Received: 26 December 2024 | Accepted: 18 May 2025

DOI: 10.1111/jog.16330

ORIGINAL ARTICLE

Lack of knowledge, not vaccine hesitancy, is the main cause of low human papilloma virus vaccination rate among systemic lupus erythematosus patients in Japan after suspension of proactive recommendation: Analysis of a patients' survey

Takashi Kurita[1] | **Akio Yamamoto**[2] | **Tadashi Hosoya**[2] | **Marina Tsuchida**[2] | **Shinsuke Yasuda**[2] | **Yoshiaki Gu**[1,3]

[1]Department of Infectious Diseases, Institute of Science Tokyo, Tokyo, Japan

[2]Department of Rheumatology, Institute of Science Tokyo, Tokyo, Japan

[3]ST Center for Infectious Disease Education and Analysis (TCIDEA), Institute of Science Tokyo, Tokyo, Japan

Correspondence
Takashi Kurita, Department of Infectious Diseases, Institute of Science Tokyo, 1-5-25, Yushima, Bunkyo-ku, 113-8510, Tokyo, Japan.
Email: kurita.cid@tmd.ac.jp

Abstract

Objective: To identify the factors that inhibit human papilloma virus (HPV) vaccination to improve the high HPV infection rate and cervical cancer incidence among SLE patients.

Methods: We conducted a questionnaire survey of female SLE patients aged 18–45 years attending our hospital to analyze factors related to HPV vaccination.

Results: We obtained responses of 88 participants. Only 5 (5.7%) were received HPV vaccination, 15 (17.0%) were uncertain of their vaccine history, and 27 (30.7%) had never even heard of HPV vaccination. The reasons for unvaccinated against HPV were "don't know" with 24 participants, "missed opportunity" with 15, and "troublesome, somehow" with 8. The most trusted source of medical information for the unvaccinated was their physician (69, 60.2%). Among the unvaccinated, those who wished to be vaccinated in the future were positively correlated with "trust of vaccine benefit" ($r = 0.561$, $p = 0.005$) and "general knowledge about HPV vaccine" ($r = 0.512$, $p = 0.013$), and negatively correlated with "negative attitudes toward vaccination and vaccine policy" ($r = -0.547$, $p = 0.007$).

Conclusion: HPV vaccination rate among SLE patients in Japan was extremely low. The main reason was lack of knowledge. The most effective solution is considered to provide accurate information and adequate recommendations of HPV vaccination by attending physicians.

KEYWORDS

immunization programs, papillomavirus vaccines, systemic lupus erythematosus, vaccination

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting all organs, epidemiologically more common in women, with a peak incidence during pregnancy and childbearing years. The prognosis for patients with SLE used to be poor, but in the past two decades, there has been a remarkable improvement in the control of disease activity with the advent of superior therapies such as novel immunosuppressive drugs and biologic agents. Statistics on SLE patients show a steady decreasing trend in deaths due to the underlying disease itself.[1] This change has resulted in a relative increase in the proportion of deaths due to malignancy, cardiovascular events, and infections. Therefore, we believe that there is a need to address these issues in order to further improve the survival rate or quality of life of SLE patients.

Multiple cohorts and meta-analyses have shown that SLE patients have a high frequency of cervical cancer and cervical intraepithelial neoplasia (CIN) than the

general population.[2–4] The odds ratio (OR) of high-grade squamous intraepithelial lesions in women with SLE compared to healthy controls has been reported to be 8.66.[5] One of the reasons for the high incidence of cervical cancer in SLE patients is the high rate of human papillomavirus (HPV) infection, which is a major cause of cervical cancer. In a meta-analysis, the HPV infection rate was higher in SLE patients compared to healthy controls (34.15% vs. 15.3%, OR 2.97, 95% confidence interval 2.25–3.76).[6] SLE patients are reported to be at risk for high-risk types of HPV, such as HPV-16/18, because of inefficient clearance of HPV according to immunosuppressive status.[7] Furthermore, immunosuppressed conditions may promote cancer development through persistent HPV infection.

The HPV vaccine is the most effective method of preventing HPV infection. Several prospective observational studies have shown that the HPV vaccine prevents the development of cervical cancer as well as CIN.[8,9] It is recommended that all SLE patients should obviously be encouraged to be vaccinated against HPV, following the above-mentioned background of SLE.[10] In fact, the 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases[11] and the 2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases[12] suggest that patients with autoimmune diseases, in particular patients with SLE, should receive vaccinations against HPV.

