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Risk for Human Papillomavirus-Associated Gynecologic Cancers Among Women of Childbearing Age With Rheumatic Diseases: A Population-Based Cohort Study

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ABSTRACT

Background: This study evaluated the risk of human papillomavirus (HPV)-associated gynecologic cancers in women with rheumatic diseases (RD) during their childbearing years.
Methods: Using the Korean National Health Insurance Service-National Health Information Database (2011–2021), we conducted a cohort study of 40,514 women with RD and 199,366 women without RD aged 20–49 years. The RD cohort included 9,932 women with systemic lupus erythematosus (SLE), 23,731 with seropositive rheumatoid arthritis (SPRA), and 6,851 with ankylosing spondylitis (AS). Incidence rates and hazard ratios (HRs) for HPV-associated gynecologic cancers, including cervical intraepithelial neoplasia grade 3, and cervical, vaginal, and vulva cancers, were estimated using Cox regression.
Results: Over the mean (standard deviation) follow-up period of 67.5 (37.7) months, the incidence rate of HPV-associated gynecologic cancers was 111.5/100,000 person-years in the RD cohort and 73.2/100,000 person-years in the non-RD cohort. The incidence rate/100,000 person-years of HPV-associated gynecologic cancers in the RD subcohorts was higher in SLE (223.6) and SPRA (83.1) and lower in AS (69.1) than in the non-RD cohort. The fully adjusted HR for HPV-associated gynecologic cancers was higher in the RD cohort (HR, 2.95; 95% confidence interval [CI], 2.44–3.57) and all the RD subcohorts (SLE: HR, 1.85; 95% CI, 1.33–2.57, SPRA: HR, 4.10; 95% CI, 3.03–5.55, and AS: HR, 1.91; 95% CI, 1.06–3.43). After adjusting for comorbidities and medication use, hazard ratios increased in SPRA and AS but decreased in SLE.
Conclusion: Korean women of childbearing age with RD have a threefold increased risk for HPV-associated gynecologic cancers compared with those without RD. Comorbidities and medication use in SLE may influence the risk. Improved screening strategies are needed for these women.

Keywords: Rheumatic Diseases; Human Papillomavirus; Gynecologic Cancer; Childbearing Age

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Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
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INTRODUCTION

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the general population.[1] The global prevalence rate of genital HPV infection in women is 2–44%, with the highest rates of incident and persistent infections observed in women aged 24–34 years.[1] HPV is a major cause of cervical cancer, which is one of the leading causes of cancer-related deaths among women globally.[2] Persistent high-risk HPV infection is a major risk factor for the development of HPV-associated gynecologic cancers in women. However, behavioral factors and comorbidities, such as risky sexual behaviors, concomitant sexually transmitted infections, tobacco smoking, and immunosuppression, also increase the risk for HPV-associated gynecologic cancer.[3-7]

Immunocompromised women with rheumatic diseases (RD) have been reported to have a higher risk for gynecologic cancers associated with HPV infection. Women with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are at an increased risk for developing high-grade cervical dysplasia and cervical cancer,[8-13] and vaginal and vulva cancers.[14] Furthermore, immunosuppressive medications used to treat severe SLE, such as cyclophosphamide, mycophenolate mofetil, azathioprine, and high doses of corticosteroids, can increase the risk for cervical dysplasia in a cumulative dose-dependent manner, resulting in persistent HPV infection.[7,15-18] RA, SLE, and ankylosing spondylitis (AS) are types of RD that frequently occur in women of childbearing age[19-21]; however, their risk for HPV-associated gynecologic cancers is not yet fully understood.

The objective of this study was to evaluate the risk of HPV-associated gynecologic cancers and to determine the impact of comorbidities and medication use on this risk in Korean women with RD during their childbearing years compared to those without RD.

METHODS

Study design and data source

This cohort study was conducted using data from the Korean National Health Insurance Service-National Health Information Database (NHIS-NHID) between 2009 and 2021. The Korean NHIS is a single insurer that provides coverage for most of the Korean population. The NHIS-NHID is composed of five databases, namely eligibility, national health screening, healthcare utilization, long-term care insurance, and healthcare provider databases, which include information on income-based insurance contributions, residential districts, national health screening, inpatient and outpatient healthcare utilization (diagnosis and treatment), claims data, and healthcare providers.[22] The NHID provides data on an annual basis, spanning from 2002 to the present.[22]

Data collected between January 1, 2009, and December 31, 2021, were used for this study. In 2009, the Republic of Korea subsidized medical expenses for patients with rare and intractable diseases through a copayment assistance policy, the Individual Copayment Beneficiaries Program (ICBP); RD, including SLE, seropositive rheumatoid arthritis (SPRA), and AS, were designated as rare diseases covered by this program. Under the ICBP, the NHIS established a registration program that included codes for targeted diseases classified according to the Korean Standard Classification of Diseases-7 (based on the International Classification of Diseases, 10th Revision [ICD-10]), date of definitive diagnosis, and

confirmatory diagnostic tests. Data after January 1, 2009, were used assuming that all patients with SPRA, SLE, and AS were accurately coded, compared to the previous NHID period from 2002 to 2008, as the ICBP registration required the classification criteria for a definitive diagnosis.

