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Short communication

Evaluation of future cervical cancer risk in Japan, based on birth year

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ABSTRACT

In 2013, following the Ministry of Health, Labor and Welfare (MHLW)'s announced suspension of its vaccine recommendation due to media reports of "adverse events", HPV vaccination dropped to almost 0%. Here, we analyzed, by birth year, the cumulative vaccinations for girls up to age 16 (maximum age for public subsidies) and the results of cervical cancer screening in Matsuyama City. The incidence of CIN3 or worse was 0.09% (7/7872) for these unvaccinated generation born between 1991 and 1993, and 0.00% (0/7389) for the vaccination generation born between 1994 and 1996. This study is the first to show the significant reduction in incidence of CIN3+depending on birth year in Japan. We must keep in mind that the unacceptable high risk for cervical cancer has already begun for an entire new generation of unvaccinated girls born in or after 2000. This data encourages a resumption of MHLW's recommendation for HPV vaccination.

1. Introduction

Cervical cancer is on the decline in many countries, but in Japan a trend for significantly decreasing age-adjusted incidence of cervical cancer (per 100,000) began in 1976 but reversed after 2000, increasing significantly to date (APC = 3.8, 95% CI: 2.7 to 4.8; age-adjusted rate: 28.0 in 1976, 9.1 in 2000, 14.1 in 2012) [1]. Despite biennial cervical cancer screening being recommended for all females 20 or older, the screening rate is extremely low.

The cervical cancer prevention vaccine for Human Papillomavirus (HPV) was expected to be a powerful preventive measure for cervical cancer. So much so that public subsidies for the HPV vaccine which targeted females aged 13–16 commenced in 2010 and the vaccine became periodical in April of 2013, targeting those aged 12–16. However, repeated news regarding so-called adverse events arose soon thereafter, stoking public doubts about the vaccine's safety. The MHLW responded by announcing a "Suspension of its active inoculation recommendation for the cervical cancer prevention vaccine" on June 14th, 20136. As of January 2019, this suspension is still ongoing, with 5 years having already passed. Due to the combination of alleged adverse events and MHLW's resulting suspension of its active recommendation, the percentage of young Japanese women receiving the HPV vaccine has now decreased sharply, leading to different immunization rate greatly depending on birth year. The vaccines had not been introduced for girls born in 1993. About 70% of girls born in 1994–1999 have been immunized with the public subsidy. About 4% of girls born in 2000, about 1% of girls born in 2001, and almost 0% of girls born after 2001 have been immunized [2,3].

The purpose of the present study was to examine the vaccination rates and the incidence of cervical intraepithelial neoplasia (CIN) in Japan, based on birth year, and observed a dramatic decrease of CIN3 following introduction of the HPV vaccine program.

2. Materials and methods

We analyzed, by birth year, the cumulative vaccinations for girls up to age 16 (maximum age for public subsidies) and the results of cervical cancer screening in Matsuyama City (population 510,000). We studied females who received screenings at age 20

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; MHLW, Ministry of Health, Labor and Welfare.

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from 2011 to 2016 (i.e., born between 1991 and 1996). In Japan, females aged 20 or older who miss their targeted year can undergo the exam the next year. In the present analysis, for the females who did not receive cervical cancer screening at the age of 20, the screening results from the following year, at age 21, were included.

3. Statistics

The rates of screening, abnormal cytology, receiving biopsy, abnormal histology were compared between those born in 1991–1993 (unvaccinated generation) and those born in 1994–1996 (vaccinated generation) by Fisher's exact test. The level of statistical significance was set at p = 0.05.

4. Results

The screening targets for cervical screening at age 20 from 2011 to 2013 were born in 1991 to 1993, thus in 2010, when public subsidies started, were over the targeted ages for receiving the HPV vaccine. The vaccination rate was 0% (0/7872) in these females (unvaccinated generation) (Fig. 1). On the other hand, among the screening targets from 2014 to 2016, who were born in 1994–1996, the vaccination rate was 79% (5837/7389) (vaccinated generation).

The screening rates were similar in both groups (p = 1.0) (Table 1). The rate of abnormal screening was significantly higher in the unvaccinated generation (5.7%) than the vaccinated one (3.0%) (p = 0.0063). Among these females, the rates of receiving biopsy were also similar in both groups (p = 1.0).

Table 1
Comparison of the results of cervical cancer screening - before and after introduction of the HPV vaccination program in Japan.

