

ORIGINAL ARTICLE

Long-term effectiveness of HPV vaccination against HPV infection in young Japanese women: Real-world data

Megumi Kurosawa¹ | Masayuki Sekine¹  | Manako Yamaguchi¹ | Risa Kudo¹ | Sharon J. B. Hanley²  | Megumi Hara³ | Sosuke Adachi¹ | Yutaka Ueda⁴ | Etsuko Miyagi⁵  | Sayaka Ikeda⁶  | Asami Yagi⁴  | Takayuki Enomoto¹ 

¹Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

²Hokkaido University Center for Environmental and Health Sciences, Sapporo, Japan

³Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga, Japan

⁴Departments of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka, Japan

⁵Department of Obstetrics and Gynecology, Yokohama City University School of Medicine, Yokohama, Japan

⁶Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

Correspondence

Masayuki Sekine, Department of Obstetrics and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori, Chuo-ward, Niigata 951-8510, Japan.
Email: masa@med.niigata-u.ac.jp

Funding information

This work was supported by the Japanese Agency for Medical Research and Development (JP21ck0106562).

Abstract

In Japan, public funding for HPV vaccination began in 2010 for girls aged 13–16 years (birth cohort years 1994–1997) and women born in 1994 who turned 25 in 2019. We aimed to verify the long-term effectiveness of the bivalent HPV vaccine in women aged 25 years. Subjects were women aged 25–26 years who underwent cervical cancer screening and HPV testing in Niigata from 2019 to 2020 (birth cohort years 1993–1994). Information on vaccination status and sexual behavior was obtained from a questionnaire and municipal records. We compared the HPV infection rates of the vaccinated and unvaccinated groups. Of the 429 registrants, 150 (35.0%) and 279 (65.0%) were vaccinated and unvaccinated, respectively. The average period from HPV vaccination to HPV testing was 102.7 months (8.6 years), with a median of 103 months (range 92–109 months). The HPV high-risk infection rate was 21.3% (32/150) in the vaccinated group and 23.7% (66/279) in the unvaccinated group ($P = 0.63$). The HPV16/18 infection rate was 0% (0/150) in the vaccinated group and 5.4% (15/279) in the unvaccinated group, showing a significant difference ($P = 0.0018$), and the vaccine effectiveness was 100%. The cross-protective type HPV31/45/52 infection rate in the vaccinated group was significantly lower than that in the unvaccinated group (3.3% vs. 10.0%, $P = 0.013$). There was no significant difference in the mean age at sexual debut and the number of previous sexual partners between the two groups. We have demonstrated the long-term 9-year effectiveness of the bivalent vaccine against HPV infection for the first time in Japan.

KEYWORDS

cervical cancer, HPV infection, HPV vaccine, Japan, long-term effectiveness

Abbreviations: ASC-US+, ASC-US or worse; CIN1+, CIN1 or worse; CIN2+, CIN2 or worse; CIN3+, CIN3 or worse; LSIL+, LSIL or worse; MHLW, the Ministry of Health, Labor and Welfare; NIP, national immunization program; VE, vaccine effectiveness.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Cancer Science* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.

1 | INTRODUCTION

In Japan, the bivalent HPV vaccine Cervarix[®] was approved in 2009 and the four-valent HPV vaccine Gardasil[®] was approved in 2011. A publicly funded HPV vaccination program began in 2010 for girls aged 13–16 years by each municipality, and HPV vaccination was included in the national immunization program (NIP) in April 2013. However, 2 months later, the Ministry of Health, Labor and Welfare (MHLW) in Japan announced that proactive recommendations for the vaccine were to be suspended. As a result, the vaccination rate, which was about 70% nationwide, decreased to less than 1%.^{1,2} Although the HPV vaccine is still included in the NIP and girls in the target age group can be inoculated with public funds, coverage remains low.^{3–5} Women born in or after 1994 were eligible for publicly funded HPV vaccination. According to a report by Nakagawa et al., the vaccination rate of women born in 1994 was 55.5%, and the rate for those born between 1995 and 1999 increased to 75.7%. After that, coverage in women born in 2000 decreased sharply to 14.3%, and it fell to less than 1% in women born after 2001.⁵

