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 srss Statistics 20 (IBM Corporation). The Student's t-test, the  $\chi^2$ -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 20 s and 30 s. 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

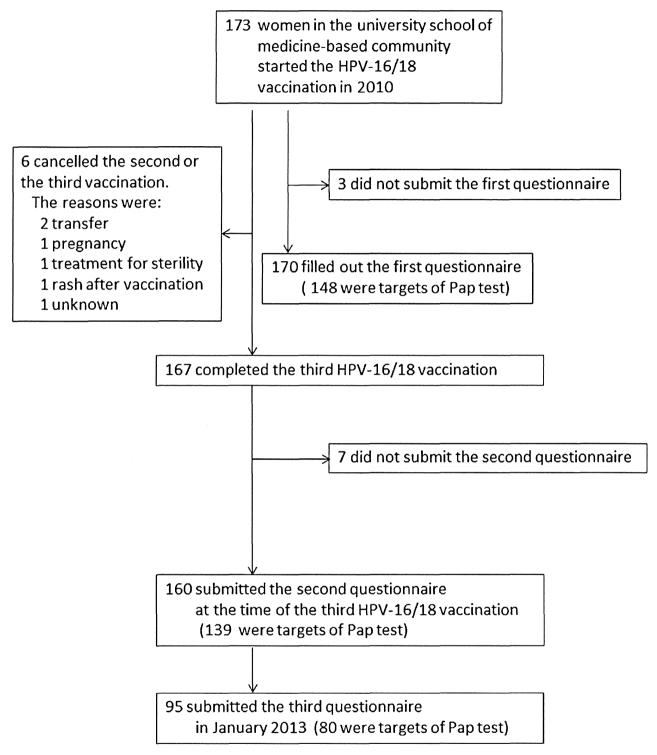
Table 1 Characteristics of 141 medical staff members and hospital employees who participated in the kickoff lecture for cervical cancer prevention at the university-hospital-based community

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 $56 (39.7\%)$ 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 $119 (84.4\%)$ HPV-related tumors $119 (84.4\%)$ Initiation of HPV vaccination in Japan in the near future $105 (74.5\%)$ Pap test experience (female $n = 122$ ) $39 (32.0\%)$ Not 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 $140 (99.3\%)$	7 1	
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%)       10 (7.1%)         Job classification       10 (7.1%)         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       140 (99.3%)	Sex	
Age (years)       43 (30.5%) $20-29$ 43 (30.5%) $30-39$ 43 (30.5%) $40-49$ 26 (18.4%) $50-$ 19 (13.5%)         Unknown       10 (7.1%)         Job classification       30 (20.7%)         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       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       140 (99.3%)	Female	122 (86.5%)
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 $(7.1\%)$ 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       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%)       10 (7.1%)         Approval for the initiation of cervical cancer prevention project in the university-hospital-based       140 (99.3%)	Male	19 (13.5%)
30–39       43 (30.5%)         40–49       26 (18.4%)         50–       19 (13.5%)         Unknown       10 (7.1%)         Job classification       (4.3%)         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       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%)       10 (7.1%)         Approval for the initiation of cervical cancer prevention project in the university-hospital-based       140 (99.3%)	Age (years)	
40–49 50– Unknown 10 (7.1%)  Job classification Nurse Nedical doctor Pharmacist Clerk Others Unknown  Knowledge about cervical cancer HPV-related tumors Initiation of HPV vaccination in Japan in the near future Pap test experience (female n = 122) Regularly screened Not regular but at least once Never screened Unknown  Approval for the initiation of cervical cancer prevention project in the university-hospital-based	20–29	43 (30.5%)
50-       19 (13.5%)         Unknown       10 (7.1%)         Job classification       (30.7%)         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       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       140 (99.3%)	30–39	43 (30.5%)
Unknown $10 (7.1\%)$ Job classification $10 (7.1\%)$ 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 cancerHPV-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 $140 (99.3\%)$	40-49	26 (18.4%)
Job classification  Nurse  Medical doctor  Pharmacist  Clerk  Others  Unknown  Knowledge about cervical cancer  HPV-related tumors  Initiation of HPV vaccination in Japan in the near future  Pap test experience (female $n = 122$ )  Regularly screened  Not regular but at least once  Never screened  Unknown  Approval for the initiation of cervical cancer prevention project in the university-hospital-based $56 (39.7\%)$ $32 (22.7\%)$ $6 (4.3\%)$ $35 (24.8\%)$ $19 (6.4\%)$ $119 (84.4\%)$ $105 (74.5\%)$ $105 (74.5\%)$ $39 (32.0\%)$ $39 (32.0\%)$ $39 (32.0\%)$ $39 (32.0\%)$ $39 (32.0\%)$ $39 (30.3\%)$ $39 (30.3\%)$ $39 (30.3\%)$ $39 (30.3\%)$	50-	19 (13.5%)
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 cancerHPV-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 $140 (99.3\%)$	Unknown	10 (7.1%)
Medical doctor $32 (22.7\%)$ Pharmacist $6 (4.3\%)$ Clerk $3 (2.1\%)$ Others $35 (24.8\%)$ Unknown $9 (6.4\%)$ Knowledge about cervical cancerHPV-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 $140 (99.3\%)$	Job classification	
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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 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	Medical doctor	32 (22.7%)
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 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	Pharmacist	6 (4.3%)
Unknown $9 (6.4\%)$ Knowledge about cervical cancer HPV-related tumors $119 (84.4\%)$ Initiation of HPV vaccination in Japan in the near future 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	Clerk	3 (2.1%)
Knowledge about cervical cancer  HPV-related tumors  Initiation of HPV vaccination in Japan in the near future  Pap test experience (female $n=122$ )  Regularly screened  Not regular but at least once  Never screened  Unknown  Approval for the initiation of cervical cancer prevention project in the university-hospital-based  119 (84.4%)  105 (74.5%)  39 (32.0%)  39 (32.0%)  37 (30.3%)  10 (7.1%)  140 (99.3%)	Others	35 (24.8%)
HPV-related tumors119 (84.4%)Initiation of HPV vaccination in Japan in the near future105 (74.5%)Pap test experience (female $n = 122$ )39 (32.0%)Regularly screened39 (32.0%)Not regular but at least once36 (29.5%)Never screened37 (30.3%)Unknown10 (7.1%)Approval for the initiation of cervical cancer prevention project in the university-hospital-based140 (99.3%)	Unknown	9 (6.4%)
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in the near future 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	HPV-related tumors	119 (84.4%)
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	Initiation of HPV vaccination in Japan	105 (74.5%)
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	in the near future	
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Never screened 37 (30.3%) Unknown 10 (7.1%) Approval for the initiation of cervical cancer prevention project in the university-hospital-based 140 (99.3%)	Not regular but at least once	36 (29.5%)
Approval for the initiation of cervical 140 (99.3%) cancer prevention project in the university-hospital-based		37 (30.3%)
cancer prevention project in the university-hospital-based	Unknown	10 (7.1%)
cancer prevention project in the university-hospital-based	Approval for the initiation of cervical	140 (99.3%)
	university-hospital-based	
	community	

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.

