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Human Immunodeficiency Virus (HIV)– and Non-HIV–Associated Immunosuppression and Risk of Cervical Neoplasia

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OBJECTIVE: To estimate the risk of cervical intraepithelial neoplasia grade 2, 2–3, 3, adenocarcinoma in situ, or cancer (CIN 2 or worse) among women with human immunodeficiency virus (HIV)– and non-HIV–associated immunosuppression.

METHODS: We performed a case–control study of 20,146 women with incident CIN 2 or worse and 5:1 age-matched, incidence-density selected women in a control group (n=100,144) enrolled in an integrated health care system from 1996 to 2014. Adjusted rate ratios (RRs) from conditional logistic regression were obtained for HIV status (stratified by CD4$^+$ T-cells), solid organ transplant history, and immunosuppressive medication use.

RESULTS: Risk of CIN 2 or worse was increased among women with HIV (n=36 women in the case group and 79 women in the control group; adjusted RR 2.0, 95% CI 1.3–3.0) compared with those without HIV and in solid organ transplant recipients (n=51 women in the case group and 68 women in the control group; RR 3.3, 95% CI 2.3–4.8) compared with women without a prior transplant. The highest risks were among women with HIV and less than 200 CD4$^+$ T-cells/microliter (n=9 women in the case group and eight women in the control group; RR 5.6, 95% CI 2.1–14.7) compared with those without HIV and in solid organ transplant recipients prescribed three or greater immunosuppressive medication classes (n=32 women in the case group and 33 women in the control group; RR 4.1, 95% CI 2.5–6.8) compared with women without a prior transplant and zero medication classes. No increased risks were observed for women with HIV and 500 or greater CD4$^+$ T-cells/microliter (n=9 women in the case group and 43 women in the control group; RR 0.8, 95% CI 0.4–1.7) compared with those without HIV or women without prior solid organ transplantation prescribed two or fewer immunosuppressive medication classes (n=1,262 women in the case group and 6,100 women in the control group; RR 0.95, 95% CI 0.89–1.01) compared with women without and a prior transplant and zero medication classes.

CONCLUSION: Risk of CIN 2 or worse is increased in women with a prior solid organ transplant or who have HIV and CD4$^+$ cells/microliter less than 500 but not in women with HIV and higher CD4$^+$ levels or in women without a prior solid organ transplant but who are prescribed only one or two immunosuppressive medication classes.

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Each author has indicated that he or she has met the journal's requirements for authorship.

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Cervical cancer screening guidelines by the American College of Obstetricians and Gynecologists (ACOG)[1] and others[2] recommend more intensive screening of all women with human immunodeficiency

virus (HIV) as a result of known increased risks of cervical neoplasia and cancer.[3] ACOG also recommends an intensive screening approach for women immunocompromised because of non-HIV causes, but acknowledges that limited direct evidence exists to guide cervical cancer screening in these women.

Key questions remain regarding cervical cancer screening among immunosuppressed women. First, it is unclear whether intensive screening is still indicated for all women with HIV given current practice of immediate initiation of antiretroviral therapy.[4] Second, non-HIV immunosuppression is broadly defined and often refers to immunosuppressive medications prescribed for a wide variety of health conditions, including solid organ transplantation, systemic lupus erythematosus, and inflammatory bowel disease. Although a few studies have indicated increased cervical neoplasia risk in these settings,[5–10] the number of classes of immunosuppressive medications has grown substantially over the past three decades and indications for their use have expanded.[11] Thus, additional research is needed to clarify which sources of immunosuppression should prompt more intensive screening.

We sought to estimate the effect of immunosuppression on risk of cervical neoplasia or cancer, including associations with HIV (stratified by $CD4^+$ T-cells), solid organ transplantation, and immunosuppressive medications (stratified by class and number prescribed). We hypothesized that the higher risk of cervical neoplasia would be limited to subsets of immunosuppressed women.

