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学 会 等 発 表 実 績

委託業務題目「HPVワクチンの有効性と安全性の評価のための大規模疫学研究」

機関名 横浜市立大学

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Web-based survey on knowledge for cervical cancer prevention among young women: comparison in Japan and Australia・口頭発表	Miyagi E, Motoki Y, Sato A. M., Morita S, Taguri M, Hirahara F, Wark J. D., Garland S. M.	EUROGIN 2015 (European Research Organization on Genital Infection and Neoplasia), Sevilla	2015, 2	国外
Trends in mortality of human papillomavirus-related cancers in 1975-2012, from the Kanagawa cancer registry, JAPAN・口頭発表	Motoki Y, Katayama K, Asai-Sato M, Miyagi E, Hirahara F	EUROGIN 2015 (European Research Organization on Genital Infection and Neoplasia), Sevilla	2015, 2	国外
Surveys on attitudes for HPV vaccination among young women in Kanagawa Prefecture, Japan・ポスター発表	Miyagi E, Sukegawa A, Motoki Y, Asai-Sato M, Ohshige K, Taguri M, Hirahara F, J. D. Wark, S. M. Garland	15th Biennial Meeting of the International Gynecologic Cancer Society (IGCS), Melbourne	2014, 11	国外
Increasing cervical cancer mortality among young Japanese women: analysis of Kanagawa cancer registry, 1975-2012・ポスター発表	Motoki Y, Mizushima S, Taguri M, Asai-Sato M, Miyagi E, Hirahara F	15th Biennial Meeting of the International Gynecologic Cancer Society (IGCS), Melbourne	2014, 11	国外
神奈川県地域がん登録に『子宮がん』と登録されていた症例の再分類結果の検討・ポスター発表	元木葉子, 水嶋春朔, 加藤久盛, 佐藤美紀子, 沼崎令子, 岡本直幸, 平原史樹, 宮城悦子	第52回日本癌治療学会学術集会, 横浜	2014, 8	国内
シンポジウム「子宮頸がん予防HPVワクチンの有効性と今後の課題」	宮城悦子	第52回日本癌治療学会学術集会, 横浜	2014, 8	国内
シンポジウム I 日本型子宮頸がん予防体制実現への地域コミュニティの役割を考える	宮城悦子, 元木葉子, 丸山康世, 時長亜弥, 佐治晴哉, 沼崎令子, 佐藤美紀子, 寺本勝寛, 加藤久盛, 平原史樹	第55回日本臨床細胞学会春期大会, 横浜	2014, 6	国内

Increase of cervical cancer risk among young Japanese female ; Analyses of Kanagawa cancer registry data 1985-2011・ポスター発表	Motoki Y, Asai-Sato M, Numazaki R, Miyagi E, Hirahara F	第66回日本産科婦人科学会学術講演会, 東京	2014, 4	国内
当院でHPVワクチン接種を受けた医療関係者の子宮頸がん検診受診動向に関する研究・ポスター発表	丸山康世, 宮城悦子, 時長亜弥, 水島大一, 元木葉子, 助川明子, 佐藤美紀子, 沼崎令子, 平原史樹	第66回日本産科婦人科学会学術講演会, 東京	2014, 4	国内

## 2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 (学会誌・雑誌等名)	発表した時期	国内・外の別
Three-year questionnaire survey on human papillomavirus vaccination targeting new female college students	Sukegawa A, Ohshige K, Arai S, Sakanashi K, Usui M, Hirahara F, Miyagi E	J Obstet Gynaecol Res	2015	国外
Web-based recruiting for a survey on knowledge and awareness of cervical cancer prevention among young women living in Kanagawa Prefecture, Japan	Miyagi E, Motoki Y, Asai-Sato M, Taguri M, Morita S, Hirahara F, Wark JD, Garland SM	Int J Gynecol Cancer	2014	国外
Attitudes toward cervical cancer screening among women receiving human papillomavirus vaccination in a university-hospital-based community: Interim 2-year follow-up results	Miyagi E, Sukegawa A, Motoki Y, Kaneko T, Maruyama Y, Asai-Sato M, Numazaki R, Mizushima S, Hirahara F	J Obstet Gynaecol Res	2014	国外

# Effect on HPV vaccination in Japan resulting from news report of adverse events and suspension of governmental recommendation for HPV vaccination

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## Abstract

**Background** Administration of the human papillomavirus (HPV) vaccine decreased dramatically in Japan after extensive news of adverse vaccine events and suspension of the governmental recommendation for the vaccine. In this study, we investigated the knowledge and acceptance of vaccinated adolescents concerning cervical cancer, cancer screening and the HPV vaccine. Furthermore, we analyzed whether and by how much the news affected acceptance of the vaccination.

**Methods** This study was conducted as a part of Osaka Clinical resEARCh of HPV vacciNe (OCEAN) study. A questionnaire was distributed to 2,777 study registrants.

**Results** The response rate was 38 %. The recognition rate of the news of the vaccine's adverse events was 80 %; it

was 68 % for awareness of the government's announcement of the suspension of its recommendation for the vaccine. Among those who had a chance to hear or see the negative news during their vaccination period, 46 (60 %) continued vaccination while knowing of the news, 22 (29 %) discontinued vaccination, and 9 (11 %) continued vaccination without an awareness of the news. Reports of the vaccine's adverse events were the main reason for not continuing the vaccination series. Those who consulted doctors after hearing the adverse news were significantly more likely to continue their vaccinations than those who did not.

**Conclusions** Our results should help in understanding the need for a strong promotion of vaccine usage and cancer screening after future retraction of the recommendation suspension. This may apply to other countries with an

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unsatisfactory rate of HPV vaccination due to fears of adverse vaccine events.

**Keywords** HPV vaccine · Adverse events · Media reports · Governmental suspension of vaccination · Japan

## Introduction

Cervical cancer, which is commonly caused by chronic infection with an oncogenic strain of human papillomavirus (HPV), was the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide in 2008 [1]. Most cases occurred in developing countries; In contrast, cervical cancer has markedly decreased in several Western countries where screening programs have long been established.

In Japan, the rate of cancer screening is quite low, which is a serious public health issue. The biennial screening rate was 32.0 % in 2010. When limited to women in their twenties, the screening rate was considerably lower, at 10.2 % in women aged 20–25 years old and 24.2 % in 26–30-year-olds. This is likely to be one of the reasons for the increase in the incidence of cervical cancer in Japan, especially in the younger generations, i.e., those in their twenties and thirties [2].

The introduction of a vaccine for HPV has made cervical cancer a largely preventable disease. HPV vaccines protect from HPV types 16 and 18, which are thought to account for roughly 60–70 % of cervical cancers [3–6]; thus the protection rate is expected to be also around 60–70 %. On the other hand, the distribution of HPV strains varies by age and region [7–10]. In Japan, HPV 16 and 18 were detected in 90 % of invasive cervical cancers of women in their twenties and in 76 % in their thirties [11]. Thus, in Japan, the accurate protection rate for the HPV vaccine may be higher than thought, although its long-term effect remains unclear.

In April 2011, the Obstetrical Gynecological Society of Osaka initiated a multi-center, prospective cohort study named OCEAN (Osaka Clinical resEArch of HPV vac-ciNe) study to evaluate the oncogenic HPV prevalence in Japan and the long-term protection rate of the HPV vaccine in patients against abnormal cervical cytology and cervical intraepithelial neoplasia. The recruitment of vaccinated participants will continue until the end of March 2015.

In the early spring of 2013, during the period of study enrolment, news of adverse events from receiving the HPV vaccine, such as syncope, complex regional pain syndrome (CRPS) and impaired mobility, was widely and repeatedly reported by the news media. In June 2013, the Japanese government announced that the HPV vaccination was no longer being actively recommended until more detailed

information became available [12]. Both the news of the adverse effects and the government announcement immediately led to fears for schoolgirls and their parents regarding the vaccine, and this fear inhibited HPV vaccination participation. For example, in June 2013, in a city with a population of 840,000 in Osaka Prefecture, the first dose vaccination rate decreased by 97 % compared with the same month in the previous year (described in detail elsewhere). Taking into account the increase in cervical cancer and the extremely low rate of cervical cancer screening in younger Japanese generations, it is crucial to encourage them to get the HPV vaccination.