Study cohorts

Women of childbearing age (defined as women between the ages of 20 and 49 years) with and without RD were selected. The RD cohort included SLE, SPRA, and AS, identified with the diagnostic codes M05, M32, and M45, respectively, based on the ICD-10 codes in the NHIS-NHID (2011–2021). Women with SLE, SPRA, and AS were included within the RD cohort as subcohorts, as they are representative diseases that occur frequently in women of childbearing age. The start of the follow-up period (i.e., the index date) was defined as the date of the first RD code identification. Women with HPV-associated gynecologic cancer within 12 months before the index date were excluded. HPV-associated gynecologic cancers included cervical intraepithelial neoplasia grade 3, cervical cancer, vaginal cancer, and vulva cancer identified with the ICD-10 codes D06, C53, C52, and C519, respectively. These cancers were included based on evidence pointing toward the increased risk for these cancers in patients with SLE and RA.[8-12]

The non-RD cohort comprised women of childbearing age who did not have RD, including SLE, SPRA, and AS, in the NHIS-NHID (2011–2021) database. Women in the non-RD cohort were matched by age and index date with women in the RD cohort and were randomly sampled in a 1:5 ratio. In the non-RD cohort, women matched by age and index date with women with SLE, SPRA, or AS were selected to serve as controls for each RD subcohort.

Women in the RD and non-RD cohorts were followed up until the earliest occurrence of any of the following events: development of HPV-associated gynecologic cancer, the end of the study database (2021), or death.

Outcome measures

The primary outcome measure was the development of HPV-associated gynecologic cancer. In addition, variables potentially associated with the risk for HPV-associated gynecologic cancer were assessed at baseline and during the follow-up period. Age, income, medical insurance, residential district, comorbidities, smoking status, and preventive medical service utilization were assessed at baseline. The age, income, medical insurance, and residential district data were obtained at the index date. Comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, and cancer, were identified with the ICD-10 codes I10-12/15, E10-14, E78, and C*, between 1 and 24 months before the index date. Smoking and preventive medical service utilization data were obtained from the NHIS health screening database within 24 months closest to the index date. Variables for the preventive medical service utilization included NHIS health screening and NHIS Papanicolaou (Pap) smear recipients.

During the follow-up period, the same comorbidities and preventive medical service utilization data assessed at baseline were evaluated in addition to the use of medication and healthcare utilization. Medications included nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, hydroxychloroquine, cyclophosphamide, immunosuppressants, and biologics. Immunosuppressants included methotrexate, leflunomide, azathioprine, cyclosporin, tacrolimus, mizoribine, and mycophenolate mofetil. The number of immunosuppressants used was also assessed. Biologics included etanercept, adalimumab,

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infliximab, golimumab, abatacept, tocilizumab, rituximab, ustekinumab, secukinumab, ixekizumab, tofacitinib, baricitinib, and upadacitinib. Variables included in healthcare utilization were the total number of outpatient department (OPD) and obstetrics and gynecology (OB/GYN) OPD visits during the follow-up period.

Statistical analysis

A descriptive analysis was performed to summarize the baseline and follow-up characteristics of the cohorts. Categorical variables are presented as frequencies and percentages, and continuous variables are presented as the mean ± standard deviation (SD). The baseline and follow-up characteristics of the RD and non-RD cohorts, as well as the RD subcohorts and their controls, were compared using the χ^2 test for categorical variables and the Student's *t*-test for continuous variables. The incidence rates (IRs) of HPV-associated gynecologic cancer in the RD cohort, non-RD cohort, and the RD subcohorts were calculated per 100,000 person-years (PYs) with a 95% confidence interval (CI) during the follow-up period. Kaplan–Meier curves were plotted for the cumulative incidence of HPV-associated gynecologic cancer in the RD cohort, non-RD cohort, and the RD subcohorts. Unadjusted and multivariate Cox proportional hazard models, which adjusted for multiple potential confounders associated with HPV infection, were used to compare the risk of HPV-associated gynecologic cancer in the RD cohort and subcohorts with the non-RD cohort and RD subcohort controls, respectively. Adjusted potential confounders associated with HPV infection included income level, medical insurance type, residential district, comorbidities, preventive medical service utilization at baseline and during the follow-up period, and comorbidities and medication use (immunosuppressant use, number of immunosuppressants used, NSAID use) during follow-up. All statistical analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA). A $P < 0.05$ was considered statistically significant.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital, South Korea (NHIMC 2024-01-007), and the study was conducted according to the principles of the Declaration of Helsinki. Since the database used in this study contains anonymized data for research purposes, informed consent was not required.

RESULTS

Characteristics of the study cohorts

The study included 41,514 women of childbearing age with RD, including 9,932 women with SLE, 23,731 with SPRA, and 6,851 with AS, as well as 199,366 women without RD. **Table 1** shows the baseline characteristics of the study cohorts. The mean follow-up duration was similar in the RD and non-RD cohorts, 67.5 ± 37.7 and 67.7 ± 37.7 months, respectively. Since age was matched, the mean age was similar in the RD (37.5 ± 8.8 years) and non-RD (37.4 ± 8.8 years) cohorts; however, the patients with SLE (33.2 ± 9.4 years) and AS (34.4 ± 8.5 years) were younger and those with SPRA (40.1 ± 7.4 years) were older than women without RD. In addition, patients in the SLE, SPRA, and AS subcohorts mostly belonged to the age groups of 20–24, 45–49, and 35–39 years, respectively. The RD cohort included more women in the lower-income segment and on medical aid than the non-RD cohort. Comorbidities and preventive medical service utilization were higher in the RD cohort than the non-RD cohort. Smoking status was not significantly different between the RD and non-RD cohorts.

