0–112) and 46.3 (95% CI = 17.4–123), respectively, demonstrating that the rates of CC were similar.[19]

Human Papillomavirus Vaccine Immunogenicity

Published studies in both pediatric/adolescent and adult populations with SOTs have no major adverse safety events other than injection site reactions. Seroconversion ranged from 45% to 72% depending upon HPV type, type of transplant, and immunosuppressive medication profile.[20,21] A Belgian study assessed seroconversion following nonavalent HPV vaccine administration in SOT recipients (56 renal, 57 heart, 58 lung) over a 7-month period; the mean age was 42 years, ranging from 18 to 55 years.[20] Overall seroconversion rates for all SOT patients were 64.3% (95% CI = 55.8%–72.2%) for HPV 6, 70.7% (95% CI = 62.7%–77.8%) for HPV 11, 69.1% (95% CI = 61.0%–76.4%) for HPV 16, 51.7% (95% CI = 43.2%–60.2%) for HPV 18, 55.9% (95% CI = 47.6%–64.0%) for HPV 31, 66.9% (95% CI = 58.8%–74.3%) for HPV 33, 46.0% (95% CI = 37.8%–54.3%) for HPV 45, 65.3% (95% CI = 57.1%–72.9%) for HPV 52, and 72.0% (95% CI = 64.1%–79.0%) for HPV 58. Seroconversion rates were lowest in lung SOT recipients likely due to the intensity of the immunosuppressive medication regimen, and those receiving mycophenolate mofetil or tacrolimus.[20] Additionally, seroconversion to at least 1 covered HPV type was higher with the full 3-series vaccine course (76.3%; 95% CI = 62.8%–89.8%) than with 1 or 2 vaccines only (61.7%; 95% CI = 47.8%–75.6%). Other studies have corroborated these differences in seroconversion.[7,21] Immunogenicity of HPV vaccine tended to be lower for vaccination a year or less after SOT compared to more than a year after (OR = 0.21; 95% CI = 0.04%–1.03%).[7] Improvements in immunogenicity with delayed vaccination need to be weighed against risk of new HPV exposure while awaiting vaccination.

In adolescent populations receiving SOTs,[21] seropositivity rates were 100% in the liver transplant recipients and 50%–75% (depending on HPV type) in the kidney transplant recipients; of note, the kidney transplant recipients were on multiple immunosuppressive agents and the liver transplant patients were only on a single agent.[21] Immunogenicity of HPV vaccine has also been compared in adolescents with chronic kidney disease (CKD), dialysis dependence, or kidney transplant[22]; at 12 months postvaccination, antibody response was 100% for all 4 HPV genotypes in the chronic kidney disease/dialysis group, whereas in the transplant patients, seropositivity at 12 months was 62.5% for HPV 6 (p = .02), 50% for HPV 11 (p = .001), 75% for HPV 16 (p = .04), and 50% for HPV 18 (p = .001).[22] Vaccination did not appear to impact the rate of rejection.[22]

One study attempted to evaluate the efficacy of catch-up HPV vaccination for ages 18–26 years to reduce rates of CIN2+ in immunosuppressed individuals (HIV infection, organ transplant recipients, systemic immunosuppressive medication use[23]). Those with 1 or more HPV vaccine doses were compared to those with no HPV vaccination with an relative risk (RR) for CIN2+ of 1.00 (95% CI = 0.71–1.42) and for CIN3+ of 1.02 (95% CI = 0.58–1.80). For nonimmunocompromised individuals, catch-up vaccine reduced CIN 2+ by 19% and in immunosuppressed by 4%.

The American Society of Transplantation Infectious Diseases Community of Practice published vaccination guidelines for SOT recipients.[12,24] Optimally, HPV vaccination should be completed prior to transplantation according to established guidelines for the general population given the reduced immunogenicity following SOT. If the complete series has not been administered prior to SOT, recipients should resume the vaccination schedule 3–6 months posttransplant[24] or initiate it a year posttransplant.[12] Persons of all ages should get a 3-vaccine course.[2,24] Timing for initiation of HPV vaccine after SOT requires balancing improved immunogenicity with delay versus risk of new HPV exposure while waiting.

Summary for HPV, SIL, CIN, and CC Risk in Patients With SOT and ESRD.

This updated review continues to show an elevated risk of HPV, SIL, and CC among patients with SOT and also now includes patients with ESRD on renal dialysis. Recommendations endorse following the CDC HIV guidelines in SOT and ESRD patients. A 3-dose HPV vaccination series should be offered at the recommended ages (ie, age 9 through 26 years with shared decision-making for those age 27 through 45 years). For SOT, HPV vaccine strategies should follow the American Society of Transplantation Infectious Diseases Community of Practice

described above. Solid organ transplant is associated with an increased risk of vulvar, anal, and vaginal cancer in addition to CC. Additionally, ESRD is associated with an increased risk of vulvar cancer.[25] These risks should be considered when providing gynecologic care.

Allogeneic Hematopoietic Stem Cell Transplantation

Two published articles were found to fulfill the criteria for review. There were no new studies of HPV and SIL risk post-HSCT between 2018 and 2022 that fit the criteria for inclusion.