MATERIALS AND METHODS

The study was conducted among women enrolled in Kaiser Permanente Northern California, a large integrated health care delivery system providing comprehensive care for more than 3.9 million members representing 28% of insured Californians in the greater San Francisco Bay area.[12] We used a nested case–control study design with cases defined as all women with a new diagnosis of cervical intraepithelial neoplasia grade 2, 2–3, 3, adenocarcinoma in situ, or cancer (CIN 2 or worse) and controls sampled from women without CIN 2 or worse at the time when each case occurred (ie, incidence density sampling). The source population for selection of both women in the case group and those in the control group included 2,142,687 women who had cytology between January 1995 and June 2014 (Fig. 1). After study exclusions (Fig. 1), the final case group included 20,146 women with CIN 2 or worse with an incident CIN 2 or worse event between July 1996 (to ensure 18 months or

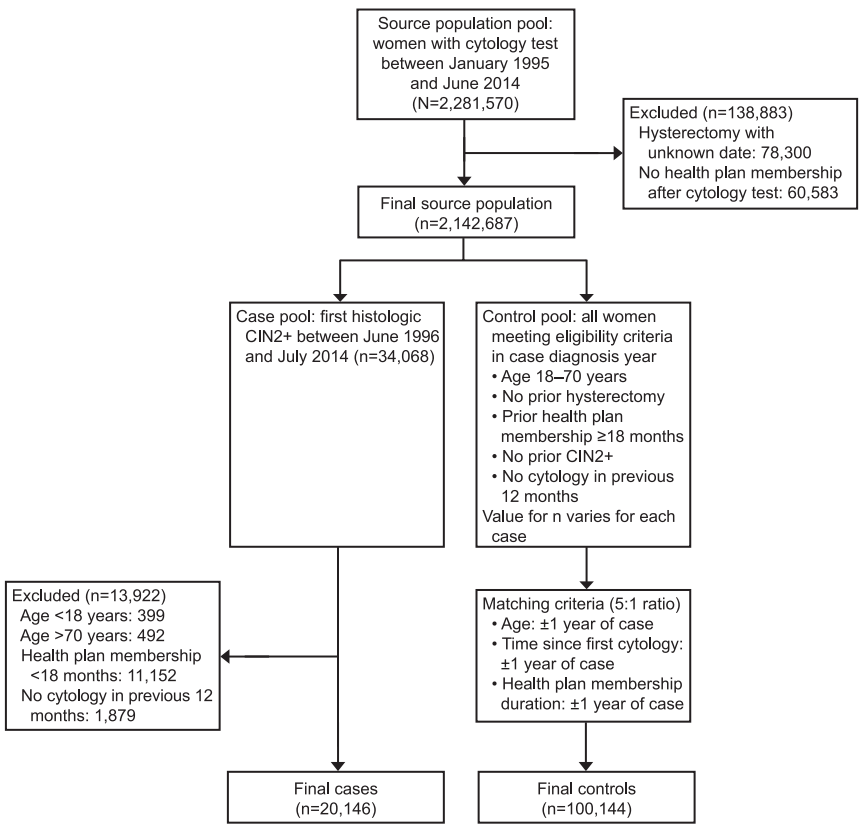

Fig. 1. The figure displays the selection of the overall source population, the case pool, and the control pool and the final case and control participants. Exclusions are shown for the case group, whereas this information varied for the control group because a separate control pool was assembled for each of 20,146 women in the case group. CIN, cervical intraepithelial neoplasia.

Silverberg. Immunosuppression and Risk of CIN. Obstet Gynecol 2018.

greater to identify incident events) and June 2014. Next, we randomly selected five women in a control group per woman in the case group meeting the same eligibility as women in the case group and frequency-matched by age (within 1 year), time since first cytology in the health system (within 1 year), and years of continuous prior health plan membership (within 1 year). The 5:1 ratio was based on a priori power calculations, which indicated 80% power to detect an odds ratio of 1.8 or greater with a hypothetical exposure prevalence of 0.1% among women in the control group, which is consistent with the observed exposure prevalence. Note that a biopsy was only required for women in the case group; women in the control group may have had no need for biopsy or a biopsy with less than CIN 2 or worse.