Japan is in the extraordinary situation with the lowest HPV vaccination rates among developed countries due to the interruption of government proactive recommendations for more than 8 years until recently, in the general population, not limited to SLE patients. The HPV vaccine in Japan was approved in October 2009, and a routine vaccination program was initiated. However, in 2013, a campaign by the domestic media to emphasize the adverse effects of the HPV vaccine heated up,[13] leading to the interruption of the government recommendation of the HPV vaccine by the Ministry of Health, Labor, and Welfare (MHLW). Since then, HPV vaccination rates among women of age eligible for vaccination in Japan have dropped sharply from the 70% range to less than 1%.[14,15] The reported safety concerns were denied in several studies, most notably the Nagoya study,[16,17] and through the criticism of Japan's vaccine policy by WHO in July 2017,[18] the interruption of proactive recommendation of the HPV vaccine in Japan finally discontinued in April 2022, and individual recommendations were resumed as for other routine vaccinations.[19,20] Since then, the HPV vaccination rate in Japan has improved but is still at a low level.[21,22] Various factors may be related, including lack of education or appropriate promotions of awareness, insufficient recommendations by health care professionals, and vaccine hesitancy. There is also concern that the strong residual effect of the negative media campaign is imprinting a distrust of the HPV vaccine on the entire population in Japan.

Our question was what strategies could be developed to increase the HPV vaccination rates of SLE patients, which are critically low in the context after such a large-scale negative campaign in Japan. Although HPV infection rates are strongly influenced by local differences, the healthcare system, and social and economic conditions,[23] it is also essential to establish a specific strategy based on a survey of the current local situation. Therefore, we designed a pilot study using a questionnaire-based investigation to identify the factors inhibiting HPV vaccination of SLE patients.

MATERIALS AND METHODS

Study design

This is a single-center, cross-sectional study using a patient questionnaire. The study was conducted between April and December 2023, and included female SLE patients aged 18 to 45, who are in the age group with proven efficacy of the HPV vaccine, and who are currently attending our rheumatology department of Science Tokyo Hospital. To ensure a high questionnaire collection rate, a questionnaire-based survey was combined with an internet survey, and each participant was given an incentive of 2000 yen. Recruitment to the survey was done through advertising by displaying posters with QR codes in outpatient settings and oral invitation from attending physicians. The answers were anonymous due to containing highly private information. We ensured anonymity by not sharing information among the attending physician, persons who collect the questionnaires, and persons who analyze the survey results, in order to prevent the linking of individual participants and their answers.

Questionnaire content

The contents of the survey included age, region of birth, history of overseas residence, educational background, annual income, incidence and prevalence of cervical cancer, gynecological examinations taken, HPV vaccination rate, what type of information sources (media, SNS, etc.) are used to gather medical information, attitude toward vaccines, accurate knowledge of vaccines, and the negative image of vaccines, etc. The assessments of attitude toward vaccines, including vaccine hesitancy, were performed using the VAX scale questionnaire items.[24] To assess accurate knowledge of vaccines, we used the total score of the quiz that we prepared in which participants made a correct or incorrect choice about HPV and vaccines. The quiz consisted of 18 original questions developed for this study, 12 for general knowledge about HPV and vaccines, and 6 questions on knowledge specific to autoimmune diseases.

Statistical analysis

The answers obtained were analyzed using a logistic regression model to investigate the factors related to HPV vaccination and the intention to administer the HPV vaccination in the future. Categorical variables were expressed as percentages and continuous variables were expressed as the mean ± standard deviation (SD) for normal distributions or medians and interquartile ranges (IQR) otherwise. In independent samples, either chi-square tests or Fisher's exact tests were used for binary data, either *t*-tests or Mann–Whitney's *U*-tests were used for continuous data. The correlation coefficient was assessed by Spearman's rank correlation coefficient method. All *p* values were two-tailed, and those of less than 0.05 were considered statistically significant. Data were analyzed with SPSS version 28.0.0.0 software (SPSS Japan, Tokyo, Japan).

RESULTS

Basic information of participants

A total of 88 valid answers were collected from 88 participants. The mean age (± SD) of participants was 35.0 ± 6.7 years. The final education level was junior high school/high school for 18 participants, junior college/professional school for 21 participants, university for 37 participants, master's degree/doctoral degree for 11 participants, and non-response for 1 participant. The annual income was less than 3 million yen with 53 participants, between 3 and 5 million yen with 23 participants, between 5 and 7 million yen with 6 participants, more than 7 million yen with 5 participants, and non-response with 1 participant. The sources of medical information (multiple choices allowed) were, in descending order: 74 primary physicians, 43 experts articles on internet, 32 medical institution's websites, 30 social networking services (SNS), 18 nurses/pharmacists charge, 16 books, 14 parents/relatives, 14 TV/radio media, 13 friends of medical professionals, 13 personal blogs, 12 pharma company websites, 12 official government websites, 11 friends, and fewer than 10 others.

Comparison of HPV vaccinated and non-vaccinated participants

HPV vaccination history consisted of 5 (5.7%) vaccinated and 83 (94.3%) unvaccinated. The mean age of HPV vaccinated participants was significantly lower than that of unvaccinated participants, which presumably reflects the routine vaccination that began in Japan in December 2009. There were no statistically significant differences in HPV vaccination status by education, annual income, or history of living abroad (Table 1). The reasons for receiving HPV vaccine were "reasonable or free of charge" with 2 participants and "it is routine vaccine" with 2 (Figure 1a). The reasons for not receiving HPV vaccine (among whom 74 responses) were "don't know" with 28 participants, "missed opportunity" with 16, and "troublesome, somehow" with 8 (Figure 1b). HPV vaccinated participants were significantly more frequent to use medical institution's websites as a source of medical information ($p = 0.003$) (Figure 2). The most trusted source of medical information among the HPV unvaccinated was their primary physician (50 participants, 69.4%), followed by medical institution's website (8 participants, 11.1%) (Figure 2).