We identified 1 article from 2013 to 2021 evaluating HPV vaccine immunogenicity in female (assigned at birth) HSCT patients, a topic not addressed in our previously published guideline.[1]

Cervical Cancer. A SEER/Medicare-based, retrospective, case-control study of 700 cases with hematologic malignancies and HSCT were matched 1:5 with 3,159 controls who did not undergo HSCT. In addition, a random sample of 5% of noncancer controls were matched to cases 5:1. Outcomes included any HPV-related genital cancers in the cervix, vagina, or vulva combined. Results showed that the proportion of HPV-related precancer or second malignancy was higher in HSCT patients than in noncancer controls (4.8% vs 1.4%, OR = 3.49; 95% CI = 1.69–7.20). Also, while chronic GVHD was included as a covariate, genital chronic GVHD was not available in the dataset and was not included as a covariate in the analysis.[26]

In a Korean study of cancer incidence in allogeneic HSCT patients, 10,354 patients were matched 1:1 with noncancer patients.[27] There was an increased risk of all gynecologic cancers at 10 years (HR = 2.69, 95% CI = 1.04–6.96, p = .041). Limitations of this study included that CC was not separated out from other gynecologic cancers and was not characterized as HPV-related. In addition, GVHD comorbidity was not measured.[27]

Human Papillomavirus Vaccine Immunogenicity. There was 1 study of the safety and immunogenicity of quadrivalent HPV vaccine after allogeneic HSCT in female (assigned at birth) patients ages 18–50 years in a single-arm nonrandomized clinical trial at the National Institutes of Health.[28] Patients and healthy controls received a 3-dose series of quadrivalent HPV vaccine. Assays for anti–HPV 6-, 11-, 16-, and 18-specific antibody levels were drawn prior to vaccination and at 2, 6, 7, and 12 months after receiving the first injection. Results showed that 18 of 23 patients receiving immunosuppression (78.3%), 20 of 21 (95.2%) not receiving immunosuppression, and all 20 healthy volunteers developed antibodies to all the HPV types present in the vaccine (p = .04). At both months 7 and 12, the change in HPV antibody levels from baseline was not significantly different between the 2 posttransplant groups, or between either the posttransplant group or the healthy group (Kruskal-Wallis test; all $p > .05$).

Summary of HPV, SIL CIN, and CC Screening in Patients With History of HSCT. This updated review continues to show an elevated risk of CC among patients with HSCT whether on immunosuppression or not. There was no new information on those with a new diagnosis of genital or chronic GVHD; however, previous data suggested increased risk for HSIL or CC for this group of patients. Recommendations endorse following the CDC HIV guidelines for screening for patients with HSCT and new diagnosis of genital and chronic GVH. A 3-dose HPV vaccination series should be offered at the recommended ages.

Inflammatory Bowel Disease

Nine articles were found to fulfill the criteria for full review. We included 1 article from 2013 evaluating HPV vaccine immunogenicity in female IBD patients, a topic not addressed in our previously published guideline.[1]

Human Papillomavirus. At a hospital-based IBD Clinic in China, HPV detection prevalence in 124 IBD patients (94 with Crohn disease, 30 with ulcerative colitis) was compared to 372 controls.[29] There was no difference in overall HPV positivity between IBD patients and controls [OR = 1.63 (95% CI = 0.87–3.05)], but IBD patients were at increased risk of infection with HPV 16/18 genotypes [OR = 29.0 (95% CI = 3.64–211.0)]. Higher odds of HPV detection were observed in IBD patients on methotrexate [OR = 4.76 (95% CI = 1.47–15.4), p = .005] and in those treated with 3 or more immunosuppressants [OR = 3.64 (95% CI = 1.25–10.6), p = .013].[29]

Squamous Intraepithelial Lesion and Cervical Intraepithelial Neoplasia. In a retrospective cohort study from Australia, compared with controls, 2,683 patients with IBD had higher rates of low-grade cytologic abnormalities [adjusted hazard ratio (AHR) = 1.19 (95% CI = 1.09–1.29)] but no significant difference in high-grade cytologic abnormalities [AHR = 1.12 (95% CI = 0.96–1.29)] or high-grade histology, defined as CIN2+ [AHR = 1.02 (95% CI = 0.85–1.24)]. Use of immunosuppressant medication was not considered in the analysis.[30] In a study of 99 German patients with IBD, only low-grade cytologic abnormalities were significantly more prevalent in 65 IBD patients on immunosuppressive therapy than in 550 healthy controls [OR = 4.96 (95% CI = 2.73–9.02)].[31]

Cervical Cancer. In a retrospective review of national datasets in England, 36,673 patients with CC were identified and, among them, 352 had IBD. Age-standardized rates showed a higher CC rate in patients with IBD (5.2 per 100,000) compared with non-IBD patients (4.6 per 100,000; p = .042). The impact of immunosuppressant medication use was not evaluated.[32]

A population-based study using a South Korean insurance claims database compared CC incidence in 12,632 patients with ulcerative colitis to 36,797 age-matched controls. Although there was no difference in likelihood of CC overall [aHR = 1.56 (95% CI = 0.97–2.50)] with stratification by age, patients ≥60 years old with ulcerative colitis had higher likelihood of CC than controls [aHR = 3.65 (95% CI = 1.54–8.66)]. There was no difference in CC rates among patients with ulcerative colitis associated with the use of immunosuppressive medications.[33]

