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RESEARCH PAPER

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The efficacy of human papillomavirus vaccination in young Japanese girls: the interim results of the OCEAN study

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ABSTRACT

Human papillomavirus (HPV) vaccine has been used to prevent chronic HPV infection, which accounts for cervical cancer. Japanese Ministry of Health, Labor and Welfare (MHLW) conducted an HPV vaccination campaign in 2010 and the Obstetrical Gynecological Society of Osaka initiated a multicenter, prospective cohort study in Osaka, Japan – OCEAN (Osaka Clinical resEArch of HPV vacciNe) study – to investigate the oncogenic HPV prevalence and the long-term protection rate of HPV vaccine. A total of 2814 participants were enrolled on their visit for HPV vaccination between 12 and 18 years old. Among them, 102 participants received HPV/Pap co-test as primary cancer screening at the age of 20–21. We compared the prevalence in two groups (the vaccinated and the unvaccinated group). HPV infection ratio was significantly lower in the vaccinated group compared to the unvaccinated (12.9% vs. 19.7%; $p = .04$). In particular, HPV 16 and 18 were not detected in the vaccinated group, while 4.9% of participants in the unvaccinated group were infected ($p = .001$), suggesting that vaccination provided effective protection against high-risk types of HPV. The cross-protection effect of HPV vaccines was also observed against HPV 31, 45, and 52. Although HPV vaccines were not contributed to the reduction of cervical intraepithelial neoplasia 1 (CIN) ($p = .28$), CIN2 or worse was not observed in vaccinated group. Our research showed that at the age of 20–21, HPV vaccine inhibited the infection of high-risk HPV and had impacted on the development to CIN2 or worse in Japan.

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Introduction

In 2018, cervical cancer was the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality in women worldwide.[1] Human papillomavirus (HPV) vaccine has been used in more than 130 countries to prevent chronic HPV infection, which accounts for almost all cases of cervical cancer.[2] Indeed, the effectiveness of HPV vaccine has been already reported in many countries.[3–5]

HPV vaccines have rendered cervical cancer a largely preventable disease. Precisely, HPV vaccine induces antibody responses at high level to HPV types 16 and 18, which are responsible for approximately 70% of cervical cancer cases globally.[6] Of note, the distribution of HPV strains varies by age and region. In Japan, HPV types 16 and 18 were reported in 90% of patients with cervical cancer in their 20 s and 76% in their 30 s.[7] Hence, the precise protection rate for HPV vaccine could be higher than anticipated in our country, although its long-term effect remains unclear.

Japanese Ministry of Health, Labor and Welfare (MHLW) conducted an HPV vaccination campaign in 2010 following the approval of clinical use of the vaccine in 2009. In April 2011, the Obstetrical Gynecological Society of Osaka initiated a multicenter, prospective cohort study in Osaka, Japan – OCEAN (Osaka Clinical resEArch of HPV vacciNe) study – to investigate the oncogenic HPV prevalence and the long-term protection rate of HPV vaccine in patients with abnormal cervical cytology and cervical intraepithelial neoplasia.

There was an acceleration in enrollment of vaccinated participants by April 2013 when HPV vaccine was added as one of the national immunization programs in Japan. Nevertheless, adverse events of HPV vaccination, including syncope, complex regional pain syndrome and impaired mobility, were

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repeatedly reported in the media. In June 2013, the Japanese Government announced discontinuation of the active recommendation for its use until the information of the adverse effects were fully investigated. Thus, we had to terminate the enrollment of study participants at the end of March 2015 as further recruitment was almost impossible due to this announcement. Over 2800 vaccinated participants were barely enrolled, that enabled our analysis of the HPV prevalence and the protective effect of HPV vaccine in the young generations.

Here, we report the scheduled interim results of OCEAN study to show the HPV prevalence and the protection rate of HPV vaccine in young Japanese girls aged 20–21 years.

Methods

Study design

Enrollment of The OCEAN study was conducted between April 2011 and March 2015. The inclusion criteria were as follows: (1) healthy women aged 12–18 years who attended for HPV vaccine [either bivalent (Cervarix, GlaxoSmithKline Biologicals, London, UK) or quadrivalent (Gardasil, Merck, Darmstadt, Germany) vaccine] at public expense, (2) women aged 20–21 who already had HPV vaccination and visited clinic/hospitals for routine cancer screening, (3) unvaccinated women aged 20–21 who attended for cancer screening. The enrollment was performed at each clinic or hospital which participated in OCEAN study. Written informed consent was obtained from all participants before commencing the study, and the written consent from parents was obligatory together with own consent in case of girls under 16 years. Vaccination records of the participants were collected from local government database or clinical record in the clinic or hospitals. The study was approved by the Ethics Committees of the Osaka University Hospital (Osaka, Japan) and other individual institutions.