We previously reported a significant preventive effect of the HPV vaccine against HPV 16/18 infection in Japanese women aged 20–22 years.^{6,7} We also analyzed the preventive effect against abnormal cytology and histology in women aged 20 years and compared pre-vaccination cohorts (those born between 1991 and 1993) to those born when public funding became available for the HPV vaccine (born between 1994 and 1996). We found that the incidence of cytological abnormalities, ASC-US or worse (ASC-US+) decreased by 24%, LSIL or worse (LSIL+) decreased by 73%, and CIN3 decreased significantly from 0.8% to 0% ($P = 0.016$) in cohorts eligible for publicly funded vaccination.^{8,9} We also estimated the likelihood of abnormal histology in women aged 20–24 years. We found that the odds ratios for those vaccinated against HPV compared to those who were not were 0.42 (95% confidence interval [CI] 0.31–0.58), 0.25 (0.12–0.54), and 0.19 (0.03–1.15) for “CIN1 or worse (CIN1+)”, “CIN2 or worse (CIN2+)”, and “CIN3 or worse (CIN3+)”, respectively. These results showed the short-term effectiveness of HPV vaccination for women in their early 20s. So far, there have been no reports in Japan of the preventive effect of the HPV vaccine after the age of 25 years.

HPV infection rates for women in their 20s was highest at 23–26 years, and is reflective of sexually activity in this age group¹⁰ (Figure S1). Therefore, it is important to verify the effect of the HPV vaccine around the age of 25 years, when exposure to HPV is high. In this study, we aimed to ascertain the effectiveness of the HPV vaccine against HPV infection about 10 years after vaccination in women aged 25–26 years.

2 | MATERIALS AND METHODS

Subjects were women aged 25–26 years who underwent cervical cancer screening in Niigata City from April 2019 to March 2020 (birth cohort years 1993–1994). Residual screening specimens were used for HPV genotype testing. All samples were tested with the BD Onclarity[™] HPV kit (Becton, Dickinson and Company, New

Jersey, USA)^{11,12} and only those samples positive for the Onclarity[™] Genotyping was performed with the MEBGEN[™] HPV kit (MBL, Tokyo, Japan).¹³ Information on vaccination status and sexual behavior (age at sexual debut, number of previous sexual partners) was obtained from a questionnaire. For women who were vaccinated with public funds, the official vaccination records of Niigata city were examined to confirm the date of vaccination and type of vaccine. We recruited participants regardless of HPV vaccination status, sexual activity, and cancer screening results to minimize selection bias. To evaluate the effectiveness of the vaccine against high-risk HPV infection, we compared the following two groups: (1) a vaccinated group to an unvaccinated group and (2) a publicly funded HPV vaccine cohort (birth cohort year 1994: publicly funded generation) to a cohort that was not eligible for publicly funded HPV vaccination (birth cohort year 1993: pre-introduction generation). We used EZR software to perform Fisher's exact test, chi-square test, *t* test, and sample size calculation. The formula for vaccine effectiveness (VE) is $VE = (1 - OR) \times 100$, where OR is the odds ratio. *P* values of <0.05 were considered to be statistically significant. The present study protocol was approved by the institutional review board of Niigata University Graduate School of Medical and Dental Sciences and registered at the UMIN Clinical Trials Registry, trial number UMIN000026769. Written informed consent was obtained from all participants.

3 | RESULTS

3.1 | Characteristics of the registrants

In Japan, national cervical cancer screening is usually done once every 2 years. Among 7100 females aged 25 and 26 years in Niigata City, 770 women underwent cervical cancer screening in 2019 ($770/7100 = 10.8\%$). All 770 women were asked to participate in the study using a document outlining the study. Of them, 482 (62.6%) were enrolled in the study.

Of the 482 registrants, 429 were included in this study; one woman who received the 4-valent vaccine and 52 who did not complete the questionnaire were excluded from the analysis. There were 150 (35.0%) women in the vaccinated group and 279 (65.0%) in the unvaccinated group. Table 1 shows the characteristics of the registrants in this study by vaccination status. The average period from HPV vaccination to HPV testing was 102.7 months (8.6 years), with a median of 103 months (range 92–109 months). When registrants were divided by year of birth, the vaccination rate was 17.7% for women born in 1993 and 77.4% for women born in 1994. There were no significant differences between the two groups in sexual experience, number of previous sexual partners, and age at sexual debut.