A multicenter Dutch cohort showed a higher detection rate of CIN2 + (included CC) [standardized detection rate (SDR) = 1.27 (95% CI = 1.05–1.52)] among 2,098 patients with IBD compared with 8,379 age-matched controls as well as a greater risk of developing CIN2+ over the study time [IRR = 1.66 (95% CI = 1.21–2.25)].[34] The individual detection rates for CIN2, CIN3, and CC was due to CIN2 rates alone, and specifically among those aged 35–44 years old. The longitudinal risk over time of developing CIN2+ was due to the combined effect of an increased risk of CIN2 and CIN3 but not of CC. An association was not observed between CIN2+ risk and history of immunomodulator or biologic treatment.[34]

Using the Dutch IBD biobank and a national registry, a retrospective cohort study including 1,318 patients with Crohn disease and 663 with ulcerative colitis found that 99 cases of CIN 2+ were diagnosed over a median follow-up of 17.2 years. There was no association between ever versus never use of the immunosuppressive medications studied and development of CIN2+.[35]

A meta-analysis of 7 cohort studies with 94,144 IBD patients and 53,661,004 controls and 4 case-control studies with 20,267 IBD patients and 60,034 controls published between 2006 and

2019 found no association between IBD and risk of CC [OR/RR = 1.54 (95% CI = 0.83–2.85).[36] A significant association was observed between IBD and risk of noncancerous cervical abnormalities [OR/RR = 2.46 (95% CI = 1.55–3.91)]. There was no analysis by immunosuppressive therapy status.[36]

In a meta-analysis of 5 population-based cohort studies published between 2001 and 2021 including 74,310 patients with IBD and 2,029,087 controls, there was no significant increase in CC risk among IBD patients [HR = 1.24 (95% CI = 0.94–1.63).[37] There was no observed difference in CC risk assessed by IBD type for ulcerative colitis or Crohn disease. Subgroup analysis of the studies that included data on cervical neoplasia showed higher risk of LSIL [HR = 1.15 (95% CI = 1.04–1.28)] but not of HSIL [HR = 1.36 (95% CI = 0.97–1.90)] in those with IBD (Mann 2022).[37]

Human Papillomavirus Vaccine Immunogenicity. We identified one study reporting on immunogenicity of HPV vaccination for patients with IBD on an immunosuppressant medication (tumor necrosis factor [TNF]-alpha inhibitor or immunomodulator) for a minimum of 1 month before enrollment.[38] In the prospective cohort study of 37 females aged 9–26 years with IBD, 33 completed the 3-dose quadrivalent HPV vaccination series with seropositivity of 100% to HPV types 6, 11, and 16, and 94% seropositivity to HPV 18 in testing 2–6 weeks after the final vaccine dose. Geometric mean titer levels were similar to historic controls without IBD.[38]

Summary of HPV, SIL, and CC Risk for Patients With Inflammatory Bowel Disease. This updated review continues to shows an increased risk for HPV and SIL, but conflicting evidence about CC risk in patients with IBD on immunosuppressive therapy. Recommendations endorse following the CDC HIV guidelines for screening in IBD patients on immunosuppressive therapy given the lack of definitive association with CC may reflect more intense screening and treatment of precancer in the populations studied. The evidence on patients not on immunosuppressive therapy is conflicting mostly because studies often lacked immunosuppressive therapy use and no additional recommendations are made than for the general population with an option for shared decision-making. A 3-dose HPV vaccination series should be offered at the recommended ages.

Systemic Lupus Erythematosus

Seven articles were found to fulfill the criteria for review. We included 6 articles from 2013 to 2021 evaluating HPV vaccine immunogenicity in female (assigned at birth) SLE patients.

Human Papillomavirus. In a meta-analysis of 9 cross-sectional studies including 751 patients with SLE and 5,144 controls, cervical HPV detection (pooled prevalence in random effects meta-analysis) in patients with SLE was 34.15% (95% CI = 19.6%–52.5%) compared with 15.3% (95% CI = 0.79%–27.8%) in controls [OR = 2.87 (95% CI = 2.20–3.76), $p < .0001$].[39] There was no difference in HPV detection prevalence among SLE patients by immunosuppressive therapy status. Four studies looked specifically at the impact of azathioprine or cyclophosphamide on HPV detection prevalence in patients with SLE compared with no immunosuppressant and also found no difference.[39]

Squamous Intraepithelial Lesions and Cervical Intraepithelial Neoplasia. In a retrospective cohort study from Australia, 702 patients with SLE or Mixed Connective Tissue Disease (MCTD) were compared to 985,583 female (assigned at birth) controls. Patients with SLE/Mixed Connective Tissue Disease had higher rates of high-grade histology (5.57 vs 3.76 per 1,000 person-years, AHR = 1.47, $p = .033$).[30]

Cervical Cancer. A prospective cohort study from China followed 8,120 patients with autoimmune diseases over 38,727 person-years between January 2006 and April 2015.[40] Patients with SLE had a standardized incidence ratio (SIR) for CC of 5.38 (95% CI = 1.97–11.71).[40] A retrospective cohort analysis of the Korean National Health Insurance Claims database reviewed claims between 2008 and 2014.[41] A total of 21,016 patients with SLE were compared to 105,080 age- and sex-matched controls. The SIR for CC among patients with SLE was 3.09–3.22 (95% CI = 2.30–4.26).[41]

