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Human papillomavirus vaccine to prevent cervical intraepithelial neoplasia in Japan: A nationwide case-control study

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Abstract

Cervical cancer remains among the most common cancers in women worldwide and can be prevented by vaccination. The Ministry of Health, Labour and Welfare of Japan suspended active recommendation of regular human papillomavirus (HPV) vaccines in 2013 because of various symptoms including chronic pain and motor impairment. This nationwide case-control study from April 2013 to March 2017 targeted women aged 20-24 years old at cervical screening. We compared HPV vaccination exposure between those with abnormal and normal cytology. Abnormal cytology was classified based on the results of histological test and 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 2483 cases and 12 296 controls (one-to-five matching) were eligible in 31 municipalities in Japan. The distribution of histological abnormalities among cases was 797 CIN1 (including dysplasia) (32.1%), 165 CIN2 (6.7%), 44 CIN3 (1.8%), and eight squamous cell carcinoma (SCC) (0.3%). The OR of HPV vaccination compared with no vaccination for abnormal cytology, CIN1+, CIN2+, and CIN3+ versus controls was 0.42 (95% CI, 0.34-0.50), 0.42 (95% CI, 0.31-0.58), 0.25 (95% CI, 0.12-0.54), and 0.19 (95% CI, 0.03-1.15), respectively, equating to a vaccine effectiveness of 58.5%, 57.9%, 74.8%, and 80.9%, respectively. Eight patients had SCC, none was vaccinated. This nationwide case-control study in Japan demonstrated a substantial risk reduction in abnormal cytology and CIN among women who did versus those who did not receive HPV vaccination.

KEYWORDS

case-control study, cervical intraepithelial neoplasia, HPV vaccine, human papillomavirus, vaccine effectiveness

1 | INTRODUCTION

Cervical cancer remains one of the most common cancers in women worldwide, and infection with high-risk types of human papillomavirus (hrHPV) is a cause of precancerous cervical lesions and cervical cancer.[1] To date, the 2vHPV (HPV type 16/18), 4vHPV (HPV type 6/11/16/18), and nonvalent (HPV type 6/11/16/18/31/33/45/52/58) vaccines have been globally approved, and large observational cohorts and randomized trials demonstrated their acceptable safety profiles and high efficacy against hrHPV infections as well as precancers.[2-8]

In Japan, there were a total of 10 490 new cases in 2014 and 2795 women died of cervical cancer in 2017.[9] The age-standardized incidence of cervical cancer has been increasing since 2000, especially in women aged <40 years.[10] Even at the precancerous intraepithelial stage, frequent biopsies can be burdensome, and conization for CIN3 can also affect the risk of preterm birth during subsequent pregnancies. The 2vHPV vaccine was launched in October 2009, followed by the 4vHPV vaccine in August 2011. Subsidies from local and national governments for a three-dose HPV vaccination program for girls aged 13-16 years old started in November 2010. However, due to the occurrence of various symptoms including chronic pain, motor impairment, and others, the Ministry of Health, Labour and Welfare (MHLW) of Japan announced the suspension of the proactive recommendation for routine use of the HPV vaccine in the national immunization program on June 2013, just two months after its inception.[11] As a result, the HPV vaccination rate among younger women has decreased sharply from a peak of about 70% in 2013 to the current rate of <1% for those born after 2002.[12] As for this circumstance in Japan, the World Health Organization's Global Advisory Committee on Vaccine Safety commented that young women have been left vulnerable to preventable HPV-related cancers.[13]

To date, the effectiveness of HPV vaccination for Japanese women has not been sufficiently investigated. There are no nationwide databases for vaccination and cancer screening registries as well as frameworks for evaluating vaccine efficacy. In addition, because most studies conducted in Japan used a self-reported vaccination history,[14] vaccine effectiveness has not been correctly estimated due to misclassification of self-reported vaccination history.[14] We, a designated research group of the MHLW of Japan, conducted a nationwide case-control study of HPV vaccine efficacy using cytology results, histology results, and vaccination history from official records in various municipalities. This study aimed to estimate the effect of the HPV vaccine against abnormal cytology and cervical intraepithelial neoplasia (CIN)1+, CIN2+, and CIN3+ in Japanese women.