In the present study, we investigated the level of knowledge about, and acceptance of, cervical cancer, HPV vaccination and cancer screening. Importantly, our registrants included those who had a chance to hear or see the news of the adverse events of the HPV vaccine and the government's announcement of suspension of its recommendation during the period of their vaccination. Therefore, a comparison with those who continued their vaccinations and those who suspended them would clarify the factors associated with their behavior toward vaccination. Regarding the strong impact of news of adverse events, it is clear that the negative feeling about HPV vaccination will not disappear easily, even if the government decides to recommend the vaccination program again in the near future. Therefore, in this situation, it is important how HPV vaccination and cancer screening should be promoted in Japan. This survey will help to facilitate HPV vaccination and cancer screening effectively after the suspension of the vaccination is retracted in Japan, and also in those countries with similar unsatisfactory rates of vaccination due to fear of adverse events.

## Patients and methods

### Study design

Women have been recruited for the OCEAN study since April 2011. Healthy women aged 12–18 years who were going to receive the HPV vaccine (either bivalent or quadrivalent vaccine; Cervarix, GlaxoSmithKline Biologicals and Gardasil, Merck, respectively) at public expense were eligible for inclusion. Since the HPV vaccine program is not school-based in Japan, recruitment has been conducted at each clinic or hospital where the vaccine was received. All participants provided either personal or parental written informed consent (parental informed consent was essential for those aged under 16 years). The OCEAN study was approved by the ethics committees of the Osaka University Hospital and other individual institutions.

## Questionnaire

In October 2013, the first questionnaire was distributed by mail to all 2,764 participants who had enrolled in the OCEAN study by the end of September 2013. The second questionnaire distribution was conducted in December 2013, and was sent only to the 2080 participants who did not reply the first time, and to 13 who were newly recruited after October 2013. In total, 2,777 registrants were sent the questionnaire. Since our participants were relatively young, it was permitted for their parents to answer the questionnaire as their representative.

A structured and closed-ended questionnaire was used, including questions about demographic data, knowledge and attitudes toward HPV vaccination and cervical cancer screening, as well as the news of adverse events and the governmental announcement of suspension of recommendation for the HPV vaccine. First, understanding of general respects of the HPV vaccine by all the responders was examined. Then, we analyzed the responses from those who had an opportunity to hear or see the news and the governmental announcement during their vaccination series. In order to explore whether the adverse news affected the participants' attitude toward vaccination, an analysis was done to compare those who continued and those who ceased their vaccination. The study was approved by the ethics committee of Osaka University Hospital.

## Statistics

Fisher's exact test was used for statistical analysis; the level of statistical significance was set at 0.05.

## Results

### Respondents

Of 2,777 registrants of the OCEAN study enrolled by 20 December 2013, 1,053 participants returned their questionnaire by 16 February 2014, when 4 months had passed after the first questionnaire was distributed. The total response rate was thus 38 %. Of 1,053 responders, answers to the questions were analyzed for 1,038 whose informed consent was obtained. The age of the responders ranged from 12 to 22 years, with the median age of 15 (Table 1).

Did the respondent have knowledge of the aim and efficacy of the HPV vaccine they received?

The aim of HPV vaccination (protection from cervical cancer) was recognized correctly by 92 % (955/1038) of the questionnaire responders. Of these 955 responders,

**Table 1** Age distribution of the survey population

Age (years)	School age	Number	%
12	6th grade (elementary school)	1	0.1
13	7th grade (junior high school)	21	2.0
14	8th grade (junior high school)	156	15.0
15	9th grade (junior high school)	202	19.5
16	10th grade (high school)	193	18.6
17	11th grade (high school)	188	18.1
18	12th grade (high school)	186	17.9
19	1st year (university, college)	71	6.8
20	2nd year (university, college)	16	1.5
21	3rd year (university, college)	3	0.3
22	4th year (university, college)	1	0.1

39 % (401/955) also answered the efficacy of the HPV vaccine (60–70 %) correctly, whereas 32 % overestimated and 24 % underestimated its efficacy (Table 2). Bivalent vaccine was inoculated in 52 % of participants, and quadrivalent in 25 %; however, 18 % did not remember which vaccine they received. The majority (88 %) received all 3 doses, and 6 % (64/1038) did not complete the vaccination (1 dose for 17, and 2 doses for 47 participants).

Permeation of news of adverse events after vaccination and governmental announcement of suspension of its recommendation

There were 830 responders (80 %) who remembered hearing or seeing the news of the adverse events during or after finishing their vaccinations. Of them, 60 % (495/830) consulted with someone after they knew the news. On the other hand, the governmental announcement of suspension of the HPV-vaccine recommendation was also widely recognized (68 %), but significantly less than the news of adverse events ( $p < 0.001$ ) (Table 2).

Knowledge and intention to receive cervical cancer screening

Most (88 %) answered correctly that HPV-vaccinated women should continue to receive cervical cancer screening (Table 2). This knowledge did not vary significantly by age (data not shown). Of those who planned to receive a cancer screening after their HPV vaccination, only 61 % (554/914) knew that, by governmental recommendation in Japan, cervical cancer screening should be started at the age of 20. Nearly a third (33 %) had intentions of getting a cervical cancer screening at the age of 20; however, over half (54 %) answered "undetermined". Younger responders tended to answer more correctly (data not shown). The most frequent reason for not receiving cervical cancer

**Table 2** Participants' characteristics

Question	Number responding	%
Aim of HPV vaccine		
Known	955	92
Unknown	19	2
Unanswered	64	6
Efficacy of HPV vaccine (protection rate from cervical cancer)		
100 %	30	3
80–90 %	300	29
60–70 %	401	39
50 %	185	18
30–40 %	48	5
10–20 %	12	1
Unknown	5	0.5
Unanswered	57	6
Type of HPV vaccine inoculated		
Bivalent	543	52
Quadrivalent	257	25
Forgotten	189	18
Unanswered	49	5
Compliance with vaccination		
1 dose	17	2
2 doses	47	4
3 doses	929	88
Forgotten	31	3
Unanswered	34	3
Awareness of news of adverse events of HPV vaccine		
Known	830	80
Unknown	180	17
Unanswered	28	3
Consulted after hearing the news of adverse events of HPV vaccine		
Yes	495	60
No	260	31
Unanswered	5	9
Persons consulted after hearing the news of adverse events after vaccination (multiple answers permitted)		
Family	417	84
Friends	172	35
Doctor	51	10
School teacher	6	1
Others	3	0.6
Unanswered	2	0.4
Awareness of governmental announcement of suspension of recommendation for HPV vaccine		
Known	704	68
Unknown	307	30
Unanswered	27	2
Cervical cancer screening (cytological check) after HPV vaccination		
Needed	914	88

**Table 2** continued

Question	Number responding	%
Unneeded	37	4
Unknown	52	5
Unanswered	35	3
Starting age of cervical cancer screening recommended in Japan		
20 years	554	61
30 years	230	25
40 years	49	5
50 years	2	0.2
60 years	1	0.1
Unknown	76	8
Unanswered	2	0.2
Intention of having cervical cancer screening at the age of 20 years		
Willing	328	33
Undetermined	557	54
Unwilling	120	12
Unanswered	23	2
Reasons for indetermination or unwillingness of cervical cancer screening at the age of 20 years (multiple answers permitted)		
Barrier to gynecologists	247	37
Anxiety about the exam	171	25
No special reasons	164	24
Bother	145	21
Cost	126	19
Impression of painful exam	95	14
Insufficient time	41	6
Unnecessary	39	6
Others	76	11

screening was having a barrier to the gynecologist (37 %). Others included anxiety about the examination (25 %), no special reasons (24 %), bother (21 %), costs (19 %), impression of painful examination (14 %), insufficient time (6 %), unnecessary (6 %), and so on.