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Table 1. Baseline characteristics of the study cohort

Characteristics	RD[a]	Non-RD[a]	*P* value	SLE	SLE control	*P* value	SPRA	SPRA control	*P* value	AS	AS control	*P* value
No. of patients	40,514	199,366		9,932	48,959		23,731	116,647		6,851	33,761	
Follow-up period, mon	67.5 ± 37.7	67.7 ± 37.7		67.5 ± 37.4	68.0 ± 37.4		69.3 ± 37.7	69.6 ± 37.6		60.8 ± 37.8	60.9 ± 37.8	
Age, yr												
Mean ± SD	37.5 ± 8.8	37.4 ± 8.8		33.2 ± 9.4	33.2 ± 9.4		40.1 ± 7.4	40.1 ± 7.5		34.4 ± 8.5	34.4 ± 8.5	
20–24	4,874 (12.0)	24,204 (12.1)		2,534 (25.5)	12,581 (25.7)		1,228 (5.2)	6,096 (5.2)		1,112 (16.2)	5,527 (16.4)	
25–29	3,820 (9.4)	18,892 (9.5)		1,292 (13.0)	6,369 (13.0)		1,377 (5.8)	6,812 (5.8)		1,151 (16.8)	5,711 (16.9)	
30–34	4,931 (12.2)	24,150 (12.1)		1,427 (14.4)	6,979 (14.3)		2,357 (9.9)	11,527 (9.9)		1,147 (16.7)	5,644 (16.7)	
35–39	7,018 (17.3)	34,429 (17.3)		1,556 (15.7)	7,653 (15.6)		4,235 (17.9)	20,757 (17.8)		1,227 (17.9)	6,019 (17.8)	
40–44	8,956 (22.1)	44,068 (22.1)		1,649 (16.6)	8,110 (16.6)		6,137 (25.9)	30,210 (25.9)		1,170 (17.1)	5,748 (17.0)	
45–49	10,915 (26.9)	53,623 (26.9)		1,474 (14.8)	7,266 (14.8)		8,397 (35.4)	41,245 (35.4)		1,044 (15.2)	5,112 (15.1)	
Income level[b], segment			< 0.0001			< 0.0001			0.001			0.001
1–3	11,513 (28.4)	53,570 (26.9)		2,929 (29.5)	13,345 (27.3)		6,665 (28.1)	31,223 (26.8)		1,919 (28.1)	9,001 (26.7)	
4–7	14,389 (35.5)	72,979 (36.6)		3,472 (35.0)	17,976 (63.7)		8,435 (35.5)	41,998 (36.0)		2,482 (36.2)	13,005 (38.5)	
8–10	13,574 (33.5)	67,861 (34.0)		3,279 (33.0)	16,420 (33.5)		8,053 (33.9)	40,570 (34.8)		2,242 (32.7)	10,871 (32.2)	
Insurance			< 0.0001			< 0.0001			< 0.0001			< 0.0001
Employee	28,050 (69.2)	139,004 (69.7)		6,930 (69.8)	34,02 (70.5)		16,225 (68.4)	80,048 (68.6)		4,895 (71.5)	24,454 (72.4)	
Self-employed	10,700 (26.4)	56,621 (28.4)		2,439 (24.6)	13,372 (27.3)		6,605 (27.83)	34,517 (29.6)		1,656 (24.2)	8,732 (25.9)	
Medical-aid	1,764 (4.35)	3,741 (1.9)		563 (5.7)	1,084 (2.2)		901 (3.8)	2,082 (1.8)		300 (4.4)	575 (1.7)	
Residential district			< 0.0001			0.976			< 0.0001			0.013
City, province	8,106 (20.0)	41,705 (20.9)		2,137 (21.5)	10,581 (21.6)		4,338 (18.3)	23,635 (20.3)		1,631 (23.8)	7,489 (22.2)	
Metropolitan city	10,388 (25.6)	50,906 (25.5)		2,507 (25.2)	12,357 (25.2)		6,199 (26.1)	30,109 (25.8)		1,682 (24.6)	8,440 (25.0)	
Special city	22,020 (54.4)	106,755 (53.6)		5,288 (53.2)	26,020 (53.2)		13,194 (55.6)	62,903 (53.9)		3,538 (51.6)	17,832 (52.8)	
Comorbidities[c]												
Hypertension	3,605 (8.9)	8,812 (4.42)	< 0.0001	1,430 (14.4)	2,452 (5.0)	< 0.0001	1,764 (7.4)	9,627 (8.3)	< 0.0001	411 (6.0)	647 (9.4)	< 0.0001
DM	2,992 (7.39)	8,031 (4.03)	< 0.0001	815 (8.21)	3,500 (7.2)	< 0.0001	1,724 (7.3)	11,396 (9.8)	< 0.0001	453 (6.61)	961 (14.0)	< 0.0001
Hyperlipidemia	12,598 (31.1)	24,033 (12.05)	< 0.0001	3.496 (35.2)	10,398 (21.2)	< 0.0001	7,124 (30.0)	31,475 (27.0)	< 0.0001	1,978 (28.87)	3,416 (49.7)	< 0.0001
Cancer	1.757 (4.34)	5,809 (2.91)	< 0.0001	516 (5.2)	1,743 (3.6)	< 0.0001	967 (4.1)	6,340 (5.4)	< 0.0001	274 (4.0)	461 (6.7)	< 0.0001
Smoking[d]			0.118			0.278			0.873			0.080
None	22,604 (90.5)	108,350 (90.9)		4,450 (89.4)	21,691 (90.0)		14,597 (91.2)	69,501 (91.3)		3,557 (89.0)	3,557 (89.0)	
Ex-smoker	958 (3.8)	4,390 (3.7)		211 (4.2)	950 (4.0)		573 (3.6)	3,692 (3.5)		174 (4.4)	174 (4.3)	
Current smoker	1,428 (5.7)	6,500 (5.5)		319 (6.4)	1,432 (6.0)		841 (5.3)	3,935 (5.2)		268 (6.7)	268 (6.7)	
Preventive medical service utilization[d]												
Number of NHIS health screenings undergone/10 years	18,328 (45.2)	84,991 (42.6)	0.927	3,579 (36.0)	17,035 (34.8)	0.018	11,825 (49.8)	54,688 (46.9)	< 0.0001	2,922 (42.7)	13,268 (39.3)	< 0.0001
Number of NHIS Pap smear tests undergone/10 years	15,800 (39)	71,490 (35.9)	< 0.0001	3,014 (30.4)	13,823 (28.2)	< 0.0001	10,252 (43.2)	46,741 (40.1)	< 0.0001	2,534 (37.0)	10,926 (32.4)	< 0.0001