3.2 | HPV infection rates in vaccinated and unvaccinated groups

Infection rates by high-risk HPV type (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 types) are shown in Table 2. The HPV

TABLE 1 Characteristics of the registrants in this study

	All (n = 429)	Vaccinated (n = 150)	Unvaccinated (n = 279)	P value
Age (y)				
Mean (\pm SD)	25.7 (\pm 0.5)	25.4 (\pm 0.5)	25.9 (\pm 0.3)	<.0001 ^b
Birth year (fiscal year)				
1993: pre-introduction generation	305 (71.1%)	54 (17.7%)	251 (82.3%)	<.0001 ^c
1994: publicly funded generation	124 (28.9%)	96 (77.4%)	28 (22.6%)	
Follow-up period (mo) ^a				
Mean \pm SD	-	102.7 \pm 3.5	-	-
Median (range)	-	103 (92–109)	-	-
Sexual intercourse, n (%)				
Experienced	413 (96.3%)	143 (95.3%)	270 (96.8%)	.44 ^c
Inexperienced	16 (3.7%)	7 (4.7%)	9 (3.2%)	
Number of sexual partners, n (%)				
\geq 10	71 (16.6%)	22 (14.7%)	49 (17.6%)	.762 ^c
6–9	80 (18.6%)	25 (16.7%)	55 (19.7%)	
2–5	197 (45.9%)	72 (48.0%)	125 (44.8%)	
1	65 (15.2%)	24 (16.0%)	41 (14.7%)	
None	16 (3.7%)	7 (4.7%)	9 (3.2%)	
Age at sexual debut, n (%)				
\leq 15	64 (14.9%)	21 (14.0%)	43 (15.4%)	.87 ^c
16–18	168 (39.2%)	58 (38.7%)	110 (39.4%)	
\geq 19	181 (42.2%)	64 (42.7%)	117 (41.9%)	
None	16 (3.7%)	7 (4.7%)	9 (3.2%)	
Mean (\pm SD)	18.3 (\pm 2.8)	18.3 (\pm 2.6)	18.2 (\pm 2.9)	.775 ^b

^aPeriod from HPV vaccination to HPV testing.

^bt test.

^cFisher's exact test.

TABLE 2 High-risk HPV infection rates in vaccinated and unvaccinated groups

	All (n = 429)	Vaccinated (n = 150)	Unvaccinated (n = 279)	OR (95% CI)	VE (95% CI)	P value ^b
	n (%)	n (%)	n (%)			
High-risk HPV ^a	98 (22.8)	32 (21.3)	66 (23.7)	0.88 (0.52 to 1.44)	12.5% (-44.4 to 47.7)	.63
HPV 16/18	15 (3.5)	0 (0.0)	15 (5.4)	0.00	100.0%	.0018
HPV 31/45/52	33 (7.7)	5 (3.3)	28 (10.0)	0.31 (0.09 to 0.84)	69.0% (16.3 to 90.9)	.013

Abbreviations: OR, odds ratio; VE, vaccine effectiveness.

^aHPV 16/18/31/33/35/39/45/51/52/56/58/59/68.

^bFisher's exact test.

high-risk infection rate was 21.3% (32/150) in the vaccinated group and 23.7% (66/279) in the unvaccinated group. Although the infection rate was slightly lower in the vaccinated group, there was no significant difference between the two groups ($P = 0.63$). The HPV16/18 infection rate was 0% (0/150) in the vaccinated group and 5.4% (15/279) in the unvaccinated group, showing a significant difference ($P = 0.0018$), and the VE was 100% (Table 2 and Figure 1). Regarding the infection rate for HPV31/45/52, types which have

been reported to offer a cross-protection effect by the bivalent HPV vaccine in Japanese women, the infection rate in the vaccinated group was 3.3% (5/150) and that in the unvaccinated group was 10.0% (28/279), thus significantly lower in the vaccinated group ($P = 0.013$). Regarding the preventive effect against HPV infection for each HPV type, there were HPV16, 18, 33, or 45 infections in the vaccinated group, showing a high infection-preventing effect (Table 3).

