

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

Etsuko Miyagi¹, Aiko Sukegawa¹, Yoko Motoki¹, Tetsuji Kaneko², Yasuyo Maruyama¹, Mikiko Asai-Sato¹, Reiko Numazaki¹, Shunsaku Mizushima³ and Fumiki Hirahara¹

¹Department of Obstetrics and Gynecology, Yokohama City University Hospital, ²Biobank, Department of Research Support and Coordination, Advanced Medical Research Center, Yokohama City University, and ³Department of Public Health, Yokohama City University Graduate School of Medicine, Yokohama, Japan

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.¹ In Japan, in 2007, 8867 women were newly diagnosed with invasive cervical cancer, and 2737

women died of cervical cancer in 2011.² 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.^{2,3} In Japan, the incidence and the mortality rates of cervical cancer have increased among

Received: June 1 2013.

Accepted: September 3 2013.

Reprint request to: Dr Etsuko Miyagi, Department of Obstetrics and Gynecology, Yokohama City University Hospital, 3-9 Kanazawa-ku, Yokohama 236-0004, Japan. Email: emiyagi@med.yokohama-cu.ac.jp

women younger than 50 years in the past decade,^{2,3} 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.⁴

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)⁵⁻⁷ and the HPV-6/-11/-16/-18 vaccine (quadrivalent; Gardasil, Merck Sharp & Dohme Corp),⁸⁻¹⁰ 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.⁵⁻¹² 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.^{11,12} 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.^{3,13} 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.¹⁴ 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 2010¹⁵ in Japan, which is one of the lowest rates among developed countries.¹⁶ 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

toward cervical cancer screening, the first questionnaire included questions about lifetime experiences with the Pap test, the time of the last Pap test and the cycles of the Pap test. The second and third questionnaires included the questions about the time, place, and the result of their last Pap test to compare with the first one. For the participants under the age of 20 years, written informed consent was also obtained from their parents. This study protocol was approved by the ethics committee of the Yokohama City University School of Medicine.

Statistical analyses were carried out using IBM spss Statistics 20 (IBM Corporation). The Student's *t*-test, the χ^2 -test, and the Mann-Whitney *U*-test were used for the analyses, and statistical significance was set at $P < 0.05$.

Results

Characteristics of the participants attending the kick-off lecture on cervical cancer prevention at the YCU Hospital

About 160 individuals working at the YCU-HC took part in the kick-off lecture in November 2009 prior to the opening of an outpatient clinic for cervical cancer prevention at the YCU Hospital in January 2010. The results of the anonymous questionnaires completed by 141 participants are summarized in Table 1. The participants consisted of 122 (86.5%) women and 19 (13.5%) men. Their occupations were: 56 nurses (39.7%), 32 medical doctors (22.7%), six pharmacists (4.3%) and 35 clerical workers (24.8%). About 60% of the participants were in their 20s and 30s. A relationship between HPV infection and cervical cancer was recognized by 84.8% of the questionnaire respondents, and 74.5% knew that the bivalent HPV vaccine had already been approved in Japan and would become available soon. Among the 122 women, 61.5% (75/122) had received a Pap test in their lifetime, but only 39 (32%) out of the 75 screened women were having a Pap test regularly, and 37 of 122 (30%) women had never received a Pap test. Regarding initiation of a cervical-cancer-prevention advocacy based at the YCU-HC, almost all participants (140/141) approved the plan.