Although a cohort study design was a viable alternative approach, we used the nested case–control design to enhance computational efficiency (a cohort study would have involved a multivariable analysis of greater than 2,000,000 women) and to allow for precise matching of risk factors between women in the case group and those in the control group (a cohort study would need to primarily rely on analytical adjustment). The choice of study design is anticipated to have minimal effect on statistical power, because the same number of cases would contribute to both designs.

The primary data source for the current study was the electronic medical record with comprehensive clinical and administrative data available since 1995, including inpatient and outpatient medical encounters, pharmacy, laboratory, procedure, health plan membership, and demographic information, all of which can be linked by a unique medical record number.

Histopathology results of cervical biopsies were ascertained by Systematized Nomenclature of Medicine topology (ie, cervix) and morphology codes. Next, text-based natural language processing of the corresponding pathology reports was used to assign the exact dysplasia diagnosis (eg, CIN 2, CIN 3). In a validation study of 162 women, this approach correctly coded 161 women (99.3%) as CIN 2 or worse and correctly coded the exact category in 154 women (96%). Cancer diagnoses were ascertained from the Surveillance, Epidemiology, and End Results-based Kaiser Permanente Northern California cancer registry.

The Kaiser Permanente Northern California HIV registry[13] includes all known cases of HIV infection dating to the early 1980s with HIV infection confirmed by chart review. The registry maintains data on HIV transmission risk factors, dates of known HIV infection, acquired immunodeficiency syndrome diagnoses, and complete HIV-related laboratory values and pharmacy data. For analyses, we ascertained the most recent (within 18 months) CD4 test result before the index date.

From pharmacy records, we ascertained recent (ie, within the past 18 months) use of 17 immunosuppressive medication drug classes: 1) corticosteroids or glucocorticoids, 2) antiproliferative agents, 3) calcineurin inhibitors, 4) tumor necrosis factor inhibitors, 5) folate antimetabolites, 6) cytotoxic agents, 7) mTOR inhibitors, 8) antilymphocyte antibodies, 9) interleukin-1 receptor antagonists, 10) interleukin-2 receptor antagonists, 11) fusion proteins, 12) alkylating agents, 13) proteasome inhibitors, 14) immunomodulator agents, 15) immunomodulatory derivatives of thalidomide, 16) small molecule inhibitors, and 17) monoclonal antibodies. Only the first six more common medication classes were analyzed individually; medication classes 7 through 17 were analyzed together as "other immunosuppressive medications." We only considered nontopical medications, except for two calcineurin inhibitors, pimecrolimus and tacrolimus, given their high potency; however, no patients had evidence of exposure to pimecrolimus and exposure to tacrolimus was rare. We did not ascertain the clinical diagnoses associated with medication use, except for solid organ transplantation, which is specifically cited by ACOG[1] as a source of non-HIV–related immunosuppression. Similar to prior studies,[14] solid organ transplantation was defined as women having two or more diagnosis or procedure codes at any time before the index.

Clinical CIN risk factors included a recent (within 18 months) history of smoking and high parity (ie, three or more live births). We also identified factors potentially associated with increased screening frequency, including number of recent outpatient visits and race and ethnicity. Finally, factors that were both clinical risk factors and associated with screening frequency included recently documented sexually transmitted infections (STIs; herpes, gonorrhea, syphilis, and chlamydia), prior human papillomavirus vaccination, and recent use of hormone therapy or oral contraceptives. With the exception of race and ethnicity, these factors were considered present if documented in the medical record and not present otherwise, because lack of such diagnoses was not routinely recorded. Thus, there was no missing information for these variables. For race and ethnicity, we created a separate unknown category, although most (97% of women in the case group and 94% of those in the control group) had known race and ethnicity. The institutional review board at Kaiser

Permanente approved this study with a waiver of written informed consent.