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**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.

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

Age (years)				2	Tob classification			
	Staff MD	Resident MD	Nurses	Pharmacists	Other medical staff members	Medical school students	Nursing school students	Total
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-		0	2	0	,(	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 ± 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.	nan the other grou	ups $(P < 0.01)$ . HI	V, human papill	omavirus; MD, me	dical 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	(n = 148)
screening targets†	
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%)

 $\ensuremath{^{\dagger}}\xspace Pap$  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. <sup>4</sup> 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 ± SD	Median age	Pap test within 2 years	Pap test in lifetime
Students $(n = 13)$	22.2 ± 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%)

<sup>\*</sup>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%)*

<sup>\*</sup>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 uptake 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

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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 worldwide5-10 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.<sup>6</sup> 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<sup>22,23</sup> and Australia,<sup>11,12</sup> 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,<sup>24</sup> 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,<sup>25</sup> 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 HPVrelated 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.

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# Three-year questionnaire survey on human papillomavirus vaccination targeting new female college students

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#### **Abstract**

*Aim:* A questionnaire survey was conducted at fixed points to describe changes over a 3-year period in the human papillomavirus (HPV) vaccination uptake rate among young women. Several factors obtained from the questionnaire were investigated in relation to HPV vaccination.

*Methods:* The study was conducted at two universities in Yokohama City, Japan. Newly enrolled female students of the universities were recruited to participate in this study in 2011, 2012 and 2013. The study participants were asked about their HPV vaccination status. They were also questioned about factors that potentially influenced HPV vaccination, such as current age, place of residence during high school, and knowledge related to cervical cancer and HPV vaccination.

**Results:** The proportion of vaccinated participants dramatically increased in 2013 (48.7%) in comparison to 2011 (5.4%) and 2012 (13.5%). Three factors were positively related to HPV vaccination: being 18 years old in 2013, which means that they were eligible for a financial support program (P < 0.001); living in the study city, in which HPV vaccination was well conducted (P < 0.001); and proper knowledge of cervical cancer and HPV vaccination (P < 0.001).

*Conclusion:* The HPV vaccination uptake rate in 2013 dramatically increased from that in 2011. Official financial support and publicity work were likely to have had an effect on the HPV vaccination uptake rate.

**Key words:** cervical cancer, fixed point observation, human papillomavirus vaccine, questionnaire survey, young women.

#### Introduction

Human papillomavirus (HPV) infection, a type of infectious disease, is known to be the main cause of cervical cancer. A worldwide investigation found that more than 70% of cases of cervical cancer were caused by the HPV 16 and/or 18 DNA genotypes (HPV16/

18).¹ A Japanese report stated that 67.1% of Japanese women who suffered from cervical cancer were infected with HPV16/18.²

Human papillomavirus infection has become preventable with the introduction of a vaccine targeting the virus. The US Food and Drug Administration licensed a quadrivalent vaccine against HPV6/11/

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16/18 in 2006 and a bivalent vaccine against HPV16/18 in 2009. Many other countries have licensed these vaccines and have begun to provide financial support to vaccination programs targeting teenage girls.<sup>3</sup> In Japan, a bivalent vaccine and a quadrivalent vaccine have been licensed since 2009 and 2011, respectively.

Every year, more than 260 000 and 2500 women die of cervical cancer in the world<sup>4</sup> and in Japan<sup>5</sup>, respectively. Although cervical cancer-prone women tend to be of middle age, there has been a recent increase in the number of young Japanese women suffering from the disease.<sup>5</sup> To prevent HPV infection, it would be best for girls to receive HPV vaccination before their first intercourse, around pre-adolescence or early adolescence. In 2010, Japan's Ministry of Health, Labor and Welfare started to provide financial support for a HPV vaccination program targeting girls aged 13-16 years. Through national government assistance, local governments initiated their own programs to facilitate HPV vaccination. These programs were expected to raise HPV vaccination uptake rates among young women, and the years of 2011–2013 were considered to be a good time period for observing the change in the HPV vaccination uptake rate.

We therefore conducted a questionnaire study at fixed points to describe the changes from 2011 to 2013 with regard to HPV vaccination knowledge and the vaccination uptake rate among young women. The relation between several factors obtained from the questionnaire study and HPV vaccination status were also investigated.

#### Methods

#### Study sites and subjects

The study was conducted at two universities in Yokohama, Japan (population of 3.69 million according to the 2010 census). Yokohama is one of the cities in Japan where HPV vaccination facilitation programs have been actively promoted. Yokohama's vaccination facilitation program, which targeted 13–18-year-old girls, was conducted from February 2011 to March 2013.

The two universities at which the study was carried out are located in the central and southern parts of the city, respectively. The percentage of students from outside of the city is 70–80%. Newly enrolled female students of the two universities were recruited to participate in this study at the start of the school year in the beginning of April in 2011, 2012 and 2013. Students who entered the universities in 2011 and 2012 received HPV vaccination at their own expense because official

assistance programs were not in place at the time in which they were vaccinated. In contrast, the female students who were 18 years old when they entered university in 2013 had been the targeted by the government-assisted program. As such, a high rate of HPV vaccination was expected among the newly enrolled students of 2013.