HPV vaccination status by generation based on vaccine policy

We analyzed HPV vaccination status and future intentions to receive the HPV vaccine, classified into three generations based on the vaccine policy in Japan (Table 2). Generation 1 is comprised of participants who were applicable before the start of routine vaccination and never had a chance to receive the HPV vaccine (i.e. ≥ 30 years old, born before 1993). Generation 2 consists of participants who were applicable from the start of routine vaccination to the interruption of the proactive recommendation, whose periods of routine vaccination do not include the suspended period of proactive recommendation (i.e., 27–29 years old, born in 1994–1996). Generation 3 includes participants affected by the interruption of the proactive recommendation, whose period of routine vaccination must include the suspended period of proactive recommendation (i.e., ≤26 years old, born after 1997). In Generation 1, no patient was vaccinated, and 21 (33.9%) were unaware of the HPV vaccine, which is the highest percentage compared to any other generation. Three (21.4%) and two (22.2%) were vaccinated in Generation 2 and Generation 3, respectively. Even among Generations 2 and 3, who are eligible for catch-up HPV vaccination in Japan, 6 (26.0%) were unaware.

Comparison of those willing to receive HPV vaccine and those not willing to receive HPV vaccine

Of the participants who had not received the HPV vaccine, 38 participants answered the question of whether they intended to receive the HPV vaccine in the future: 14 (36.8%) were willing to receive the HPV vaccine, 9 (23.7%) were not willing to receive the HPV vaccine, and 15 (39.5%) were unable to decide. No statistically significant differences were found in background, such as education, annual income, or history of living abroad, between those who were willing to receive the HPV vaccine and those who were not (Table 3).

TABLE 1 Characteristics of participants.

	HPV vaccinated ($N = 5$)	HPV unvaccinated or unknown ($N = 83$)	p value
Age (mean, SD)	26.6 ± 1.7	35.5 ± 6.7	0.003*
History of cervical cancer	0 (0%)	0 (0%)	–
History of CIN	0 (0%)	5 (6.0%)	0.668
History of cervical cancer screening	3 (60.0%)	39 (47.0%)	0.917
Final education level			
Junior high school (*N*, %)	0 (0%)	1 (1.2%)	0.054
High school (*N*, %)	1 (20.0%)	16 (19.3%)	0.587
Junior college/professional school (*N*, %)	0 (0%)	21 (25.3%)	0.454
University (*N*, %)	4 (80.0%)	33 (39.8%)	0.192
Master/Doctoral degree (*N*, %)	0 (0%)	11 (13.3%)	0.862
Annual income (million yen)			
<3.0 (*N*, %)	1 (20.0%)	52 (62.7%)	0.155
3.0–5.0 (*N*, %)	4 (80.0%)	19 (22.9%)	0.138
5.0–7.0 (*N*, %)	0 (0%)	6 (7.2%)	0.862
>7.0 (*N*, %)	0 (0%)	5 (6.0%)	0.668
History of living abroad (*N*, %)	1 (20.0%)	11 (13.3%)	0.807
Influenza vaccinators (last season)	4 (80.0%)	40 (48.2%)	0.357
COVID-19 vaccinators	5 (100.0%)	72 (86.7%)	0.862

Note: Continuous values are shown as mean ± SD. Binary values are presented as number (%) unless otherwise indicated. p values were calculated for comparison between HPV vaccinated and unvaccinated participants using chi-square tests for binary data, t-tests for continuous data.
Abbreviations: CIN, cervical intraepithelial neoplasia; COVID-19, coronavirus disease 2019; HPV, human papilloma virus; *N*, numbers; SD, standard deviation.
*p values less than 0.05.