Characteristics of the study participants regarding follow-up on their cervical cancer screening status after their HPV vaccinations

Figure 1 shows a flow chart of the present study. In 2010, 173 YCU-HC women aged 18 years and over

Table 1 Characteristics of 141 medical staff members and hospital employees who participated in the kick-off lecture for cervical cancer prevention at the university-hospital-based community

Sex	
Female	122 (86.5%)
Male	19 (13.5%)
Age (years)	
20–29	43 (30.5%)
30–39	43 (30.5%)
40–49	26 (18.4%)
50–	19 (13.5%)
Unknown	10 (7.1%)
Job classification	
Nurse	56 (39.7%)
Medical doctor	32 (22.7%)
Pharmacist	6 (4.3%)
Clerk	3 (2.1%)
Others	35 (24.8%)
Unknown	9 (6.4%)
Knowledge about cervical cancer	
HPV-related tumors	119 (84.4%)
Initiation of HPV vaccination in Japan in the near future	105 (74.5%)
Pap test experience (female $n = 122$)	
Regularly screened	39 (32.0%)
Not regular but at least once	36 (29.5%)
Never screened	37 (30.3%)
Unknown	10 (7.1%)
Approval for the initiation of cervical cancer prevention project in the university-hospital-based community	140 (99.3%)

HPV, human papillomavirus.

received the bivalent HPV vaccine at the YCU hospital and agreed to participate in the study. Among them, 98.3% (170/173) filled out the questionnaire at the first vaccination. The response rate of the second questionnaire at the third vaccination and of the third questionnaire in January 2013 was 95.8% (160/167) and 59.4% (95/160), respectively. The participants' age distributions and occupations are summarized in Table 2. Their median age was 27.5 years, and the median ages of the medical and nursing school students were 22.0 and 19.0 years, respectively. The third vaccination was completed by 167 of 173 (96.5%) individuals, and 160 (95.8%) answered the second questionnaire (Fig. 1). Baseline characteristics of the participants are shown in Table 3. A total of 88.2% (150/170) of the women were sexually active, 88.8% (151/170) had no parity, and 80.6% (137/170) were unmarried. Among 148 women who were 20 years and older and sexually active, corresponding to the targets of the Pap test, 59.5% (88/148) had received the test at least once in their lifetime.