#### Questionnaire survey

A questionnaire was developed for female students. It included questions on age, place of residence during high school and HPV vaccination status. In the questionnaire, respondents were asked whether they had received education on sexually transmitted infections (STI) and cervical cancer when they were in junior high school or high school. To assess their attitudes toward and acceptance of vaccination, they were also asked whether they received the mumps and rubella (MR) vaccine when they were in high school. The survey comprised nine questions on knowledge of cervical cancer and nine questions on HPV vaccination. Students were requested to answer the questions with 'yes' or 'no'. In the third year, to clarify who or what had affected the students' attitudes toward HPV vaccination, the question, 'How do you know about the HPV vaccine?' was added.

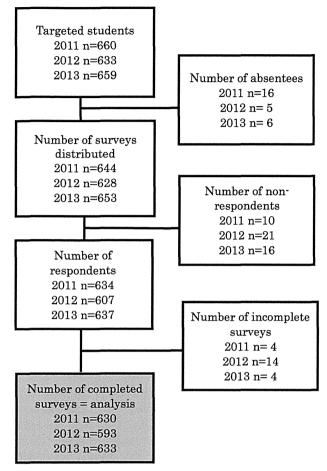
#### Statistical analyses

Differences in HPV vaccination knowledge and the HPV vaccination uptake rate among students of each year were tested by  $\chi^2$ -test. Changes in the rates over the 3 years were analyzed by  $\chi^2$ -test for trend. When differences in characteristics were compared between groups,  $\chi^2$ -test and Mann–Whitney *U*-test were used. Correct answer rates of each yes/no question were described with a 95% confidence interval (CI). Logistic regression analysis was conducted targeting students who entered the universities in 2013 to investigate relevant factors for HPV vaccination. A P-value of less than 0.05 for a two-tailed test was considered to indicate statistical significance.  $\chi^2$ -tests for trend were conducted using R version 2.15.1 (The R Foundation for Statistical Computing). IBM SPSS Statistics 21 (IBM, Armonk, NY, USA) was used for non-parametric tests and the logistic regression analyses.

#### **Ethical considerations**

The questionnaire study was conducted anonymously. Subjects were fully informed of the aim of the study. Students who gave consent filled out the questionnaire.

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**Figure 1** Flow diagram of participation in 2011, 2012 and 2013. The number of questionnaire respondents was 630 (95.5% of targeted students) in 2011, 593 (93.7%) in 2012 and 633 (96.1%) in 2013.

The study was approved by the Research Ethics Committee of Yokohama National University and Yokohama City University.

#### Results

A flow diagram of the study is shown in Figure 1. The number of questionnaire respondents was 630 (95.5% of targeted students) in 2011, 593 (93.7%) in 2012 and 633 (96.1%) in 2013. The mean ages of the participants in years were 18.7 (range, 18–46; median, 18) in 2011, 18.4 (range, 18–48; median, 18) in 2012 and 18.3 (range, 18–45; median, 18) in 2013 (Table 1).

Most of the participants answered that they had received an education on STI (95.9% in 2011, 98.0% in 2012 and 97.8% in 2013). The proportion of participants

who answered that they had received education on cervical cancer increased in both 2012 and 2013 (25.2% in 2011, 38.6% in 2012, 58.9% in 2013). Approximately 80% of participants answered that they had received MR vaccination when they were in high school (Table 1).

The proportion of participants who answered that they knew that HPV vaccination could be received in Japan gradually increased from 49.5% in 2011 to 71.2% in 2013 (P < 0.001 by the test for trend). In 2013, there was a dramatic increase in the proportion of participants who answered that they had received HPV vaccination (48.7%) in comparison with 2011 (5.4%) and 2012 (13.5%). The increasing trend was found to be statistically significant (P < 0.001) (Fig. 2).

Participants of the study conducted in 2013 were divided into two groups based on HPV vaccination status: 308 students who answered that they had received the vaccination (HPV vaccination group) and 291 students who answered that they had not (HPV non-vaccination group); 34 students did not answer the question on HPV vaccination. The characteristics of the two groups are summarized in Table 2. The proportion of students in the HPV vaccination group whose age was 18 years old was 87.3%, which is significantly higher than that in the HPV non-vaccination group (55.7%) (P < 0.001). The proportion of students who had lived in the study city, Yokohama, during high school was also significantly higher in the HPV vaccination group (27.9%) than in the HPV non-vaccination group (10.0%) (P < 0.001). Although no significant difference was observed in experiences of education on STI between the groups, a significant difference was observed in experiences of education on cervical cancer (P < 0.001). The proportion of students who had received MR vaccine was 79.5% in the HPV vaccination group and 74.6% in the HPV non-vaccination group, and a statistical difference was observed (P = 0.004). Students who belonged to the HPV vaccination group tended to answer questions on cervical cancer and HPV vaccination correctly in comparison with students who belonged to the HPV non-vaccination group (P < 0.001).

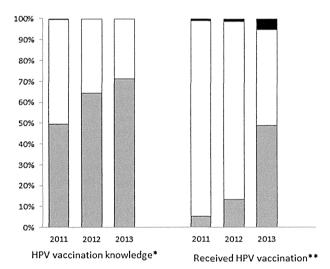
Correct answer rates to the 18 questions on cervical cancer and HPV vaccination are shown with 95% CI for each of the two groups (Fig. 3a,b). The correct answer rates of the HPV vaccination group were significantly higher than those of the non-vaccination group for several questions, including: 'It would be best for young girls to receive HPV vaccination before their first intercourse (Question no. 13; Correct answer: Yes);'

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Table 1 Characteristics of students entering the target universities in 2011, 2012 and 2013

Year of admission		$2011 \ (n = 630)$	$2012 \ (n = 593)$	$2013 \ (n = 633)$
Age (years)	Mean	18.7	18.4	18.3
	Median	18	18	18
	Range	18-46	18-48	18-45
Place of residence during high school	Median 18 18 18 Range 18-46 18-48 of residence during high school Yokohama 102 (17 Outside Yokohama No investigation 329 (55 No answer 162 (27 Station on STI Given 605 (95.9%) 581 (98 Not given 22 (3.5%) 11 (1.1 No answer 4 (0.6%) 1 (0.1 No answer 4 (0.6%) 1 (0.1 Station on cervical cancer Given 159 (25.2%) 229 (38 Not given 465 (73.7%) 362 (61 No answer 7 (1.1%) 2 (0.2 station on cervical cancer Received 491 (77.8%) 484 (81	102 (17.2%)	118 (18.6%)	
0 0	Outside Yokohama	No investigation	329 (55.5%)	393 (62.1%)
	No answer	O	162 (27.3%)	122 (19.3%)
Education on STI	Given	605 (95.9%)	581 (98.0%)	619 (97.8%)
	Not given	22 (3.5%)	11 (1.9%)	12 (1.9%)
		4 (0.6%)	1 (0.1%)	2 (0.3%)
Education on cervical cancer	Given	159 (25.2%)	229 (38.6%)	373 (58.9%)
	Not given	465 (73.7%)	362 (61.0%)	252 (39.8%)
	W	7 (1.1%)	2 (0.3%)	8 (1.3%)
MR vaccination	Received	491 (77.8%)	484 (81.6%)	483 (76.3%)
Education on cervical cancer	Not received	122 (19.3%)	102 (17.2%)	124 (19.6%)
	No answer	18 (2.9%)	7 (1.2%)	26 (4.1%)

MR, mumps and rubella; STI, sexually transmitted infection.



