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ORIGINAL ARTICLE

Human papillomavirus vaccine to prevent CIN3 or worse (CIN3+): A nationwide case–control study in Japan

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Abstract

An increase in cervical cancer incidence has been reported in Japan. The Ministry of Health, Labor, and Welfare of Japan has resumed the active recommendation of regular HPV vaccines in 2022. In Japan, the preventive effect of CIN3+ in the real world has not yet been demonstrated in age-adjusted cohort or case–control studies. This study aimed to estimate the effect of the HPV vaccine against CIN3+ in Japanese women. This nationwide case–control study from April 2013 to March 2020 targeted women aged 20–26 years old at the time of cervical screening. We compared HPV vaccination exposure between those with abnormal and those with normal cytology. Abnormal cytology was classified into cervical intraepithelial neoplasia (CIN)1+, CIN2+, and CIN3+. We calculated the odds ratio (OR) and 95% confidence interval (CI) of the above endpoints and vaccination exposure using the conditional logistic regression model and estimated vaccine effectiveness using the formula (1 −OR) × 100. A total of 2790 cases and 13,990 controls (one-to-five matching) were eligible in 37 municipalities in Japan. In this study, 61 CIN3 (2.2%) and 10 squamous cell carcinomas (SCC) (0.4%) were found. The OR for CIN3+ versus controls was 0.14 (95% CI, 0.03–0.75), equating to a vaccine effectiveness of 86%. Of the 10 patients who had SCC none were vaccinated. This nationwide case–control study in Japan demonstrated a substantial risk reduction in CIN3+ among women who did versus those who did not receive HPV vaccination.

KEYWORDS
case–control studies, human papillomavirus viruses, papillomavirus vaccines, uterine cervical dysplasia, vaccine efficacy

1 | INTRODUCTION

Human papilloma virus (HPV) infections can lead to several types of cancers, among which cervical cancer is currently a common and serious one. To counter this threat, the bivalent HPV vaccine, which covered the two most-high-risk cervical cancer-causing strains of HPV, types 16 and 18, was approved in Japan in October 2009, and the broader-acting quadrivalent vaccine (covering HPV

types 6, 11, 16, and 18) in July 2011.[1] Subsidies from local and national governments for a HPV vaccination program commenced in 2010 in Japan, and the use of the HPV vaccine became a routine in the national immunization program for girls aged 12–16 years in April of 2013.[2] However, reports arose of various post-vaccination symptoms, such as chronic pain. So, just 2 months after Japan's national vaccine recommendation, in the spring of 2013, as a causal relationship with the vaccine could not be ruled out, the Ministry of Health, Labor, and Welfare (MHLW) decided to suspend its proactive recommendation for routine vaccination until the frequency and cause of the adverse reactions could be determined and appropriate information provided to the public.[3] This suspension caused the HPV vaccination rate for eligible girls to drop sharply, from its peak of about 70% earlier in 2013 to less than 1% for those born in 2002 and afterward.[4] The suspension lasted for approximately 8 years. Finally, in November 2021, it was confirmed that there were no significant safety concerns for the HPV vaccines and that the effectiveness of HPV vaccination clearly outweighed any risk of adverse events. The MHLW notified the suspension of active recommendations was terminated.[5] As a retroactive response to those who had missed their opportunity to be vaccinated, catch-up vaccination began being offered, a program that will continue until March 2025.[6] Furthermore, in April 2023, a subsidized nine-valent HPV vaccine became available. Thus, HPV vaccination, at a standstill for nearly 8 years, has recently resumed, with a better vaccine, but HPV vaccination coverage in Japan has remained low.[7]

The number of cervical cancer cases in Japan is increasing, especially among young women.[8] There is no national HPV vaccination registry in Japan, so there are only scattered investigative reports regarding the preventive effects of HPV vaccination, and the lack thereof due to the 8-year suspension gap, on HPV-related precancerous cervical lesions. We previously conducted a nation-wide case–control study and reported that the HPV vaccine had an effectiveness of 57.9% for preventing CIN1+ and 74.8% for CIN2+ in 2021.[9] We have, in this second-stage study, used data from a nationwide registry in Japan to examine the effectiveness of HPV vaccination for preventing CIN3+ in Japan.

2 | METHODS

2.1 | Study overview

We conducted a case–control study using data obtained from privacy-protected municipal cervical cancer screening. This database was initially constructed and managed independently by each municipality, as were personal records of cervical cancer vaccination history.

All 80 of Japan's municipalities, mainly in the prefectural capitals of each prefecture, were invited to participate in the study, and 37 municipalities participated.