2 | MATERIALS AND METHODS

2.1 | Study overview

In Japan, cervical cancer screening has been provided in residential areas, workplaces, and individual health check-ups. Cytology using conventional methods and liquid sample methods has been widely used as a cervical cancer screening method. The resident screening is conducted and managed mainly by each municipality (city, town or village). The screening target population was women aged ≥ 20 years old since April 2004 and municipalities maintain individual records of screening histories. Similarly, individual cervical cancer vaccination records are also managed by each municipality.

In the present study, case-control analysis was carried out using data on cervical cancer screening and HPV vaccination history obtained from 31 municipalities. We announced study participation to all 80 municipalities, centering on the prefectural capital in each prefecture; of them, 31 agreed to participate. Figure 1 shows the study subjects and study framework. The girls shown in the dotted areas were the age group widely vaccinated under public subsidies by an HPV vaccination program started for girls aged 13-16 years in 2010-2013 who would have a high percentage of cervical cancer vaccine inoculation. In contrast, those in the diagonally lined areas were the age group at the time of vaccination cessation as a result of suspension of the governmental recommendation in 2013, so it is assumed that the vaccination rate would be low. The study period was set from April 1, 2013 to March 31, 2017 and the target population was women aged 20-24 years at the time of cervical screening. As a result, women born between 1994 and 1997 shown in the dot-framed areas (aged 20-23 years in 2014-2017) had a chance to get immunized, whereas those born between 1990 and 1993 in the thick-framed areas (aged 20-24 years in 2013-2017) did not. We compared proportions of HPV vaccinated between abnormal cytology and normal cytology groups to analyze the association between HPV vaccination and cervical precancerous lesions.

2.2 | Case-control definitions

The participant enrolment process is shown in Figure 2. Individual data of cervical cancer screenings of women aged 20-24 years from the fiscal years of 2013-2017 were obtained from 31 municipalities across Japan. According to the Community Health Business Report, the total number of cervical cancer screening examinees among women with our target age in these research municipalities was a total of 93 937 women during the study period (15 455 in fiscal year 2013, 25 356 in fiscal year 2014, 19 946 in fiscal year 2015, 16 685 in fiscal year 2016, and 16 495 in fiscal year 2017, respectively).[15]The case-controls status was determined from the cervical cancer screening results. The results were coded according to Bethesda coding.[16] Patients with abnormal cytology (atypical squamous cells of undetermined significance [ASC-US]+ of Bethesda) were selected as "cases," while "controls" were selected from those with normal cytology (negative for intraepithelial lesion or malignancy [NILM] of Bethesda). Five controls matched with the exact birth year and closest examination date were selected for each case in each municipality. As a result, 2817 cases and 13 988 controls were available.

This study excluded women with any of the following characteristics: history of abnormal cytology, unknown Bethesda, and history