**Figure 2** Changes in rates of knowledge on human papillomavirus (HPV) vaccine and HPV vaccine uptake from 2011 to 2013. \*Test of homogeneity on knowledge:  $\chi^2 = 65.8$ , P < 0.001; test for trend of rates:  $\chi^2 = 68.0$ , P < 0.001. \*\*Test of homogeneity on vaccination:  $\chi^2 = 378.8$ , P < 0.001; test for trend of rates:  $\chi^2 = 336.7$ , P < 0.001. Black, no answer; white, no; gray, yes.

'HPV vaccination requires inoculation of 3 times (Question no. 16; correct answer: Yes);' and 'There is no system of public assistance for HPV vaccination in Japan (Question no. 18; correct answer: No)'.

The results of the multivariate logistic regression analysis, which was performed to investigate relevant factors for HPV vaccination and to adjust for confounding factors, are shown in Table 3. In the logistic analysis model, the dependent variable was set to '1' if the stu-

dents answered that they had received vaccination and to '0' if otherwise. The analysis was conducted with five independent variables. There was no evidence of multicollinearity. The sample correlation coefficient between any pair of variables was less than +0.70 and greater than -0.70. Being 18 years of age on entry to university, and thereby being eligible for assistance from the national financial support program, was positively related to HPV vaccination (P < 0.001). Residing in the study city (Yokohama) during high school (independent variable set to '1' if the student resided in Yokohama and '0' if elsewhere) was significantly related to HPV vaccination (P < 0.001). Having received education on cervical cancer (variable set to '1' if she had received education and '0' if otherwise) implied a positive influence to HPV vaccination; however, statistical significance was not achieved (P = 0.059). There was no statistical relation between MR vaccination and HPV vaccination. The number of correct answers was included in the analysis model as a numerical independent variable; the result showed the positive relation between the number of correct answers and HPV vaccination uptake (P < 0.001).

#### Discussion

The present 3-year questionnaire survey showed a dramatic increase of young women who had received HPV vaccination. Among newly enrolled female students, the HPV vaccination uptake rate jumped to 48.7% in 2013 from 13.5% in 2012 and 5.4% in 2011. This study attempted to show the factors that contributed to this increase.

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Table 2 Characteristics of two groups in 2013: students who received HPV vaccination and students who did not

HPV vaccination		Received $(n = 308)$	Not received $(n = 291)$	P-value
Age	18 years	269 (87.3%)	162 (55.7%)	<0.001*
Ü	≥19 years	18 (5.8%)	98 (33.7%)	
	No answer	21 (6.8%)	31 (10.7%)	
Place of residence during high school	Yokohama	86 (27.9%)	29 (10.0%)	<0.001*
	Outside Yokohama	172 (55.8%)	197 (67.7%)	
	No answer	50 (16.3%)	65 (22.3%)	
Education on STI	Given	304 (98.7%)	282 (96.9%)	0.106*
	Not given	3 (0.9%)	8 (2.6%)	
	No answer	1 (0.3%)	1 (0.3%)	
Education on cervical cancer	Given	204 (66.2%)	147 (50.5%)	<0.001*
	Not given	100 (32.5%)	141 (48.5%)	
	No answer	4 (1.3%)	3 (1.0%)	
MR vaccination	Received	245 (79.5%)	217 (74.6%)	0.004*
	Not received	46 (14.9%)	74 (24.0%)	
	No answer	17 (5.5%)	0 (0.0%)	
No. of correct answers to questions	Median	15	15 `	<0.001**
on cervical cancer and HPV vaccination	Range	10–18	3–18	

<sup>\*</sup>P-value obtained by Pearson's  $\chi^2$ -test ('no answer' cases are excluded from the analysis); \*\*P-value obtained by Mann–Whitney *U*-test. MR, mumps and rubella; STI, sexually transmitted infection.

Human papillomavirus vaccination knowledge is, as a matter of course, an essential factor for increasing the vaccination uptake rate. Half of the newly enrolled students in 2011 and two-thirds of the newly enrolled students in 2012 knew of the vaccine. Japan's Ministry of Health, Labor and Welfare started a HPV vaccination financial assistance program in November 2010. Although newly enrolled students in 2011 and 2012 were not covered by the program, commencement of the national program probably raised their awareness of HPV vaccination. The media likely influenced their HPV vaccination knowledge because they frequently took up the topic of HPV vaccination around the time that the vaccine program was introduced. Hilton et al. reported that media coverage surrounding the introduction of the HPV vaccination program should be welcomed as it is likely to contribute towards influencing public perceptions about the acceptability of and need for HPV vaccination.6

Many investigations have shown expense to be one of the barriers against vaccination.<sup>7–10</sup> Financial support is considered to be an important factor for increasing the HPV vaccination uptake rate. There was a dramatic increase in 2013 in the percentage of students who reported that they had received vaccination; the decreased expense is likely to be one of the reasons. Hayashi *et al.* reported that a high HPV vaccination uptake rate (90.7%) was achieved in the city of Shiki in the south of Saitama Prefecture (population of 69 611

according to the 2010 census), which started full subsidization for HPV vaccination before the national program.<sup>11</sup> In the present study, multivariate logistic regression analysis, which targeted newly enrolled students in 2013, was conducted to investigate the influence of financial support on HPV vaccination. The students who were 18 years of age when they entered the study universities and who were eligible for financial support from the national program were more likely to have received the vaccination than older students (odds ratio [OR], 4.52; 95% CI, 2.97–6.88; Table 3).