#### Effects on vaccination of the news of adverse vaccine events and the negative governmental announcement

The news of adverse events was most frequent on the news media around March 2013. Thus, those who started HPV vaccination after September 2012 had a chance to hear or see the alarming news and the governmental announcement. Of 77 responders who started vaccination after September 2012, 46 (33 %) continued vaccination with knowledge of the news, 22 (16 %) discontinued their vaccination, and 9 (11 %) continued vaccination without knowing of the news (Table 3). The news of adverse events was widely recognized in both the continued and the

**Table 3** Comparison between the vaccine-continued and the vaccine-discontinued groups

Question	Continued (n = 46)	Discontinued (n = 22)	p value
Awareness of news of adverse events of HPV vaccination			0.096
Known	45 (98 %)	19 (86 %)	
Unknown	1 (2 %)	3 (14 %)	
Awareness of governmental announcement of suspension of recommendation of HPV vaccine			0.17
Known	40 (87 %)	22 (100 %)	
Unknown	6 (13 %)	0 (0 %)	
Reasons for discontinuation of vaccination			–
News of adverse events of HPV vaccine	–	7 (32 %)	
Governmental announcement of suspension of recommendation of HPV vaccine	–	2 (9 %)	
Both	–	13 (59 %)	
Type of vaccine inoculated <sup>a</sup>			1.0
Bivalent	8 (20 %)	4 (21 %)	
Quadrivalent	33 (80 %)	15 (79 %)	
Decision process of starting vaccination <sup>b</sup>			0.073
Self-determined	14 (30 %)	2 (10 %)	
Parent-determined <sup>c</sup>	32 (70 %)	19 (90 %)	
Person consulted upon hearing the news of adverse events after vaccination (multiple answers permitted) <sup>d</sup>			0.021
Doctor	17 (47 %)	3 (15 %)	
Others	19 (53 %)	17 (85 %)	
Requirement for resuming injection (multiple answers permitted)			–
Detailed information about adverse events of HPV vaccine	–	10 (45 %)	
Governmental announcement of restart of recommendation of HPV vaccine	–	10 (45 %)	
Encouraging announcement from experts	–	7 (32 %)	
Friends resuming injection	–	2 (9 %)	
Other	–	3 (14 %)	
Never to resume	–	5 (23 %)	
Intention of having cervical cancer screening at the age of 20 years <sup>e</sup>			0.82
Willing	16 (36 %)	9 (41 %)	
Undetermined	26 (58 %)	11 (50 %)	
Unwilling	3 (7 %)	2 (9 %)	

<sup>a</sup> Seven cases of ‘forgotten’ and a single case of ‘unanswered’ were removed from statistical analysis

<sup>b</sup> A single case of ‘unanswered’ was removed from statistical analysis

<sup>c</sup> Including the cases in which decision was made in consultation with the vaccinated participant

<sup>d</sup> Two cases of ‘unanswered’ were removed from statistical analysis

<sup>e</sup> A single case of ‘unanswered’ was removed from statistical analysis

discontinued group (98 and 86 %, respectively). The governmental announcement of suspension of its recommendation for HPV vaccine was also acknowledged similarly in both groups (87 % for the continued and 100 % for the discontinued group). The news of adverse events affected the attitude toward vaccination more strongly than the governmental announcement (91 and 68 %, respectively:  $p = 0.13$ ).

#### Factors affecting attitude about HPV vaccination

Factors which affected the respondents’ attitudes to HPV vaccination were then analyzed. There was no statistical difference between the types of vaccine received ( $p = 1.0$ ); however, those who consulted doctors after hearing the news were significantly more likely to stay on their vaccination schedule than those who consulted only with others ( $p = 0.021$ ). Of 46 respondents in the continued group, 17 (47 %) consulted with doctors; however, only 3 (15 %) did do so in the discontinued group. Those who decided their vaccination by themselves tended to continue their vaccination ( $p = 0.073$ ).

#### Future intentions of HPV vaccination and cervical cancer screening

Those who discontinued their vaccination schedule were asked what would be needed in order for them to resume their vaccinations. Detailed information on adverse effects and government announcement of restarting recommendation for HPV vaccine were mostly required (45 % for each). Of those who suspended their vaccinations, 23 % answered that they would never resume vaccination.

There was no statistical difference in intention to have cervical cancer screening between the continued and the discontinued group ( $p = 0.82$ ); however, those who were willing to receive cervical screening were few in both groups (36 and 41 %, respectively:  $p = 0.82$ ).

#### Discussion

Human papillomavirus (HPV) vaccine, currently the only approved vaccine for protection from cancer, was licensed in Japan in 2009 for the bivalent HPV vaccine and in 2011 for the quadrivalent. At first, both vaccines were available to private patients at their own expense, then a nationwide HPV vaccine program began in 2011, funded equally by the national and regional governments. Finally, in April 2013, HPV became a routine/universal vaccination. However, around the same time, news of certain adverse events of the HPV vaccine was on the media repeatedly, which induced an immediate and drastic reduction in HPV

vaccination rates in adolescents. This trend has been accelerated by the suspension of the recommendation for HPV vaccination by the Japanese government in June 2013. In one city, the vaccination rate dropped by 97 % compared with the same month in the previous year, and this trend has persisted. The Global Advisory Committee on Vaccine Safety (GACVS) and the International Federation of Gynecologic and Obstetrics (FIGO) proclaimed the safety of HPV vaccines in June and August, respectively [13, 14]; however, to date, they have not been able to overcome the fear of the adverse events.

Our results show that the news of adverse events was significantly more recognized than the government announcement of suppression of the HPV vaccine (80 and 68 %, respectively:  $p < 0.001$ ). Moreover, the news of adverse events had more effect on the attitude towards vaccination than the government announcement (91 and 68 %, respectively:  $p = 0.13$ ). This indicates that having concerns about side effects is certainly a big barrier to vaccination. In fact, in the USA, the concern about safety of the HPV vaccine grows with each year. This concern was the second most common reason given by parents for not vaccinating their daughters (4.5 % in 2008 to 16.4 % in 2010) [15], and it was the most common reason in Hong Kong [16]. In Greece, there is year by year an increasing fear of adverse events that was reported to inhibit their intention to vaccinate more frequently, although the rate of insufficient knowledge of the vaccine decreased for those not being vaccinated [17]. The media is a powerful tool for informing the public about health issues, but it does not always provide balanced information, and sometimes it misinforms [18]. It is thus required to notify both parents and their daughters of the correct information.

First, educational interventions on adolescents and their parents are important in order to promote vaccination. Indeed, parents require more information before vaccinating their children [19]. Recent systematic reviews show that individuals' knowledge and attitudes toward the vaccine are associated with its uptake [20]. Considering that those who are inoculated with HPV vaccine are relatively young, education is required for parents as well as adolescents. However, in our study, those who determined to receive the vaccine by themselves tended more to continue vaccination even if young; thus, they must always be informed about the meaning of the vaccine within their understanding.

Second, the physician's recommendation is considered to be important to HPV vaccine acceptance. In our study, consultation with doctors significantly affected those bent on continuing vaccination ( $p = 0.021$ ; Table 3). Numerous studies also reported that a physician recommendation was an important predictor of HPV vaccine uptake [21–23]. Since HPV vaccination is not conducted as a school-based

system in Japan, the physician recommendation has a considerable effect on the decision of HPV vaccine uptake. HPV vaccine is offered more by physicians (51 %) and pediatricians (19 %) than by gynecologists (12 %) in Japan [24]. On the other hand, fewer family physicians and pediatricians strongly recommended the vaccine for 11–12-year-old patients than for older [25], and more than half of pediatricians were not confident discussing HPV-related issues and needed more knowledge or training [26]. The American Academy of Pediatrics (AAP) recently published what pediatricians should answer to questions about the effectiveness and safety of HPV vaccine [27]. Our results revealed that the vaccinated adolescents and their mothers wanted to know precise information on adverse events of the vaccine. Doctors can allay their fears by giving them correct information on efficacy as well as on the good safety record of the HPV vaccine with evidence of the relatively low frequency of the serious adverse events. The AAP stated that “acceptance of HPV vaccination can be enhanced by a strong recommendation from the health care professional” [27]. Thus education should also be targeted towards physicians and pediatricians as well as gynecologists.