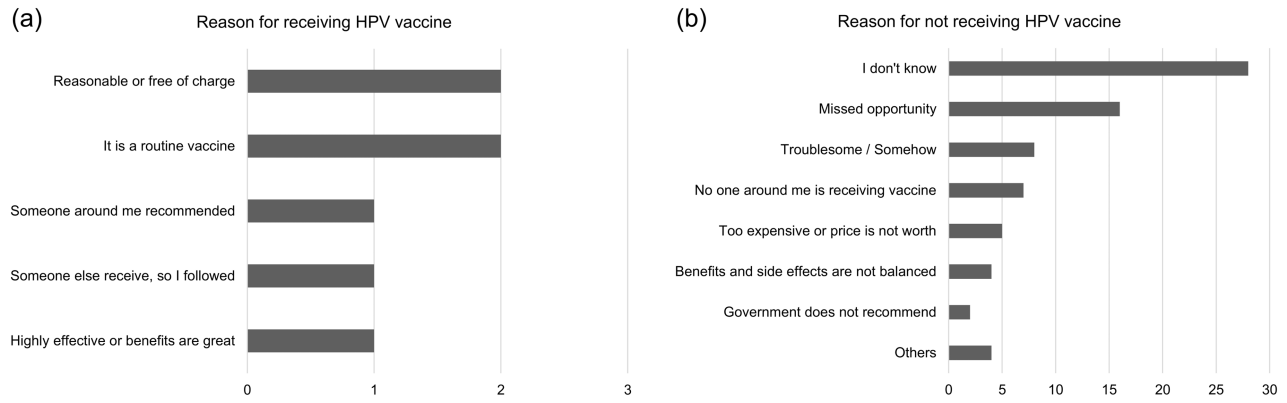

FIGURE 1 Reason for receiving HPV vaccine. We asked the reasons for receiving HPV vaccine among the HPV vaccinated participants, and reasons for not receiving HPV vaccine among the HPV unvaccinated participants. (a) Answers by HPV vaccinated participants. (b) Answers by HPV unvaccinated participants. HPV, human papilloma virus.

Vaccine attitude, vaccine hesitancy, and vaccine knowledge

Table 4 showed the correlations between vaccine attitude, vaccine hesitancy (evaluated by VAX scale), or vaccine knowledge (evaluated by quiz correctness) among the HPV vaccinated and unvaccinated, and among the unvaccinated with and without intention to receive HPV vaccine, respectively. No significant correlations were found between HPV vaccinators and vaccine attitudes, vaccine hesitancy, or vaccine knowledge (Table 4). Among the unvaccinated participants, "willing to receive HPV vaccine" was positively correlated with "trust of vaccine benefit" ($r = 0.561$. $p = 0.005$) and "general knowledge about HPV and vaccines" ($r = 0.512$, $p = 0.013$), and negatively correlated with "negative attitude toward vaccination and vaccine policy" ($r = -0.547$, $p = 0.007$) (Table 4).

DISCUSSION

In this study, we found that the main reason for not receiving the HPV vaccine is due to a lack of knowledge, but not to vaccine hesitancy in Japanese SLE patients.

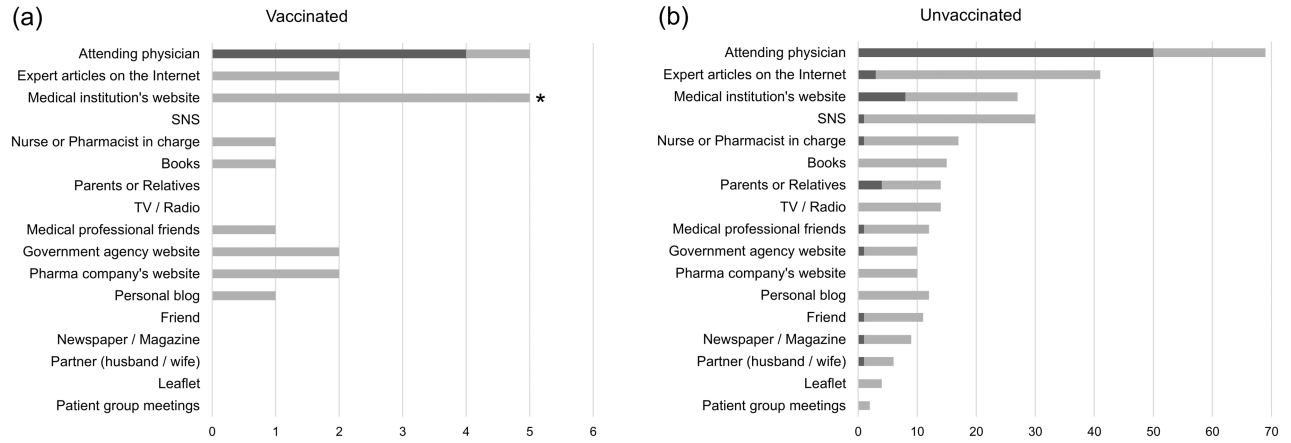

FIGURE 2 Sources of medical information for HPV vaccinated and unvaccinated participants. We asked which informational tools participants use to gather medical information. The most trusted sources are indicated by dark bars; others are indicated by light bars. * indicates significant differences between HPV vaccinated and unvaccinated participants ($p < 0.05$, chi-square test). (a) Answers by HPV vaccinated participants. (b) Answers by HPV unvaccinated participants. HPV, human papilloma virus; SNS, social networking service; TV, television.

TABLE 2 HPV vaccination status by generation based on vaccine policy in Japan.