Publicity is also considered to be important for increasing the HPV vaccination uptake rate. Fujiwara et al. investigated the effect of various communitybased interventions in Tochigi Prefecture and reported that school-based vaccinations and public subsidies are the most effective methods to improve HPV vaccination coverage, with the combination of a free ticket, direct mail and recalls with public subsidies also being important factors.<sup>12</sup> Although the Ministry of Health, Labor and Welfare began to subsidize the HPV vaccination for girls aged 13-16 years in November 2010 as a transient HPV vaccination program, only approximately 60% of local governments had started the program by the end of fiscal year 2010, which ended in March 2011.13 Yokohama City started the vaccination program in February 2011, and the target age was extended to 18 years in fiscal year 2012, which is thought to be one of the reasons why students from

	Question	Correct answer	40%	60%	80%	100
4	Patients with cervical cancer are increasing among	Yes	Received			96.4%
ı	women in their 20s and 30s.	res	Not receive			96.6%
_	The most common cancer in women-specific 20-39	Yes	Received	51.3%		
_	years old is cervical cancer.	res	Not receive	56.4%		
3	Human papillomavirus (HPV) is related to	V	Received		83.19	-
3	the development of cervical cancer.	Yes	Not receive		75.3%	
4	In Japan, more than 2,500 women die of cervical		Received		74.0%	
4	cancer every year.	Yes	Not receive		71.5%	
5	No girl gets cervical cancer under twenty years of	No	Received		7 11.070	96.8%
5	age.	110	Not receive			95.5%
	Surgery in the only tweetment for now just accord	No	Received		84.4	
6	Surgery is the only treatment for cervical cancer.	INO	Not receive		82.1%	
7	Woman who have had cervical cancer have no	No.	Received		75.0%	
′	chance of pregnancy.	No	Not receive		74.6%	
	HPV infection is related to sexual intercourse.		Received		78.9%	
8	mry injection is related to sexual intercourse.	Yes	Not receive		74.6%	
_	HPV is only related to the development of cervical	N-	Received		84.1	<u>_</u>
9	cancer.	No	Not receive			9%

	Question	Correct answer	40%	60% 80% 100
	LIDV		Received	73.1%
10	HPV vaccine can prevent all types of HPV.	No	Not receive	69.4%
			Received	80.2%
11	There are two kinds of HPV vaccine.	Yes	Not receive	75.3%
	In Japan, women can receive HPV vaccination.		Received	99.0%
12		Yes	Not receive	96.2%
	It would be best for young girls to receive		Received	91.6%
13*	It would be best for young girls to receive HPV vaccination before their first intercourse.	Yes	Not receive	82.8%
14	HPV vaccination can completely prevent		Received	89.3%
14	cervical cancer.	No	Not receive	84.5%
	Even when inoculated with HPV vaccine after		Received	79.2%
15	having sex experience, effects of HPV infection can be expected.	Yes	Not receive	78.0%
10*	HPV vaccine is required inoculation of 3 times.		Received	88.0%
16		Yes	Not receive	70.4%
17	After receiving the HPV vaccine, there is no		Received	95.8%
17	risk of sexually transmitted infection.	No	Not receive	93.8 %
10*	There is no system of public assistance for		Received	94.2%
10"	HPV vaccination in Japan	No	Not receive	83.5%

Figure 3 (a) Correct answer rates to questions on cervical cancer are shown for two groups, students who received human papillomavirus (HPV) vaccination and students who did not. The 95% confidence interval of the correct answer rates, which are indicated by bars, overlaps between the groups on the nine questions. (b) Correct answer rates to questions on HPV vaccination are shown for two groups, students who received HPV vaccination and students who did not. The 95% confidence interval of the correct answer rates, which are indicated by bars, do not overlap between the groups on the questions 13, 16 and 18\*.

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Table 3 Multivariate logistic regression analysis on relative factors to HPV vaccination

Factors (variables)	Coefficient	Standard error	P-value	Adjusted OR (95% CI)
Age of 18 years on entry to university	1.509	0.214	< 0.001	4.52 (2.97–6.88)
Resided in the target city, Yokohama, as a high school student	1.032	0.240	< 0.001	2.81 (1.75–4.50)
Received education on cervical cancer	0.341	0.180	0.059	1.41 (0.99-2.00)
Received MR vaccine as a high school student	0.058	0.213	0.784	1.06 (0.70–1.61)
No. of correct answers to the 18 questions on cervical cancer and HPV vaccination	0.167	0.045	< 0.001	1.18 (1.08–1.29)

CI, confidence interval; HPV, human papillomavirus; MR, mumps and rubella; OR, odds ratio.

Yokohama City had a higher HPV vaccination rate. The city government sent information on the vaccination by mail that targeted girls and informed recipients that the total cost of the vaccination was being subsidized by the city and the national government. The present study showed that 72.9% of students (86/118 students) who were 18 years old and resided in Yokohama during high school had received the HPV vaccine. The results of the logistic regression analysis show a positive relation between place of residence and vaccination uptake rate (OR, 2.81; 95% CI, 1.75–4.50; Table 3). This result indicates that the city's public works influenced the HPV vaccination uptake rate.

Proper knowledge of cervical cancer is important for its prevention. The present study showed that the proportion of students who received education on cervical cancer increased from 2011 to 2013 (Table 1). Although knowledge of cervical cancer and the HPV vaccination may not be directly linked to HPV vaccination uptake, as noted by Ratanasiripong et al.,8 many investigations have shown that knowledge of cervical cancer positively influences the rate of HPV vaccination uptake. 14-17 In the present study, the logistic regression model included factors of education and knowledge. Although education on cervical cancer did not have a statistically significant influence on vaccination uptake rate (OR, 1.41; 95% CI, 0.99-2.00; Table 3), there was a significant positive relation between the number of correct answers to the questions on cervical cancer and HPV vaccination and the HPV vaccination uptake rate (OR, 1.18; 95% CI, 1.08–1.29; Table 3). This positive relation implies the importance of young women being properly educated on cervical cancer and the HPV vaccination to raise the vaccination uptake rate. However, the actual influence of correct knowledge on acceptance of HPV vaccination, namely, a cause and effect, is not clear. Students who passively received HPV vaccination without correct knowledge of cervical cancer and/or HPV vaccination might have had the opportunity to obtain such knowledge at the time of the vaccination. For instance, correct knowledge regarding the number of vaccine inoculations (Question no. 16) or public assistance for HPV vaccination (Question no. 18) was likely obtained from an experience with HPV vaccination. However, a prospective study is needed to clarify the actual influence of knowledge on the acceptance of HPV vaccination.