Birth Year Screening Year at age 20	1991–1993 2011–2013	1994–1996 2014–2016	*p*-value
Target of cervical cancer screening	7872	7389	
Receiving cervical cancer screening	890 (11%)	806 (11%)	0.43
Abnormal screening results	51 (5.7%)	24 (3.0%)	0.0063
ASC-US	26	13	0.076
LSIL	14	10	0.68
ASC-H	2	1	1.0
HSIL	9	0	0.0042
HSIL+	9	0	0.0042
Receiving Biopsy	35 (69%)	17 (71%)	1.0
CIN1	7	9	0.62
CIN2	5	2	0.46
CIN3	7	0	0.016
Others*	16	6	0.083
CIN1+	19	11	0.20
CIN2+	12	2	0.014
CIN3+	7	0	0.016

(Fisher's exact test).
* : No malignancy (cervicitis, polyp etc.).

The incidence rate of HSIL was significantly higher in the unvaccinated generation (9/7872) than the vaccinated one (0/7389) (p = 0.0042). The incidence of CIN (CIN1+) tended to be higher in the unvaccinated generation (19/7872) than the vaccinated one (11/7389) (p = 0.20). Especially, CIN3 or worse (CIN3+) for these unvaccinated girls was 0.09% (7/7872) (Fig. 1). On the other hand, among screening targets from 2014 to 2016, born in 1994 to 1996,

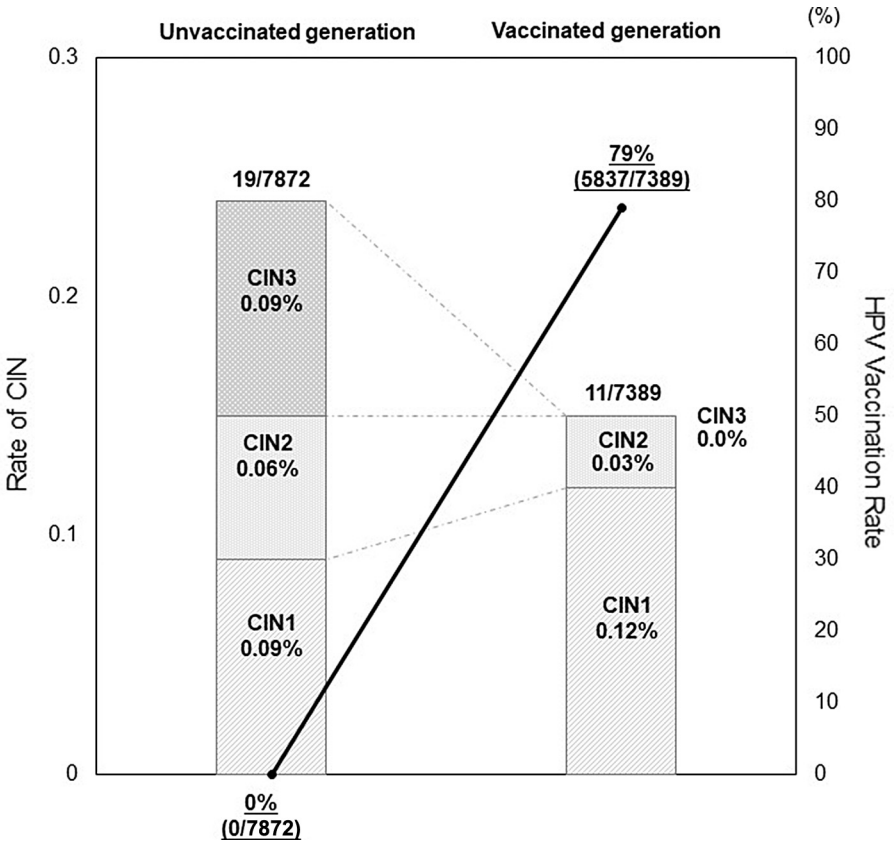

Fig. 1. Comparison of the HPV vaccination rate and the results of cervical cancer screening between the unvaccinated and vaccinated generations. Public subsidies for HPV vaccination started in 2010; by 2012, vaccination rates of 70% were achieved. In March of 2013, media reports of potential 'adverse events' caused the government, in June of 2013, to 'temporarily' suspend recommendation for HPV vaccination, resulting in a discontinuity in HPV and cervical cancer protection that is linked to an unfortunate year of birth in Japan.

there were no cases of CIN3+. This reduction in incidence of CIN3+ in the vaccinated cohort was statistically significant ($p = 0.016$).

5. Discussion

The protective effects of human papillomavirus (HPV) vaccines against HPV-linked precancerous lesions of the uterine cervix have been widely and incontrovertibly demonstrated. Recently, it has been shown that this vaccination protects invasive HPV-associated cancers as well [4]. However, there are only a few studies for verification of effectiveness of HPV vaccine in Japan. In an analysis using the results of pap tests for 20 to 24-year-old females in Miyagi Prefecture, the statistically significant association between with or without immunization and abnormal cytology was demonstrated ($p = 0.03$) [5]. We previously analyzed the statistical data for each birth year, for the cumulative HPV vaccination rates achieved as of age 16, and for the corresponding results of cervical cancer screening at age 20. The rate of abnormal findings in cervical cytology increased slightly from 3.68% in 2010 (birth year: 1990) to 4.35% in 2013 (birth year: 1993); however, it dynamically dropped to 2.99% in 2014 (birth year: 1994) and 3.03% in 2015 (birth year: 1995) [6].