Human immunodeficiency virus–associated immunosuppression was analyzed as 1) women with HIV compared with those without HIV and 2) women with HIV stratified by recent $CD4^+$ T-cell levels compared with those without HIV. $CD4^+$ T-cell counts were stratified as less than 200, 200–499, and 500 or greater cells/microliter and ranged from a low of 7 to a high of 1,861 cells/microliter. Non-HIV–associated immunosuppression was analyzed as 1) any prescription of immunosuppressive medications compared with no prescription; 2) number of immunosuppressive medication classes: zero (reference), one, two, or three or greater; 3) any solid organ transplantation compared with no transplantation; 4) a combined variable of transplantation and number of immunosuppressive medication classes; and 5) individual medication class prescribed compared with no prescription of that medication class. Bivariate and multivariable conditional logistic regression was used to estimate odds ratios, which represents unbiased estimates of rate ratios (RRs) in a nested case–control study with incidence density sampling.[15] Cervical intraepithelial neoplasia 2 and CIN 2–3 represent key clinical events that often prompt treatment; CIN 3 is considered a true precursor for cancer, although it is much less common. Thus, we evaluated CIN 2 or worse as the primary outcome and CIN 3 or worse as a secondary outcome. Adjusted models included terms for: recent smoking (yes or no); recent hormone therapy or oral contraceptives (yes or no); race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other, unknown); recent STIs (yes or no); any prior human papillomavirus vaccination (yes or no); three or more live births (yes or no); and prior outpatient visits (continuous). All analyses were conducted using the logistic procedure in SAS 9.3.

RESULTS

The study population included 20,146 women with CIN 2 or worse (cases) and 100,144 women in the control group. Among women in the case group, 19,580 cases (97.2%) had five matched women in the control group, 548 women in the case group (2.7%) had four matched women in the control group, 17 women in the case group (0.1%) had three matched women in the control group, and one woman in the case group (0.0%) had one matched woman in the control group. Some women in the control group (n=6,848) matched to more than one woman in the case group, and other women in the control group (n=1,034) became cases at a later date. Women in the case group were more likely than women in the control group to be recent smokers and hormonal therapy or oral contraceptive users and had a higher prevalence of recent STIs, three or more live births, and a lower percentage with prior human papillomavirus vaccination (Table 1). Of 20,146 women with CIN 2 or worse, 10,109 (50%) had CIN 3, and 646 (3%) had cancer (Table 2).

Among women in the case group and those in the control group, 36 (0.2%) and 79 (0.1%) women ($P<.001$), respectively, had HIV (Table 3). In unadjusted analyses, the higher risk of CIN 2 or worse among women with HIV compared with those without HIV was seen in women with 200–499 $CD4^+$ T-cells/microliter ($P<.001$) and less than 200 $CD4^+$ T-cells/microliter ($P<.001$), but not those with 500 or greater $CD4^+$ T-cells/microliter ($P=.56$). Prior solid organ transplantation was present in 51 (0.3%) women in the case group (34 kidney, eight liver, seven lung, two heart) and 68 (0.1%; $P<.001$) women in the control group (56 kidney, nine liver, one lung, two heart), and the transplant occurred at a mean of 5.6 years and 6.1 years before the index for women in the case group and those in the control group, respectively. Recent immunosuppressive medication prescriptions were common with 1,370 (6.8%) and 6,353 (6.3%) of women in the case group and those in the control group recently exposed ($P=.013$). The most common immunosuppressive medication class was corticosteroids with 5.9% and 5.6%, of women in the case group and those in the control group exposed ($P=.08$). Women with CIN 2 or worse had a higher prevalence of antiproliferative agents ($P<.001$), calcineurin inhibitors ($P<.001$), folate antimetabolites ($P=.015$), and cytotoxic agents ($P=.003$). Finally, women in the case group had a higher prevalence of two (0.4% compared with 0.3%; $P=.004$) or three or greater (0.5% compared with 0.2%; $P<.001$) immunosuppressive medication classes compared with women in the control group.

In adjusted models, women with HIV were at overall increased risk for CIN 2 or worse compared with those without HIV (RR 2.0, 95% CI 1.3–3.0; Fig. 2). A significant elevated CIN 2 or worse risk by HIV status was also observed for women with HIV and 200–499 $CD4^+$ T-cells/microliter (RR 3.0, 95% CI 1.6–5.5) and less than 200 cells/microliter (RR 5.6, 95% CI 2.1–14.7), but not for those with 500 or greater $CD4^+$ T-cells/microliter (RR 0.8, 95% CI 0.4–1.7; Fig. 2). The magnitudes of RRs for HIV immunosuppression were similar for CIN 3 or worse (Appendices 1 and 2, available online at http://links.lww.com/AOG/B37).