It is important that mothers or parents who obtained proper information on HPV vaccination recommend that their daughters receive the vaccine. L6-18 Among the 451 students who answered that they knew about the HPV vaccination in 2013, 135 students answered that they heard about the vaccine from their parents. Eighty-six of the 135 answered that they had received HPV vaccination. Because the target age for HPV vaccination is early adolescence, the attitude of parents, especially mothers, has an effect on the decision to receive vaccination. L8-21 It is very important that health providers provide sufficient information to parents on HPV vaccination.

There is a limitation of the study. Because the participants of this survey were university students, the study population may not be fully representative of general women of the same age, and there could be differences in the rates of HPV vaccination knowledge and vaccination uptake rate. However, the fixed point observational survey conducted in the present study allowed us to observe the changes in HPV vaccination knowledge and vaccination uptake rates over the 3-year period in Japan. Additionally, in Japan, severe adverse events after HPV vaccinations, including chronic pain, were widely reported in 2013, resulting in the suspension of approval for HPV vaccines as part of a national vaccination program since June 2013. We are planning to conduct a new survey to determine the influence of this situation in the near future.

In conclusion, the HPV vaccination uptake rate among newly enrolled female students dramatically increased in 2013 in comparison with 2011. Official financial support and publicity work are likely to have had a great effect on the increase in the HPV vaccination uptake rate.

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OPEN

### Web-based Recruiting for a Survey on Knowledge and Awareness of Cervical Cancer Prevention Among Young Women Living in Kanagawa Prefecture, Japan

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Objectives: Cervical cancer (CC) incidence and mortality among young women have been increasing in Japan. To develop effective measures to combat this, we assessed the feasibility of using a social networking site (SNS) to recruit a representative sample of young women to conduct a knowledge and attitude study about CC prevention via an internet-based questionnaire. Methods: From July 2012 to March 2013, advertising banners targeting women aged 16 to 35 years in Kanagawa Prefecture were placed on Facebook in a similar manner as an Australian (AUS) study conducted in 16- to 25-year-olds in 2010 and on a homepage to advertise our CC advocacy activities. Eligible participants were emailed instructions for accessing our secure Web site where they completed an online survey including demographics, awareness, and knowledge of human papillomavirus (HPV) and CC. Data for the study population were compared with the general Japanese population and the AUS study. Results: Among 394 women who expressed interest, 243 (62%) completed the survey, with 52% completing it via Facebook. Women aged 26 to 35 years, living in Yokohama City, with an education beyond high school, were overrepresented. Participants had high awareness and knowledge of HPV and CC, comparable with the AUS study participants. However, the selfreported HPV vaccination rate (22% among participants aged 16-25 years) and the recognition rate of the link between smoking and CC (31%) were significantly lower than in the AUS study (58% and 43%, respectively) (P < 0.05). Significant predictors of high knowledge scores about HPV included awareness of HPV vaccine (P < 0.001) and self-reported HPV vaccination (P < 0.05).

**Conclusions:** The SNS and homepage are efficient methods to recruit young women into health surveys, which can effectively be performed online. A nationwide survey using SNSs would be an appropriate next step to better understand the current lack of uptake of the national HPV vaccine program by young women in Japan.

Key Words: Cervical cancer, HPV, Young female, Social networking sites, Advocacy

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The increasing incidence and mortality rates of cervical cancer (CC) are set as cancer (CC) among young Japanese (JPN) women are a serious health problem. 1,2 This situation is thought to be a result of low uptake of the CC cytology screening program. With a population of approximately 65,600,000 women, Japan reported in 2007 that 8867 women were newly diagnosed with invasive CC, whereas 2737 women died from the disease in 2011.1 To establish effective prevention strategies in Japan, we require a broader understanding of reproductive and sexual health behaviors among young people, because the risk for CC begins at the first intercourse.3 The recruitment of representative samples of young people is challenging as this population is increasingly mobile and, in general, indifferent to medical issues. Moreover, traditional strategies, such as random digit dialing and media advertising campaigns, have limitations, including low participation rates due to reduced landlines and high costs.<sup>4–7</sup> Recently, a study conducted by us in Australia showed that using the social networking site (SNS), Facebook (FB), was an effective strategy to identify a representative sample of young women.<sup>8,9</sup> This Australian (AUS) study demonstrated the potential of using SNSs in a cost-effective way to engage young women in health research and to penetrate nonurban communities. In Japan, SNSs, including FB, are rapidly being embraced among younger generations with 72% in their teens and 64% in their 20s being reported as regular users. 10 Furthermore, around 42% of JPN women aged 10 to 39 years have their own FB account with 50% of them being daily users. 11

In this study, our objectives were to measure (1) the feasibility of recruiting a representative sample of young women aged 16 to 35 years living in Kanagawa Prefecture (population of 9,084,000<sup>12</sup>) using an SNS for a health study and (2) the knowledge and attitudes of that representative sample of young women toward CC prevention. The data were compared with the AUS study, where very comprehensive CC screening and human papillomavirus (HPV) vaccine programs are established. <sup>13,14</sup>

#### MATERIALS AND METHODS

#### Recruitment

Inclusion criteria were being female; having an age of 16 to 35 years; living in Kanagawa Prefecture, Japan; and a written consent for completing an online survey. As minors are legally defined as 19 years and younger in Japan, girls aged 16 to 19 years required written parental consent for participation in the study.