Categorial values are provided as numbers (%) and numerical quantitative data are provided as the mean ± SD. Variables were obtained at the index date unless otherwise indicated.
RD = rheumatic diseases, SLE = systemic lupus erythematosus, SPRA = seropositive rheumatoid arthritis, AS = ankylosing spondylitis, SD = standard deviation, DM = diabetes mellitus, NHIS = National Health Insurance Service, Pap = Papanicolaou.
[a]RD and non-RD cohorts were matched for age and index date. The RD cohort included patients with SLE, SPRA, and AS.
[b]Income levels were determined according to the decile method (8–10 refers to the low-income group).
[c]Comorbidities were identified with diagnostic code based on the International Classification of Diseases 10th revision between 1 and 24 months before the index date.
[d]Smoking and preventive medical service utilization data were obtained from the NHIS Health Screening Examination Database within 24 months closest to the index date.

Characteristics recorded during the follow-up period are shown in **Table 2**. All comorbidities and medication use were higher in the RD cohort than in the non-RD cohort. The same pattern of comorbidities and medication use was observed in the RD subcohorts compared with their controls, except for cyclophosphamide use in the AS subcohort, which was not significantly different compared with the control. The total number of OPD and OB/GYN OPD visits was higher in the RD cohort than the non-RD cohort (23.0 ± 20.6 vs. 11.3 ± 12.6 and 1.5 ± 3.8 vs. 1.4 ± 3.3, respectively) (all $P \leq 0.0001$). The number of Pap smear tests undergone/10 years was also higher in the RD cohort than in the non-RD cohort (1.13 ± 2.12 vs. 1.07 ± 2.09, $P \leq 0.0001$). However, the number of NHIS health screenings undergone/10 years was not significantly different between the RD and non-RD cohorts (2.17 ± 3.25 vs. 2.17 ± 3.30, $P = 0.927$). Among the RD subcohorts, the total number of OPD and OB/GYN OPD visits/year was higher in all RD subcohorts than their controls, with the exception of the total number of OB/GYN visits/year in the SPRA subcohort, which was similar to the number in its control. The number of NHIS health screenings and Pap smear tests undergone were significantly different among the RD subcohorts. The number of NHIS health screenings undergone/10 years was lower in the SLE and higher in the SPRA subcohorts than in their respective controls, but not different in the AS subcohort. In contrast, the number of Pap smear tests undergone/10 years was higher in the SPRA and AS subcohorts than their respective controls, but not different in the SLE subchohort.

Incidence rates and cumulative incidence of HPV-associated gynecologic cancers

The follow-up period was 67.5 ± 37.7 months, during which the IR of HPV-associated gynecologic cancers between the cohorts was 111.5/100,000 PYs in the RD cohort and 73.2/100,000 PYs in the non-RD cohort. Among the RD subcohorts, the IR/100,000 PYs of HPV-associated gynecologic cancers was higher in women with SLE (223.6) and SPRA (83.1) than their respective controls; however, it was lower in women with AS (69.1) (**Fig. 1A**). Kaplan–Meier curves comparing the cumulative incidence of HPV-associated gynecologic cancers between the RD and non-RD cohorts revealed similar results, showing an increased risk for HPV-associated gynecologic cancers in the RD cohort, with the highest cumulative incidence observed in the SLE subcohort (**Fig. 1B**).