In a systematic review and meta-analysis of prospective studies, 48 cohort studies involving 247,575 patients to assess cancer risk and cancer mortality among SLE patients were included.[42] Among the 20 prospective cohort studies looking at CC risk, the CC risk was higher among patients with SLE (RR = 2.17, 95% CI = 1.53–3.07).[42] This study updates a prior meta-analysis from the same group that included articles that were not restricted to prospective cohort studies. That paper, published in 2018, showed an increased risk of CC among patients with SLE (SIR = 1.56, 95% CI = 1.29–1.88) across 11 included studies.[43] Another systematic review and meta-analysis found a similar increased relative risk of 1.66 (95% CI = 1.16–2.36) for CC across 14 studies and 103,845 participants.[44]

Human Papillomavirus Vaccine Immunogenicity. Multiple small prospective studies have reported satisfactory immunogenicity and safety with the quadrivalent HPV vaccine series (4vHPV) for patients with SLE. Among 16 females aged 12–26 years old with SLE with baseline seronegative status who completed the 3-dose 4vHPV series, seropositivity was >94% for all HPV types in all but 1 subject who had received rituximab during the vaccine series.[45] Another study reported 100% seroconversion for all HPV types after the 3-dose 4vHPV series among 34 participants aged 19–50 years old with minimally active or inactive SLE.[46]

A multicenter prospective study evaluated the 4vHPV vaccine as a 2- ($n = 30$) or 3-dose series ($n = 180$) in 9- to 20-year-old females with SLE. The 2-dose group had 93% seropositivity to HPV 16 and 83% to HPV 18 compared with 97% and 91%, respectively, to HPV 16 and 18 in the 3-dose group. Healthy controls ($n = 35$) received the 3-dose series and had 100% seroconversion to HPV 16 and 18.[47]One study reported on antibody response to a 3-dose 4vHPV vaccine series in 50 patients aged 18–35 years old with stable SLE, most on an immunomodulator, compared with healthy controls.[6] At 7 months after vaccine series initiation, seroconversion from a negative baseline for HPV 16 was 92% for patients with SLE versus 98% for controls ($p = .34$), and for HPV 18 was 76% for patients with SLE versus 93% for controls ($p = .06$).[6] In a follow-up study 5 years later, seropositivity to HPV 16 persisted in 94% and to HPV 18 in 96% in the SLE group compared with 100% ($p = .49$) and 96% ($p = 1.0$) among the control group.[48] A meta-analysis of 6 studies reported pooled seroconversion rates for SLE patients at 7 months after 3-dose HPV vaccine series initiation for HPV 16 as 96.4% (95% CI = 0.93–1.00) and for HPV 18 as 91.8% (95% CI = 0.85–1.00).[49]

Summary of HPV, SIL CIN, and CC Screening in Patients With Systemic Lupus Erythematosus. This updated review continues to show an elevated risk of HPV, SIL, and CC among patients with SLE whether on immunosuppressants

or not. Recommendations endorse following the CDC HIV guidelines for CC screening with or without immunosuppressant use and 3-dose HPV vaccination series should be offered at the recommended ages.

Rheumatoid Arthritis

Three articles published since the 2019 guidelines were found to fulfill the criteria for review. We did not identify any articles evaluating HPV detection risk after the prior guidelines were developed, nor any that investigate vaccine immunogenicity in adult female RA patients. We identified 2 studies that looked at these outcomes among adolescents with Juvenile Idiopathic Arthritis (JIA), which we included as a proxy for a similar disease process in a vaccine-eligible population.

Squamous Intraepithelial Lesions and Cervical Intraepithelial Neoplasia. Two of the studies examined the risk of SIL among women with RA, and found no increased risk. One of the studies was retrospective comparing 1,426 patients with RA to 985,583 female controls.[30] Use of immunosuppressants was not addressed in this study. The second was a prospective cohort study that examined the association of biologic therapy with rates of CIN and found no statistically significant differences in rates of high-grade CIN between patients exposed to biologic Disease-Modifying Therapies (b-DMTs) compared to b-DMT–naive patients (1.3% vs 1.0%, 95% CI = −2–10).[50]

Cervical Cancer. The study referred to above in Chinese patients with autoimmune diseases[40] showed that patients with RA had an SIR of 9.50 (95% CI = 4.91–16.59) for CC. No data were given on use of immunosuppressants.

Human Papillomavirus Vaccine Immunogenicity. Two prospective studies showed safety and immunogenicity of the 3-dose bivalent vaccine among adolescent females with JIA was no different from what was observed among healthy females after 3 doses. The numbers of JIA patients on methotrexate or TNF inhibitors was too small to observe any effect of medication.[51,52] In both studies, there were similar rates of local reactions to the vaccine and no difference in JIA disease progression.

Summary of Risk of HPV, SIL, CIN, and CC Screening in Patients With Rheumatoid Arthritis. This updated review continues to show an increased risk for HPV, SIL, and CC in patients with RA on immunosuppressive therapy. Recommendations endorse following the CDC HIV guidelines for CC screening for patients with RA on immunosuppressive therapy. The data on patients not on immunosuppressive therapy continue to be conflicting but studies often did not include the status of immunosuppressant use and therefore, recommendations are no different than the general population with an option for shared decision-making. A 3-dose HPV vaccination series should be offered at the recommended ages for all patients.