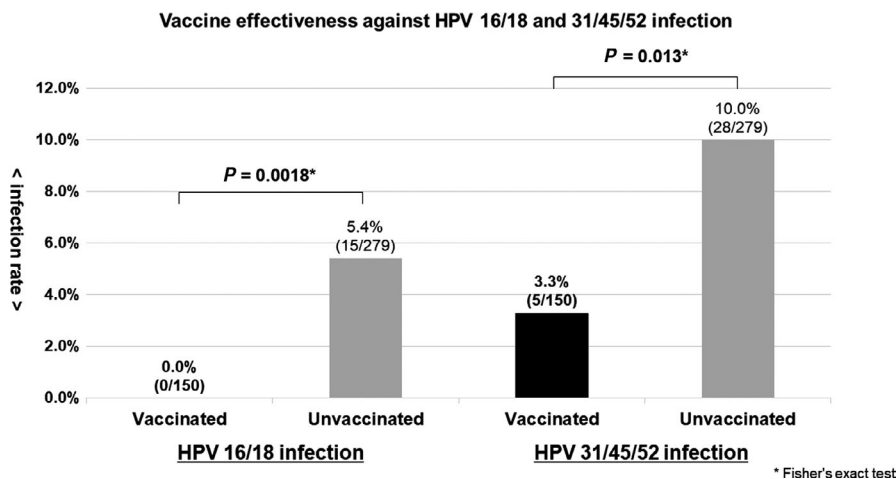


FIGURE 1 Vaccine effectiveness against HPV 16/18 and 31/45/52 infection in vaccinated and unvaccinated groups. The HPV16/18 infection rate was 0% (0/150) in the vaccinated group and 5.4% (15/279) in the unvaccinated group, showing a significant difference ($P = 0.0018$). Regarding the cross-protection effect of the bivalent vaccine, the HPV31/45/52 infection rate in the vaccinated group was 3.3% (5/150) and that in the unvaccinated group was 10.0% (28/279), therefore it was significantly lower in the vaccinated group ($P = 0.013$)

TABLE 3 Type-specific HPV infection rates in vaccinated and unvaccinated groups

	All (n = 429)	Vaccinated (n = 150)	Unvaccinated (n = 279)
	n (%)	n (%)	n (%)
HPV 16	14 (3.3)	0 (0.0)	14 (5.0)
HPV 18	2 (0.5)	0 (0.0)	2 (0.7)
HPV 31	11 (2.6)	1 (0.7)	10 (3.6)
HPV 33	2 (0.5)	0 (0.0)	2 (0.7)
HPV 35	0 (0.0)	0 (0.0)	0 (0.0)
HPV 39	14 (3.3)	5 (3.3)	9 (3.2)
HPV 45	2 (0.5)	0 (0.0)	2 (0.7)
HPV 51	18 (4.2)	7 (4.7)	11 (3.9)
HPV 52	24 (5.6)	4 (2.7)	20 (7.2)
HPV 56	17 (4.0)	6 (4.0)	11 (3.9)
HPV 58	18 (4.2)	5 (3.3)	13 (4.7)
HPV 59	6 (1.4)	2 (1.3)	4 (1.3)
HPV 68	13 (3.0)	3 (2.0)	10 (3.6)

In addition, we show the results of cytology of the registrants in Table S1. There was no significant difference in the rate of abnormal cytology between the vaccinated and unvaccinated groups.

3.3 | HPV infection rates in the publicly funded generation and pre-introduction generation

The registrants in the publicly funded generation (birth year 1994) and pre-introduction generation (birth year 1993) were 124 (28.9%) women in the former and 305 (71.1%) women in the latter, respectively (Table S2). The HPV vaccination rate was 77.4% (96/124) for the former and 17.7% (54/305) for the latter ($P < 0.0001$). There was no significant difference in the mean age at sexual debut and

the number of previous sexual partners between the two groups. The high-risk HPV infection rate was 24.2% (30/124) in the former and 22.3% (68/305) in the latter. There was no significant difference between the two groups ($P = 0.70$). The HPV16/18 infection rate was 0% (0/124) for the publicly funded generation, which was significantly lower than the 4.9% (15/305) for the pre-introduction generation ($P = 0.0077$). Regarding the cross-protective effect on HPV31/45/52, the infection rate in the publicly funded generation was 4.8% (6/124), which was lower than that in the pre-introduction generation (27/305 = 8.9%), but not statistically significant ($P = 0.23$).