Risk of HPV-associated gynecologic cancers

The unadjusted hazard ratios (HRs) with 95% CI for HPV-associated gynecologic cancers were increased in the RD cohort (HR, 1.83; 95% CI, 1.42–2.6), including the SLE (HR, 2.00; 95% CI, 1.15–3.45) and SPRA (HR, 2.68; 95% CI, 1.81–3.97) subcohorts but not the AS subcohort (HR, 0.77; 95% CI, 0.44–1.36). After full adjustment for possible confounders, the HRs for HPV-associated gynecologic cancers were increased in the RD cohort (HR, 2.95; 95% CI, 2.44–3.57) and all RD subcohorts (SLE: HR, 1.85; 95% CI, 1.33–2.57, SPRA: HR, 4.10; 95% CI, 3.03–5.55, and AS: HR, 1.91; 95% CI, 1.06–0.43). In the RD subcohorts, the HR was reduced in the SLE subcohort but increased in the SPRA and AS subcohorts after adjustment for comorbidities and medication use during the follow-up period (**Fig. 2**, **Supplementary Table 1**).

Sensitivity analysis

Supplementary Fig. 1 demonstrates the possible effect of residual confounding on our findings, evaluated using the rule-out method.[23] Unless there are exceptionally strong risk factors for HPV-associated gynecologic cancers that are unmeasured and unaccounted for between the cohorts in our fully adjusted models, the increased HRs associated with SLE, RA, and AS cannot be attributed to residual confounding.

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Table 2. Comorbidities, medication, and healthcare and preventive medical service utilization during the follow-up period

Variables	RD[a]	Non-RD[a]	*P* value	SLE[a]	SLE control[a]	*P* value	SPRA[a]	SPRA control[a]	*P* value	AS[a]	AS control[a]	*P* value
No. of patients	40,514	199,366		9,932	48,958		23,731	116,647		6,851	33,761	
Comorbidities												
Hypertension	6,662 (16.4)	16,208 (8.1)	< 0.0001	2,924 (29.4)	3,136 (6.4)	< 0.0001	3,128 (13.2)	11,164 (9.6)	< 0.0001	610 (8.9)	1,908 (5.7)	< 0.0001
DM	7,308 (18.0)	21,276 (10.7)	< 0.0001	1,873 (18.9)	4,394 (9.0)	< 0.0001	4,423 (18.6)	14,058 (12.1)	< 0.0001	1,012 (14.8)	2,824 (8.4)	< 0.0001
Hyperlipidemia	20,016 (49.4)	54,004 (27.1)	< 0.0001	4,444 (44.7)	11,921 (24.4)	< 0.0001	12,426 (52.4)	34,394 (29.5)	< 0.0001	3,146 (45.9)	7,689 (22.8)	< 0.0001
Cancer	3,650 (9.0)	11,733 (5.9)	< 0.0001	1,013 (10.2)	2,502 (5.11)	< 0.0001	2,152 (9.1)	7,621 (6.5)	< 0.0001	485 (7.1)	1610 (4.8)	< 0.0001
Medication use												
NSAIDs	32,218 (79.5)	48,182 (24.2)	< 0.0001	4,598 (46.3)	10,347 (21.1)	< 0.0001	21,413 (90.2)	31,564 (27.1)	< 0.0001	6,209 (90.6)	6,217 (18.6)	< 0.0001
Corticosteroids	29,045 (71.7)	9,383 (4.7)	< 0.0001	7,697 (77.5)	2,087 (4.3)	< 0.0001	18,978 (80.0)	6,060 (5.2)	< 0.0001	2,370 (34.6)	1,236 (3.7)	< 0.0001
Hydroxychloroquine	23,904 (59.0)	447 (0.2)	< 0.0001	8,527 (85.9)	75 (0.2)	< 0.0001	15,196 (64.0)	310 (0.3)	< 0.0001	181 (2.6)	62 (0.2)	< 0.0001
Cyclophosphamide	1,166 (2.9)	804 (0.4)	< 0.0001	965 (9.7)	145 (0.3)	< 0.0001	176 (0.7)	567 (0.5)	< 0.0001	25 (0.4)	92 (0.3)	0.193
Immunosuppressant[b]	23,017 (56.8)	1,135 (0.6)	< 0.0001	4,808 (48.4)	278 (0.6)	< 0.0001	17,516 (73.8)	704 (0.6)	< 0.0001	693 (10.1)	153 (0.5)	< 0.0001
No. of immunosuppressant[b]			< 0.0001			< 0.0001			< 0.0001			< 0.0001
1–2	20,537 (50.7)	1,108 (0.6)		4,349 (43.8)	271 (0.6)		15,512 (65.4)	684 (0.6)		676 (9.9)	153 (0.5)	
> 2	2,480 (6.1)	27 (0.01)		459 (4.6)	7 (0.01)		2,004 (8.4)	20 (0.02)		17 (0.3)	0	
Biologics[c]	5,533 (13.7)	164 (0.08)	< 0.0001	131 (1.3)	38 (0.08)	< 0.0001	3,381 (14.3)	110 (0.09)	< 0.0001	2,021 (29.5)	16 (0.05)	< 0.0001
Healthcare utilization												
Number of total OPD, visits/yr	23.0 ± 20.6	11.3 ± 12.6	< 0.0001	24.8 ± 21.8	10.5 ± 11.3	< 0.0001	22.0 ± 18.5	11.8 ± 13.4	< 0.0001	23.9 ± 25.2	10.6 ± 11.7	< 0.0001
Number of OB/GYN OPD, visits/yr	1.5 ± 3.8	1.4 ± 3.3	< 0.0001	1.8 ± 5.0	1.5 ± 3.5	< 0.0001	1.4 ± 3.1	1.3 ± 3.1	0.182	1.8 ± 3.6	1.7 ± 3.5	< 0.0001
Preventive medical service utilization												
Number of NHIS health screenings undergone/10 years	2.17 ± 3.25	2.17 ± 3.30	0.927	1.56 ± 2.88	1.73 ± 3.05	< 0.0001	2.48 ± 3.37	2.42 ± 3.39	0.022	1.97 ± 3.19	1.94 ± 3.24	0.395
Number of NHIS Pap smear tests undergone/10 years	1.13 ± 2.12	1.07 ± 2.09	< 0.0001	0.78 ± 1.84	0.80 ± 1.88	0.571	1.32 ± 2.22	1.24 ± 2.19	< 0.0001	0.96 ± 2.06	0.88 ± 2.00	0.003