Third, scientific evidence shown by experts will help to promote vaccination. In our study, 32 % answered that encouraging announcements from experts was required for resuming HPV vaccination (Table 3). It is desirable that those announcements by expert societies would be reported correctly and widely on the media.

There are some limitations in our study. First, most of the enrolments in the OCEAN study were recruited by gynecologists rather than physicians and pediatricians, which perhaps gives a selection bias. The analysis by comparing 3 groups was difficult since the sample in each group was too small. Second, the study was conducted using a mailed questionnaire, and thus some information bias may have occurred. Larger-scale studies are needed to obtain population-based data. Thus, we conducted an internet survey in the general population and now are attempting to analyze it.

In conclusion, this study showed that the adverse events of the vaccine decreased the vaccine uptake significantly. Acceptance would be higher following a detailed explanation by physicians. Education about the HPV vaccine and cervical cancer as well as encouragement for cancer screening is required for physicians, adolescents and their parents. Fear of adverse events has become a barrier to HPV vaccination worldwide; understanding the attitude of adolescents and their parents towards adverse events will be more and more important.

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## Original Article



## Evaluation of a Free-Coupon Program for Cervical Cancer Screening Among the Young: A Nationally Funded Program Conducted by a Local Government in Japan

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### ABSTRACT

**Background:** Finding ways to improve the cervical cancer screening rates among young women has been seen as a critical national health problem in many countries, including Japan. The aim of the present study was to evaluate the effects of a free-coupon program for cervical cancer screening conducted by a local government under financial support from the Japanese national government.

**Methods:** The personal cervical cancer screening information was analyzed for all female residents of Toyonaka City, including any past screening history and clinical results since the year 2009, when a free-coupon program for screening was started. These results were compared to results from 2008, prior to implementation of the free-coupon screening program.

**Results:** The screening rates of women eligible for the free-coupon peaked dramatically compared to women of similar age who paid for their screening; however, the rates for the ineligible-age population also increased significantly in parallel to those in the free-coupon program, possibly by indirect peer and publicity effects. In women aged 20 to 25 years, the consecutive screening rate after a free-coupon screening was significantly lower than for those women who received a regular residential screening. After a free-coupon screening, the rate for participating in consecutive screenings depended significantly on the institution where the participant received her first screening test.

**Conclusions:** These results suggest that, for a generation of young women 20–25 years of age, a free-coupon program for cervical cancer screening was effective in increasing the first-time participation rate for screening; however, the increase in first-time participation did not lead to the expected increase in consecutive screenings.

**Key words:** cervical cancer screening; free-coupon; screening rate; consecutive screening

### INTRODUCTION

Cancer of the cervix is the second most common cancer in women worldwide, with about 500 000 new cases and 250 000 deaths each year.<sup>1</sup> Almost 80% of cases occur in low-income countries.<sup>1</sup> Although a vaccine against the human papillomavirus (HPV) effectively prevents human papillomavirus infection and thus reduces the risk of cervical cancer by around 70%,<sup>2</sup> about 30% will still develop cervical cancer.

In some countries, including the United States and the United Kingdom, the cervical cancer screening rate is roughly 80%; however, in Japan it is only 25%.<sup>3</sup> Of particular concern, the screening rate for women aged 20–29 years is less than 10%.<sup>4</sup> Further, the incidence of cervical cancer among this 20- to 29-year age group has recently been increasing dramatically.<sup>5</sup> Finding ways to improve the screening rates among this younger generation has been seen as a critical national health problem.

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In Japan, it is recommended that women start receiving cervical cancer screening at age 20, to be repeated every 2 years. Even if women skip a screening test in the appropriate second year, they can still undergo a screening test the following year. The local government covers part of the screening costs, and the participant pays the rest, which usually amounts to ¥500 to ¥2000 (approximately \$5 to \$20 in United States' dollars [USD]). In 2009, a free-coupon program for screening for cervical and breast cancers was introduced in Japan as a national policy. In this program, a coupon or voucher for a free cervical cancer screening was sent by mail to women aged 20, 25, 30, 35, and 40. The program costs were covered by local governments, with financial support from the national government. Because this free-coupon program was terminated at the end of 2013, all citizens aged 20–44 years in Toyonaka had received a free-coupon only once between 2009 and 2013. A woman aged 20 in 2009, for example, would have received a free-coupon screening in 2009 and undergone a regular screening in 2011 and 2013.

There is an evidence gap as to whether removal of out-of-pocket costs and receipt of an individual invitation letter would be effective for increasing the cervical cancer screening rate, especially in Asia.<sup>6–9</sup> However, the reason for this inconsistency is unclear.

Toyonaka is an urban city located in Osaka prefecture. In October 2013, Toyonaka had an area of 38.6 km<sup>2</sup> and a population of 394 004. Toyonaka is officially acknowledged by the national government of Japan as a core city. In the present study, we evaluated the effectiveness of the free-coupon program in improving cervical cancer screening rates among the younger population of Toyonaka.

It was recently reported that removal of out-of-pocket costs for cervical cancer screening was an effective means of increasing the screening attendance of eligible women.<sup>6</sup> In the present study, we analyzed for the first time the effects of the free-coupon on the screening rate not only for the eligible women but also for the coupon-ineligible women, as well as the results of the screening tests and the consecutive screening rates following the free-coupon screening.

## MATERIALS AND METHODS

The personal screening information of all female residents aged 20–49 in Toyonaka, including screening history and test results since 2009 (when the registration system was renewed and the free-coupon program was started), was available at an individual level. Only the screening rates aggregated by age groups of 20–24, 25–29, 30–34, 35–39, and 40–44 years were recorded for the year 2008. In Toyonaka, participants in the regular cervical cancer screening program typically paid ¥600 (about \$6 USD) for a standard cervical cancer screening.

The rate of cervical cancer screening among the young generation of women (defined here as women aged 20–44 years) for each year between 2009 and 2012 was analyzed.

During the period from 2009 to 2012, a free-coupon program was conducted for women at 5-year age intervals, beginning at the recommended starting age of 20 years (ie, ages 20, 25, 30, 35, and 40 years). These screening rates were compared to that of each age group during the index year of 2008, which was just prior to the start of the free-coupon program. A comparison of the rates for those requiring further diagnostic workups and for cancer detections between the free-coupon and regular screening programs was also conducted. The screening histories of the free-coupon group and regular screening program group were analyzed for changes in consecutive screening rates and any links between those rates and the screening sites where the previous screening was performed.

This study was approved by the Institutional Review Board and the Ethics Committee of the Osaka University Hospital.

## Statistical analysis

MedCalc software (MedCalc Software, Mariakerke, Belgium) was used for the statistical analysis. Increases in the screening rate for each age or age group were evaluated by the logistic regression model. Differences in the rates of further diagnostic workups and cancer detection between the free-coupon group and the regular screening group were evaluated using Fisher's exact test. Differences in consecutive screening rates between a free-coupon group and a regular screening group and between screening sites were also evaluated using Fisher's exact test. Results were considered to be significant when the *P*-value was less than 0.05.

## RESULTS

### Effect of a free-coupon on young women's participation in cervical cancer screening

Figure and Table 1 show the yearly rate of cervical cancer screening for 20- to 44-year-old women between the years of 2009 and 2012, when the free-coupon program was being conducted. The screening rates for free-coupon-eligible 20-, 25-, 30-, 35-, and 40-year-old women formed peaks. Compared to screening rates in the year 2008 (prior to the free-coupon program), which were calculated for the age groups of 20–24, 25–29, 30–34, 35–39, and 40–44 years, the screening rates for the 20-, 25-, 30-, 35-, and 40-year-old women exhibited statistically significant increases (rate ratio [RR] 7.1, 95% confidence interval [CI] 5.9–8.6; RR 6.4, 95% CI 5.2–7.1; RR 3.1, 95% CI 2.9–3.3; RR 3.3, 95% CI 3.1–3.5; and RR 3.0, 95% CI 2.8–3.2, respectively; Table 2). The RRs of the 20- and 25-year-olds were especially high, relative to those of the 30-, 35-, and 40-year-olds.