	Generation 1 (before routine vaccination)	Generation 2 (after start of routine vaccination)	Generation 3 (affected by the interruption)
N	62	14	9
HPV vaccinated	0/62 (0%)	3/14 (21.4%)	2/9 (22.2%)
HPV unvaccinated	33/62 (53.2%)	3/14 (21.4%)	2/9 (22.2%)
Unknown vaccine history	8/62 (12.9%)	4/14 (28.5%)	3/9 (33.3%)
Not aware of HPV vaccine	21/57 (33.9%)	4/14 (28.5%)	2/9 (22.2%)
Future Intentions of HPV vaccine among unvaccinated (exclude non-respondents)			
Willing to receive vaccine	12/33 (36.3%)	1/3 (33.3%)	1/2 (50.0%)
Not willing to receive vaccine	8/33 (24.2%)	1/3 (33.3%)	0/2 (0%)
Unable to decide	13/33 (39.3%)	1/3 (33.3%)	1/2 (50.0%)

Note: Binary values are presented as number (%) unless otherwise indicated.
Abbreviations: HPV, human papilloma virus; *N*, numbers.

We interpret that the impact of the negative campaign is not as serious in many SLE patients as health care providers believe.

This study also revealed that the HPV vaccination rate among SLE patients in Japan is extremely low at 5.7%. To the best of our knowledge, this is the first report investigating the HPV vaccination rate among SLE patients in Japan, although the crude survey method is by voluntary reporting using a questionnaire. We cannot precisely discuss whether the overall vaccination rate of SLE patients in this study is an outlier or not, because there are not sufficient data on the HPV vaccination rate among the healthy population in the generation before the start of routine vaccination in Japan (i.e. Generation 1). If we discuss only the generations eligible for routine vaccinations (i.e., Generation 2 and 3), the cumulative first vaccination rate in whole Japan is 9%–80%, indicating that the vaccination rate in this study is about the same level.[25] A cohort of the United States at 2015 also had a similarly low HPV vaccination rate (10.7%) among SLE patients as in our study.[26] This suggests that health care professionals, including rheumatologists, may underestimate the risk of CIN and cervical cancer, and/or overestimate the risk of HPV vaccination.

Most unvaccinated participants in this study considered health care professionals, especially their primary physicians, as their main source of medical information. Furthermore, accurate knowledge about HPV vaccination was significantly higher among those who intend to be vaccinated in the future, and these intentions were independent of concerns about the unknown adverse effects of the vaccine. Thus, to provide appropriate "vaccine literacy" by attending physicians is probably the most effective approach to increase HPV vaccination rates. While it is important to remove concerns about adverse events when providing information about HPV vaccination, our study indicates that the most important approach is to ensure the vaccine benefits and efficacy.

There is a strong concern that the importance of HPV vaccination in SLE patients is not well recognized not

TABLE 3 Comparison of background according to HPV vaccine intention.

	Willing to receive HPV vaccine ($N = 14$)	Not willing to receive HPV vaccine, or unable to decide ($N = 24$)	p value
Age (average, SD)	37.3 ± 6.5	38.1 ± 5.7	0.691
History of cervical cancer	0 (0%)	0 (0%)	–
History of CIN	2 (14.3%)	2 (8.3%)	0.977
History of cervical cancer screening	8 (57.1%)	11 (45.8%)	0.737
Final education level			
Junior high school	0 (0%)	0 (0%)	–
High school	1 (7.1%)	4 (16.7%)	0.734
Junior college/professional school	4 (28.6%)	5 (20.8%)	0.884
University	6 (42.9%)	13 (54.2%)	0.737
Master/doctoral degree	3 (21.4%)	2 (8.3%)	0.513
Annual income (million yen)			
<3 million yen	10 (71.4%)	16 (66.7%)	0.954
3–5 million yen	2 (14.3%)	3 (12.5%)	0.954
5–7 million yen	1 (7.1%)	2 (8.3%)	0.945
>7 million yen	1 (7.1%)	3 (12.5%)	0.977
History of living abroad	5 (35.7%)	2 (8.3%)	0.096

Note: Continuous values are shown as mean ± SD. Binary values are presented as number (%) unless otherwise indicated. p values were calculated for comparison between those who is willing to receive HPV vaccine and those who is not willing to receive HPV vaccine or unable to decide, using chi-square tests for binary data, t-tests for continuous data.
Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; N, numbers; SD, standard deviation.

TABLE 4 Correlations between HPV vaccinated or vaccine intentions and vaccine knowledge/attitudes.

	Between HPV vaccinated ($N = 5$) and others ($N = 83$)		Between willing to receive HPV vaccination ($N = 14$) and others ($N = 24$)	
	Correlation coefficient	p value	Correlation coefficient	p value
Attitude toward vaccines				
Trust of vaccine benefit	0.133	0.218	0.561	0.005*
Worries over unforeseen future effects	−0.157	0.143	−0.377	0.076
Concerns about commercial profiteering	−0.037	0.729	−0.069	0.755
Preference for natural immunity	−0.054	0.620	0.171	0.435
Negative attitude toward vaccination and vaccine policy	−0.075	0.485	−0.547	0.007*
Knowledge of vaccines				
General knowledge about HPV and vaccines	0.031	0.775	0.512	0.013*
Knowledge specific to autoimmune diseases	−0.064	0.556	−0.113	0.607