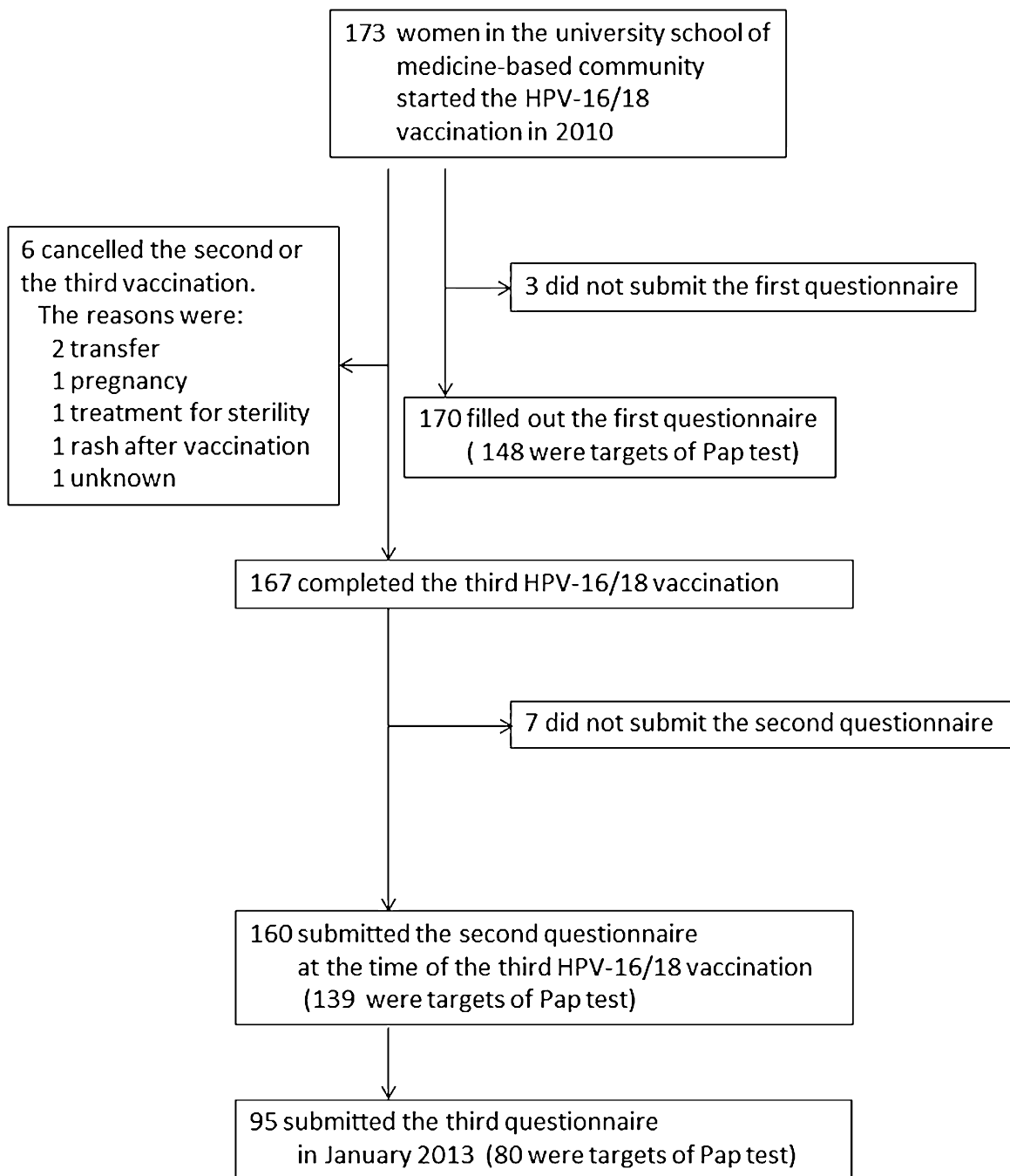


Figure 1 Flow chart of the present study. The third vaccination was completed by 167 out of 173 (96.5%) women who participated in the study. The response rates to the first, second and third questionnaires were 98.3% (170/173), 95.8% (160/167) and 59.4% (95/160), respectively. HPV, human papillomavirus.

Table 2 Age distribution and job classification of the study participants at the first HPV vaccination

Age (years)	Job classification							Total
	Staff MD	Resident MD	Nurses	Pharmacists	Other medical staff members	Medical school students	Nursing school students	
18-19	0	0	0	0	0	2	7	9 (5.3%)
20-29	17	24	25	4	10	15	4	99 (58.2%)
30-39	22	2	20	4	10	0	0	58 (34.1%)
40-	1	0	2	0	1	0	0	4 (2.4%)
Total number	40 (23.5%)	26 (15.3%)	47 (27.6%)	8 (4.7%)	21 (12.4%)	17 (10.0%)	11 (6.5%)	170 (100%)
Mean age \pm SD	31.1 \pm 4.1	26.8 \pm 1.9	29.8 \pm 6.7	31.0 \pm 5.9	30.3 \pm 5.6	21.9 \pm 2.07	19.3 \pm 1.4	28.3 \pm 5.9
Median age (range)	31 (26-48)	27 (24-33)	29 (22-59)	29.5 (25-39)	29.5 (22-42)	22.0 (19-25)*	19.0 (18-22)*	27.5 (18-59)

*Significantly younger than the other groups ($P < 0.01$). HPV, human papillomavirus; MD, medical doctors.

Table 3 Baseline characteristics of study participants and their cervical cancer screening status at the first HPV vaccination

Sexual intercourse	($n = 170$)
Not experienced	19 (11.2%)
Experienced	150 (88.2%)
Unknown	1 (0.6%)
Parity	($n = 170$)
No	151 (88.8%)
Yes	18 (10.6%)
Unknown	1 (0.6%)
Marital status	($n = 170$)
Unmarried	137 (80.6%)
Married	33 (19.4%)
Pap smear experience of the screening targets†	($n = 148$)
Never screened	57 (38.5%)
Screened at least once	88 (59.5%)
Unknown	3 (2.0%)
Pap test status	($n = 88$)
Only once	23 (26.1%)
Every 1-2 years	35 (39.8%)
Every 3-5 years	23 (26.1%)
Unknown	7 (8.0%)

†Pap smear targets were defined as the women aged 20 years and older who were sexually active.