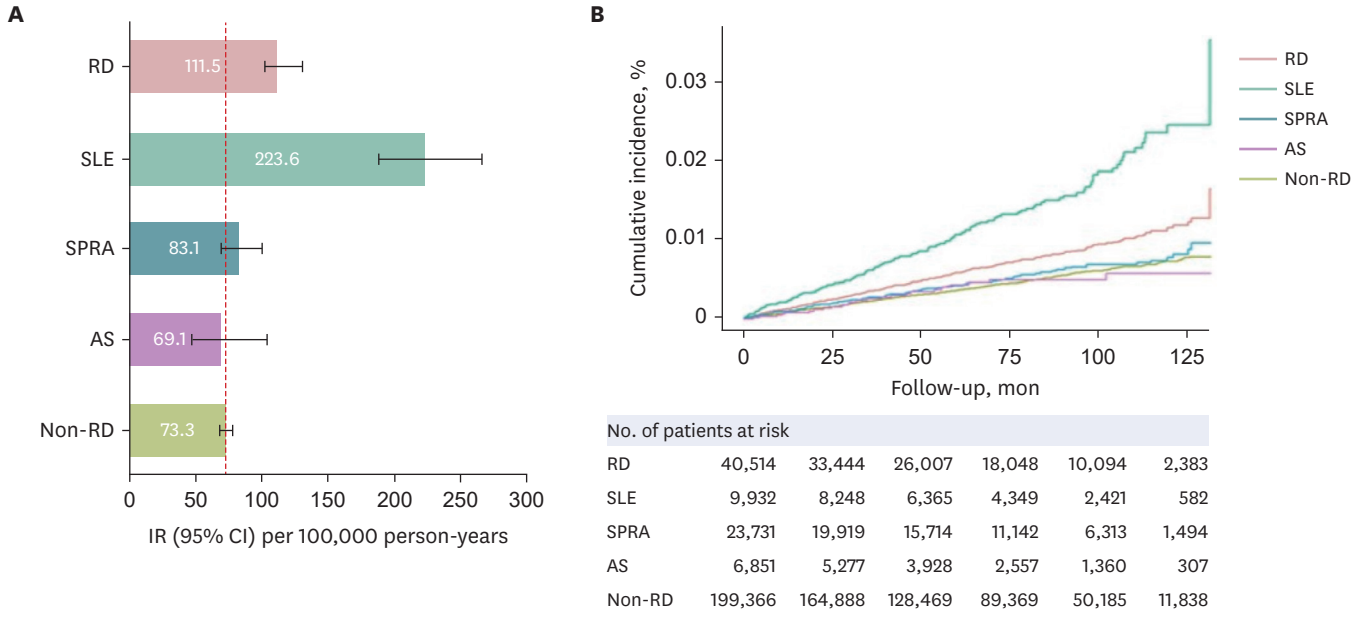
Categorial values are provided as numbers (%) and numerical quantitative data are provided as mean ± standard deviation.

RD = rheumatic diseases, SLE = systemic lupus erythematosus, SPRA = seropositive rheumatoid arthritis, AS = ankylosing spondylitis, DM = diabetes mellitus, NSAIDs = nonsteroidal anti-inflammatory drugs, OPD = outpatient department, OB/GYN = obstetrics and gynecology, NHIS = National Health Insurance Service, Pap = Papanicolaou.

[a]RD and non-RD, SLE and SLE control, SPRA and SPRA control, and AS and AS control are age- and index date-matched, RD include SLE, SPRA, and AS.

[b]Immunosuppressants include MTX, leflunomide, azathioprine, cyclosporin, tacrolimus, mizoribine, MMF.

[c]Biologics include etanercept, adalimumab, infliximab, golimumab, abatacept, tocilizumab, rituximab, ustekinumab, secukinumab, ixekinumab, tofacitinib, baricitinib, upadacitinib.



No. of patients at risk						
RD	40,514	33,444	26,007	18,048	10,094	2,383
SLE	9,932	8,248	6,365	4,349	2,421	582
SPRA	23,731	19,919	15,714	11,142	6,313	1,494
AS	6,851	5,277	3,928	2,557	1,360	307
Non-RD	199,366	164,888	128,469	89,369	50,185	11,838

Fig. 1. Incidence rates and cumulative incidence of HPV-associated gynecologic cancers. IRs per 100,000 person-years (**A**) and Kaplan–Meier curves for the cumulative incidence (**B**) of HPV-associated gynecologic cancers. The RD and non-RD cohorts are matched for age and index date. HPV-associated gynecologic cancers included cervical intraepithelial neoplasia grade 3, cervical cancer, vaginal cancer, and vulva cancer. The RD cohort included patients with SLE, SPRA, and AS.
IR = incidence rate, HPV = human papillomavirus, RD = rheumatic diseases, SLE = systemic lupus erythematosus, SPRA = seropositive rheumatoid arthritis, AS = ankylosing spondylitis, CI = confidence interval.