Multiple Sclerosis

We identified 38 articles that examined the relationship between MS and HPV, SIL, and CC. As this topic was not reviewed for the last publication, articles were reviewed beginning in 2000.

Human Papillomavirus. Only 1 study analyzed the risk of HPV in individuals with MS. An analysis of electronic health records at Vanderbilt University demonstrated no impact of MS on the incidence of HPV positivity in a case-control study, although the percentage of those with HPV was extremely low (0.4% of cases vs 0.2% of controls).[53]

Squamous Intraepithelial Lesion and Cervical Intraepithelial Neoplasia. A retrospective observational cohort study in Australia included 1,426 patients with MS.[30] They found no increase in the incidence of SIL, although there were some significant differences between patients with MS and controls, including the number of cytology tests performed. The impact of DMTs was not evaluated. A registry-based cohort study in Sweden compared MS patients on fingolimod, natalizumab, and rituximab to the general population.[54] Although follow-up was only 2–4 years depending upon the cohort, no difference in hazard ratio was seen for natalizumab (1.29; 95% CI = 0.71–2.34) or rituximab (1.15; 95% CI = 0.66–2.02). A numerical, but not statistical, increase was seen in association with fingolimod (1.63; 95% CI = 0.94–2.82), which was similar to the overall risk of developing any cancer while on fingolimod (1.53; 95% CI = 0.98–2.38).

Cervical Cancer. A population-based registry study was performed linking information from the Danish Multiple Sclerosis Register and the Danish Cancer Register.[55] Overall, 1,037 cancers were observed in 11,817 patients with MS. The overall cancer risk, and the risk of CC specifically, were similar between cases and controls (40 cases of CC compared to an expected 36.05 cases; p = 1.11 [0.81–1.41]). Another Danish Registry study also evaluated patients with MS and, among 14,403 patients, demonstrated similar CC risk to that of the general population (SIR = 1.2; 95% CI = 0.9–1.6).[56] Another study examined 1,218 female (assigned at birth) Swedish patients with MS in a case-control series and reported no difference in risk of CC (HR = 0.83; 95% CI = 0.64–1.07) (Bahmanyar 2009).[57] Another Swedish study also found no difference in CC risk between cases and controls (SIR = 0.92; 95% CI = 0.54–1.45).[58] This study also found no difference in the risk of death from CC (HR = 1.81; 95% CI = 0.91–3.62). A linked abstraction of hospital and mortality data from the UK included 2,812 patients with MS.[59] No change in incidence of CC was seen either before the diagnosis (ARR = 0.8; 95% CI = 0.3–1.7) or after the diagnosis (ARR = 1.3; 95% CI = 0.5–2.8) of MS. Three other studies identified no difference in the risk of CC among MS patients compared to the general population.[60–62] Use of DMTs was not included in these studies.

A registry-based study compared 6,949 Norwegian MS patients to 37,922 patients in the general population during the time periods of 1953–1995 (before the introduction of DMTs) and 1996–2017 (after the introduction).[63] The earlier cohort demonstrated a similar incidence rate ratio of both overall cancer (IRR = 1.11; 95% CI = 0.90–1.37) and female (assigned at birth) genital organ cancer (IRR = 0.78; 95% CI = 0.48–1.27). In the latter cohort, the overall incidence rate ratio of cancer was higher among those with MS (IRR = 1.38; 95% CI = 1.28–1.52). The incidence rate ratio for female (assigned at birth) genital organ cancer was also increased (IRR = 1.40; 95% CI = 1.09–1.80). The authors concluded that the use of DMTs increased the risk of cancer among patients with MS. An obvious limitation of this study, however, is that it did not separate out CC from other female (assigned at birth) genital organ cancers—although this would also include other cancers such as vaginal and vulvar cancer, which may also be HPV-related and are rarer than CC. A similar analysis performed evaluated MS patients and matched controls in Ontario, Canada, during the years 1998–2007 and 2008–2017.[64]

Age-standardized incident rates of CC were no different from the general population in either time cohort [1998–2007 (IRR = 0.92 (95% CI = 0.52–1.63)] and 2008–2017 [IRR = 0.84 (95% CI = 0.53–1.33)]. There were no data on the use of DMTs.

HPV Vaccine Immunogenicity

There were no available data on the efficacy of HPV vaccination in patients with MS. In general, inactivated (nonlive) vaccines can be safely administered in patients with MS regardless of their concomitant use of immunologic therapies. Additionally, routine vaccination with inactivated vaccines is not associated with an increase in risk of MS relapse.[65]

Summary of Risk of HPV, SIL, CIN, and CC Screening in Patients With MS. This review on MS is new to the CC screening guidelines on non–HIV-immunosuppressed patients. There is no strong evidence to support that MS alone increases cervical SIL or CC risk. In contrast, immunosuppressant or DMT (see below) does seem to increase the risk, although results are conflicting regarding the risk associated with individual DMTs. The lack of association with CC risk may also be due to the intense screening in patients with MS, which would have led to enhanced detection and treatment of preinvasive lesions. We conclude that MS patients not on immunosuppressive treatment have no greater risk than the general population and those on immunosuppressive treatment may reflect a greater risk of CC than the general population. The recommendation for CC screening of patients with MS on immunosuppressive therapy should follow the CDC HIV CC screening guidelines; the recommendation for patients not on immunosuppressive therapy should follow CC screening guidelines for the general population with an option for shared-decision making. A 3-dose HPV vaccination series should be offered at the recommended ages for all patients.