However, only 39.8% (35/88) of them had received regular Pap tests at least every 2 years, as recommended by the Japanese cervical cancer screening guideline.⁴ Among the screening targets, 48.4% (30/62) of medical doctors, 53.3% (24/45) of nurses and 38.5% (5/13) of the medical and nursing school students had received a Pap test within the last 2 years (Table 4). During their lifetime, 64.5% (40/62) of medical doctors, 62.2% (28/45) of nurses and 46.2% (6/13) of the students had received a Pap test (Table 4). Although the median age of the targets for cervical cancer screening was significantly lower in the student group compared with the other groups (Mann-Whitney U -test, $P < 0.001$), no significant differences were shown between the groups in the frequency of Pap tests both within 2 years and lifetime (Table 4).

Changes in Pap test experiences before and after HPV vaccinations

We analyzed the changes in Pap test experiences among 139 women of the screening targets who had finished the third HPV vaccination (Table 5). Although 53 out of 139 women (38.1%) had never had a Pap test at the time of their first HPV vaccination in 2010, the rate decreased significantly to 20.9% (29/139) at the time of the third vaccination and 8.8% (7/80) in January

Table 4 Baseline cervical cancer screening experience of the screening targets within 2 years and lifetime at the first HPV vaccination

Job classification	Mean age \pm SD	Median age	Pap test within 2 years	Pap test in lifetime
Students ($n = 13$)	22.2 \pm 1.3*	22.0 (20–24)*	5 (38.5%)	6 (46.2%)
Medical doctors ($n = 62$)	29.5 \pm 4.0	28.5 (24–48)	30 (48.4%)	40 (64.5%)
Nurses ($n = 45$)	29.8 \pm 6.8	28.5 (22–59)	24 (53.3%)	28 (62.2%)
Others ($n = 28$)	30.8 \pm 5.6	30.0 (22–42)	10 (35.7%)	14 (50.0%)
Total ($n = 148$)	28.1 \pm 2.4	28.0 (21–59)	69 (46.6%)	88 (59.5%)

*Significantly younger than the other groups ($P < 0.01$). SD, standard deviation.

Table 5 Changes in cervical cancer screening status among participants of Pap test targets who completed the third vaccination

	At the first vaccination in 2010 ($n = 139$)	At the third vaccination ($n = 139$)	Survey in January 2013: response rate 57.6% (80/139)
Never	53 (38.1%)	29 (20.9%)*	7 (8.8%)*
2 or more years ago	17 (12.2%)	9 (6.5%)	18 (22.5%)
Within past 2 years	63 (45.3%)	99 (71.2%)*	54 (67.5%)*
Time unknown	4 (2.9%)	0	0
No answer	2 (1.4%)	2 (1.4%)	1 (1.3%)
Total experiences of Pap test	84 (60.4%)	108 (77.7%)*	72 (90.0%)*

* $P < 0.001$.

2013. The frequency of Pap tests within 2 years was 45.3% (63/139) at the first HPV vaccination; it increased significantly to 71.2% (99/139) 6 months later at the third vaccination ($P < 0.001$), and was 67.5% (54/80) 2 years later ($P < 0.001$). The lifetime Pap test experience also increased significantly from 60.4% (84/139) to 77.7% (108/139) ($P < 0.001$) during the 6 months after HPV vaccination, and reached 90.0% (72/80). In 24 out of 53 women (45.3%) who had never had a Pap test at the time of their first HPV vaccination, their first Pap test was followed by their HPV vaccination. During the 6-month vaccination period, five women were found to have abnormal Pap test results; three were diagnosed with cervical intraepithelial neoplasms (CIN), one with CIN1 and two with CIN2, and were under observation. None of the participants were revealed to have CIN3 or invasive cervical cancer, or received treatment for cervical lesions.