DISCUSSION

This is the first study to evaluate the risk for HPV-associated gynecologic cancers among women of childbearing age with RD. After adjusting for possible confounders, this study found that Korean women of childbearing age with RD have a threefold higher risk for HPV-associated gynecologic cancers than those without RD.

This study demonstrated that the IR of HPV-associated gynecologic cancers in Korean women of childbearing age with RD was 111.5/100,000 PYs, which is approximately 1.6 times higher than the IR of age-matched women without RD (73.2/100,000 PYs). A direct comparison of the IR of HPV-associated gynecologic cancer between women of childbearing age with RD with RD of all ages is challenging. However, it has been reported that women aged ≥ 18 years with systemic inflammatory diseases have an IR of 94.2/100,000 PYs of high-grade cervical dysplasia and cervical cancer.[8] This rate is lower than the IR of HPV-associated gynecologic cancers in women of childbearing age with RD found in this study. Additionally, after adjusting for potential confounders such as demographics, preventive medical service utilization, comorbidities, and medication use, this study found that women of childbearing age with RD have a 2.95 times greater risk of developing HPV-associated gynecologic cancers, whereas Kim et al.[8] reported that women aged ≥ 18 years with SLE and RA had a 1.5 times greater risk of high-grade cervical dysplasia and cervical cancer than those without systemic inflammatory diseases. These findings suggest that women of childbearing age with RD seem to be at a higher risk than women of all ages with RD.

In addition, this study found that women of childbearing age with SPRA have the highest risk of developing HPV-associated gynecologic cancers with an HR of 2.95, followed by those with

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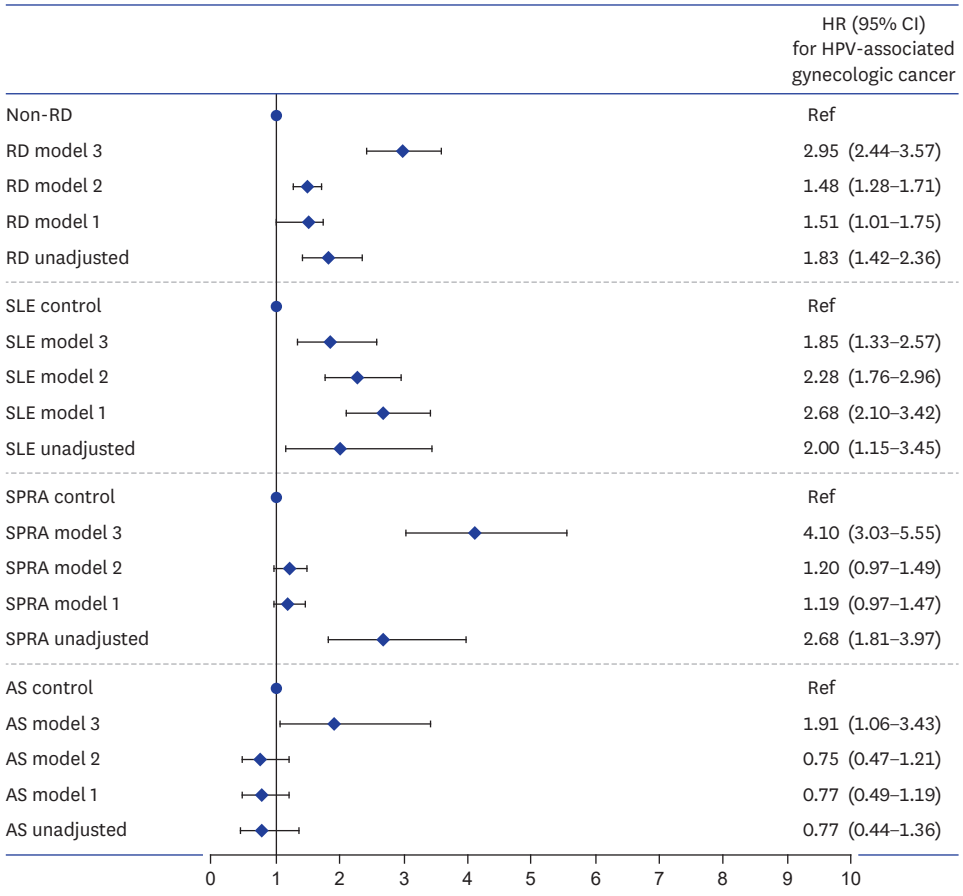


Fig. 2. HRs for HPV-associated gynecologic cancers: multivariate Cox regression models. A step down in HR after adjusting for variables in each model indicates that the adjusted variables increased the risk, whereas a step up in HR indicates that the adjusted variables decreased the risk.
Model 1 was adjusted for income level, medical insurance type, residential district, comorbidities, and preventive medical service utilization at baseline. Model 2 was adjusted for healthcare and preventive medical service utilization during the follow-up period in addition to the variables in Model 1. Model 3 (fully adjusted model) was adjusted for comorbidities and medication use (immunosuppressant use, number of used immunosuppressants, NSAID use) during follow-up in addition to the variables in Model 2. The RD and non-RD cohorts were matched for age and index date. HPV-associated gynecologic cancers included cervical intraepithelial neoplasia grade 3, cervical cancer, vaginal cancer, and vulva cancer. The RD cohort included patients with SLE, SPRA, and AS.
HR = hazard ratio, HPV = human papillomavirus, NSAID = non-steroidal anti-inflammatory drug, RD = rheumatic diseases, SLE = systemic lupus erythematosus, SPRA = seropositive rheumatoid arthritis, AS = ankylosing spondylitis, CI = confidence interval.