Disease Modifying Therapies Including Monoclonal Antibodies. The increased use of DMTs in the treatment of autoimmune diseases and hematologic malignancies have improved disease-specific outcomes but can be associated with B-cell depletion, secondary hypogammaglobulinemia via plasma cell depletion, and heightened risk for viral infection. These therapies may also result in T-cell inactivation, cytokine modulation, and altered immunosurveillance of malignancy. Together, these effects could theoretically inhibit HPV viral clearance and promote CC progression (reviewed below in detail). Few publications have adequately addressed these risks, however, and individual study results demonstrate a mixed impact, secondary to methodological flaws. Limitations have included combining patients on different therapies that have varying mechanisms of action and therefore varying risk profiles, inclusion of patients on agents that are no longer in use, inclusion of patients who have changed therapies throughout the study, and short overall follow-up. Additionally, because of the rarity of CC in Western countries, many studies have looked at the combined risk of multiple malignancies including CC. It is therefore impossible to compile a complete list of DMTs or to pinpoint the impact that any individual drug may have on HPV persistence or the development of high-grade cervical neoplasia or CC. What follows is a brief review of the available data.

Disease-Modifying Therapies in General

No studies have specifically addressed the risk of DMTs and HPV infection. Two studies evaluated the risk of progression of cervical neoplasia to cancer in patients receiving DMTs. The first study reported on 951 patients with spondyloarthritis followed for 9.2 ± 5.9 years, 34 of whom developed cervical neoplasia (including both SIL and CC).[66] Neither the risk of developing cervical neoplasia nor the risk of progression of SIL to CC were related to the use of conventional or biologic DMTs. The second study reported on 806 Danish patients with inflammatory arthritis (RA, ankylosing spondylitis, psoriatic arthritis, or other) who also had a history of cervical neoplasia.[67] None of the patients experienced progression to CC, including those on DMTs. The authors believed that their data were limited by short follow-up and small numbers, concluding that larger numbers of patients and longer follow-up are required to assess the risk associated with DMTs.

Several publications reported on the CC risk associated with unspecified DMTs or classes of DMTs. A national Swedish registry-based cohort study of patients with SLE treated with either immunosuppressive DMTs or antimalarials found an increase in cervical neoplasia and CC in the cohort receiving immunosuppressants (HR = 1.83; 95% CI = 1.15–2.91), but no increase in CIN 2+ (HR = 1.44; 95% CI = 0.82–2.54).[68] All 5 cases of invasive CC occurred in the immunosuppressants cohort, thus statistical evaluation was not performed. Among 341,758 Danish patients with various autoimmune disorders reported that the use of antimetabolites, systemic corticosteroids, or immunosuppressants, other than azathioprine, were not associated with the risk of CC.[56] Treatment with a cumulative high dose of azathioprine (>300 mg defined daily doses) was associated with a hazard ratio of 2.2 (95% CI = 1.2–3.9). Of note, this analysis included patients during the period of 1995–2010, which likely did not include many of the drugs currently used to treat patients with autoimmune disorders. A cohort study of greater than 400,000 patients with RA treated with either biologic or nonbiologic DMTs identified 22,267 matched pairs.[69] Ninety-two percent of patients treated with a biologic DMT received a TNF inhibitor, most commonly etanercept. The most common nonbiologic DMT was methotrexate. Mean duration of treatment ranged from 1 to 2 years. The authors concluded that treatment with a biologic DMT was associated with a "numerically significant, but not statistically significant, increase in the risk of high-grade cervical neoplasia or CC" compared to treatment with a nonbiologic DMT. Short duration of treatment, however, limits the ability to draw conclusions from this study.

Another study identified 238 subjects with a history of previously treated HSIL among 11,738 patients with RA treated with either a nonbiologic DMT (48/2654) or a TNF inhibitor (190/9084).[70] Only 2 incident female genital cancers were reported during follow-up: 1 case each of metastatic squamous cell carcinoma of the vulva and metastatic CC, both in the nonbiologic DMT cohort. In each case, cervical SIL had occurred 13 years prior to the development of the incident cancer. The authors stated that a limitation of the study was the lack of power to detect a clinically important difference in cancer risk between cohorts. A Swedish nationwide register-based cohort study by Wadström et al. included 9,629 patients with RA beginning TNF inhibitor, 34,984 biologics-naïve patients with RA, and 300,331 general-population controls.[71] Patients were followed for up to 13 years. Compared to the biologics-naïve cohort, the TNF inhibitor cohort had a higher rate of CIN 2+ (HR = 1.36; 95% CI = 1.01–1.82) and a doubled risk of invasive CC (HR = 2.10; 95% CI = 1.04–4.32).