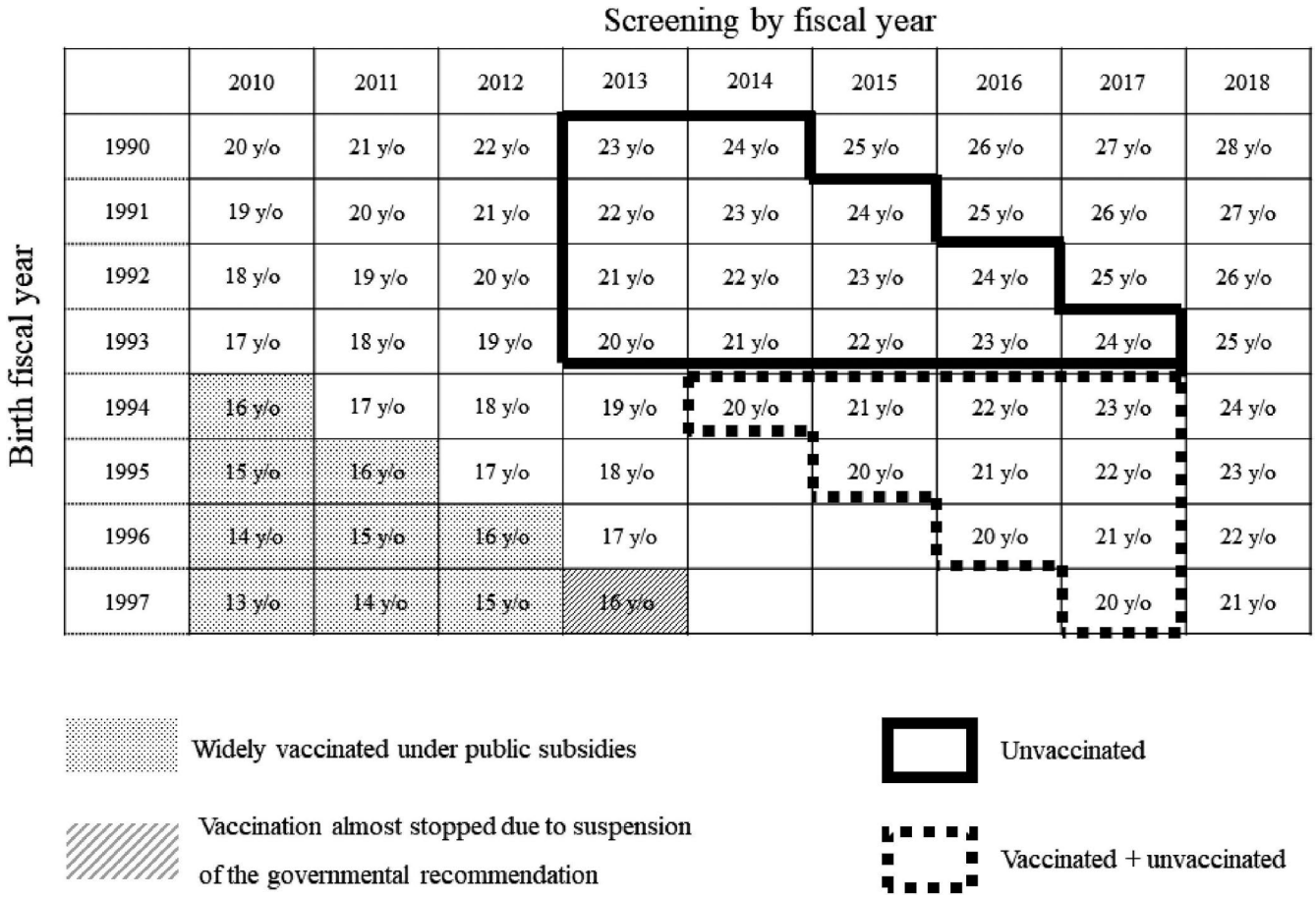

FIGURE 1 Research subjects and research framework. Girls shown in the dotted areas (aged 13-16 years in 2010-2012) were in the widely vaccinated group, whereas those in the diagonally lined areas (aged 16 years in 2013) were in the vaccination cessation group. As a result, women born between 1994 and 1997 shown in the dot-framed areas (aged 20-23 years in 2014-2017) had the chance to get immunized, whereas those born between 1990 and 1993 in the thick-framed areas (aged 20-24 years in 2013-2017) did not

of moving into a municipality since November 2010, and unclear HPV vaccination history. In addition, the controls whose matched cases met the exclusion criteria were also excluded. As a result, a total of 2483 cases and 12 296 controls were finally eligible for this analysis. Among 1014 cases of those with histological abnormalities, 132 cases were described as dysplasia only (without definite classification of CIN) and classified as CIN1 in this study. As the exact age and date of birth were not provided to the research group because of protection rules for personal information in some municipalities (305 cases, 2200 controls), in our analysis, these cases and controls were categorized as "the non-specific age group".

2.3 | Vaccination record survey

Because Japan has no national vaccine registry, each municipality manages its own official immunization records. Therefore, information about individual vaccination status including the date of inoculation, lot number, and number of doses was linked with the data of the cervical cancer screening by the public health center of each municipality. In this study, researchers received anonymous linked datasets from each municipality and integrated them for our analysis. As the vaccination history in other municipalities could not be collected, subjects with a history of moving in from other municipalities were excluded from our analyses.

2.4 | Statistical analysis

Data are shown as mean ± standard deviation for continuous values and their percentages for categorical values by age or fiscal year for the eligible women. A conditional logistic regression model was used to calculate the odds ratio (OR) for preventing cytology/histology abnormalities. Abnormalities were classified into abnormal cytology, CIN1+, CIN2+, and CIN3+, and we estimated the OR due to vaccination exposure for each status. As for women having dysplasia without grading CIN, we classified it as CIN1+ in this analysis, because they had at least CIN1. We also estimated vaccine effectiveness using the formula $(1 - OR) \times 100$. As a sensitivity analysis, OR and its effectiveness were calculated excluding two municipalities in which most pathological results were missing, All P values were two-sided and those <0.05 were considered statistically significant.