Note: p values were calculated using Spearman's rank correlation coefficient between HPV vaccinated and others, and between willingness to receive HPV vaccination and others, respectively.
Abbreviations: HPV, human papilloma virus; N, numbers.
*p values less than 0.05.

only among patients but also among rheumatologists, in considering the approach of providing information from the attending physician to increase the HPV vaccination rate. The participants in our study were not educated enough about the HPV vaccination, even though they were considered an exemplary population with a high level of health literacy, since they had the same or higher rates of influenza or COVID-19 vaccination and cervical cancer screening compared to the general population. As reported by Sakanishi et al., accurate knowledge of vaccination by healthcare providers is associated with appropriate recommendations of HPV vaccination.[27] Although some experts are concerned about vaccine safety in SLE patients due to case reports of disease flare-ups after vaccination or newly onset vaccine-triggering autoimmune events, multiple studies have demonstrated the evidence of vaccine safety.[28,29]

Therefore, we must increase the awareness of rheumatologists about this problem and control the HPV vaccination

process in a systematic approach. There are still no academic statements or recommendations in Japan to guide appropriate vaccination against autoimmune diseases, unlike in Europe or the United States. Recommendations by governments and health care professionals have also been demonstrated to promote vaccination, as previously reported.[30–32] Although it is estimated that Japan could reduce cervical cancer deaths by 60% through catch-up vaccination,[33] we should recognize that the benefit of the HPV vaccine generally decreases with increasing age of vaccination. So, it is important to provide information as early as possible, while it is unclear whether the appropriate age for vaccination in the general population applies to patients with SLE. Multifaceted interventions should be necessary in the future, such as the establishment of clinical evidence and academic recommendations for vaccines, public health interventions, and appropriate education and promotional campaigns for both health care providers and patients.

This study has several limitations. First, this study is statistics from a single center in the Tokyo metropolitan area, so these results may not be applicable to the entire area of the country or world, especially in the rural area. Rural areas generally have lower HPV vaccination rates than urban areas,[34] and education about HPV and the vaccine is poorly developed.[35,36] Second, we did not collect information about what information the participants had previously been provided by health care providers including attending physicians, regarding HPV vaccination. We also do not have any data on the priority level of HPV vaccination for SLE patients by their attending physicians. In the United States, approximately half of pediatric rheumatologists sometimes or always recommend HPV vaccines to their patients.[37] Considering that half of the participants missed opportunities or did not know about HPV vaccines, presumably a sufficient proportion of those patients are not recommended for vaccination. Third, the questionnaire on vaccine knowledge was not validated in advance. Although the nature of the quiz reflects a certain level of accurate knowledge, we admit the limitation of its validity and reliability. Fourth, our study may have insufficient power for some factors since the sample size was not calculated as required for statistical significance. For example, we might have potentially underestimated the impact of groups who are reluctant to receive vaccinations due to concerns about adverse events such as vaccine-triggered flares of SLE, so this might require further investigation with a large sample size. In addition, it should be considered that self-reporting bias might have led to a higher proportion of participants who were cooperative with their primary physicians or who had a positive attitude toward vaccines. Fifth, the immunogenicity of the HPV vaccine was not evaluated. Despite adequate vaccination, SLE patients may not be sufficiently immunized due to the disease itself or to the immunosuppressive status induced by therapeutic agents. Mok CC et al. reported significantly lower HPV vaccine antibody titers in SLE patients and higher incidence of primary vaccine failure or seroreversion, which were associated with disease flares and cumulative doses of immunosuppressive agents.[38] In order to achieve the true goal of improving the prognosis and quality of life of SLE patients, future issues should also include investigating the regular monitoring of antibody titers or requirements for indication of booster vaccination.

Our study might indicate that low HPV vaccination rates, which are important for SLE patients, are potentially attributed to a lack of knowledge rather than vaccine hesitancy. It is essential to increase the HPV vaccination rate to improve the prognosis of patients with SLE. The resumption of proactive recommendation of routine HPV vaccination in Japan provides a very good opportunity. However, learning from the great loss of opportunities for HPV vaccination in Japan, additional public health interventions by the government or medical organization(s) are also essential, such as providing further catch-up vaccination opportunities or preventing biased media reporting. We believe that the most effective strategy is providing adequate guidance and support to each patient by the attending physician about the efficacy and safety of the HPV vaccination. For this purpose, we must increase the awareness of rheumatologists about HPV vaccination, understand its importance, and establish a consensus based on the local situation.

AUTHOR CONTRIBUTIONS

Takashi Kurita: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing – original draft. **Akio Yamamoto:** Data curation; writing – review and editing. **Tadashi Hosoya:** Data curation; writing – review and editing. **Marina Tsuchida:** Data curation; writing – review and editing. **Shinsuke Yasuda:** Data curation; writing – review and editing. **Yoshiaki Gu:** Methodology; project administration; supervision; writing – review and editing.