Table 1. Baseline Characteristics, Women With Cervical Intraepithelial Neoplasia and Matched Women in a Control Group, Kaiser Permanente, 1996–2014

Characteristic	Women in the Case Group (n=20,146)	Women in the Control Group* (n=100,144)
Age† (y)	35.6±11.3	35.6±11.3
Years of prior health plan membership†	6.4±4.4	6.6±4.5
Index year†		
1996–2000	3,725 (18.5)	18,540 (18.5)
2001–2005	4,718 (23.4)	23,424 (23.4)
2006–2010	7,033 (34.9)	34,957 (34.9)
2011–2014	4,670 (23.2)	23,223 (23.2)
Outpatient visits/y	7.6±6.1	7.1±5.5
Race and ethnicity		
Non-Hispanic white	10,452 (51.9)	46,206 (46.1)
Non-Hispanic black	1,642 (8.2)	8,522 (8.5)
Hispanic	3,881 (19.3)	20,035 (20.0)
Other	3,546 (17.6)	19,660 (19.6)
Unknown	625 (3.1)	5,721 (5.7)
Smoking		
Recent‡	3,925 (19.5)	12,660 (12.6)
Ever	5,555 (27.6)	20,445 (20.4)
Hormonal therapy or oral contraceptive use		
Recent‡	9,937 (49.3)	43,660 (43.6)
Ever	14,020 (69.6)	66,352 (66.3)
Sexually transmitted infection§		
Recent‡	719 (3.6)	2,132 (2.1)
Ever	2,193 (10.9)	7,125 (7.1)
3 or more live births	2,135 (10.6)	9,928 (9.9)
Any prior HPV vaccination among all patients	433 (2.2)	2,433 (2.4)
Any prior HPV vaccination among eligible‖ patients	429 (9.9)	2,408 (11.1)

HPV, human papillomavirus.
Data are mean±SD or n (%).
* $P<.05$ for all variables comparing women in the case group and those in the control group based on bivariate conditional logistic regression models. Not computed for matching variables.
† Matching variable.
‡ Within 18 months before index.
§ Herpes, gonorrhea, syphilis, chlamydia.
‖ Index date in 2006 or later and age 26 years or younger as of January 1, 2006; N=4,357 women in the case group and 21,773 women in the control group.

For non-HIV immunosuppression, prior transplantation conferred a threefold higher risk (RR 3.3, 95% CI 2.3–4.8; Fig. 2). Whereas any recent immunosuppressive medication prescription was not associated with CIN 2 or worse, we observed an increasing risk as the number of medication classes increased (Fig. 2): RR 0.9 (95% CI 0.9–1.0), RR 1.2 (95% CI 1.0–1.5), and RR 1.7 (95% CI 1.3–2.2) for those with one, two, and three or greater recent medication classes prescribed, respectively, compared with no immunosuppressive medication prescribed. In unadjusted models (Table 3), an increased risk was observed for women with no prior transplantation who were prescribed three or greater classes (RR 1.5, 95% CI 1.2–2.1) compared with women with no prior transplantation or immunosuppressive medication prescriptions; the corresponding results were not statistically significant in adjusted models (Fig. 2). For transplant recipients, RRs ranged from 1.9 (95% CI 0.7–5.3) for those without immunosuppressive medications prescribed to 4.1

Table 2. Histologic Diagnostic Category of Cervical Intraepithelial Neoplasia Grade 2 or Worse Cases, Kaiser Permanente, 1996–2014 (n=20,146)

Category	n (%)
CIN 2	3,463 (17.2)
CIN 2–3	5,408 (26.8)
CIN 3	10,109 (50.2)
Adenocarcinoma in situ	520 (2.6)
Adenocarcinoma	243 (1.2)
Squamous cell carcinoma	379 (1.9)
Other cancer	24 (0.1)

CIN, cervical intraepithelial neoplasia.