Opinions about factors for increasing cervical cancer screening up take in Japan

At the time of their first HPV vaccination, 170 women were asked which factors they considered to be important for increasing participation in regular cervical cancer screening in Japanese women. The question was presented as multiple choices from five items. Free-of-

charge screening was selected by 82.4% (140/170), detailed information about facilities by 57.1% (97/170), and detailed information about cervical cancer screening methods by 54.7% (93/170). Less than 50% chose the Pap test performed by a female doctor (76/170, 44.7%) and less than 40% selected a paid holiday for the screening (65/170, 38.2%).

Discussion

Local communities are considered to have a critical role in promoting population-based health initiatives.^{17–19} Yokohama City is the capital of Kanagawa Prefecture having about 3 700 000 people,²⁰ and YCU has the only public school of medicine in Kanagawa Prefecture. The YCU-HC, on which we focused in this study, had 1059 students (442 medical, 394 nursing, and 223 graduate students) in the school of medicine and approximately 1000 full-time employees in the school and the hospital in 2010. Women accounted for over 1200 (60%) of the community members. In this study, we analyzed our interim data obtained from the YCU-HC women who had begun HPV vaccination in 2010, because the availability of HPV vaccines and the attitude toward vaccination changed significantly in Japan in 2011, following the start of a temporary national HPV vaccination

program for girls aged 13–16 years and the lack of bivalent HPV vaccines in 2011. In addition, since the quadrivalent HPV vaccine became available in August 2011 in Japan, women who hope to prevent not only cervical cancer but also genital warts caused by HPV types 6 and 11 infections are coming to receive HPV vaccinations in our clinic. Because under present conditions the precise degree of participation in cervical cancer screening of Japanese women of different vocations is unclear in Japan, YCU-HC women were expected to show a high participation rate in the screening, as in the other developed countries, before we tabulated the results of this survey. Far from our expectations, our interim results showed that about 30% of the YCU-HC women older than 20 years who attended the lecture and 40% of those who had catch-up HPV vaccinations had never previously had a Pap test. These data strongly suggest that a systematic education regarding cervical cancer prevention is necessary for Japanese young adult women, even for medical professionals. In addition, our results had great impact on the health-care providers in the community in encouraging them to be cooperative in launching a community-based health-care promotion.

Two HPV vaccines are reported to have high efficacy against infection by HPV types 16 and 18 in young women not yet infected with the relevant HPV types at enrollment, both in randomized controlled multicenter studies worldwide^{5–10} and in a Japanese study on the bivalent HPV vaccine.²¹ In addition, catch-up vaccination of women, including sexually active women without regard to HPV infection, has been proven effective to some extent in large-scale clinical trials of the two HPV vaccines.^{5–7,9,10} A recent 4-year end-of-study report on the large-scale bivalent HPV vaccine clinical trial, which enrolled women aged 15–25 years, showed 45.6% (95% confidence interval 28.8–58.7) vaccine efficacy against CIN3 or greater, irrespective of HPV DNA in the lesion, in a group comprising women in a catch-up population that included sexually active women.⁶ This efficacy was lower than the astonishing report of 93.2% (95% confidence interval 78.9–98.7) efficacy in women who were HPV naïve at baseline,⁶ although it was significantly effective compared with the control group. In addition, cervical cancer screening of young adult women has been shown to still be important even after receiving either of the HPV vaccines. At present, catch-up HPV vaccination among young adult women is thought to be important in Japan, as it is in Western countries^{22,23} and Australia,^{11,12} for the purpose of not

only decreasing individual cervical cancer risk, but also of increasing nationwide herd immunity. According to the HPV vaccine recommendations published in the Guidelines for Gynecological Practice in Japan in 2011,²⁴ which referred to the report by Konno on the cost-effectiveness of adding HPV vaccination to the current cervical cancer screening that is in place in Japan,²⁵ the vaccination of girls and women in three age groups is considered cost-effective; the first group includes 10–14-year-old girls, the second group includes women 15–26 years of age who should receive catch-up vaccinations, and the third group comprises women 27–45 years of age.