Figure 1 shows the study subjects and the framework of the study. The women indicated by the dashed line are the age group who were widely vaccinated with the anti-cervical cancer HPV vaccine through the publicly funded HPV vaccination program for girls aged 13–16 years that ran from 2010 to 2013. The subjects enclosed by the black line are the group whose recommendation for vaccination was discontinued beginning in 2013 and therefore had a low overall vaccination rate. The study period was from April 1, 2013 to March 31, 2020, and the subjects were cervical cancer screening recipients, born in 1991–1996 and therefore aged 20–26 years.

Women born between 1994 and 1996 are shown in the dashed-framed area (aged 20–26 years in 2014–2020); they had an opportunity to get immunized, whereas those born between 1991 and 1993 in the black-framed area (aged 20–26 years in 2013–2019) passed through subsidized eligibility before the HPV vaccine was introduced in Japan and were unlikely to have been immunized. We compared the proportions of HPV vaccinated subjects between the abnormal cytology and normal cytology groups to analyze the association between HPV vaccination and cervical precancerous lesions, especially lesions beyond CIN3.

2.2 | Data collection and HPV vaccination history

The participant enrolment process is shown in Figure 2. Individual data on cervical cancer screening among women aged 20–26 years

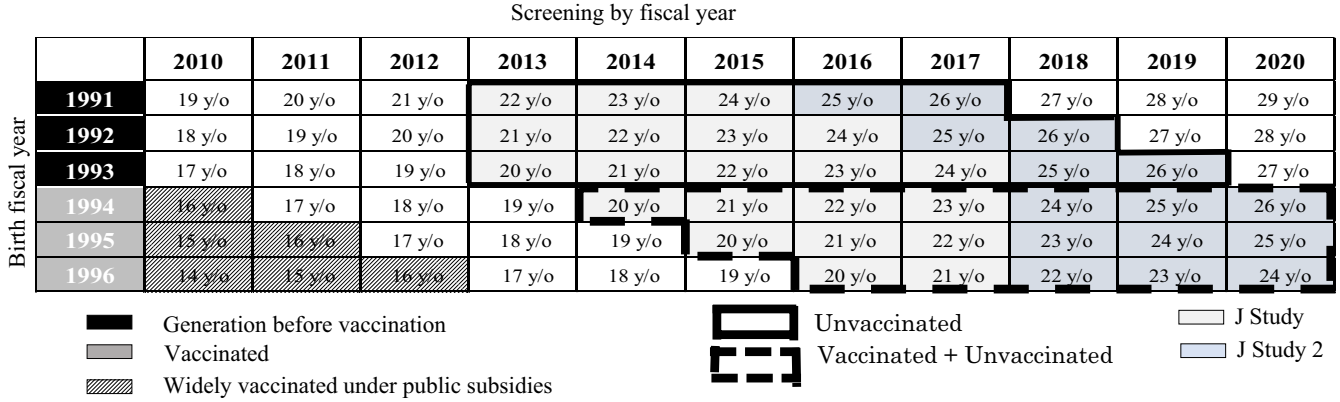

FIGURE 1 The study subjects and the framework.

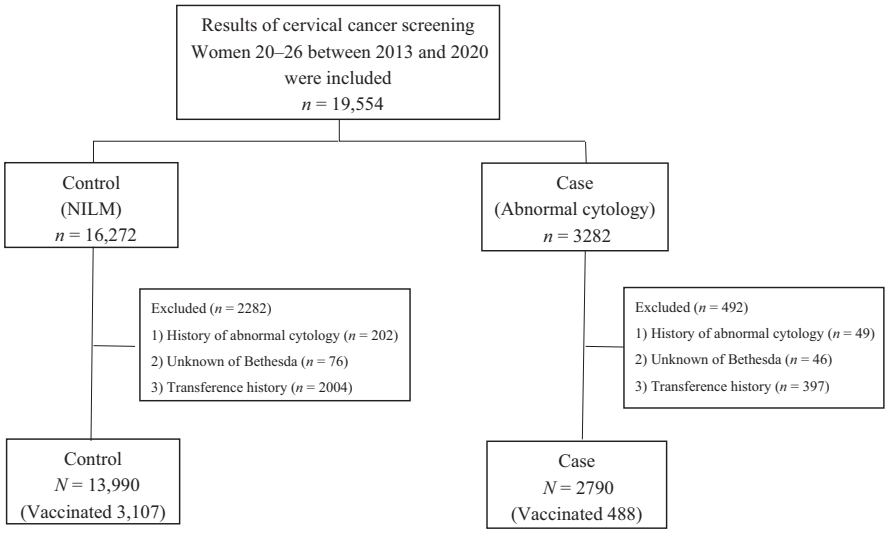

FIGURE 2 The participant enrolment process.

in 2013–2020 were obtained from 37 participating municipalities across the country. Case management status was determined from cervical cancer-screening results. Results were graded according to Bethesda coding. Patients with abnormal cytology (atypical squamous cells of undetermined significance [ASC-US]+in Bethesda) were considered "cases," and those with normal cytology (negative for intraepithelial lesion or malignancy [NILM]) were selected as "controls." For each case in each municipality, five controls were selected who matched the exact year of birth and closest examination date. This resulted in 3282 cases and 16,272 controls, for a total of 19,554 cases in our study.