### Effect of a free-coupon program on participation rates in cervical cancer screening by the ineligible population

Interestingly, the screening rates for the coupon-ineligible population also increased during the study period (Figure).

**Table 1. Yearly rate of cervical cancer screening for 20- to 44-year-old women between the years of 2008 and 2012**

Age (years)	2008	2009	2010	2011	2012
20		174/2016 (8.6%)	183/1868 (9.8%)	220/1731 (12.7%)	175/1778 (9.8%)
21		24/1921 (1.2%)	40/1994 (2.0%)	25/1879 (1.3%)	69/1746 (4.0%)
22	137/9573 (1.4%)	34/1989 (1.7%)	54/1950 (2.8%)	63/2006 (3.1%)	76/1910 (4.0%)
23		51/2077 (2.5%)	76/2015 (3.8%)	60/1960 (3.1%)	101/2004 (5.0%)
24		44/2082 (2.1%)	86/2071 (4.2%)	65/1997 (3.3%)	108/1925 (5.6%)
25		408/2290 (17.8%)	409/2049 (20.0%)	495/2091 (23.7%)	440/2003 (22.0%)
26		78/2240 (3.5%)	89/2237 (4.0%)	79/2068 (3.8%)	133/2104 (6.3%)
27	360/11 031 (3.3%)	85/2293 (3.7%)	154/2255 (6.8%)	136/2241 (6.1%)	168/2110 (8.0%)
28		100/2335 (4.3%)	151/2328 (6.5%)	156/2246 (6.9%)	184/2311 (8.0%)
29		145/2473 (5.9%)	205/2364 (8.7%)	185/2385 (7.8%)	239/2279 (10.5%)
30		578/2628 (22.0%)	639/2494 (25.6%)	616/2393 (25.7%)	593/2518 (23.6%)
31		235/2793 (8.4%)	249/2578 (9.7%)	199/2541 (7.8%)	282/2390 (11.8%)
32	1032/13 232 (7.8%)	170/2836 (6.0%)	247/2765 (8.9%)	220/2627 (8.4%)	226/2602 (8.7%)
33		278/2952 (9.4%)	349/2858 (12.2%)	284/2775 (10.2%)	317/2654 (11.9%)
34		208/3233 (6.4%)	269/3019 (8.9%)	174/1896 (6.0%)	274/2801 (9.8%)
35		874/3574 (24.5%)	873/3219 (27.1%)	863/3054 (28.3%)	736/3016 (24.4%)
36		244/3404 (7.2%)	219/3468 (6.3%)	158/3283 (4.8%)	212/3079 (6.9%)
37	1334/16 753 (8.0%)	381/3558 (10.7%)	389/3460 (11.2%)	362/3415 (10.6%)	375/3308 (11.3%)
38		223/3335 (6.7%)	299/3579 (8.4%)	238/3480 (6.8%)	319/3465 (9.2%)
39		322/3314 (9.7%)	352/3357 (10.5%)	352/3526 (10.0%)	374/3462 (10.8%)
40		807/3422 (23.6%)	832/3309 (25.1%)	865/3361 (25.7%)	773/3599 (21.5%)
41		346/3223 (10.7%)	312/3362 (9.3%)	294/3308 (8.9%)	266/3386 (7.9%)
42	1277/15 900 (8.0%)	196/2607 (7.5%)	240/3234 (7.4%)	239/3379 (7.1%)	242/3293 (7.3%)
43		349/2932 (11.9%)	262/2594 (10.1%)	330/3240 (10.2%)	395/3371 (11.7%)
44		214/3014 (7.1%)	233/2954 (7.9%)	174/2612 (6.7%)	244/3248 (7.5%)

Compared with the screening rate in 2008, the screening rates in the off years from 2009 to 2012 for the coupon-ineligible women in the 21–24, 26–29, 31–34, 36–39, and 41–44 year age groups also significantly increased at the same time that the free-coupon was sent to the eligible 20-, 25-, 30-, 35-, and 40-year-old women (Table 1). The RRs for the 21–24 and 26–29 year age groups were around 2.0 (RR 2.2, 95% CI 1.8–2.6 and RR 1.9, 95% CI 1.7–2.1, respectively); however, those of the 31–34, 36–39, and 41–44 year age groups were around 1.1 (RR 1.2, 95% CI 1.1–1.2; RR 1.1, 95% CI 1.1–1.2; and RR 1.1, 95% CI 1.0–1.2; Table 2).

In order to analyze the reasons for the increased screening rates observed among coupon-ineligible women, the screening history of members of the ineligible population (ie, 21-, 22-, 23-, 24-, 26-, 27-, 28-, and 29-year-old women) post-2009, when the free-coupon program started, who attended screening in 2012 ( $n = 799$ ) was investigated (Table 3). Among 799 women, excluding in-migrants, 531 (66%) had no prior history of screening, while 156 (20%) had a history of an ordinary program screening alone, and 111 (14%) had a history of a free-coupon program screening.

### Quality evaluation of cervical cancer screening in a free-coupon program

In order to compare the characteristics of women who received a free-coupon screening and those who were screened in a regular program, the rate of further diagnostic workups and that of cancer detection were analyzed in both groups. The women aged 20, 25, 30, 35, and 40 years were all eligible for a free-coupon, so there were no women among these groups who received a regular program screening and who paid for the costs. The rates of further diagnostic workups and cancer detection during 2009 to 2012 were compared between the women aged 20, 25, 30, 35, and 40 years who

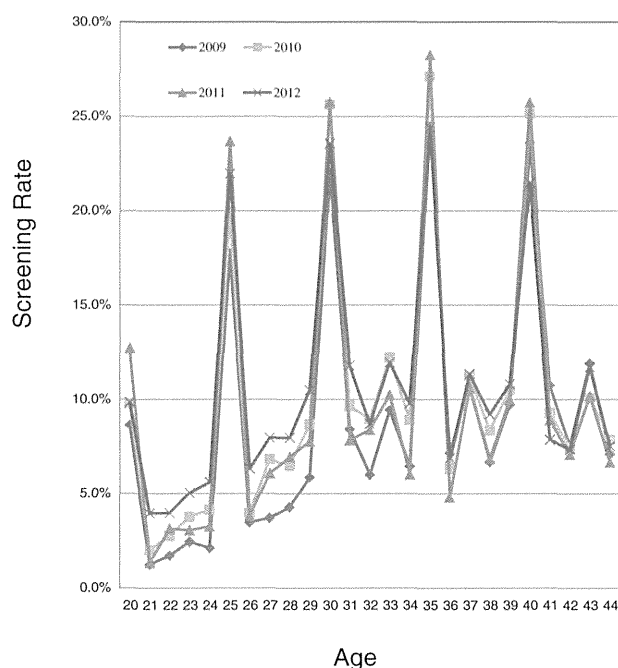


Figure 1. The rate of cervical cancer screening in women 20 to 44 years old in Toyonaka between 2009 and 2012.

received screening with a free-coupon versus those aged 21, 26, 31, 36, and 41 years who received screening in a regular paid program. The rate of requiring further diagnostic workups was 2.0% (240/11 793) in the free-coupon group and 2.3% (80/3553) in the regular program group, indicating no significant difference between the two groups ( $P = 0.43$  by Fisher's exact test). The rate of cancer detection was 8.4 per 100 000 (10/11 793) in the free-coupon group and 8.9 per 100 000 (3/3553) in the regular program group, indicating no significant difference between the two groups ( $P = 1.0$  by Fisher's exact test).