As for a population-based cervical cancer screening program using conventional Pap smears in Japan, it was started in Japan for all female residents aged 40 years or over under the Health Service Law for the Aged in 1982. In 2003, the target age group was lowered from the previous age of ≥ 30 years to ≥ 20 years, and the screening interval was lengthened from every year to every 2 years.³ Since 2009, cost-free Pap smear coupons have been distributed by the Japanese government to women aged 20, 25, 30, 35 and 40 years in order to increase their participation. However, data collected in the national census year of 2010 revealed that the self-reported rate of Pap test experience in Japan during the previous 2 years was only about 32% among women aged ≥ 20 years and 40% among women aged 20–69 years.¹⁵ This was still far less than the 60–90% reported in Western developed countries.¹⁶ In the present study, it was found that only 32% of the women who participated in the lecture about cervical cancer prevention had regular Pap smears, which was almost the same rate as that reported in the national survey. Considering these data together with our results that participation in Pap tests within 2 years was 46.6%, even among the YCU-HC women who received HPV vaccination, it is apparent that the importance of regular screening is not fully recognized by the Japanese women. We estimate that this situation is caused not only because of insufficient medical information provided by the Japanese government, but also because few Japanese women have been effectively educated and informed to understand the risk of cervical cancer related to HPV infection. Information about HPV-related diseases is not included in the routine educational programs on sexual and reproductive health in Japanese junior-high and/or high schools. In our study, self-reported participation in Pap tests within 2 years increased to 77.7% after HPV vaccinations, to which the proposal of opportunistic screening at

women's work or study sites might have contributed. This phenomenon also suggests that knowing both the limitation of HPV vaccine efficacy and the significance of the Pap test encouraged these women to have their cervical cancer screening performed after the vaccination. In fact, 75% (18/24) of the women who had received the first Pap test between their first and third vaccinations were in their 20 s. It was also informative that 80% of the participants thought cost-free screening is an important incentive for obtaining regular Pap tests in Japan.

Just after the start of this study, we also started to collaborate with local administrations and several groups involved in the cervical cancer prevention advocacy to start the large-scale Yokohama-Kanagawa cervical cancer prevention project. Together with our interim results and various data provided by local administrations in Kanagawa Prefecture, we are paying much attention to how various segments of the young adult female population can be informed about cervical cancer prevention. The successful outcome of our collaboration with the local administrations should be verified in the near future through increased screening participation in Yokohama City and Kanagawa Prefecture, and then followed by a decrease in the prevalence of CIN 3 and invasive cervical cancer in the district.

The limitations of the present study were that the data were obtained from one limited medical community, and the collection rate of the questionnaire decreased to 57.6% at 2 years after the study participants' vaccinations, because most of the participants were young temporary staff members or students. Nevertheless, the results showed the present status and attitudes toward cervical cancer prevention in young adult women who have some medical knowledge and received HPV catch-up vaccinations. This study suggests that urgent drastic changes are needed in the cervical cancer prevention strategy for young adult women, who are older than the targets of the national HPV vaccine program in Japan.

Acknowledgments

This study was partly supported by 2011 & 2012 Grants-in-Aid from the Ministry of Health, Labour, and Welfare of Japan.

We thank Dr A. Kadowaki, Dr R. Kitayama, Ms K. Fukumoto, Ms E. Araki, and Ms Y. Uchiyama for their support to continue our project.

Disclosure

Dr Etsuko Miyagi received lecture fees from Merck Sharp & Dohme Corp K. K.