Summary of Risk of HPV, SIL, CIN, and CC Screening in Patients on DMTs. Data regarding CC risk associated with individual DMTs are limited and often contradictory. Limitations of the available data include short time of follow-up, limited number of patients, and the confounding caused by switching from one medication to another during study periods. In addition,

TABLE 1. Summary of Cervical Cancer Screening and Vaccination Recommendations

	General-population cervical cancer screening	Increased screening[a] with immunosuppressant use	Increased screening[a] regardless of immunosuppressant use	HPV vaccination[b]
Solid organ transplant			X	X
End-stage renal disease			X	X
Hematopoietic stem cell transplant[c]			X	X
Systemic lupus erythematosus			X	X
Rheumatoid arthritis	X[d]	X		X
Inflammatory bowel disease	X[d]	X		X
Multiple sclerosis	X[d]	X		X
Disease-modifying therapies or monoclonal antibodies	X[e]	X[e]		X

[a]Increased screening recommendations are noted on Table 2.

[b]Human papillomavirus (HPV) vaccination ages per ACIP recommendations, starting at age 9 and extending up to age 26, with an option to vaccinate up to age 45 with shared decision-making. Recommend a 3-vaccine course in immunosuppressed adolescents rather than a 2-vaccine series. For solid organ transplant (SOT) candidates, administer HPV vaccination before the transplant when possible. See SOT section for further recommendations regarding vaccination around time of SOT. If HPV vaccination was given before hematopoietic stem cell transplantation (HSCT), the vaccine series should be restarted and can be administered up to age 45, following ACIP guidelines.

[c]Exceptions for HSCT recipients: if graft versus host disease develops, test cervical cytology annually until 3 consecutive normal results at which time perform cytology every 3 years. Alternatively, if aged 30 years or more, perform cotest at diagnosis and if cytology is normal and HPV is negative, perform cotesting every 3 years.

[d]Due to lack of data, shared decision-making about increased screening is reasonable for women with inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and multiple sclerosis not on chronic immunosuppressant medication.

[e]Shared decision-making about increased screening should also be implemented for any women on DMT/MAB.

most of the women were followed very closely, hence early diagnosis and treatment of precancers may have masked the increased risk in CC. In many instances, recommendations are based on extrapolation from the risk associated with other viral infections such as herpes and hepatitis. Given the uncertainty of the risk associated with exposure to any individual DMT, we conclude that the evidence is insufficient to make a recommendation so shared decision-making is needed to individualize screening.

DMTs, MAB, and HPV Vaccine Immunogencity. Healthy plasma cells are an integral component of humoral immunity and the production of serum antibodies following vaccination. No data are available for the impact of DMTs or MAB on HPV vaccination specifically. In a limited study[72] of 30 patients with relapsed refractory multiple myeloma, there were no differences in antigen-specific antibody responses to *Streptococcus pneumoniae* and *Haemophilus influenzae* type B vaccinations between those who were daratumumab-naïve (55.6% and 62.5%, respectively) versus daratumumab-treated (68.8% and 66.7%, respectively; $p = .509$ and $p = .842$). In contrast, another study showed higher rates of nonresponse to pneumococcal polysaccharide vaccine (OR = 9.51 [95% CI = 2.68–33.80]. Another group administered vaccines to 102 patients with relapsing MS randomized to receive either ocrelizumab, interferon B, or no DMT.[73] Exposure to ocrelizumab attenuated the response to tetanus toxoid-containing vaccine and 23-valent pneumococcal polysaccharide vaccine.

In a study evaluating humoral response to COVID-19 vaccination in 912 Sardinian MS patients on various DMTs, those treated with natalizumab, teriflunomide, azathioprine, fingolimod, ocrelizumab, and rituximab showed significantly lower response compared to untreated controls.[74] No differences in response were seen for those treated with dimethyl fumarate, interferon, alemtuzumab, or glatiramer acetate. In a separate study evaluating humor response 1 month after the second dose of COVID-19 vaccine in 140 patients on a variety of DMTs, all patients treated with first-line DMTs (natalizumab, cladribine, alemtuzumab) developed a measurable humoral response.[75] Among patients treated with ocrelizumab and fingolimod, the immune response was significantly lower and some failed to develop a measurable response. Time from last DMT infusion to vaccination was positively correlated with immune response. There were no significant side effects to vaccination regardless of DMT exposure.

Summary of HPV Vaccine Immunogenity and DMTs/MAB.. The impact of these therapies on patients previously vaccinated against HPV is unknown. In Australia, a 3-dose regimen of an HPV vaccine is recommended for immunocompromised patients of any age, including those on immunotherapies.[76] A 3-dose series of the HPV vaccine is recommended for all patients on DMTs at the recommended ages. If this can be performed prior to starting a DMT, this would be ideal.

Limitations

There are many limitations as pointed out in each section. The limitations include publications with small sample sizes, lack of inclusion of type of immunosuppressive therapies, short follow-up periods, and lack of histologic endpoints.

Summary of recommendations for each group reviewed is listed in Table 1. These summaries took into account the increased risk of cervical precancers and cancers for women living with SOT, HSCT, and SLE, hence the recommendations for enhanced screening frequency. It was also felt that there was both a theoretical risk as well as some evidence in the literature for any immunosuppressant use including DMT/MABs increasing risk for patients with RA, IBD, and MS, hence the recommendation for enhanced screening frequency in this group as well. The literature on RA, IBD, and MS not on immunosuppressants was very limited because the use of immunosuppressants were not always available. However, overall there did not appear to be an increased risk; therefore,

we recommended following the guidelines for general populations with the caveat that shared decision-making for those with RA, IBD, and MS not on immunosuppressants is also appropriate. This was also true for all patients on any DMT or MABS since the literature for all other disease was scant. Given the theoretical risks and conflicting data, any women on DMT or MABS should have shared decision-making regarding screening frequency. We also emphasize that the CDC HIV CC guidelines include enhanced screening through the woman's lifetime as defined in Table 2. Human papillomavirus vaccination at the CDC target age should not change the recommendations for increased CC screening surveillance. Data identify an increased risk of vulvar cancer in SOT and ESRD, and this risk may extend to other immunocompromised groups[25] covered by this guideline, though studies are lacking. Potential for vulvar cancer should be considered during gynecologic care.