### Rate of consecutive cervical cancer screening after a free-coupon screening

The screening rates of the women aged 20 and 25 years were dramatically increased by the free-coupon program (Figure and Table 1). To assess whether these increased screening rates resulted in increased rates of consecutive screening, the data were analyzed regarding whether or not those women who underwent a free-coupon screening at the ages of 20 or

Table 2. Comparison of the cervical cancer screening rate between the index year of 2008 and the free-coupon program years of 2009–2012

Age, years	2008	2009–2012		
	Rate of screening	Rate of screening	Rate ratio	95% CI
20	1.4%	10.2%	7.1	5.9–8.6
21–24		3.1%	2.2	1.8–2.6
25	3.3%	20.8%	6.4	5.7–7.1
26–29		6.3%	1.9	1.7–2.2
30	7.8%	24.2%	3.1	2.9–3.3
31–34		9.0%	1.2	1.1–1.2
35	8.0%	26.0%	3.3	3.1–3.5
36–39		8.8%	1.1	1.1–1.2
40	8.0%	23.9%	3.0	2.8–3.2
41–44		8.7%	1.1	1.0–1.2

Table 3. Past screening history of the population ineligible for a free coupon who received a screening in a regular local program in 2012

Age, years	Number screened (in 2012)	Fixed domicile resident	No history of screening	History of screening with free-coupon	History of screening without free coupon
21	69	65	56 (86%)	9 (14%)	0 (0%)
22	76	65	56 (86%)	9 (14%)	0 (0%)
23	101	79	54 (68%)	19 (24%)	6 (8%)
24	108	90	72 (80%)	0 (0%)	18 (20%)
Subtotal	354	299	237 (80%)	37 (12%)	24 (8%)
26	133	112	81 (72%)	5 (4%)	26 (23%)
27	168	90	28 (31%)	40 (44%)	22 (24%)
28	184	134	88 (66%)	29 (22%)	17 (13%)
29	239	164	97 (59%)	0 (0%)	67 (41%)
Subtotal	724	500	294 (59%)	74 (15%)	132 (26%)
Total	1078	799	531 (66%)	111 (14%)	156 (20%)

**Table 4. Rates of consecutive cervical cancer screening after a free-coupon screening and a regular screening**

	Screening number	Out-migrant within 2 years	Repeated screening within 2 years
Free coupon in 2009			
20 years old	174	19/174 (11%)	10/152 <sup>a</sup> (6.5%) <sup>b</sup>
25 years old	408	92/408 (23%)	40/311 <sup>a</sup> (13%) <sup>c</sup>
Total	582	111/582 (19%)	50/463 <sup>a</sup> (11%) <sup>d</sup>
Regular program in 2009			
21 years old	24	3/24 (13%)	7/21 <sup>a</sup> (33%) <sup>b</sup>
26 years old	78	17/78 (22%)	18/61 <sup>a</sup> (30%) <sup>c</sup>
Total	102	20/102 (20%)	25/82 <sup>a</sup> (30%) <sup>d</sup>

<sup>a</sup>Cases that required further diagnostic workups on initial screening are excluded.

<sup>b,c,d</sup> $P < 0.001$  by Fisher's exact test.

25 years returned for a subsequent screening. The rate of consecutive cervical cancer screening was compared between the women aged 20 and 25 years who received screening with a free-coupon in the year 2009 and those aged 21 and 26 years who received screening in a regular program in 2009.

In order to investigate the rate of consecutive screening, we excluded from analysis women who out-migrated after a free-coupon screening. In the urban city of Toyonaka, the number of out-migrants was relatively high. Among 582 women aged 20 or 25 years who received a free-coupon screening in the year 2009, 111 persons (19%) moved out of the city within 2 years (Table 4). Among the 102 coupon-ineligible women aged 21 or 26 years who received a screening in a regular program in the year 2009, 20 persons (20%) moved out of the city within 2 years.

After excluding the out-migrants, the continuous screening rate was analyzed. In Japan, women aged 20 years or older are invited for cervical cancer screenings at consecutive two-year intervals, with financial support from their local government. The consecutive screening rate of women aged 20 and 25 within the 2-year interval following the introduction of the free-coupon screening program in 2009 was 6.5% for the 20-year-olds (10/152) and 13% for the 25-year-olds (40/311). On the other hand, the rates of re-visits for women aged 21 or 26 years within a similar 2-year period following a screening in the regular program in the year 2009 were significantly higher: 33% for the 21-year-olds (7/21;  $P < 0.001$ ) and 30% for the 26-year-olds (18/61;  $P < 0.001$ ).

When for some reason a person does not receive a screening after a 2-year interval, she can still undergo a screening in the 3rd year with the same financial support. The consecutive screening rate of women aged 20 and 25 within the 3-year interval following the introduction of the free-coupon screening program in 2009 was 16% for the 20-year-olds (24/142) and 22% for the 25-year-olds (63/277; data not shown). On the other hand, the rates of re-visits for women aged 21 or 26 years within a similar 3-year period following screening in the regular program in the year 2009 were significantly higher: 56% for the 21-year-olds (10/18;  $P <$

**Table 5. Differences in rates of consecutive screening are related to the screening sites where the previous screening was performed**

	Clinic A	Other institutions	<i>P</i> -value
Free coupon in 2009			
Subsequent screening within 2 years	22/88 (25%) <sup>b</sup>	28/375 <sup>a</sup> (7%) <sup>b</sup>	$< 0.001$
Ordinary program in 2009			
Subsequent screening within 2 years	13/32 (41%) <sup>c</sup>	12/50 <sup>a</sup> (24%) <sup>c</sup>	0.11

<sup>a</sup>The cases that required further diagnostic workups on initial screening were excluded.

<sup>b</sup> $P < 0.001$  by Fisher's exact test.

<sup>c</sup> $P = 0.07$  by Fisher's exact test.

0.001) and 60% for the 26-year-olds (31/52;  $P < 0.001$ ; data not shown).

### Effect of screening site on rate of repeating cervical cancer screening

Next, we investigated the effect of where the screening tests were performed on the consecutive screening rate of women aged 20 or 25 years who received a free-coupon screening and that of those aged 21 or 26 years who received a screening through the regular program in 2009. There were 22 clinics and 6 screening centers where cervical screening test were provided in Toyonaka; however, only 18 of the 22 clinics participated in the 2009 program.

Interestingly, the consecutive screening rates of the 20- and 25-year-olds screened for free at clinic A within the 2-year interval was 25% (22/88), which was significantly higher than the 7% (28/375) reported from the other institutions ( $P < 0.001$ ; Table 5). On the other hand, the consecutive screening rates for 21- and 26-year-olds after a paid screening were slightly (but not significantly) higher at clinic A than at the other screening sites ( $P = 0.11$ ).

The consecutive screening rates of the 20- and 25-year-olds screened for free at clinic A within the 3-year interval was 46% (37/80), which was significantly higher than the 15% (50/339) reported from the other institutions ( $P < 0.001$ ; data not shown). On the other hand, the consecutive screening rates for 21- and 26-year-olds after a paid screening were slightly (but not significantly) higher at clinic A than the other screening sites ( $P = 0.07$ ).

## DISCUSSION

There is a critical need to improve the rate of cervical cancer screening among younger women in Japan, as well as in many developing countries. The screening rate of women aged 20 to 29 years is still less than 10%,<sup>4</sup> despite the increasing incidence of cervical cancer in this group.<sup>5</sup> In addition, due to a media blitz about adverse events following HPV vaccination and a statement by the Ministry of Health, Labor, and Welfare of Japan in June 2013 regarding the suspension of an aggressive recommendation for HPV vaccination, the rate of HPV vaccination has dramatically decreased. Given these

situations, the need for improvement in the cervical cancer screening rate among younger women is attracting serious attention. National and local governments therefore enacted a program in which a free cervical screening coupon was sent to 20-, 25-, 30-, 35-, and 40-year-old women to address this problem.