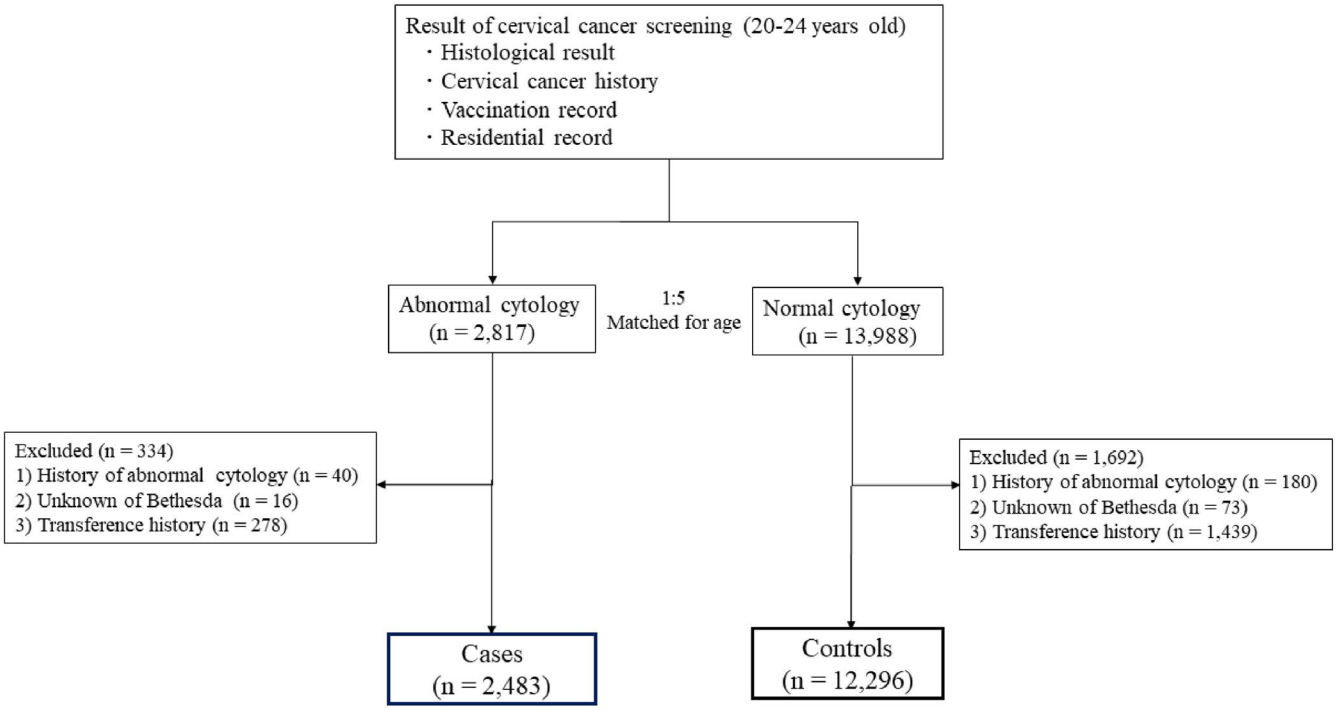

FIGURE 2 Patient enrollment process

All statistical analyses were carried out using STATA version 14.0 SE software (Stata Corp LP).

2.5 | Ethical issues

This study was approved by the Ethics Review Board at Osaka University Graduate School of Medicine (approval number 15248-7). The requirement for individual informed consent was waived.

3 | RESULTS

Table 1 presents the number of cytology/histology results by age. There were 2483 cases of abnormal cytology. The age distribution between cases and controls was similar. In terms of histological results, there were 797 cases (32.1%) of CIN1 (including dysplasia), 165 cases (6.7%) of CIN2, 44 cases (1.8%) of CIN3, and eight cases (0.3%) of squamous cell carcinoma. The proportion of patients who did not undergo a histological examination did not differ by age, and the proportion of CIN1 (including dysplasia) and CIN2 also did not change among age. However, the number of CIN3 cases tended to increase with age (from 0.9% in women aged 20 years to 2.0% in those aged 24 years).