ACKNOWLEDGMENTS

We thank all the medical staff in the department of rheumatology section and in the infection control center of our hospital for their contributions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions. This is because our raw data analyzed in this manuscript have been anonymized, but we have not obtained consent from the participants to disclose them in a publicly accessible setting, and have not received ethics committee approval for disclosure. The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from each participant. Our study complied with the principles of the Declaration of Helsinki and was approved by the local ethics committee (Permission number C2022-035).

ORCID

Takashi Kurita https://orcid.org/0000-0002-4670-405X

REFERENCES

1. Moreno-Torres V, Tarín C, Ruiz-Irastorza G, Castejón R, Gutiérrez-Rojas Á, Royuela A, et al. Trends in hospital admissions and death causes in patients with systemic lupus erythematosus: Spanish national registry. J Clin Med. 2021;10(24):5749. https://doi.org/10.3390/jcm10245749
2. Han J-Y, Kim H, Jung S-Y, Jang EJ, Cho S-K, Sung Y-K. Increased risk of malignancy in patients with systemic lupus erythematosus: population-based cohort study in Korea. Arthritis Res Ther. 2021;23(1):270. https://doi.org/10.1186/s13075-021-02648-y
3. Song L, Wang Y, Zhang J, Song N, Xu X, Lu Y. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther. 2018;20(1):270. https://doi.org/10.1186/s13075-018-1760-3
4. Kim SC, Glynn RJ, Giovannucci E, Hernández-Díaz S, Liu J, Feldman S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Ann Rheum Dis. 2015;74(7):1360–7. https://doi.org/10.1136/annrheumdis-2013-204993
5. Zard E, Arnaud L, Mathian A, Chakhtoura Z, Hie M, Touraine P, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: a meta-analysis of the literature. Autoimmun Rev. 2014;13(7):730–5. https://doi.org/10.1016/j.autrev.2014.03.001
6. García-Carrasco M, Mendoza-Pinto C, Rojas-Villarraga A, Molano-González N, Vallejo-Ruiz V, Munguía-Realpozo P, et al. Prevalence of cervical HPV infection in women with systemic lupus erythematosus: a systematic review and meta-analysis. Autoimmun Rev. 2019;18(2):184–91. https://doi.org/10.1016/j.autrev.2018.09.001
7. Lee Y-H, Choe J-Y, Park S-H, Park YW, Lee SS, Kang YM, et al. Prevalence of human papilloma virus infections and cervical cytological abnormalities among Korean women with systemic lupus erythematosus. J Korean Med Sci. 2010;25(10):1431–7. https://doi.org/10.3346/jkms.2010.25.10.1431
8. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383(14):1340–8. https://doi.org/10.1056/NEJMoa1917338
9. Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Bernal J, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet. 2021;398(10316):2084–92. https://doi.org/10.1016/S0140-6736(21)02178-4
10. Grein IHR, Groot N, Lacerda MI, Wulffraat N, Pileggi G. HPV infection and vaccination in systemic lupus erythematosus patients: what we really should know. Pediatr Rheumatol Online J. 2016;14(1):12. https://doi.org/10.1186/s12969-016-0072-x
11. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(1):39–52. https://doi.org/10.1136/annrheumdis-2019-215882
12. Bass AR, Chakravarty E, Akl EA, Bingham CO, Calabrese L, Cappelli LC, et al. 2022 American College of Rheumatology Guideline for vaccinations in patients with rheumatic and musculoskeletal diseases. Arthritis Care Res. 2023;75(3):449–64. https://doi.org/10.1002/acr.25045
13. Okuhara T, Ishikawa H, Okada M, Kato M, Kiuchi T. Newspaper coverage before and after the HPV vaccination crisis began in Japan: a text mining analysis. BMC Public Health. 2019;19(1):770. https://doi.org/10.1186/s12889-019-7097-2
14. Nakagawa S, Ueda Y, Yagi A, Ikeda S, Hiramatsu K, Kimura T. Corrected human papillomavirus vaccination rates for each birth fiscal year in Japan. Cancer Sci. 2020;111(6):2156–62. https://doi.org/10.1111/cas.14406
15. Yagi A, Ueda Y, Kakuda M, Nakagawa S, Hiramatsu K, Miyoshi A, et al. Cervical cancer protection in Japan: where are we? Vaccines (Basel). 2021;9(11):1263. https://doi.org/10.3390/vaccines9111263
16. Suzuki S, Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. Papillomavirus Res. 2018;5:96–103. https://doi.org/10.1016/j.pvr.2018.02.002
17. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. 2018;5(5):CD009069. https://doi.org/10.1002/14651858.CD009069.pub3
18. Global Advisory Committee on Vaccine Safety (WHO). Safety of HPV vaccines. [cited 2024 Apr 16]. Available from: https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety
19. Ministry of Health, Labour and Welfare. Future response to regular vaccinations related to HPV infection. [cited 2024 Apr 16]. Available from: https://www.mhlw.go.jp/content/000875155.pdf
20. Haruyama R, Obara H, Fujita N. Japan resumes active recommendations of HPV vaccine after 8.5 years of suspension. Lancet Oncol. 2022;23(2):197–8. https://doi.org/10.1016/S1470-2045(22)00002-X
21. Namba M, Kaneda Y, Kawasaki C, Shrestha R, Tanimoto T. Underlying background of the current trend of increasing HPV vaccination coverage in Japan. Glob Health Med. 2023;5(4):255–6. https://doi.org/10.35772/ghm.2023.01010
22. Prevention of cervical cancer and other HPV-related cancers fact sheet. National Cancer Center NI of CCJ. [cited 2024 Apr 16]. Available from: https://www.ncc.go.jp/html/icc/hpvcancer/index.html
23. Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. RMD Open. 2019;5(2):e001041. https://doi.org/10.1136/rmdopen-2019-001041
24. Martin LR, Petrie KJ. Understanding the dimensions of anti-vaccination attitudes: the vaccination attitudes examination (VAX) scale. Ann Behav Med. 2017;51(5):652–60. https://doi.org/10.1007/s12160-017-9888-y
25. Ueda Y. Study on the HPV vaccination status (in Japanese). Adverse reaction study subcommittee, subcommittee on immunization and vaccine. [cited 2024 Apr 16]. Available from: https://www.mhlw.go.jp/content/10601000/001198130.pdf
26. Feldman CH, Hiraki LT, Lii H, Seeger JD, Kim SC. Human papillomavirus vaccine uptake among individuals with systemic inflammatory diseases. PLoS One. 2015;10(2):e0117620. https://doi.org/10.1371/journal.pone.0117620
27. Sakanishi Y, Takeuchi J, Suganaga R, Nakayama K, Nishioka Y, Chiba H, et al. Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan. BMJ Open. 2023;13(11):e074305. https://doi.org/10.1136/bmjopen-2023-074305
28. Infante V, Miyaji KT, Soarez PC, Sartori AMC. Systematic review and meta-analysis of HPV vaccination in women with