Although many interventions have attempted to remove some of the barriers to cervical cancer screening,<sup>10-16</sup> out-of-pocket costs for screening remain a barrier to access in the United States and Japan.<sup>7</sup> Recently, Tabuchi et al. demonstrated that removal of the out-of-pocket costs by providing a free-screening coupon improved cervical cancer screening participation in Japan.<sup>6</sup> However, they did not analyze how the screening rate was affected for women who had out-of-pocket costs (because of ineligible age for the free screening). In the present study, the screening rates during 2009 to 2012 were shown to rise sharply among those receiving free screening compared to the rates among those of the same age during the pre-program index year of 2008, especially in the two youngest age groups studied (ie, the women aged 20 or 25; Figure and Table 1). However, the screening rate among coupon-eligible women did not increase significantly between 2009 and 2012 (data not shown). This might imply a limitation of the effect of removal of out-of-pocket costs.

We demonstrated for the first time that the screening rates of the population who were paying for their screening (because they were an ineligible age) also increased significantly during the period of this program. While the rates among coupon-ineligible women did not increase as dramatically as those among coupon-eligible women, there was still a significant improvement over 2008 rates.

Possible reasons for the increased screening rates of the youngest of the free-coupon ineligible population during the free-coupon program might be a return visit for screening in a regular program 1 to 3 years after an initial free-coupon screening, or due to indirect effects of the free-coupon program, including improved education and understanding of cervical (and breast) cancer and enhanced motivation for cancer screening. Peer pressure from family, friends, and colleagues to participate in screening between members of the two groups is also likely.

The rate of repeat screening after receiving a previous free-coupon screening among the women who received a regular screening in 2012 was only 14%. This low rate of repeat screening suggests that the significant increase of screening rates seen among 21- to 24-year-old and 26- to 29-year-old women (RR 2.2 and 1.9, respectively; Table 2) cannot be explained by return visits for a regular screening 1 to 3 years after initial free-coupon screening. The increased screening rates of the ineligible population after the free-coupon program started might be caused by indirect publicity effects of the free-coupon program, including improved understanding of cervical cancer and enhanced motivation for

cancer screening in young women (Table 2). This somewhat unexpected effect of the free-coupon program should be confirmed in the future.

It was also demonstrated that the rate of requiring a diagnostic workup and the rate of cancer detection due to the screenings were not markedly different between the free-coupon and paid screening program groups. Perhaps more importantly, it was demonstrated for the first time that the follow-up screening rates were significantly lower in the free-coupon group than in the regular screening group (Table 4). This result shows that the complete removal of out-of-pocket costs for cervical cancer screening dramatically inspires young women to attend an initial screening; however, it does not translate to following through for a repeat screening 2 years later. This may be a limitation of the effect of a free-coupon cervical cancer screening program. On the other hand, the women who paid some amount of money for a regular screening program were shown to have a consecutive screening than those who attended a free-coupon screening. These results suggest that the largest problem now is how to inspire women to maintain a regular schedule of subsequent screenings. Understanding why the free-coupon group failed to improve rates of consecutive screening will help in providing a solution.

Interestingly, the consecutive screening rate after a free-coupon screening varied depended on where the participants received their previous screening test. This link to the screening experience may provide a partial explanation for the lack of improvement in consecutive screening rates. In the clinic where the rate of follow-up screening was significantly higher, the doctors and staff had spent enormous time and effort to educate the patient about the importance of the screening test to detect cervical cancer; however, it is difficult to statistically compare these educational efforts with those of other institutions. Education is but a part of the screening experience. Institutional reputation, location, scheduling convenience, and waiting room and screening room ambiance all play a role in whether the patient perceives the screening experience as worth repeating. These features of the screening experience are all difficult to quantify and compare statistically.

The Community Preventive Services Task Force demonstrated effectiveness of removal of out-of-pocket costs for breast cancer screening in increasing screening rates for breast cancer; however, evidence with respect to improving cervical cancer screening rates was insufficient.<sup>17</sup> The present study provided some evidence that a free-coupon program is also effective in improving cervical cancer screening rates.

In the present study, the effects of a free-coupon program on the screening rate of both eligible and ineligible women, the rates of requiring further diagnostic workups and cancer detection of a free-coupon screening, and the consecutive screening rate following a free-coupon screening in Toyonaka were analyzed. However, data from only one urban city were analyzed, which is a limitation of the present study. A larger, nation-wide study is necessary to confirm our findings.

**ONLINE ONLY MATERIAL**

Abstract in Japanese.

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## Japan's failure to vaccinate girls against human papillomavirus

**OBJECTIVE:** Human papillomavirus (HPV) vaccination has proven to be effective for prevention of HPV infection and HPV-associated precancerous cervical lesions.<sup>1</sup> However, HPV vaccination rates have remained flat, and whether or not to vaccinate has become a social issue. In the United States in 2013, HPV vaccine coverage for girls ages 13-17 years was only 57%.<sup>2</sup> A notable inhibitory factor to getting vaccinated has been reports of possible adverse effects. Safety concerns among US parents have increased (4.5% in 2008 to 16.4% in 2010), as have intentions not to vaccinate their daughters against HPV (39.8% in 2008 to 43.9% in 2010; odds ratio for trend, 1.08; 95% confidence interval, 1.04–1.13).<sup>3</sup>

**STUDY DESIGN:** In Japan, financial support of the government was initiated from 2011, and recommendation was initiated in April 2013. However, Japan has failed to capitalize on the HPV vaccine's potential for cervical cancer prevention. Japanese media reports in May and June 2013 concerning the vaccine's potential for adverse effects including complex regional pain syndrome and suspension of the government's recommendation for the vaccination on June 14, 2013, have led to public distrust and a dramatic decrease in HPV vaccination rates.<sup>4</sup> To demonstrate the depth of the problem, we analyzed the HPV vaccine coverage for 7th-grade girls in Sakai, Japan. We looked at those who had initiated their 3-dosage series either before or after the negative media reports ran. Girls from 7-11th grade were vaccination targets, with vaccinations at the 7th-grade level being the most desirable.

**RESULTS:** The first trimester of the Japanese school year runs from April 1 through late July; the summer break is about 6 weeks. The adverse Japanese media reports and the Ministry of Health, Labor, and Welfare suspension announcement occurred about 40 days prior to summer vacation, during which the girls in Sakai were expected to go to a clinic for HPV vaccination. During the summer vacation period of 2012, nearly half of the 7th-grade girls got an inoculation. However, in 2013, the number of girls vaccinated in May began to decrease following the news reports, and by late June it was almost 0 (Figure, A). The vaccination rates of the 7-10th graders who had an opportunity for vaccination prior

to the media reports were between 57.8-74.8% (2012). However, following the adverse reports, the rate plunged from 65.4% (2012) to 3.9% (2013) (incidence rate ratio, 0.060; 95% confidence interval, 0.051–0.071) (Figure, B). The girls received HPV vaccination mostly in the 7th grade. The rate of the number of those vaccinated in 7th grade was 70.4% (7th grade: 2632; and 8-10th grade: 1105) in 2012. In 2013, not only the number of those vaccinated in 7th grade but also those in 8-10th grades decreased significantly (7th grade: 158; and 8-10th grade: 90).