4 | DISCUSSION

We have demonstrated the long-term effectiveness of the bivalent vaccine against HPV infection in Japanese women aged 25-26 years, 9 years after vaccination, with real-world data. Sexual activity in Japanese women in their mid-20s is high.¹⁰ HPV 16/18 infection accounts for 84.8% of the cause of cervical cancer in Japan, but in the younger generation aged 20-29 years the proportion is even higher, accounting for 90.0%.¹⁴ HPV vaccines are included in the NIP of more than 100 countries around the world,¹⁵ and effectiveness against high-risk HPV infection and precancerous lesions has been reported.^{16,17} Furthermore, in October 2020 it was reported that invasive cervical cancer was reduced by 88% in women vaccinated under the age of 17 years in Sweden.¹⁸ Currently, there are widespread HPV vaccination programs worldwide, with most programs primarily targeting girls under the age of 17 years. The risk of HPV infection depends on the sexual activity of the woman and the risk continues not only during the first sexual intercourse but also during sexually active periods. Therefore, it is very important to investigate the long-term effect of the HPV vaccine for assessing the reduction in cervical cancer risk over a woman's life.

According to previous reports on the long-term efficacy for precancers in clinical trials,¹⁹ the observation period for the bivalent

vaccine was 3.6 years in HPV 001,²⁰ 6.4 years in HPV 007,²¹ 8.4 years in HPV 023,²² 9.4 years in the Extension HPV023,²³ and 11.1 years in the Costa Rica Vaccine Trial.²⁴ In the Costa Rica Vaccine Trial for assessing the efficacy of the bivalent vaccine, women aged 18–25 years were enrolled in a randomized, double-blind, controlled trial. As a result, cumulative VE against HPV 16/18-associated CIN2+ and CIN3 specifically over the 11-year period was 97.4% (95% CI 88.0–99.6) and 94.9% (73.7–99.4), respectively.²⁴ So far, this report shows the longest efficacy of the bivalent vaccine.

For the 4-valent vaccine, the observation period is 3.6 years in FUTURE I,²⁵ 5 years in HPV-P007,²¹ 8 years in Nordic P015²⁵ and 14 years in FUTURE II.²⁶ So far, the longest observation period for vaccine efficacy has been 14 years for the 4-valent vaccine. In a 14-year long-term follow-up of women aged 16 to 26 years, no cases of HPV16/18-related CIN2+ and cervical cancer were observed in the per-protocol effectiveness population during the entire study. VE of 100% was demonstrated with a trend toward continued protection through 14 years post-vaccination. Seropositivity rates of HPV6, 11, 16, and 18 types were 90.6%, 91.1%, 98.3%, and 52.4%, respectively.²⁶ Regarding the long-term cross-protective effectiveness, on the Australian study showed that prevalence of HPV31/33/45 was also lower among vaccinated (4%) compared with unvaccinated (7%) women (OR = 0.51, 95% CI 0.29–0.89).

On the other hand, regarding the long-term effectiveness in real-world data, the observation period for the 4-valent vaccine was 10 years in a Danish study,²⁷ and 12 years in an Australian study.²⁸

We previously reported that the VE of the bivalent vaccine was more than 90% against HPV 16/18 type infection in Japanese women aged 20–22 years,⁶ and the results provided the Japanese public with reliable scientific data on the effectiveness of the HPV vaccine in Japan. The present survey confirmed the long-term effectiveness against HPV 16/18 and 31/45/52 infection at the age of 25–26 years, which is when sexual activity is high.

There are several limitations to this study. The first is that antibody titers were not measured. No HPV 16/18-infected individuals were found in the vaccinated group, however, it has not been confirmed whether the preventive effect is due to a sustained antibody titer. The correlation between the immunological effect of the antibody and the clinical effect of preventing HPV infection has not yet been established, and it is unclear if maintaining a high antibody level really prolongs the prevention period of HPV infection. Furthermore, the minimum amount of antibody required to prevent HPV infection is still unclear. Second, we compared the HPV 16/18 infection rate between vaccinated and unvaccinated groups, and also between a publicly funded cohort and a cohort not eligible for publicly funded HPV vaccination. However, it may be difficult to discuss the herd immunity effect of the HPV vaccine in this analysis. More cases and years of follow-up may be needed to discuss the herd immunity effect. The third limitation is selection bias in the cohort study. There is concern that women who undergo cancer screening and participate in epidemiological studies tend to be more health conscious. Regarding the correlation between the intention to undergo cancer screening and HPV vaccination, Taniguchi et al. reported that vaccinated women had a higher rate of cervical cancer screening.²⁹ However, the HPV vaccination rate in the