Table 3. Human Immunodeficiency Virus (HIV)– and Non-HIV–Associated Immunosuppression Prevalence and Unadjusted Rate Ratios Among Women With Cervical Intraepithelial Neoplasia Grade 2 or Worse and Matched Women in a Control Group, Kaiser Permanente 1996–2014

	Women in the Case Group (n=20,146)	Women in the Control Group (n=100,144)	RR (95% CI)*
HIV-associated immunosuppression			
Women with HIV	36 (0.2)	79 (0.1)	2.3 (1.5–3.4)
Women with HIV, by recent† CD4+ T-cells			
Less than 200 CD4+ cells/microliter	9 (0.04)	8 (0.01)	5.6 (2.2–14.6)
200–499 CD4+ cells/microliter	18 (0.09)	28 (0.03)	3.2 (1.8–5.8)
500 or greater CD4+ cells/microliter	9 (0.04)	43 (0.04)	1.0 (0.5–2.1)
Women without HIV (reference)	20,110 (99.8)	100,065 (99.9)	1
Non-HIV–associated immunosuppression			
Any recent† immunosuppressive medication use	1,370 (6.8)	6,353 (6.3)	1.1 (1.02–1.2)
Corticosteroids	1,186 (5.9)	5,600 (5.6)	1.1 (0.99–1.1)
Antiproliferative agents	86 (0.4)	177 (0.2)	2.4 (1.9–3.1)
Calcineurin inhibitors	109 (0.5)	374 (0.4)	1.5 (1.2–1.8)
TNF inhibitors	35 (0.2)	133 (0.1)	1.3 (0.9–1.9)
Folate antimetabolites	65 (0.3)	228 (0.2)	1.4 (1.1–1.9)
Cytotoxic agents	131 (0.7)	487 (0.5)	1.3 (1.1–1.6)
Other immunosuppressive medication	38 (0.2)	141 (0.1)	1.3 (0.9–1.9)
No. of recent† immunosuppressive medication classes			
0 (reference)	18,778 (93.2)	93,794 (93.7)	1
1	1,188 (5.9)	5,812 (5.8)	1.0 (0.96–1.1)
2	88 (0.4)	310 (0.3)	1.4 (1.1–1.8)
3	77 (0.4)	195 (0.2)	2.0 (1.6–2.6)
4	14 (0.1)	29 (0.0)	
5	1 (0.0)	4 (0.0)	
Previous solid organ transplant recipient	51 (0.3)	68 (0.1)	3.7 (2.6–5.4)
Solid organ transplant status and number of recent immunosuppressive medication classes			
No prior solid organ transplant			
0 medication classes	18,773 (93.2)	93,781 (93.6)	1
1–2 medication classes	1,262 (6.3)	6,100 (6.1)	1.0 (0.97–1.1)
3 or greater medication classes	60 (0.3)	195 (0.2)	1.5 (1.2–2.1)
Prior solid organ transplant			
0 medication classes	5 (0.0)	13 (0.0)	2.0 (0.7–5.5)
1–2 medication classes	14 (0.1)	22 (0.0)	3.1 (1.6–6.1)
3 or greater medication classes	32 (0.2)	33 (0.0)	4.9 (3.0–7.9)

RR, rate ratio; HIV, human immunodeficiency virus; TNF, tumor necrosis factor.
Data are n (%) unless otherwise specified.
* Based on bivariate conditional logistic regression models.
† Within the prior 18 months.

(95% CI 2.5–6.8) for those with three or more prescribed classes compared with women with no transplantation or immunosuppressive medication prescription. The magnitudes of RRs were similar for CIN 3 or worse (Appendices 1 and 2, available online at http://links.lww.com/AOG/B37). Finally, significant associations with CIN 2 or worse were found for antiproliferative agents (RR 2.0, 95% CI 1.5–2.6) and calcineurin inhibitors (RR 1.3, 95% CI 1.00–1.6; Table 4). After excluding women with prior transplantation, only antiproliferative agents remained statistically significant (RR 1.5, 95% CI 1.1–2.1). Corticosteroids, the most commonly prescribed immunosuppressive medication in our study, conferred a small decreased risk (RR 0.93, 95% CI 0.87–1.0).