Participants were recruited for 9 months, from July 2, 2012, to March 20, 2013, using FB advertisements targeted by age and place of residence, in addition to a banner on the homepage (HP) (http://kanagawacc.jp/) to advertise our CC prevention project, which started in 2011 as the Yokohama-Kanagawa CC Prevention Project (YKCCPP). The YKCCPP was announced via public lectures, television, and brochures, whereas FB advertisements were displayed only for FB users whose profiles met the inclusion criteria. We chose the "cost-per-click" option for FB advertisements, which charged each time the advertisement was clicked on. When someone clicked on the advertisement, they were redirected to our secure study Web site that contains

detailed study information. Potential participants expressed their interest by giving their name, residential and email addresses, age, and telephone number on a form on the study Web site. After receiving information from potential participants, a consent form was sent to their residential address by mail. All potential participants who furnished signed consent forms had their final eligibility confirmed by telephone or email; those who did not respond to a second notification by email within 2 months were considered to have withdrawn their expression of interest (EoI). Eligible participants were then emailed instructions for accessing the online survey. The online survey tool SurveyMonkey with the enhanced security option of Secure Socket Layers encryption was used to administer the survey to participants. For further protection of privacy, research assistants, who were not qualified to access the questionnaire data, provided each participant with a unique study ID to access the survey, so that the researchers could not connect a participant's name with the unique ID. As compensation for participants' time in the online survey, a gift card worth JPY 1,000 (US \$1 = JPY 80 in June 2012) was sent to those completing it.

#### Questionnaire

The survey contained questions on demographic variables (date of birth, marital status, country of birth, educational background, and residential address); self-reported height and weight; how participants found the study; sexual history; and experience and knowledge of chlamydia, HPV, HPV vaccine, and CC. With the exception of several questions about CC, these questionnaires were almost identical to the study in Australia conducted in 2010 (AUS study). 8,9

#### **HPV** and **CC** Knowledge Scores

The HPV and CC knowledge were evaluated using the same method as the AUS study. 8,9 The HPV awareness was defined by a "yes" response to the question "Do you know what HPV is?". The HPV knowledge was evaluated only among participants who responded "yes" to the question "Do you know what HPV is?", using 6 subsequent "true/false/don't know" questions. One point was given for each correct answer. and a knowledge scale (0–6, from no to high) was constructed. Participants who did not know what HPV was were automatically given a score of 0. The HPV knowledge scale was divided into 3 groups according to the participants' scores: low (0-2), moderate (3-4), and high (5-6). The CC knowledge was also assessed using 7 "yes/no/don't know" questions about the factors that reduce a person's risk for CC. One point was given for each correct answer, and a knowledge scale (0-7) was constructed. The CC knowledge scale (0-7) was divided into 3 groups: low (0-2), moderate (3-4), and high (5-7).

#### **Statistical Analysis**

Statistical analysis was performed using SPSS version 20 (IBM Corporation, Armonk, NY). We used Japanese Bureau of Statistics 2010 census data<sup>12</sup> to compare our study group with the distribution of the general population. Regarding women's educational background and body mass index (BMI), data from the Employment Status Survey 2012 from the Japanese Bureau of Statistics and National Health<sup>16</sup>

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and the Nutrition Survey 2010 from Ministry of Health, Labour and Welfare 17 were cited, respectively. We compared demographic characteristics in our samples with those of the general population using Fisher exact test. Odds ratios, adjusted odds ratios, 95% confidence intervals (CIs), and 2-sided P values were estimated using binomial logistic regression analysis. In all analyses, we defined a 2-sided P < 0.05 as statistically significant. Data were treated as missing if no response was given or "don't know" was selected. Binomial logistic regression analysis was used to identify independent predictors of HPV and CC knowledge.

#### **Ethical Considerations**

After users were directed to our secure study Web site, all subsequent study procedures took place outside the SNSs. This study protocol was approved by the institutional ethics committee of Yokohama City University School of Medicine.

#### RESULTS

#### Recruitment

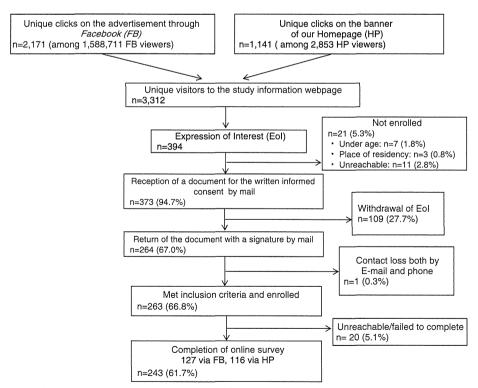
The FB advertisements were displayed 5,698,440 times from July 2012 until April 2013, resulting in 1,588,711 viewers and 2171 clicks on the advertisement that directed respondents to the study Web page. There were 2853 visitors to the YKCCPP HP, with 1141 visitors being directed to the study Web page. Of the total 3312 unique visitors to the study Web

page, 394 (204 via FB, 190 via HP) showed an EoI in sending individual information from the Web page. We collected signed consents from 264 of those 394 women (67% of EoIs), and 243 (62% of EoIs) women completed the survey. Overall, 52% (127/243) were recruited through FB, and the remainder was recruited through the HP: the demographics were not different between the 2 groups except that the number of virgins was greater and the proportion of age of first sexual intercourse being 16 to 18 years was lower in the HP (data not shown). The detailed recruitment steps are shown in Figure 1.

## Participants' General Demographic Characteristics

The participants' general demographic characteristics are shown in Table 1. Compared with the general target population,  $^{12}$  participants aged 16 to 21 years were underrepresented, whereas those aged 22 to 25 years were representative, and those aged 26 to 35 years were overrepresented (P < 0.05).

Residents in the capital (Yokohama City) were overrepresented compared with the other cities and towns (P < 0.05). Most participants were born in Japan (97.1%), which was similar to the target population (P = 0.46). As for educational background, 5 (2.1%) participants were high school students, 47 (19.3%) were high school graduates, and 190 (78.2%) had an educational level higher than high school graduate (P < 0.05). Another parameter of significant difference was that 23% of the study participants were underweight



**FIGURE 1.** Summary of recruitment steps. Sampling and response steps are shown. Percentages are calculated using the number of EoIs (n = 394). The EoI was defined to give their name, residential address, age, email address, and telephone number on a form on the study Web site.