subjects of this analysis was 77.4%, which was lower than the vaccination rate in women born in 1994 in Niigata City (93.1%). Of the cancer screening examinees aged 25–26 years in Niigata City, 7.7% (59/770) of women needed to make a detailed examination (ASC-US+ 7.7%, LSIL+ 5.2%) in 2019, whereas 6.8% (29/429) of the females needed to make a detailed examination (ASC-US+ 6.8%, LSIL+ 4.0%) among the participants in this study. The difference was not significant, therefore we consider that there is no clear interaction between HPV vaccination and the outcome of cancer screening, and it is unlikely that a selection bias has occurred. The fourth limitation is confounding factors for age and vaccination status. Women aged 26 years (born in 1993) have a very low vaccination rate because they are the generation before the introduction of publicly funded vaccination. On the other hand, women aged 25 years (born in 1994) have a vaccination rate of 77.4% due to the introduction of publicly funded vaccination. In Niigata City, the cancer screening rate was 5.0% at age 25 and 17.0% at age 26 in 2019. On the other hand, the registration rate was 76.9% at the age of 25 and 58.2% at the age of 26. Considering that women aged 25 years have a lower screening rate and higher registration rate than women aged 26 years, there may be differences in population characteristics between women aged 25 and 26 years. For example, if a person who had a cancer screening at the age of 25 was more health conscious and had a higher vaccination rate than the age of 26, it is possible that the VE is highly estimated in the analysis. On the other hand, if women aged 25 years have more symptoms and/or HPV infections than women aged 26 years, VE may be estimated to be low due to the high vaccination rate in women aged 25 years. Regarding the statistical power in this analysis, we predicted that the HPV16/18 infection rate in 25-year-old women would be 4% in the unvaccinated group and 0.1% in the vaccinated group based on our previous data,¹⁵ thus we considered 480 cases were required for the analysis. In the actual analysis, 150 subjects (infection rate 0%) in the vaccinated group and 279 subjects (infection rate 5.4%) in the unvaccinated group were analyzed, and the statistical power was 0.817. Therefore, we consider that the statistical power is sufficiently maintained.

In conclusion, we consider that the NIP for HPV vaccination in Japan will help prevent cervical cancer in young Japanese women, however almost all adolescent Japanese girls have not been vaccinated due to the discontinuation of proactive recommendation of the vaccine. Now, they are over 20 years old and are about to enter a period of high sexual activity. After the MHLW in Japan has resumed proactive recommendation for HPV vaccination, the following actions are required: accurate and scientific information dissemination in the media, enlightenment activities using a behavioral economics approach, policies for catch-up vaccination, and inclusion of 9-valent vaccine in the NIP. We will continue this survey to verify the long-term effectiveness of the HPV vaccine against cervical precancers in women at the age of 25–26 years and the long-term effectiveness of the 9-valent vaccine in the future.

ACKNOWLEDGEMENTS

We would like to thank Ms. Yuka Watanabe, Ms. Sachiko Ono, Ms. Anna Ishida, and the administrator of Niigata city for their support in conducting the survey.

CONFLICT OF INTEREST

M.Y., Y.U., and T.E. have received lecture fees from Merck Sharp and Dohme. E.M. received honoraria and lecture fees from Roche Diagnostics, Hologic Japan, and Merck Sharp and Dohme. All other authors report no potential conflicts.

ORCID

Masayuki Sekine  <https://orcid.org/0000-0003-0751-6395>
 Sharon J. B. Hanley  <https://orcid.org/0000-0002-7554-004X>
 Etsuko Miyagi  <https://orcid.org/0000-0002-5492-0844>
 Sayaka Ikeda  <https://orcid.org/0000-0001-7948-8990>
 Asami Yagi  <https://orcid.org/0000-0002-3222-5963>
 Takayuki Enomoto  <https://orcid.org/0000-0003-4538-5541>