The proportion of HPV vaccinated are compared between cases and controls in Table 2. A total of 404 of 2483 (16.3%) cases received the vaccination versus 2605 of 12 296 (21.2%) controls. Among women aged 20-23 years, the vaccination rate was higher in the controls than in the cases. The detailed pattern of controls who received vaccines by fiscal year and birth fiscal year is noted in Table 3. The generation born after 1994 is the group when the subsidies for HPV vaccination started, and the vaccination rate in that age group was 52.9%. The vaccination rate of the unspecified age group was 16.1% in cases and 16.5% in controls.

The effectiveness of HPV vaccine against histological abnormality for eligible Japanese women is shown in Table 4. The OR for abnormal cytology was 0.42 (95% CI, 0.34-0.50), equating a vaccine effectiveness of 58.5%. The OR in CIN1+ was 0.42 (95% CI, 0.31-0.58) and in CIN2+ was 0.25 (95% CI, 0.12-0.54), equating to a vaccine effectiveness of 57.9% and 74.8%, respectively. In addition, the OR in CIN3+ was 0.19 (95% CI, 0.03-1.15) and vaccine effectiveness was 80.9%. In this study, there were five patients with squamous cell carcinoma and three patients with invasive cancer, but none was vaccinated.

In a sensitivity analysis excluding data from two municipalities in which most pathological results were missing, the results were almost the same (Table S1).

4 | DISCUSSION

In this case-control study, the association between HPV vaccine inoculation and cervical precancerous lesions was examined by cervical cancer screening between 2013 and 2017. We estimated that the HPV vaccine provided a 58.5% reduction against cytological abnormality, 57.9% protection for CIN1+, and 74.8% for CIN2+. As for CIN3+, the vaccination tended to show an 80.9% reduction, although it was not statistically significant. Importantly, no cases of invasive cancer were observed among the HPV vaccinated women.

TABLE 1 Number of cytology/histology results by age

Age	No. histological examination	Histological abnormality							Cases	Controls
		Negative	Dysplasia	CIN1	CIN2	CIN3	SCC	Others		
20 y/o	85 (24.8%)	51 (14.9%)	20 (5.8%)	87 (25.4%)	18 (5.2%)	3 (0.9%)	1 (0.3%)	78 (22.7%)	343 (13.8%) (100%)	1633 (13.3%)
21 y/o	149 (25.6%)	80 (13.8%)	46 (7.9%)	131 (22.6%)	42 (7.2%)	5 (0.9%)	0 (0.0%)	128 (22.0%)	581 (23.4%) (100%)	2710 (22.0%)
22 y/o	92 (25.0%)	57 (15.4%)	22 (5.9%)	95 (25.7%)	28 (7.6%)	7 (1.9%)	1 (0.3%)	67 (18.2%)	369 (14.9%) (100%)	1629 (13.3%)
23 y/o	140 (26.2%)	68 (12.7%)	32 (6.0%)	135 (25.3%)	35 (6.6%)	11 (2.1%)	3 (0.6%)	109 (20.5%)	533 (21.5%) (100%)	2330 (18.9%)
24 y/o	86 (24.4%)	43 (12.2%)	9 (2.6%)	110 (31.3%)	18 (5.1%)	7 (2.0%)	1 (0.3%)	78 (22.1%)	352 (14.2%) (100%)	1794 (14.6%)
Unspecified age	73 (23.9%)	44 (14.4%)	3 (1.0%)	107 (35.1%)	24 (7.9%)	11 (3.6%)	2 (0.7%)	41 (13.4%)	305 (12.3%) (100%)	2200 (17.9%)
Total	625 (25.1%)	343 (13.8%)	132 (5.3%)	665 (26.8%)	165 (6.7%)	44 (1.8%)	8 (0.3%)	501 (20.2%)	2483 (100%)	12 296 (100%)

Abbreviations: CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

Dysplasia includes those for whom the details of histological results are unknown. Others include benign diseases such as cervicitis and polyps and those with follow up only.

Misclassification between self-reported status and official HPV vaccination records in Japan was reported by Yamaguchi et al.[14] In their paper, 14.8% (140/949) of participants having confirmed vaccination in the official vaccination record remembered incorrectly that they had not been vaccinated. In contrast, 40.2% (113/281) of participants not having confirmed vaccination in the official record remembered that they had been vaccinated. They argued that possible reasons for this discrepancy were: (i) incorrect recognition of other vaccines, such as influenza or Japanese encephalitis; (ii) vaccination in a different municipality due to changing address; and (iii) vaccination not using official subsidies, such as catch-up vaccination. It seems that reason (i) accounted for the most cases, although possibilities for reasons (ii) and (iii) may remain.