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TABLE 1. General demographic characteristics of study participants

Characteristic	No.	Rate, %	95% CI	<b>Target Population</b>	Rate, %	P
Age group, y*						
16–17	4	1.6	0.0 - 3.2	77,499	7.4	< 0.001
18–21	29	11.9	7.9-16.0	176,271	16.8	
22–25	45	18.5	13.6-23.4	193,250	18.4	
26–30	75	30.9	25.1-36.7	274,747	26.2	
31–35	90	37.0	31.0-43.1	324,620	31.0	
Geographic region*						
Yokohama city	143	58.8	52.7-65.0	422,338	40.4	< 0.001
Kawasaki and Sagamihara city	44	18.1	13.3-22.9	275,998	26.4	
The other cities and towns	56	23.0	17.8-28.3	348,051	33.3	
Country of birth*						
Japan	236	97.1	95.0-99.2	1,013,379	96.8	0.459
Others	5	2.1	0.3 - 3.8	33,008	3.2	
No answer	2	0.8	0.0 - 2.0			
Educational level†						
<high graduate<="" school="" td=""><td>5</td><td>2.1</td><td>0.3 - 3.8</td><td>16,500</td><td>16.9</td><td>&lt; 0.001</td></high>	5	2.1	0.3 - 3.8	16,500	16.9	< 0.001
High school graduate	47	19.3	14.4-24.3	338,000	34.5	
>High school graduate	190	78.2	73.0-83.4	463,100	47.3	
No answer	1	0.4	0.0 - 1.2	12,800	1.3	
BMI, kg/m <sup>2</sup> : 16–35 years old‡						
<18.5 (underweight)	56	23.0	17.8-28.3	137	16.7	0.030
18.5–25 (normal)	166	68.3	62.5-74.2	598	72.7	
25-30 (overweight)	15	6.2	3.1-9.2	87	10.6	
>30 (obese)	2	0.8	0.0 - 2.0			
No answer	4	1.6	0.0 - 3.2			
BMI, kg/m <sup>2</sup> : 16–25 years old§						
<18.5 (underweight)	17	21.8	12.6-31.0	80	20.2	0.853
18.5–25 (normal)	55	70.5	60.4-80.6	284	71.7	
25-30 (overweight)	4	5.1	0.2 - 10.0	32	8.1	
>30 (obese)	1	1.3	0.0 - 3.8			
No answer	1	1.3	0.0-3.8			

Data for the study population were compared with the target population.

(BMI < 18.5 kg/m²), compared with 16.7% of the women in the target population, according to the National Health and Nutrition survey<sup>17</sup> (P < 0.05). However, for the participants aged 16 to 25 years, the BMI distribution was comparable with the target population (P = 0.85).

## Critical Characteristics of Participants Related to CC Compared With the AUS Study

The analyses of critical characteristics of participants related to CC in the JPN study in comparison with data from

the AUS study are shown in Table 2. The significant differences among participants aged 16 to 25 years were the age of first intercourse in 12 to 15 years old (JPN, 7.7% vs AUS, 20.5%; P < 0.001), chlamydia awareness (JPN, 89.7% vs AUS, 77.7%; P < 0.05), and self-reported HPV vaccination status (JPN, 21.8% vs AUS, 58.3%; P < 0.001). The rates of HPV awareness (JPN, 67.9% vs AUS, 62.2%; P = 0.895) and awareness of HPV vaccines (JPN, 79.8% vs AUS, 75.5%; P = 0.303) were comparable in the 2 studies. Self-reported CC screening status was asked only in the JPN study: 65.0% (158/

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<sup>\*</sup>Target population data of Kanagawa Prefecture from the Ministry of Internal Affairs and Communications Statistics Bureau Census 2010.<sup>12</sup>

<sup>†</sup>Target population data range 15 to 34 years old from distribution of educational background in Kanagawa Prefecture. 16

<sup>‡</sup>Target population data range 15 to 39 years old from the National Health and Nutrition Survey 2011. 17

<sup>§</sup>Target population data range 15 to 29 years old from the National Health and Nutrition Survey 2011.<sup>17</sup>

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TABLE 2. Comparison of critical characteristics of participants related to CC between JPN and AUS studies

		Japan (16–35 Years n = 243	Old),		Japan (16–25 Years n = 78	Old),		Australia (16–25 Years n = 278		
Characteristic	No.	Rate, %	95% CI	No.	Rate, %	95% CI	No.	Rate, %	95% CI	$P^*$
Age at first vaginal into	ercourse, y				100000000000000000000000000000000000000					
Never	31	12.8	8.6-17.0	24	30.8	24.2-37.4	62	22.3	17.4-27.2	
Age not specified	21	8.6	5.1-12.1	6	7.7	1.8-13.6	21	7.6	4.5-10.8	
12–15	14	5.8	2.9-8.7	6	7.7	1.8 - 11.0	57	20.5	15.8-25.2	< 0.001
16–18	71	29.2	23.5-34.9	13	16.7	8.4-21.4	99	35.6	30.0-41.2	
19–24	98	40.3	34.1-46.5	29	37.2	26.5-43.3	39	14.0	9.9-18.1	
25–30	8	3.3	1.1-5.5	NA			NA			
31–35	0	0.0		NA			NA			
Chlamydia awareness										
No	17	7.0	3.8-10.2	8	10.3	3.6-17.0	61	22.3	17.4-27.2	0.023
Yes	226	93.0	89.8-96.2	70	89.7	83.0-96.4	213	77.7	72.8-82.6	
Awareness of HPV vac	cines									
No	47	19.3	14.4-24.3	14	17.9	9.4-26.5	65	23.4	18.4-28.4	
Yes	194	79.8	74.8-84.9	62	79.5	70.5-88.5	210	75.5	70.4-80.6	0.303
No answer	2	0.8	0.0 - 2.0	2	2.6	0.0 - 6.1	3	1.1	0.0 - 2.3	
Self-reported HPV vac	cination sta	itus								
No	206	84.8	80.3-89.3	59	75.6	66.1-85.2	62	22.3	17.4-27.2	
Yes	30	12.3	8.2-16.5	17	21.8	12.6-31.0	162	58.3	52.5-64.1	< 0.001
Don't know	6	2.5	0.5-4.4	2	2.6	0.0-6.1	54	19.4	14.8-24.0	
No answer	1	0.4	0.0-1.2	0	0.0		0	0.0		
Self-reported CC screen	ning status									
No	51	21.0	15.9-26.1	35	44.9	33.9-55.9	NA			
Yes	158	65.0	59.0-71.0	25	32.1	21.7-42.5	NA			
Don't know	1	0.4	0.0-1.2	0	0.0		NA			
No answer	33	13.6	9.3-17.9	18	23.1	13.7–32.5	NA			

<sup>\*</sup>Compared with the data of 16 to 25 years old between Japan and Australia. NA, not applicable.