Up until now, in Japan, the preventive effect of the HPV vaccine for HPV-associated diseases of the uterine cervix has been demonstrated only for CIN1+ and CIN2+. The rates of CIN2+ were 0.10% (1/1002) with vaccination and 0.69% (34/4922) without vaccination. The reduction rate of CIN2+ was 85.51% ($p = 0.0261$). However, significant decrease of CIN3+ was not demonstrated [5].

A verification research for effectiveness of HPV vaccine, called Japan Municipal Case-control Study, or J-Study, conducted by a Japan MHLW research team, aims to show the protective effect of HPV vaccine for CIN1+ or CIN2. The other cohort studies called OCEAN STUDY and NIIGATA STUDY has been conducted to compare the incidence rate of CIN2+ between the vaccinated and the unvaccinated groups.

For the first time, we have clearly shown the preventive effect of the HPV vaccine for CIN3+ in Japan. We also found that there will be a reduction in the risk for future cervical cancer in women with birth years enjoying past public subsidies for the HPV vaccine (vaccinated generation born in 1994–1999). Our present data encourages a resumption of MHLW's recommendation for HPV vaccination. Our findings are consistent with our previous survey, which analyzed by birth year the rates of vaccination and abnormal cytology [6]. The risk of cervical cancer morbidity, for girls born in 2000 or later, is expected to increase to the same levels as for previous generations of unvaccinated women, because their vaccination rate is again almost 0% [7,8]. In Japan, despite statements by the World Health Organization and respected academic societies in support of the safety and efficacy of the HPV vaccine, the recommendation suspension continues. We must keep in mind that the unacceptable high risk for HPV infection and cervical cancer has already begun for an entire new generation of unvaccinated girls.

6. Declaration of interest

The author declares that there is no conflict of interest.

7. Conflict of interest

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References

[1] Yagi A, Ueda Y, Kakuda M, Tanaka Y, Ikeda S, Matsuzaki S, et al. Epidemiological and clinical analyses of cervical cancer using data from the population-based Osaka cancer registry. Cancer Res 2019. https://doi.org/10.1158/0008-5472.CAN-18-3109.
[2] Yagi A, Ueda Y, Tanaka Y, Nakae R, Kakubari R, Morimoto A, et al. Time-dependent changes of the intention of mothers in Japan to inoculate their daughters with the HPV vaccine after suspension of governmental recommendation. Hum Vaccin Immunother 2018;14:2497–502.
[3] Sekine M, Kudo R, Adachi S, Yamaguchi M, Ueda Y, Takata T, et al. Japanese crisis of HPV vaccination. Int J Pathol Clin Res 2016;2:039.
[4] Luostarinen T, Apter D, Dillner J, Eriksson T, Harjula K, Natunen K, et al. Vaccination protects against invasive HPV-associated cancers. Int J Cancer 2018;142:2186–218.
[5] Ozawa N, Ito K, Tase T, Shibuya D, Metoki H, Yaegashi N. Lower incidence of cervical intraepithelial neoplasia among young women with human papillomavirus vaccination in Miyagi, Japan. Tohoku J Exp Med 2017;243:329–34.
[6] Ueda Y, Yagi A, Nakayama T, Hirai K, Ikeda S, Sekine M, et al. Dynamic changes in Japan's prevalence of abnormal findings in cervical cytology depending on birth year. Sci Rep 2018;8:5612.
[7] Tanaka Y, Ueda Y, Egawa-Takata T, Yagi A, Yoshino K, Kimura T. Outcomes for girls without HPV vaccination in Japan. Lancet Oncol 2016;17:868–9.
[8] Yagi A, Ueda Y, Egawa-Takata T, Tanaka Y, Nakae R, Morimoto A, Terai Y, Ohmichi M, Ichimura T, Sumi T, Murata H, Okada H, Nakai H, Mandai M, Matsuzaki S, Kobayashi E, Yoshino K, Kimura T, Saito J, Hori Y, Morii E, Nakayama T, Suzuki Y, Motoki Y, Sukegawa A, Asai-Sato M, Miyagi E, Yamaguchi M, Kudo R, Adachi S, Sekine M, Enomoto T, Horikoshi Y, Takagi T, Shimura K. Realistic fear of cervical cancer risk in Japan depending on birth year. Hum Vaccin Immunother 2017;201(13):1700–4.