Some reports have shown the protective effectiveness of HPV vaccines against HPV infections and intraepithelial lesions in Japan.[17-26] Except for the study by Kudo and colleagues, they are based on the memory of vaccination history. Kudo and colleagues estimated the vaccine efficacy of HPV 16/18 infection prevention. They did not evaluate abnormalities in cytology and histology, and their outcomes were different from ours. Furthermore, they used municipal vaccination records, but the target population was the residents who lived in only six cities in Niigata Prefecture; Niigata, Nagaoka, Joetsu, Shibata, Mitsuke, and Sanjo cities.[17] Matsumoto and colleagues analyzed the reduction of HPV 16/18 prevalence in intraepithelial lesions by the HPV vaccine based on a self-report. This was not a study that directly verified the efficacy of HPV vaccine to prevent precancerous lesions. Because there were no data of participants without abnormal cytology, its vaccine effectiveness could not be estimated. In addition, it was not a population-based study because they collected data from 21 medical institutions.[19] Ozawa and colleagues reported that vaccinated women showed a significant decrease in CIN1+ of 64.9% and CIN2+ of 85.5% in a limited area, Miyagi prefecture, with a small sample size of 5924 women.[25] Konno and colleagues used data from 16 branches out of 46 branches in 47 prefectures, and evaluated the efficacy of the vaccine based on personal memory of vaccination history among the subjects.[26] The proportion of people in their late twenties, who were mostly unvaccinated, is high (64%). As a result, only four cases of HSIL+ with vaccination were reported in the study by Konno and colleagues, which was considerably less than the 25 cases with CIN2+ with vaccination in our study.

Furthermore, in a systematic review and meta-analysis reporting the effect at 5-9 years after HPV vaccination, CIN2+ decreased significantly by 51% (relative risk, 0.49; 95% CI, 0.42-0.58) among screened girls aged 15-19 years and decreased significantly by 31% (relative risk, 0.69; 95% CI, 0.57-0.84) among women aged 20-24 years. In our study, a 74.8% efficacy was observed for CIN2+. One possible reason for the less efficacy of HPV vaccine in systematic review than this study is that a systematic review included the single-cohort vaccination and low routine vaccination coverage country.[8] Another possible reason is that the prevalence of HPV16 and/or HPV18 was the highest in women aged 20-29 years in Japan.[27]

TABLE 2 Comparison of HPV vaccination rates between cases and controls by age at screening

	Cases		Controls	
Age	Number	Vaccinated	Number	Vaccinated
20	343	115 (33.5%)	1633	703 (43.0%)
21	581	172 (29.6%)	2710	1119 (41.3%)
22	369	36 (9.8%)	1629	261 (16.0%)
23	533	29 (5.4%)	2330	148 (6.4%)
24	352	3 (0.9%)	1794	11 (0.6%)
Unspecified age	305	49 (16.1%)	2200	363 (16.5%)
Total	2483	404 (16.3%)	12 296	2605 (21.2%)

Abbreviation: HPV, human papillomavirus.

TABLE 3 Attained age, number of NILM and HPV vaccination positives in controls according to birth year and screening year

	Screening year				
	2013	2014	2015	2016	2017
Birthyear					
1990	23y/o, 78 (0)	24y/o, 564 (0)			
1991	22y/o, 157 (0)	23y/o, 909 (17)	24y/o, 445 (11)		
1992	21y/o, 314 (0)	22y/o, 406 (2)	23y/o, 541 (11)	24y/o, 314 (0)	
1993	20y/o, 265 (0)	21y/o, 651 (1)	22y/o, 421 (0)	23y/o, 421 (9)	24y/o, 462 (0)
1994		20y/o, 403 (42)	21y/o, 550 (284)	22y/o, 391 (83)	23y/o, 381 (111)
1995			20y/o, 273 (175)	21y/o, 550 (313)	22y/o, 254 (176)
1996				20y/o, 343 (200)	21y/o, 645 (521)
1997					20y/o, 349 (286)

Abbreviations: HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.
Number of HPV vaccination positives in parentheses. Birth year and screening year are counted as fiscal year.