Data collection

We started with encouraging participants of the criteria (1) above to attend cervical cancer screening at the age of 20–21 years by sending invitation mails. Cervical screening was performed at clinics and hospitals that were in the lists of OCEAN study. At each medical facility, HPV testing using HCII (QIAGEN, Venlo, Netherland) in combination with cervical cytology (HPV/Pap co-test) was performed. Colposcopic diagnosis and biopsy were added in case of abnormal cytology result (atypical squamous cells of undetermined significance (ASC-US) with positive result of HPV, low-grade squamous intraepithelial lesion (LSIL), or more).

Statistical analysis

The statistical analysis was performed using Fisher's exact test. We set the level of statistical significance at 0.05.

Results

A total of 2814 participants were enrolled on their visit for HPV vaccination between 12 and 18 years old. Among them, 102 participants received HPV/Pap co-test as primary cancer screening, after being encouraged to receive test at the age of 20–21. In addition, 68 vaccinated cases were newly enrolled after 2015 when they received HPV/Pap co-test. We also recruited 877 unvaccinated women aged 20–21 as control. The characteristics of all participants were shown in Supplementary Table S1. Firstly, we examined HPV infection prevalence, which was significantly lower in the vaccinated group compared to the unvaccinated (12.9% vs. 19.7%; p = .04; Table 1). In particular, HPV 16 and 18, which are known as the two most common oncogenic types, were not detected in the HPV-vaccinated group, while 4.9% of participants in the unvaccinated group were infected (OR = 0.61; 95% CI, 0.38 to 0.98; Table 2), suggesting that vaccination provided effective protection against high-risk types of HPV. HPV vaccine is known to exert a cross-protection effect against other types of HPV, except for HPV 16 and 18.[5,8] It has been reported that both bivalent and quadrivalent HPV vaccines exert a cross-protection effect against HPV 31, 33, 35, 39, 45, 52, 58, and 59.[5,9–12] Thus, in our study, we examined the prevalence of other types of HPV as well. Table 3 shows prevalence of various HPV types detected both in vaccinated and unvaccinated individuals. Compared with the unvaccinated group, the prevalences of HPV 31, 45, and 52 were lower in the HPV-vaccinated group. In contrast, the prevalence of HPV

Table 1. The ratio of high-risk HPV infection.

	non-vaccinated (n = 877)	vaccinated (n = 170)	OR (95% CI)
HPV (-)	704 (80.3%)	148 (87.1%)	
high risk HPV	173 (19.7%)	22 (12.9%)	0.61 (0.38–0.98)

In vaccinated group, the ratio of high-risk HPV infection was significantly decreased compared to non-vaccinated group. (OR; odds ratio, CI; confidence interval)

Table 2. The ratio of HPV 16 and 18 infection.

	non-vaccinated (n = 877)	vaccinated (n = 170)	OR (95%CI)
high risk HPV	173 (19.7%)	22 (12.9%)	0.61 (0.38–0.98)
HPV 16 and 18	43 (4.9%)	0 (0%)	0.06 (0.003–0.92)

In vaccinated group, the infection of HPV 16 and 18 was not observed in vaccinated group. (OR; odds ratio, CI; confidence interval).

Table 3. The cross-protection effect of HPV vaccines.

HPV type	non-vaccinated (n = 877)	vaccinated (n = 170)	OR (95%CI)
16	33 (3.76%)	0 (0%)	0.07 (0.005–1.21)
18	13 (1.48%)	0 (0%)	0.19 (0.01–3.17)
31	14 (1.6%)	0 (0%)	0.17 (0.01–2.94)
33	5 (0.57%)	1 (0.59%)	1.03 (0.12–8.89)
35	5 (0.57%)	3 (1.76%)	3.13 (0.74–13.24)
39	24 (2.74%)	3 (1.76%)	0.64 (0.19–2.14)
45	5 (0.57%)	0 (0%)	0.48 (0.03–8.71)
48	0 (0%)	0 (0%)	-
51	17 (1.94%)	4 (2.35%)	1.22 (0.41–3.67)
52	45 (5.13%)	5 (2.94%)	0.56 (0.22–1.43)
56	21 (2.39%)	9 (5.29%)	2.28 (1.03–5.07)
58	37 (4.22%)	4 (2.35%)	0.55 (0.19–1.56)
59	17 (1.94%)	1 (0.59%)	0.30 (0.04–2.26)
67	0 (0%)	0 (0%)	-
68	12 (1.37%)	2 (1.18%)	0.86 (0.19–3.87)