**CONCLUSION:** Improved education around the critical importance of HPV vaccine and screening for cervical cancer prevention is needed worldwide. ■

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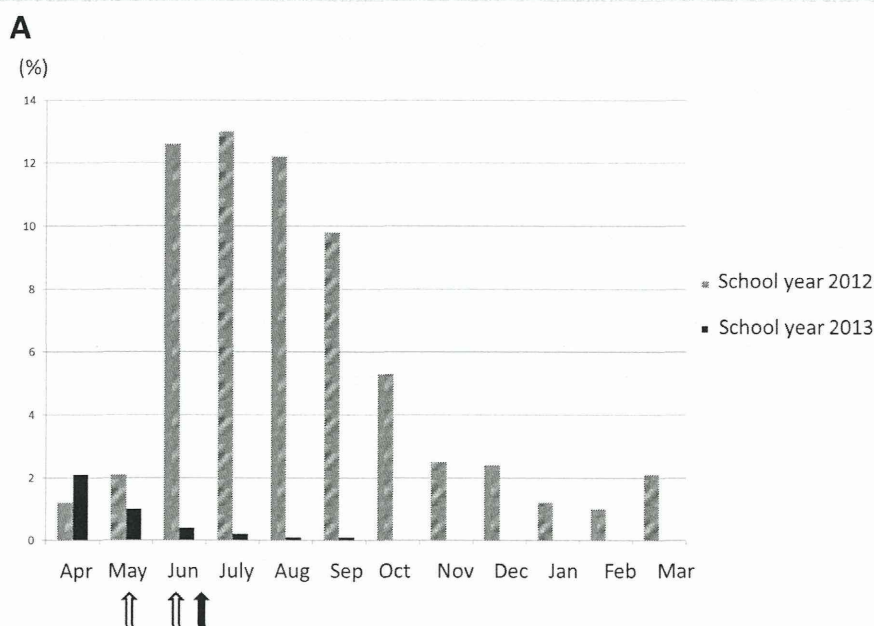
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**FIGURE**  
**HPV vaccination rates in 2012 and 2013**



**B**

Grade	School Year	
	2012	2013
7th grade (junior high school)	65.4%	3.9%
8th grade (junior high school)	74.8%	66.5%
9th grade (junior high school)	65.3%	75.4%
10th grade (high school)	57.8%	65.0%

**A**, Comparison of proportion of 7th-grade girls in Sakai, Japan who received at least 1 dose of human papillomavirus (HPV) vaccine during months of 2012 or 2013. *White arrow* = intense airing of media reports of severe adverse effects in May and June 2013. *Black arrow* = governmental announcement on June 14, 2013, of its suspension of its active recommendation for HPV vaccination. **B**, Total accumulated vaccination rates of girls in 7-10th grades in Sakai, Japan in 2012 vs 2013.

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# Attitudes toward cervical cancer screening among women receiving human papillomavirus vaccination in a university-hospital-based community: Interim 2-year follow-up results

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## Abstract

**Aim:** This study investigated the status of cervical cancer screening among women in a university hospital-based community who received catch-up human papillomavirus (HPV) vaccinations as a basic element of our community-based cervical cancer prevention advocacy.

**Methods:** Self-administered questionnaires were distributed to 173 women working or studying in the community at their first HPV vaccination in 2010, at the third vaccination, and 2 years later. Their demographics and attitudes toward the Pap test were analyzed.

**Results:** The median age of the participants was 27.5 years and 88.2% were sexually active. Before the first vaccination, 38.5% (57/148) of the screening targets had never had a Pap test. Among the women who completed the third vaccination, Pap test experiences within the recent 2 years increased from 45.3% (63/139) at the first vaccination to 71.2% (99/137) at the third vaccination, and 67.5% (54/80) 2 years later. In 45.3% of the screening targets who had never had a Pap test at the time of their first HPV vaccination, their first Pap test was followed by their vaccination.

**Conclusions:** Having biennial Pap tests in accordance with the Japanese national cancer screening guideline was shown to be difficult even for the women in the medical community; however, education about the Pap test and the efficacy of HPV vaccination in providing opportunistic screening encouraged them to have their first or suspended Pap test. Our interim data suggest the need for urgently changing the cervical cancer prevention strategy for young adult women who are excluded from the national HPV vaccine program.

**Key words:** cervical cancer, HPV vaccines, Papanicolaou smear, prevention and control, public advocacy.

## Introduction

About half a million women in the world develop uterine cervical cancer each year, and half of those die as a result.<sup>1</sup> In Japan, in 2007, 8867 women were newly diagnosed with invasive cervical cancer, and 2737

women died of cervical cancer in 2011.<sup>2</sup> Taking into consideration the cases reported as uterine cancer together with endometrial and cervical cancer, more than 3500 women are estimated to die from cervical cancer every year.<sup>2,3</sup> In Japan, the incidence and the mortality rates of cervical cancer have increased among

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women younger than 50 years in the past decade,<sup>2,3</sup> even though cervical cancer is a disease for which an effective population-based Papanicolaou test (Pap test or Pap smear) screening program has decreased the mortality rate in many countries, unlike most other cancers.<sup>4</sup>

As a part of the drastic changes in cervical cancer prevention strategies, the efficacies of two human papillomavirus (HPV) vaccines against precursors of cervical cancer have been published. These vaccines are the HPV-16/18 vaccine (bivalent; Cervarix, Glaxo-SmithKline Biologicals)<sup>5-7</sup> and the HPV-6/-11/-16/-18 vaccine (quadrivalent; Gardasil, Merck Sharp & Dohme Corp),<sup>8-10</sup> both of which have been licensed in many countries. Population-wide HPV vaccination programs for girls are estimated to reduce the incidence of cervical cancer all over the world in the future, and catch-up HPV vaccination of young adult women has also been shown to be effective in recent years.<sup>5-12</sup> Australia conducted a national vaccination program for all women aged 12–26 years between 2007 and 2009 and achieved a high level of vaccination coverage.<sup>11,12</sup> In Japan, voluntary inoculation using both HPV bivalent (since 2009) and quadrivalent (since 2011) vaccines became available for women at their own expense. A nationwide HPV vaccine program was announced by the Japanese government in November 2010 and was widely initiated beginning in 2011, mainly targeting girls aged 13–16 years. The program was funded 50% by the national government and 50% by each regional government until March 2013; total coverage by the Japanese government has just begun in April 2013. The program has been proceeding successfully, and a high prevalence of vaccination – above 70% among the targets – is reported.<sup>3,13</sup> On the other hand, the efficacy of HPV vaccines is mainly valid for the targeted HPV types, which are reported to be the cause of about 70% of cervical cancer in the world.<sup>14</sup> Therefore, the screening program for adult women is still important even in vaccinated women.

Acceptance of cervical cancer screening via the Pap test is seriously low in young adult Japanese women. The self-reported coverage rate of the Pap test in targeted women aged 20–69 years and over during the recent 2-year period was 37.7% in 2010<sup>15</sup> in Japan, which is one of the lowest rates among developed countries.<sup>16</sup> To establish an integrated and effective cervical cancer prevention system in Japan, basic data are needed from various segments of the population whose medical knowledge varies. Our project aimed to reveal the attitudes toward cervical cancer screening in

women who belonged to a university-hospital-based community (Yokohama City University Hospital Community [YCU-HC]) and received catch-up HPV vaccinations at their own expense in the hospital. This group of women is estimated to have a higher level of information about preventive medicine compared with the general population. We report here the first interim results of our comprehensive cervical cancer prevention project, launched at the YCU-HC in 2009, focusing on the attitude toward cervical cancer screening of women in the community who received the HPV vaccination.

## Methods

In November 2009, just after the approval of the bivalent HPV vaccine by the Ministry of Health, Labour and Welfare in Japan, a kick-off lecture about cervical cancer prevention was given to the staff members at the YCU-HC. The participants filled out anonymous questionnaires during the lecture to examine their knowledge about cervical cancer, experiences with the Pap test and their opinions about starting a cervical-cancer-prevention advocacy project in our community. Subsequently, we started an outpatient clinic for cervical cancer prevention in our hospital in January 2010 to provide bivalent HPV vaccinations for the YCU-HC women (staff and students) and female patients who had received some form of medical treatment at the YCU Hospital. They received the vaccine at their own expense of about 13 000 yen (about 135 US dollars at the exchange rate in April 2010) for one administration. Opportunistic cervical cancer screening using the Pap test and HPV testing (Hybrid Capture 2; QIAGEN) was provided to applicants only one time during their vaccinations at their own expense of about 10 000 yen (about 104 US dollars at the exchange rate in April 2010). At the first HPV vaccination, the limitations of the HPV vaccine effectiveness and the necessity of regular Pap tests were explained by gynecological doctors at the clinic. In 2010, 173 women in the YCU-HC received the bivalent HPV vaccine and were scheduled to receive two additional vaccinations at 1 and 6 months later. At the first vaccination in 2010, at the third vaccination 6 months later and in January 2013 (more than 2 years after the third vaccination), YCU-HC women aged 18 years and over, who were enrolled in this study with their written consent, completed questionnaires about their individual background, Pap test experiences and awareness of cervical cancer prevention. As for the survey about attitudes