TABLE 4 HPV vaccination status and effectiveness

	Cases (with histological result)				
	Negative	CIN1	CIN2	CIN3	SCC/invasive
Vaccination (+)	70	136	22	3	0
Vaccination (–)	273	661	143	41	8

		Cumulative number of cases (with histological result)		
	Controls	Cases	CIN1+	CIN2+	CIN3+
Vaccination (+)	2605	404	161	25	3
Vaccination (–)	9691	2079	853	192	49
Odds ratio		0.42	0.42	0.25	0.19
95% confidence interval		0.34-0.50	0.31-0.58	0.12-0.54	0.03-1.15
Vaccine effectiveness		58.5%	57.9%	74.8%	80.9%

Abbreviation: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
CIN1+ = CIN1(including dysplasia) + CIN2 + CIN3 + SCC/invasive. CIN2+ = CIN2 + CIN3 + SCC/invasive. CIN3+ = CIN3 + SCC/invasive.

One of the main strengths of this large-scale study is that administrative databases of 31 municipalities, 23 prefectures out of 47 prefectures from Hokkaido to Kagoshima, covering approximately 11% of the population enabled us to conduct comprehensive evaluation of the effect of HPV vaccination at the national level. In addition, immunization status was confirmed by municipal records, not

by individual memory to avoid misclassification of vaccination history. As mentioned before, according to the report by Yamaguchi et al, the memory difference was confirmed quite often regarding the presence or absence of vaccination.[14] To ensure that the immunization status was correct, we excluded participants with a history of moving into a municipality after the initiation of HPV vaccination program in November 2010 in the records of the municipalities. Moreover, as we aimed to evaluate the efficacy of the HPV vaccine focusing on the cases with newly diagnosed CIN, we excluded women with a history of abnormal cytology. These efforts lead to a more accurate assessment of HPV vaccine effectiveness. In this study, we evaluated cervical intraepithelial lesions, rather than verifying the efficacy of HPV vaccines to prevent HPV infection.

As described above, although the efficacy of HPV vaccine is reported worldwide, in some cases, various symptoms after vaccination have also been reported. Thus, for the safety of HPV vaccination, analyses have been carefully performed of various symptoms reported after vaccination such as chronic pain, movement disorders, and orthostatic dysregulation.[28] In Japan, a national epidemiological study was also conducted to evaluate the safety of HPV vaccination by the other MHLW research group. In December 2016, the safety results were reported. In this report, even girls who did not receive the HPV vaccination showed various non-specific symptoms similar to those reported in inoculated girls.[29]

This study has some limitations, however. First, as sexual behavior was not included in the survey items, if women vaccinated after their sexual debut were included in this study, the vaccine might be less effective, whereas if they were excluded, vaccine effectiveness might be overestimated. Second, regarding the histological results, there was only a description of dysplasia and in some municipalities the specific diagnosis was unknown. However, we obtained similar results despite excluding data from two municipalities without detailed histological results. Third, we could not find data on how many women had vaccinated as catch-up vaccination in Japan. Although it is an extreme assumption, if a 40% false-positive rate in the report by Yamaguchi and colleagues is used as the proportion of catch-up vaccinations and applied to those who have not been vaccinated in this study, the odds ratio was estimated to be 0.88 (0.82, 0.97), which indicates the effectiveness of the vaccination with statistical significance. Therefore, the effectiveness of the HPV vaccine was shown even when the catch-up vaccination was taken into consideration.

Notably, in a modelling study in 2019, the prediction of cervical cancer age-adjusted morbidity reached an estimated 2099 at the end of the 21st century according to predictions using the current HPV vaccination and cervical cancer screening rates. Globally, the higher the national development index, the lower the prevalence.[30] According to the modelling study, Japan is in the group with the highest national development index, but the predicted value of cervical cancer incidence is positioned as the highest in that group.[30] In Japan, cervical cancer, especially refractory adenocarcinoma, has been increasing in young women.[10] Therefore, we believe that our findings showing the effectiveness of HPV vaccination in Japan are very important data when considering the resumption of recommendations by the MHLW of Japan and increasing the vaccination rate thereafter.

In conclusion, this nationwide case-control study in Japan demonstrated a risk reduction of 58% for CIN1+ and 75% for CIN2+ among women with versus those without HPV vaccination. In Japan, the HPV vaccination rate is approaching zero, and cervical cancer has been increasing among younger women. To avoid tragedy that can be prevented by HPV vaccination, our findings suggest that resurgence of the proactive recommendation of MHLW for nationwide HPV vaccinations is needed in Japan.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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