Compared with the unvaccinated group, the prevalence of HPV 31, 45, 52, and 59 were lower in the HPV-vaccinated group. (OR; odds ratio, CI; confidence interval)

Table 4. The incidence of abnormal cytology.

	non-vaccinated (n = 877)	vaccinated (n = 170)	OR (95%CI)
NILM	844 (96.2%)	164 (96.5%)	0.94 (0.39–2.27)
ASC-US	18 (2.1%)	2 (1.2%)	0.57 (0.13–2.47)
LSIL	14 (1.6%)	4 (2.4%)	1.49 (0.48–4.57)
HSIL	1 (0.1%)	0 (0%)	1.71 (0.07–42.24)
Abnormal cytology	33 (3.8%)	6 (3.5%)	0.94 (0.39–2.27)

Although abnormal cytology was observed in 3.5% in vaccinated group, there was no significant difference compared to non-vaccinated group. (NILM; Negative for intraepithelial lesion or malignancy, ASC-US; Atypical squamous ceils of undetemined significance, LSIL; Low-grade squamous intraepithelial lesion, HSIL; High-grade squamous intraepithelial lesion, OR; odds ratio, CI; confidence interval)

Table 5. The incidence of cervical intraneoplasia (CIN).

	non-vaccinated (n = 877)	vaccinated (n = 170)	OR (95%CI)
CIN1	11 (1.3%)	4 (2.4%)	1.90 (0.60–6.03)
CIN2	4 (0.5%)	0 (0%)	0.57 (0.03–10.622)
CIN3	0 (0%)	0 (0%)	-
total	15 (1.8%)	4 (2.4%)	1.38 (0.45–4.22) (Fisher's exact test)

In the unvaccinated group, CIN1 and CIN2 were detected in 1.3% and 0.5% of participants, respectively. In contrast, CIN1 was detected in 2.4% in the HPV-vaccinated group while CIN2 was not detected. (CIN; cervical intraepitherial neoplasia, OR; odds ratio, CI: confidence interval)

56 was significantly higher in the HPV-vaccinated group (OR = 0.06; 95% CI, 0.003 to 0.92; Table 3), which achieved similar results as published data.

Secondly, we analyzed the incidence of abnormal cytology. In the unvaccinated group, abnormal cytology results were found in 3.8% of participants (Table 4). In the HPV-vaccinated group, abnormal cytology was also observed in 3.5% of participants (OR = 0.94; 95% CI, 0.39 to 2.27), indicating that HPV vaccine did not contribute to a reduction in the incidence of abnormal cytology.

We thirdly compared the incidence of cervical intraepithelial neoplasia (CIN). In the unvaccinated group, CIN1 and CIN2 were detected in 1.3% and 0.5% of participants, respectively. In contrast, CIN1 was detected in 2.4% in the HPV-vaccinated group, while CIN2 was not detected (OR = 1.90; 95% CI, 0.60 to 6.03, OR = 0.57; 95% CI, 0.45 to 4.22, respectively; Table 5). These findings suggested that the HPV vaccine did not reduce total number of patients with CIN, but might have impacted on the development to CIN2.

Our results showed the effect of HPV vaccine in young Japanese girls; however, the limitations of this intermediate report are also revealed. In this report, we could not show the reduction of cervical cancer by HPV vaccine. Although the number of cases of young cervical cancer have been increasing in Japan, it still accounts 2/100,000 in the girls aged 20 to 25. Five years later, we plan to analyze the prevalence of HPV infection, CIN and cervical cancer in the participants of this study at the age of 25–26; however, the analysis at the age of 30 and more might be needed.