AS and SLE (HR of 1.91 and 1.85, respectively). However, Kim et al.[8] reported a higher risk of high-grade cervical dysplasia and cervical cancer in women with SLE (HR, 1.53) than women with RA (HR, 1.49). This discrepancy may be because of the difference in age groups in the 2 studies. The present study focused solely on women of childbearing age, but the study by Kim et al.[8] included women across all age groups. Women over 65 years of age are more likely to experience long-term persistence of HPV infection,[24] increasing their likelihood of developing cervical cancer.[25] In the present study, women with SPRA had the highest mean age among women of childbearing age, whereas those with SLE had the lowest mean age. This disparity in age distribution might have contributed to the increased risk of HPV-associated gynecologic cancers in women with SPRA. However, considering all age groups, the lifetime risk for women with SLE seems to be higher than that for women with RA.

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A multivariable analysis was conducted to examine the impact of medication use and comorbidities on the risk of HPV-associated gynecologic cancers in women with RD of childbearing age. The results showed that for women with SLE, the use of medications and the presence of associated comorbidities during the follow-up period significantly increased the risk of developing HPV-associated gynecologic cancers. Women of childbearing age with SLE have been reported to have a greater burden of comorbidities and immunosuppressive drug use than those with SPRA and AS.[26] This is because SLE is a multisystem disease that necessitates immunosuppressive medication for treating severe organ involvement.[27,28] Our findings are supported by previous studies showing that women with SLE who are exposed to immunosuppressive are at a higher risk of developing cervical dysplasia and vaginal and vulva cancers, particularly with cumulative exposure to cyclophosphamide.[15-18] Notably, the presence of comorbidities and the use of medications appeared to decrease the risk of HPV-associated gynecologic cancers in women with SPRA and AS. This may be attributed to the widespread use of NSAIDs for managing inflammatory arthritis in patients with RA and AS. The *COX-2* gene has been implicated in early cervical carcinogenesis and tumor progression,[29,30] and few small clinical trials have suggested that COX-2 inhibitors may play a positive role in preventing cervical cancer.[31,32]

A key strength of this study is that the risk of HPV-associated gynecologic cancers in women of childbearing age with RD could be determined despite methodological challenges associated with assessing uncommon exposures and outcomes. This was made possible by utilizing a large population-based NHIS-NHID database, which contains health information of most of the Korean population. One limitation of this study is that behavioral characteristics, such as sexual activity, or HPV vaccination status, which are known risk factors for HPV infection, could not be determined. This is because the NHIS-NHID database does not include these variables. Additionally, while understanding the association between HPV infection and the development of gynecologic cancers is important, the prevalence of gynecologic cancers in the RD and non-RD cohorts could not be determined. Finally, this study was unable to directly ascertain the impact of individual drugs or comorbidities on the risk of developing HPV-associated gynecologic cancers.

The Korean government offers complimentary biennial cervical cancer screening to all women over the age of 20 years[33] and offers free HPV vaccines to female adolescents aged 12–17 years and to low-income women aged 18–26 years.[34] However, the national cancer screening program should be tailored to meet the needs of populations who are at a high risk of developing gynecologic cancers. Currently, there are no specific recommendations for gynecologic cancer screening and prevention for women with RA and AS. For women with SLE and/or AS, the European League Against Rheumatism recommends a Pap smear examination yearly for heavily immunosuppressed patients or according to the local screening program, if they are considered low-risk patients.[35] However, regular uptake of cervical cancer screening is reported to be low in Korea (18.9%).[36] Additionally, the national HPV vaccination initiation rate is low, with a reported rate of only 35.7%.[37] Studies conducted in Canada and the United States of America have shown that subgroups of women with SLE, typically Caucasian, younger, with a lower education level, and with high SLE damage, may exhibit poor adherence to preventive health screening programs.[38,39] We need more studies addressing these issues to implement effective healthcare policies and provide better gynecologic cancer screening and prevention programs for women of childbearing age with RD, as they are a highly vulnerable population for gynecologic cancers.

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In conclusion, Korean women of childbearing age with RD face an increased risk for HPV-associated gynecologic cancers. This risk may be further increased by comorbidities and medication use during the follow-up period, particularly in patients with SLE. Therefore, it is essential to develop prevention strategies for HPV-associated gynecologic cancer in women with RD of childbearing age, and healthcare providers should focus more on HPV-associated gynecologic cancer surveillance and education.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Age-stratified HRs for HPV-associated gynecologic cancer[a]: multivariate Cox regression models

Supplementary Fig. 1

Sensitivity analysis of residual confounding: rule-out approach.

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