DISCUSSION

We found that cervical neoplasia risk was increased in women with HIV and less than 500 but not 500 or greater CD4+ T-cells/microliter. For non-HIV–associated immunosuppression, we observed increased risks for women with prior solid organ transplantation with the strongest association among those prescribed three or greater medication classes. Because obstetrician–gynecologists often care for women who have been prescribed a single

Table 4. Use of Immunosuppressive Medication Classes Within the Prior 18 Months and Risk of Cervical Intraepithelial Neoplasia 2 or Worse

	Adjusted*		Adjusted (Excluding Solid Organ Transplant Recipients)*	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Corticosteroids	0.93 (0.87–1.0)	.04	0.92 (0.86–0.99)	.027
Antiproliferative agents	2.0 (1.5–2.6)	<.001	1.5 (1.1–2.1)	.024
Calcineurin inhibitors	1.3 (1.00–1.6)	.049	1.1 (0.8–1.4)	.70
TNF inhibitors	1.0 (0.7–1.4)	.88	1.0 (0.7–1.5)	.98
Folate antimetabolites	1.2 (0.9–1.6)	.21	1.2 (0.9–1.6)	.21
Cytotoxic agents	1.1 (0.9–1.4)	.38	1.1 (0.9–1.4)	.21
Other medication	1.0 (0.7–1.5)	.97	1.0 (0.6–1.4)	.86

RR, rate ratio; TNF, tumor necrosis factor.

* Rate ratios obtained from conditional logistic regression models with reference group of no use of medication class within the prior 18 months. Adjusted models include terms for smoking, hormone therapy or oral contraceptives, race and ethnicity, sexually transmitted infections, prior human papillomavirus vaccination, parity, number of prior outpatient visits.

immunosuppressive agent (eg, corticosteroids) for medical conditions such as systemic lupus erythematosus, our finding of no increased CIN 2 or worse risk in those prescribed immunosuppressive medications for conditions other than solid organ transplantation has potential clinical importance.

For HIV-associated immunosuppression, a prior study in Kaiser Permanente Northern California noted a low CIN 2 or worse risk following a negative human papillomavirus cotest, although no comparison group was included.[16] Our findings are consistent with prior publications showing that women with HIV, compared with women without HIV, are at increased risk of abnormal cytology,[17] high-grade precancerous lesions,[18] and invasive cervical cancer[3] compared with those without HIV. Similar to our study, data from the Women's Interagency HIV Study also noted a decreasing risk of CIN with higher $CD4^+$ T-cell levels, but their magnitude of effect was greater.

Regarding non-HIV immunosuppression, our finding of a threefold higher risk of CIN 2 or worse for transplant recipients is consistent with data from the U.S. Transplant Cancer Match Study showing a similar increased risk of in situ lesions,[5] but not invasive cancer.[5,19] A Swedish cancer registry study similarly noted only marginally increased risks of in