This study excluded women with a history of abnormal cytology or unknown Bethesda score. In addition, having a history of moving into a municipality since November 2010 was a reason for exclusion because it created an uncertainty, as the HPV vaccination history could not be collected from other municipalities. In addition, the controls whose matched cases met the exclusion criteria were also excluded. As a result of these exclusions, a final total of 2790 cases and 13,990 controls were eligible for our analysis. The exact dates of birth were not provided to the research group because of protection rules for personal information in some municipalities; therefore, these cases and controls were categorized in our analysis as an "unspecified age group."

There is no national vaccine registry in Japan, as each municipality maintains its own official vaccination records. Therefore, information on individual vaccination status was linked to cervical cancer screening data by each municipal health center. In this study, researchers received anonymous linked datasets from each municipality and integrated them for analysis.

2.3 | Statistical analysis

Data are presented as mean±standard deviation for continuous values and as a percentage of categorical value by age or fiscal year for eligible women. A conditional logistic regression model was used to calculate the odds ratio (OR) for the prevention of histological abnormalities. Abnormalities were categorized as CIN1+, CIN2+, and CIN3+, and the OR due to vaccination exposure was estimated for each condition. Women with dysplasia that was not classified as CIN were classified as CIN1+ in this analysis because they had at least CIN1. Women with a history of at least one dose of vaccination were considered to have been vaccinated, and the vaccine effectiveness was estimated using the formula (1 −OR)×100. As a sensitivity analysis, the OR and its effectiveness were calculated by excluding the two municipalities where the most pathological results were missing; all probability (p) values were two sided, and values below 0.05 were considered to be statistically significant. All statistical analyses were performed using STATA version 14.0 SE software (STATA Corp LP).

2.4 | Ethical issues

The study was approved by the Ethics Review Committee of the Osaka University Graduate School of Medicine (approval number 15248-7). The requirement for individual informed consent was waived because of maintained privacy procedures.

3 | RESULTS

Our study population included 16,780 women aged 20–26 years, 3595 of whom had received at least one dose of HPV vaccination during the study period.

Table 1 shows the number of controls and the cervical screening histology results by age. There were 2790 cases with abnormal cytology. Histological results showed that 880 (31.5%) had CIN1 (including dysplasia), 189 (6.8%) had CIN2, 61 (2.2%) had CIN3, and 10 (0.4%) had squamous cell carcinoma. The proportion of CIN1 (including dysplasia) did not change with age. However, although CIN2 did not change with age below 25 years, it increased at age 26. There was

TABLE 1 Number of cytology/histology results by age.

	NILM	Case	CIN1	CIN2	CIN3	SCC
20 y/o	1702 (12.2%)	354 (12.7%) (100%)	110 (31.1%)	18 (5.1%)	3 (0.8%)	1 (0.3%)
21 y/o	3007 (21.5%)	633(22.7%) (100%)	187 (29.5%)	43 (6.8%)	8 (1.3%)	0 (0.0%)
22 y/o	1762 (12.6%)	386 (13.8%) (100%)	122 (31.6%)	28 (7.3%)	7 (1.8%)	1 (0.3%)
23 y/o	2604 (18.6%)	583(20.9%) (100%)	181 (31.0%)	41 (7.0%)	13 (2.2%)	3 (0.5%)
24 y/o	1888 (13.5%)	355(12.7%) (100%)	123 (34.6%)	20 (5.6%)	10 (2.8%)	2 (0.6%)
25 y/o	367 (2.6%)	80(2.9%) (100%)	25 (31.3%)	4 (5.0%)	2 (2.5%)	1 (1.3%)
26 y/o	461 (3.3%)	95 (3.4%) (100%)	22 (23.2%)	11 (11.6%)	7 (7.4%)	0 (0.0%)
Unspecified	2199 (15.7%)	304(10.9%) (100%)	110 (36.2%)	24 (21.8%)	11 (3.6%)	2 (0.7%)
Total	13,990 (100%)	2790 (100%)	880 (31.5%)	189 (6.8%)	61 (2.2%)	10 (0.4%)