systemic lupus erythematosus (SLE). Expert Rev Vaccines. 2021; 20(3):309–18. https://doi.org/10.1080/14760584.2021.1889375
29. Hersh AO, Alarcón GS, Bonetto C, Pernus YB, Kucuku M, Santuccio C, et al. Systemic lupus erythematosus: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(51):6572–81. https://doi.org/10.1016/j.vaccine.2016.09.031
30. Lelliott M, Sahker E, Poudyal H. A review of parental vaccine hesitancy for human papillomavirus in Japan. J Clin Med Res. 2023;12(5):2004. https://doi.org/10.3390/jcm12052004
31. Rositch AF, Liu T, Chao C, Moran M, Beavis AL. Levels of parental human papillomavirus vaccine hesitancy and their reasons for not intending to vaccinate: insights from the 2019 National Immunization Survey-Teen. J Adolesc Health. 2022; 71(1):39–46. https://doi.org/10.1016/j.jadohealth.2022.01.223
32. Hansen PR, Schmidtblaicher M, Brewer NT. Resilience of HPV vaccine uptake in Denmark: decline and recovery. Vaccine. 2020; 38(7):1842–8. https://doi.org/10.1016/j.vaccine.2019.12.019
33. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. Lancet Public Health. 2020;5(4):e223–34. https://doi.org/10.1016/S2468-2667(20)30010-4
34. Goessl CL, Christianson B, Hanson KE, Polter EJ, Olson SC, Boyce TG, et al. Human papillomavirus vaccine beliefs and practice characteristics in rural and urban adolescent care providers. BMC Public Health. 2022;22(1):1322. https://doi.org/10.1186/s12889-022-13751-3
35. Mohammed KA, Subramaniam DS, Geneus CJ, Henderson ER, Dean CA, Subramaniam DP, et al. Rural-urban differences in human papillomavirus knowledge and awareness among US adults. Prev Med. 2018;109:39–43. https://doi.org/10.1016/j.ypmed.2018.01.016
36. Barbieri V, Wiedermann CJ, Lombardo S, Plagg B, Gärtner T, Ausserhofer D, et al. Rural-urban disparities in vaccine hesitancy among adults in South Tyrol, Italy. Vaccines (Basel). 2022;10(11): 1870. https://doi.org/10.3390/vaccines10111870
37. Hofstetter AM, Lappetito L, Stockwell MS, Rosenthal SL. Human papillomavirus vaccination of adolescents with chronic medical conditions: a national survey of pediatric subspecialists. J Pediatr Adolesc Gynecol. 2017;30(1):88–95. https://doi.org/10.1016/j.jpag.2016.08.005
38. Mok CC, Ho LY, To CH. Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus. Vaccine. 2018;36(23):3301–7. https://doi.org/10.1016/j.vaccine.2018.04.056

How to cite this article: Kurita T, Yamamoto A, Hosoya T, Tsuchida M, Yasuda S, Gu Y. Lack of knowledge, not vaccine hesitancy, is the main cause of low human papilloma virus vaccination rate among systemic lupus erythematosus patients in Japan after suspension of proactive recommendation: Analysis of a patients' survey. J Obstet Gynaecol Res. 2025;51(6):e16330. https://doi.org/10.1111/jog.16330