Nuances for Those Living With an HSCT

It is recommended that if an individual is being screened with cytology only and develops genital GVHD, the screening return to annual cytology for 3 consecutive screenings and, if normal, thereafter every 3 years for cytology screening. If being screened with cotesting, and no test was performed in the last year, a repeat with cotesting should be performed.

HPV Vaccine Recommendations. A 3-dose series of the HPV vaccine is recommended for all age-eligible patients described above. As with the general population, vaccination at early ages is more likely to prevent HPV-related morbidity and mortality. Routinely vaccinating young patients, starting at 9 years of age, is recommended with catch-up to 26 years of age. Vaccination

TABLE 2. Recommendations[1] for Cervical Cancer Screening for Patients With HIV in the United States

Patients living with HIV aged <30 y
- Screening is recommended to start at the age 21 y
- Patients living with HIV aged 21–29 y should have a cytology test after initial diagnosis.
- Cytology test should be performed at baseline and every 12 mo (BII).
- If results of 3 consecutive cytology tests are normal, follow-up cytology tests can be performed every 3 y (BII)
- Cotesting (cytology test and HPV test) is not recommended for patients younger than 30 y.
- If ASCUS/HPV+ or LSIL or worse is found, referral to colposcopy is recommended (AII)
- If HPV-negative ASCUS or ASCUS with no HPV test, repeat cytology test in 6–12 mo. (AII)
- Refer to colposcopy if repeat abnormal (AII)

Patients living with HIV aged ≥30 y cytology testing only
- After initial HIV diagnosis, cytology test should be performed at baseline and every 12 mo (BII).
- If results of 3 consecutive cytology tests are normal, follow-up cytology tests can be performed every 3 y (BII).
- Follow-up of abnormal test as for <30 y

Or

Cytology test and HPV cotesting:
- After initial HIV diagnosis, cytology test and HPV cotesting should be performed at baseline (BII).
- If result of the cytology test is normal and HPV cotesting is negative, follow-up cytology test and HPV cotesting can be performed every 3 y (BII).
- If the result of the cytology test is normal but HPV cotesting is positive:

Either
- Follow-up test with cytology test and HPV cotesting should be performed in 1 y.
- If the 1-y follow-up cytology test is abnormal or HPV cotesting 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 cotest in 1 y is recommended. If the follow-up HPV test is positive or cytology test is abnormal, colposcopy is recommended.

Or

Cytology test and HPV 16 or HPV 16/18 specified in cotesting:
- Perform HPV genotyping.
- If positive for HPV 16 or HPV 18, colposcopy is recommended.
- If negative for HPV 16 and HPV 18, repeat cotest in 1 y is recommended. If the follow-up HPV test is positive or cytology test is abnormal, colposcopy is recommended.

Or

Cytology test and HPV 16 or HPV 16/18 specified in cotesting:
- After initial HIV diagnosis, cytology test and HPV 16 or 16/18 cotesting should be performed at baseline (BII).
- If result of the cytology test is normal and HPV 16 or 16/18 cotesting is negative,

follow-up cytology test and HPV cotesting can be performed every 3 y (BII).

*If initial test or followup test is positive for HPV 16 or 16/18, referral to colposcopy is recommended (BII).

Screening is currently recommended through a patient's lifetime with discontinuation based on shared decision-making and quality of life.

ASCUS indicates atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

from age 27 up to age 45 years as approved in the ACIP guidelines should be considered in shared decision-making.

For SOT, when possible, HPV vaccine series should be initiated and completed before the SOT. If complete vaccination is not possible pretransplant, 1 dose should ideally be administered pretransplant, and the series should be resumed 6 months after SOT. Risk of acquiring HPV versus deferring HPV vaccination should be taken into account.

For HSCT, if the HSCT occurred after the HPV vaccine was administered, the vaccine series should be readministered up to age 45 years as approved in the ACIP guidelines.

For DMT/MCA, the HPV vaccine series should be initiated before starting treatment when possible.

Clinical and Public Health Implications

Key clinical implications include the need for more frequent screenings at an earlier onset, enhanced HPV vaccination monitoring, and interdisciplinary collaboration among health care providers. Public health considerations involve allocating resources for timely screenings, tracking vaccination outcomes, addressing health disparities through customized screening initiatives for varied communities, and ensuring access to specialized care to facilitate management of abnormal cells. Overall, improving CC outcomes in this specific population requires a comprehensive approach that combines clinical care among gynecologists, primary care providers, oncologists, pediatricians, and immunologists with culturally proactive public health strategies.

Future Directions

As immunosuppressants become less toxic and more personalized, it will be critical to continue to examine the literature. Large databases or registries that are able to collect data on specific immunosuppressant agents and HPV vaccination histories are most likely to contribute to solid evidence for CC risk.

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