Abbreviations: NILM, negative for intraepithelial lesion or malignancy; SCC, squamous cell carcinoma; y/o, years old.

also a trend toward an increase with age for CIN3 (0.8% at age 20 and 7.4% at age 26). Table 2 shows the proportion of HPV vaccination in cases and controls by age. Overall, 488 of the 2790 abnormal cytology cases (17.5%) were vaccinated, compared with 3107 of 13,990 controls (22.2%). Vaccination coverage was higher in the control group than in the abnormal cytology cases for all the ages covered by the study. In the age-unknown group, vaccination coverage was 17.5% in cases and 22.2% in controls. The effectiveness of the HPV vaccine against histological abnormalities in the Japanese women we studied is presented in Table 3. The OR for CIN1+ was 0.44 (95% CI, 0.32–0.59), for CIN2+ was 0.23 (95% CI, 0.12–0.46), and for CIN3+ was 0.14 (95% CI, 0.03–0.75), equating to a vaccine effectiveness of 56%, 77%, and 86%, respectively. This study included 10 patients with invasive cancer, none of whom were vaccinated.

A sensitivity analysis excluding the data from two municipalities where most pathology results were missing showed almost identical results.

4 | DISCUSSION

This case control study is the second phase of our work in 2020[9] reporting on the association between HPV vaccination and cervical intraepithelial lesions in Japan. This time we were evaluating the efficacy of HPV vaccination against development of CIN3 or higher cervical lesions in 20–26-year-olds who underwent cervical cancer screening between 2013 and 2020. We estimated that HPV vaccination has provided a statistically significant 86% protection against CIN3+ in this population. As the target age group was set slightly higher than in the first phase of our study and the study period was extended, it is considered that the result of this analysis showed a statistically significant difference for CIN3+.

In Japan, CIN3 is an indication for conization,[10] which significantly increases the risk for preterm delivery.[11–14] Therefore, the results of this study are important from the perspective of preterm birth prevention. Furthermore, all 10 cases of invasive cancer in this study were in women who were unvaccinated against HPV.

The high potential of HPV 16 and 18 to cause cancer in young women could also be a factor in the lack of invasive cancer appearance in this study. Although it is possible that a small number of cancers associated with other HPV types that cannot be prevented by the HPV vaccine or the cross protection used at the time may remain and the course of cervical disease, including the long-term effects of the HPV vaccine, needs to be monitored, our current results of this study are considered to be medically significant. In this study, the number of cases and controls tended to decrease with increasing age, possibly due to a shift in the study population from community screening to workplace screening.

There have been several reports regarding Japan and the effectiveness of HPV vaccination, including a reduction in HPV infection and precancerous lesions.[9,15–19] In addition, it has been reported that the incidence of CIN3+ was obviously lower in the vaccinated generation than in the pre-introduction generation in terms of changes over time in the rate of abnormal histological examination in cervical cancer screening at age 20 years,[20] which is consistent with our results in the present study.

Overseas, studies linking cancer registries and immunization in Sweden have reported significant reductions in cumulative cervical cancer incidence, with an 88% reduction among those who received the HPV vaccine by age 16 or younger and a 53% reduction among those who received the vaccine between 17 and 30 years.[21] Similarly, in Denmark, a significant cumulative cervical cancer incidence reduction of 86% has been reported for HPV vaccination at age 16 years or younger. However, the trend is only decreasing

TABLE 2 Comparison of human papilloma virus (HPV) vaccination rates between cases and controls by age at screening.

	Case		Control	
Age	Number	Vaccinated	Number	Vaccinated
20	354	117 (33.1%)	1702	730 (42.9%)
21	633	193 (30.5%)	3007	1250 (41.6%)
22	386	50 (13.0%)	1762	322 (18.3%)
23	583	49 (8.4%)	2604	235 (9.0%)
24	355	15 (4.2%)	1888	117 (6.2%)
25	80	13 (16.3%)	367	63 (17.2%)
26	95	2 (2.1%)	461	27 (5.9%)
Unspecified age	304	49 (16.1%)	2199	363 (16.5%)
Total	2790	488 (17.5%)	13,990	3107 (22.2%)

TABLE 3 Human papilloma virus (HPV) vaccination status and effectiveness.