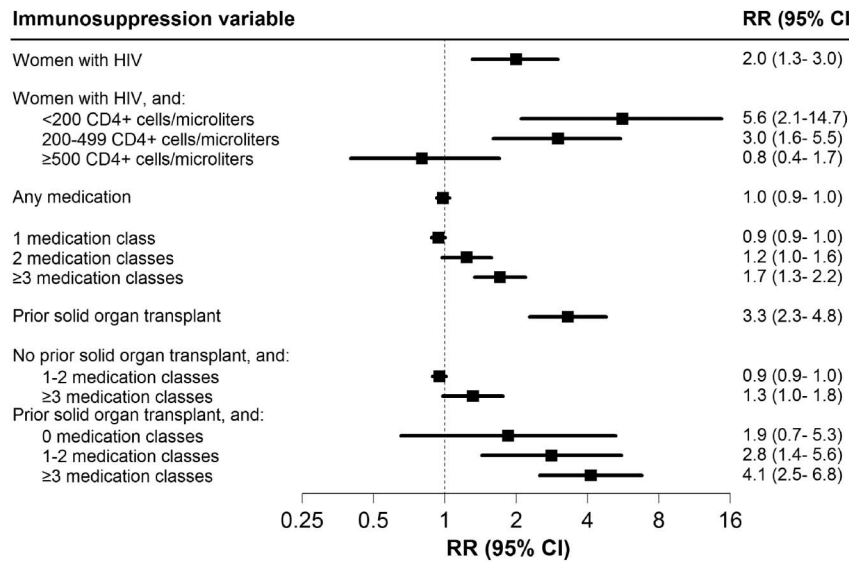

Fig. 2. Immunosuppression and adjusted rate ratios (RRs) for cervical intraepithelial neoplasia (CIN) grade 2 or worse. RRs are shown for CIN 2 or worse by human immunodeficiency virus (HIV) status (reference: Women without HIV); HIV status and recent $CD4^+$ T-cells/microliter (reference: Women without HIV); any recent (within 18 months) immunosuppressive medication use (reference: no recent use); number of immunosuppressive medication classes (reference: 0 medication classes); prior solid organ transplant recipient (reference: no history); and solid organ transplant status and number of immunosuppressive medication classes (reference: no history and zero medication classes). RRs from conditional logistic regression models adjusted for smoking, hormone therapy or oral contraceptives, race and ethnicity, recent sexually transmitted infections, any prior human papillomavirus vaccination, parity, and prior outpatient visits.

Silverberg. Immunosuppression and Risk of CIN. Obstet Gynecol 2018.

situ lesions or invasive cancer.[6] A few noted a high risk of CIN among transplant recipients[20–23]; however, these studies were limited by small sample sizes and lack of control groups. Others with control groups have noted significant increases in risk of CIN among transplant recipients,[24,25] whereas some have shown no statistically significant differences.[26,27] Few have evaluated immunosuppressive medication prescriptions in transplantation recipients, with the U.S. Transplant Cancer Match Study noting no association with in situ or invasive cervical cancer risk[5] and smaller studies noting both a higher[28] and lower[29] risk of various cervical outcomes. Finally, limited data exist regarding the association of cervical outcomes and other immunosuppressive conditions, including inflammatory bowel disease[10] and systemic lupus erythematosus.[7–9] Although the strongest association of immunosuppressive medications was found here in the subset of women with a solid organ transplantation history, it remains possible a similar association exists with these other conditions.

Some study limitations should be acknowledged. First, for certain subgroups such as women with HIV and 500 or greater $CD4^+$ T-cells/microliter, we were likely underpowered to observe a difference in risk if one existed. Other subsets (eg, less than 500 $CD4^+$ T-cells/microliter) were associated with an increased risk, but were represented by small samples. Thus, subgroup results should be interpreted with caution. In addition, study measurements such as smoking were collected from routine clinical practice. Other measurements based on pharmacy or laboratory data (eg, oral contraceptives or STIs) were more accurately ascertained, but care received outside of the health plan would have been missed. Thus, it is possible that residual confounding influenced results, although any bias is likely conservative. Next, it is possible that increased screening vigilance among immunosuppressed women affected results. However, women in the case group and those in the control group were carefully matched to reflect similar engagement in the health plan. In addition, the health plan screening guidelines currently recommend the same screening approach for women with and without HIV. An additional limitation was that we did not evaluate immunosuppressive therapy dosing, relative potency, simultaneous medication class use, or individual therapies within medication classes. However, the positive signals observed here can help guide more detailed future studies. We also acknowledge the short time window (18 months) for measurement of key exposures (eg, $CD4^+$ T-cells and use of immunosuppressive therapies). We chose the 18-month window to ensure equal opportunity for ascertainment of these exposures among women in the case group and those in the control group while maximizing our sample size.

In summary, our study provides a comprehensive evaluation of immunosuppression and the risk of CIN 2 or worse in a large sample of women with uniform access to comprehensive care. We identified novel evidence indicating that the current recommendation for more intensive screening may not apply equally to all immunosuppressed women, although additional studies are needed to confirm our findings. Future studies should also take into account both screening benefits and harms to clarify the optimal screening approaches for immunosuppressed women.

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