References

1. International Agency for Research on Cancer. *IARC Handbook of Cancer Prevention*. Lyon, France: IARC Press, 2005; 1–9.
2. Matsuda A, Matsuda T, Shibata A *et al.* Cancer incidence and incidence rates in Japan in 2007: A study of 21 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2013; 43: 328–336.
3. Hayashi Y, Shimizu Y, Netsu S, Hanley S, Konno R. High HPV vaccination uptake rates for adolescent girls after regional governmental funding in Shiki City, Japan. *Vaccine* 2012; 30: 5547–5550.
4. Hamashima C, Aoki D, Miyagi E *et al.* The Japanese guideline for cervical cancer screening. *Jpn J Clin Oncol* 2010; 40: 485–502.
5. Paavonen J, Naud P, Salmerón J *et al.* Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. *Lancet* 2009; 374: 301–314.
6. Lehtinen M, Paavonen J, Wheeler CM *et al.* Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 2012; 13: 89–99.
7. Wheeler CM, Castellsagué X, Garland SM *et al.* Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 2012; 13: 100–110.
8. Garland SM, Hernandez-Avila M, Wheeler CM *et al.* Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; 356: 1928–1943.
9. Muñoz N, Manalastas R Jr, Pitisuttithum P *et al.* Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: A randomised, double-blind trial. *Lancet* 2009; 373: 1949–1957.
10. Castellsagué X, Muñoz N, Pitisuttithum P *et al.* End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. *Br J Cancer* 2011; 105: 28–37.
11. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: An ecological study. *Lancet* 2011; 377: 2085–2092.
12. Garland SM, Skinner SR, Brotherton JM. Adolescent and young adult HPV vaccination in Australia: Achievements and challenges. *Prev Med* 2011; 53: S29–S35.
13. An interim nationwide vaccine program, Japan Ministry of Health, Labour and Welfare Japan. 2012. [Cited 26 May

- 2013.] Available from URL: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/vaccine_kouhukin_enchou.pdf
14. Smith JS, Lindsay L, Hoots B *et al*. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. *Int J Cancer* 2007; 121: 621–632.
 15. Vital statistics of Japan. 2010. Ministry of Health, Labour & Welfare, Japan. [Cited 26 May 2013.] Available from URL: <http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa10/toukei.html>
 16. Screening, survival and mortality for cervical cancer. OECD. 2011. in *Health at a Glance 2011*: OECD Indicators, OECD Publishing. [Cited 26 May 2013.] Available from URL: http://dx.doi.org/10.1787/health_glance-2011-en
 17. Manderson L, Hoban E. Cervical cancer services for Indigenous women: Advocacy, community-based research and policy change in Australia. *Women Health* 2006; 43: 69–88.
 18. Sherris J, Agurto I, Arrossi S *et al*. Advocating for cervical cancer prevention. *Int J Gynaecol Obstet* 2005; 89 (Suppl): S46–S54.
 19. Brotherton JM, Mullins RM. Will vaccinated women attend cervical screening? A population based survey of human papillomavirus vaccination and cervical screening among young women in Victoria, Australia. *Cancer Epidemiol* 2012; 36: 298–302.
 20. Vital statistics of Yokohama City. Yokohama City. 2010. [Cited 26 May 2013.] Available from URL: <http://www.city.yokohama.lg.jp/ex/stat/census/kokucho1010/01jinko-kihon/jinko-kihon-gaiyo.pdf>
 21. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: Final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; 20: 847–855.
 22. Dunne EF, Datta SD, E Markowitz L. A review of prophylactic human papillomavirus vaccines: Recommendations and monitoring in the US. *Cancer* 2008; 113 (Suppl): 2995–3003.
 23. Vergote I, van der Zee AG, Kesic V *et al*. ESGO statement on cervical cancer vaccination. *Int J Gynecol Cancer* 2007; 17: 1183–1185.
 24. Takeda T, Wong TF, Adachi T *et al*. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists 2011 edition. *J Obstet Gynaecol Res* 2012; 38: 615–631.
 25. Konno R, Sasagawa T, Fukuda T *et al*. Cost-effectiveness analysis of prophylactic cervical cancer vaccination in Japanese women. *Int J Gynecol Cancer* 2010; 20: 385–392.