	Control	CIN1	CIN2	CIN3	SCC
Vaccinated	3107	157	25	4	0
Unvaccinated	10,883	723	164	57	10
		Cumulative number of cases (with histological results)			
	Control	CIN1+	CIN2+	CIN3+	SCC
Vaccinated	3107	186	29	4	0
Unvaccinated	10,883	954	231	67	10
Odds ratio		0.44	0.23	0.14	
95% confidence interval		0.32–0.59	0.12–0.46	0.03–0.75	
Vaccine effectiveness		56%	77%	86%	

for those aged 17 years and older.[22] Furthermore, analyses linking cancer registries and immunization in Scotland have also reported no cases of invasive cancer in women vaccinated at 12 or 13 years of age, regardless of the number of vaccinations, and a significant reduction in cancer incidence in women who received three doses of bivalent vaccine between 14 and 22 years of age compared with unvaccinated women.[23] What these studies have in common is that there is a significant risk reduction in younger cohorts, especially if vaccinated at 16 years or younger.

The strengths of this study are that the analysis was conducted on a national scale, with linking of cervical cancer screening records with official vaccination history. In Japan, cancer screening results and vaccination histories are managed separately, and they are not integrated. A certain discrepancy between self-reported HPV vaccination history and municipal vaccination records has been reported,[24] and this study using official records has led to a more accurate assessment of the effectiveness of the HPV vaccine. Furthermore, the fact that data were provided by 37 municipalities across the country, from Hokkaido to Kagoshima, is considered to have enabled a more comprehensive analysis. To ensure HPV vaccination status, participants with a history of moving to the municipality after the start of the HPV vaccination program in November 2010 were excluded from the analysis if their vaccination history prior to moving was not officially confirmed. Furthermore, women with a previous history of abnormal cytology were excluded if the records could be verified, regardless of the time period, and only newly diagnosed cases of CIN were included. These efforts may have led to a more accurate assessment of the efficacy of the HPV vaccine.

However, this study has limitations. First, the sexual history of the target population was not known. Therefore, it is possible that those who received the HPV vaccine only after initiating sexual intercourse, and thus may have already been infected, may have been included. Second, in this study, people with at least one vaccination were analyzed as vaccinated, and details such as whether they were vaccinated with the bivalent or the quadrivalent vaccine and how many doses they had been vaccinated with were also unknown because many municipalities did not provide detailed data. If these details had been known, further analysis, such as differences based on the number of vaccinations or the type of vaccine received, may have been possible. In addition, there were cases where the histological examination results were only for dysplasia and no details were available, and several surgical cases referred to a higher-level medical institution were included, but the detailed results were not available and were analyzed as CIN1, assuming that at least CIN1 was present. Therefore, it is likely that analyzing some cases as CIN1 would be inaccurate in assessing the efficacy of the HPV vaccine, but the results of the analysis would not change if these data were excluded from the analysis, and the exclusion of these cases would not affect the results for CIN3 or

worse. Lastly, the study did not include catch-up vaccination subjects, and thus future work will be required to confirm the efficacy of age-appropriate vaccinations.

In conclusion, this nationwide case–control study in Japan demonstrated that HPV vaccination reduces the risk of CIN3+ by 86%. In Japan, active HPV vaccination recommendation by the MHLW has resumed and catch-up vaccination is also now available for a limited period of 3 years. However, HPV vaccination uptake coverage in Japan remains well below international norms. The analysis predicting HPV-induced cancer incidence rates up to 2030 revealed a favorable downward trend in most other target countries. However, Japan has reported an increasing trend.[25] Cervical cancer is on the rise among young women[8] and is needed to monitor the incidence rates and vaccine effectiveness over a longer period. To reduce conization for CIN3, a risk factor for preterm delivery, and to avoid tragedies that could be prevented by HPV vaccination, HPV vaccination coverage needs to be improved and male vaccination made routine.

AUTHOR CONTRIBUTIONS

Sayaka Ikeda: Conceptualization; data curation; formal analysis; investigation; project administration; visualization; writing – original draft; writing – review and editing. **Yutaka Ueda:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; supervision; validation; writing – review and editing. **Asami Yagi:** Conceptualization; data curation; funding acquisition; investigation; writing – review and editing. **Taichi Mizushima:** Investigation; writing – review and editing. **Akiko Sukegawa:** Investigation; writing – review and editing. **Risa Kudoh:** Investigation; writing – review and editing. **Manako Yamaguchi:** Investigation; writing – review and editing. **Megumi Kurosawa:** Investigation; writing – review and editing. **Etsuko Miyagi:** Investigation; writing – review and editing. **Masayuki Sekine:** Conceptualization; investigation; writing – review and editing. **Takayuki Enomoto:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Review Board: This study was approved by the Ethics Review Board at Osaka University Graduate School of Medicine (approval number 15248-11).

Informed Consent: The requirement for individual informed consent was waived.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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