Discussion

The efficacy of HPV vaccine against CIN and cervical cancer has been extensively reported worldwide. In the report from Scotland, HPV-vaccinated women exhibited more than 80% reduction in prevalence of CIN.[3] It was reported in Finland that the HPV vaccine also significantly inhibited the development of HPV-related cancer, including cervical cancer.[4] Similar effects have been already reported in several countries.[13–15] Against residual or persistent CIN, two or more doses of HPV vaccine have been demonstrated to exert an inhibitory effect.[16,17] All the studies mentioned above established the preventive effect of the HPV vaccine against CIN and cervical cancer. In our study, the HPV vaccine reduced the prevalence of HPV infection including HPV 16 and 18, although unfortunately HPV vaccine did not significantly decrease the incidence of abnormal cytology and CIN. There was a certain limitation in our study since the prevalence of CIN generally remains low around 20 years old;[18] thus, we did not observe a statistical difference in the CIN prevalence between the HPV-vaccinated and unvaccinated groups. In contrast, vaccines inhibited the progression to CIN2 or worse, which could indicate that this cohort study demonstrated the long-term effect of HPV vaccines against progression to cervical cancer.

Kudo et al. revealed that both bivalent and quadrivalent HPV vaccines exerted a significant cross-protection effect against HPV 31, 45, and 52.[10] In addition, Vincenzo et al. reported the potential of a cross-protection effect of HPV vaccine against HPV 31, 33, 35, 45, 52, 58, and 59, due to high homology of protein in the certain types of viruses with the one in vaccines.[19] In our study, HPV vaccine markedly decreased the prevalence of HPV 52, and also showed a reducing trend in HPV 31, 45, 52, 58, 59, and 68 infections. On the other hand, our findings showed a slight increase in the prevalence of HPV 35 and 56; these two HPV types have been listed as high-risk types for cervical cancer.[20,21] Prevalence of HPV 56 in our study could have contributed to the incidence of abnormal cytology in our HPV-vaccinated group. Among CIN cases in the HPV-vaccinated group, those with CIN1 showed positive for HPV 39, 51, and 52, which are not categorized in high-risk HPV types. In addition, there was no CIN2 and more aggressive disease in the vaccinated, implying that HPV vaccine exhibited high degree of effectiveness against CIN3 or worse, which are the therapeutic targets. Future studies will be targeted all high-risk HPV types covered by new HPV vaccines with direct and cross-protection effect in order to eradicate HPV and related cancer. A 9-valent HPV vaccine has been recently approved by Japan's MHLW; thus, further reduction in the prevalence of HPV infection will be expected.

In Japan, the HPV vaccination rate in younger generation has been dropped to less than 1%[22] because of the series of media reports on adverse events and the suspension of HPV vaccine recommendation by the MLHW in 2013. Following the withdrawal, there were several studies which investigated correlation between HPV vaccination and its adverse events such as syncope. In the report by Suzuki et al., there was no causal correlation between the HPV vaccine and previously reported symptoms.[23] Sobue et al. also reported similar results in the study granted by the MLHW. All these continuous efforts to establish the safety and efficacy of HPV vaccination have been accumulated enough to restart the standard immunization program as conducted in the other countries. Nevertheless, the HPV

vaccination rate in young girls still remains low, and during these off-vaccination years, unvaccinated generations have been undoubtedly increased. In Australia, the government has conducted a project named The Australian National HPV Vaccination Program (NHVP), that resulted in significant decrease in the incidence of cervical cancer to currently seven cases per 100,000 women, and it is predicted to reach the level below a potential elimination threshold of fewer than four new cases per 100,000 women annually by 2028.[24] Moreover, in Sweden, it was reported that the risk of invasive cervical cancer was decreased by quadrivalent HPV vaccine.[25] Thus we, obstetricians and gynecologists in Japan, have responsibility to take action on MHLW to restart HPV vaccination program, as well as enhance social awareness of cervical cancer and its prevention.

This study was first aimed at HPV-vaccinated girls born between 1994 and 1999, and later by chance, we encountered unvaccinated populations after 1999 due to discontinuation of the active recommendation of HPV vaccine; this phenomenon enabled us to remove lead time bias and compare the impact of HPV vaccines in three generations (unvaccinated, vaccinated, and suspended generations). Such research is usually unacceptable from an ethical point of view; however, this thought-provoking situation was incidentally occurred in Japan.

The ultimate goal of the recruitment of girls at the age of 20–21 is 1,500 participants for vaccinated and unvaccinated group, respectively, and when participants are at the age of 25–26, we encouraged screen cervical cancer again.

As final report, our data will demonstrate the efficacy of the HPV vaccine without lead-time bias and highlight the difference among vaccinated, unvaccinated and suspended girls. Our further studies will be conducted to compare the prevalence of HPV-related diseases among four groups including the population that receive vaccination after recommencement of national immunization program in the near future.

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