REFERENCE

- Sekine M, Kudo R, Adachi S, et al. Japanese crisis of HPV vaccination. *Int J Pathol Clin Res*. 2016;2(2):2469-5807.
- Hanley SJ, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. *Lancet*. 2015;385:2571.
- Tanaka Y, Ueda Y, Egawa-Takata T, Yagi A, Yoshino K, Kimura T. Outcomes for girls without HPV vaccination in Japan. *Lancet Oncol*. 2016;17:868-869.
- Sekine M, Kudo R, Yamaguchi M, et al. Japan's ongoing crisis on HPV vaccination. *Vaccines (Basel)*. 2020;8(3):362.
- 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;111:2156-2162.
- Kudo R, Yamaguchi M, Sekine M, et al. Bivalent human papillomavirus vaccine effectiveness in a Japanese population: high vaccine-type-specific effectiveness and evidence of cross-protection. *J Infect Dis*. 2019;219:382-390.
- Sekine M, Yamaguchi M, Kudo R, et al. Epidemiologic Profile of Type-Specific Human Papillomavirus Infection after Initiation of HPV Vaccination. *Vaccines (Basel)*. 2020;8(3):425.
- Ueda Y, Yagi A, Nakayama T, et al. Dynamic changes in Japan's prevalence of abnormal findings in cervical cytology depending on birth year. *Sci Rep*. 2018;8:5612.
- Yagi A, Ueda Y, Ikeda S, et al. Evaluation of future cervical cancer risk in Japan, based on birth year. *Vaccine*. 2019;37:2889-2891.
- Yamaguchi M, Sekine M, Hanley SJB, et al. Risk factors for HPV infection and high-grade cervical disease in sexually active Japanese women. *Sci Rep*. 2021;11:2898.
- Li T, Wu Z, Jiang M, et al. Clinical performance of Onclarity HPV assay and Cobas HPV test in detection of cervical precancer and cancer in Chinese women. *Gynecol Oncol*. 2020;157:202-208.
- Bonde JH, Pedersen H, Quint W, Xu L, Arbyn M, Ejegod DM. Clinical and analytical performance of the BD onclarity HPV assay with surepath screening samples from the danish cervical screening program using the VALGENT framework. *J Clin Microbiol*. 2020;58(2):e01518-e01519.
- Ozaki S, Kato K, Abe Y, et al. Analytical performance of newly developed multiplex human papillomavirus genotyping assay using Luminex xMAP™ technology (Mebgen™ HPV Kit). *J Virol Methods*. 2014;204:73-80.
- Onuki M, Matsumoto K, Iwata T, et al. Human papillomavirus genotype contribution to cervical cancer and precancer: Implications for screening and vaccination in Japan. *Cancer Sci*. 2020;111:2546-2557.
- WHO; Immunization, Vaccines and Biologicals. [https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/human-papillomavirus-vaccines-\(HPV\)](https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/human-papillomavirus-vaccines-(HPV)) (accessed on 10th February 2022).
- Drolet M, Bénard É, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet*. 2019;394:497-509.
- Luostarinen T, Apter D, Dillner J, et al. Vaccination protects against invasive HPV-associated cancers. *Int J Cancer*. 2018;142:2186-2187.
- Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 2020;383:1340-1348.
- De Vincenzo R, Conte C, Ricci C, Scambia G, Capelli G. Long-term efficacy and safety of human papillomavirus vaccination. *Int J Womens Health*. 2014;6:999-1010.
- Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004;364:1757-1765.
- Romanowski B, de Borja PC, Naud PS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet*. 2009;374:1975-1985.
- Roteli-Martins CM, Naud P, De Borja P, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. *Hum Vaccin Immunother*. 2012;8:390-397.
- Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. *Hum Vaccin Immunother*. 2014;10:2147-2162.
- Porras C, Tsang SH, Herrero R, et al. Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer: long-term follow-up results from the Costa Rica Vaccine Trial. *Lancet Oncol*. 2020;21:1643-1652.
- GlaxoSmithKline Biologicals Cervarix. https://gskpro.com/content/dam/global/hcpportal/ja_JP/products-info/cervarix/cervarix.pdf (accessed on 10th February 2022)
- Kjaer SK, Nygård M, Sundström K, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four Nordic countries. *EclinicalMedicine*. 2020;23:100401.
- Thamsborg LH, Napolitano G, Larsen LG, Lynge E. High-grade cervical lesions after vaccination against human papillomavirus: A Danish cohort study. *Acta Obstet Gynecol Scand*. 2020;99:1290-1296.
- Shilling H, Garland SM, Atchison S, et al. Human papillomavirus prevalence and risk factors among Australian women 9-12 years after vaccine program introduction. *Vaccine*. 2021;39:4856-4863.
- Taniguchi M, Ueda Y, Yagi A, et al. Cervical cancer screening rate differs by HPV vaccination status: An interim analysis. *Vaccine*. 2019;37:4424-4426.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Kurosawa M, Sekine M, Yamaguchi M, et al. Long-term effectiveness of HPV vaccination against HPV infection in young Japanese women: Real-world data. *Cancer Sci*. 2022;113:1435-1440. doi:[10.1111/cas.15282](https://doi.org/10.1111/cas.15282)