

The effect of self-sampled HPV testing on participation in cervical cancer screening on a remote island

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Aim: Self-sampling devices for oncogenic human papillomavirus (HPV) testing may be useful for improving participation in cervical cancer screening. The aim of this study was to investigate the effects of HPV self-sampling devices for non-attenders, who have not participated in regular cervical cancer screening.

Methods: To determine whether HPV self-sampling devices improve participation in cervical cancer screening on a remote island, non-attenders aged 20–49 years were included in this study. Participation was defined as returning a self-sampling device and/or participating in a conventional cytology-based cervical cancer screening. From April 2014 to May 2015, written informed consent for participation in this study was obtained from 249 of 2,986 non-attenders in the Goto Islands and randomly assigned to the “re-call” group (n=124) or the self-sampling group (n=125).

Results: The participation (by returning the HPV self-sampling device and/or attending a cervical cancer screening) rate was 12.1% (n = 15) in the “re-call” group and 76.0% (n = 95) in the self-sampling group. Only 50% of HPV-positive women (n=5) underwent cytological testing, and abnormal cytological findings were detected in two cases. For these two patients with abnormal cytology, carcinoma in situ was detected and treated.

Conclusions: Offering HPV self-sampling devices may improve participation in cervical cancer screening on remote islands in Japan.

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Key words: carcinoma in situ; cervical cancer screening; non-attenders; participation rate; HPV, self-sampling

Introduction

Significant reduction of the incidence of invasive cervical carcinoma have been observed with cervical cancer screening based on gynecological cytology.¹ Because persistent oncogenic human papillomavirus (HPV) infection is a major cause of cervical cancer, HPV testing has been used in cervical cancer screening programs, and HPV vaccines have been used for the prevention of cervical cancer.² In randomized controlled trials, cervical cancer screening based on oncogenic HPV testing has been shown to provide greater protection against cervical cancer, compared with gynecological cytology.³ Based on the existing evidence, a cervical cancer

screening program using gynecological cytology and oncogenic HPV testing has been implemented in selected areas in Japan.

Those who do not regularly participate in cervical cancer screening (non-attenders) are at risk for cervical cancer onset and invasion.⁴ To provide the effective cervical cancer screening program, the participation rate for cervical cancer screening is the most important factor, but the cervical cancer screening participation rate in Japan has been low.⁵ The participation rate for cervical cancer screening in Japan, at 30%–40%, is lower than the participation rate of 70%–80% in the West.^{6,7} Following media reports on adverse events associated with HPV vaccination, recommendations for the

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HPV vaccine were suspended in Japan in June 2013. There is an urgent need to increase participation in cancer screening programs.⁸

There are several remote islands in Nagasaki Prefecture, located on the western coast of Japan. The Goto Islands, literally meaning “five-island archipelago,” are Japanese islands in East China Sea and part of Nagasaki Prefecture. Participation in cervical cancer screening in the Goto Islands is only 20%—lower than the 36.4% participation in the Nagasaki city. In this study, we aimed to investigate whether the HPV self-sampling improves participation in cervical cancer screening program on remote islands. HPV self-sampling devices allow women to check for HPV, using a cervical brush by themselves.⁹ An advantage of HPV self-sampling devices is the possibility for women on remote islands to perform self-sampling without traveling to a medical institution. Because of this advantage, HPV self-sampling devices are considered an effective method on remote islands.¹⁰

The purpose of this study was to assess the effect of HPV self-sampling devices among non-attenders. Because there are few medical institutions in the Goto Islands, data on all non-attenders is maintained by the Goto city government. Therefore, the Goto Islands were considered an ideal research location for our study.

Methods

Screening system in the Goto Islands

This study was conducted in the Goto Islands, Nagasaki, Japan, where non-attenders were invited to participate in a regular cervical cancer screening every other year. A total of 2,986 women aged 20 to 49 years who had not undergone cervical cytology-based screening in the past 2 years were invited to participate in the study.

Study population and randomization

Our study population was comprised of non-attenders who were scheduled for participation in the cervical cancer screening program from April 2014 to May 2015. We defined “non-attenders” as women aged 20 and 49 years who had no gynecological cytology result recorded by the Goto city government over the past 2 years. These women were invited at least once but were not screened.

In May 2014, 2,986 non-attenders who missed the last round of cervical screening were identified with the assistance of the Goto city government. At first, we sent all of 2,986 non-attenders two kinds of letters; one is a letter to attend

regular cytology screenings as the first-call, and the other is a letter requesting their written consent for participation in this study using a HPV self-sampling device. We received written consent from 249 women who agreed to participate in this study using a HPV self-sampling device. The remaining 2,737 non-attenders served did not agree to participate in the study using a HPV self-sampling device. Subsequently, we randomly assigned the 249 women who agreed to participate to the “re-call group” or the “self-sampling group”. The “re-call group” was defined as the women, who were invited again by letter to attend regular cytology screenings. The “self-sampling group” was defined as the women, who got a HPV self-sampling device with a letter to attend regular cytology screenings.

In June 2015, after the random assignment of the participating women to the two groups, HPV self-sampling devices were sent by mail to the 125 non-attenders in the self-sampling group. The devices were sent along with pictorial instructions and a pre-paid return envelope. The 124 women in the “re-call” group were invited again by letter to attend regular cytology screenings (Figure 1).

Ethical statement

The study was approved by the Nagasaki University Regional Ethical Committee in 2014 (No. 14032482). Signed informed consent was obtained from all participants in the “re-call” with self-sampling group included in the study.

HPV testing using self-sampling devices

The Evalyn Brush (Rovers Medical Devices BV, Netherlands) self-sampling device was used in this study. All self-sampled specimens for oncogenic HPV testing were returned within 1 month. All samples were processed and analyzed using QIAgen’s Hybrid Capture II test. The 13 types of HPV (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) designated as oncogenic HPV are defined as carcinogenic or probably carcinogenic to humans.¹¹ Results were communicated as “positive/negative,” without genotyping.

Cytology

Cervical cytology was conducted by smear method, and all results of the cytological findings were read by the same screener at Goto City Hospital. Results were reported according to the “Bethesda classification,” the standard classification system for cytology in Japan.¹² If the cytology showed abnormal results, women were referred for further examination. Normal results included negative for intraepithelial lesion or malignancy (NILM). Abnormal results included low-grade squamous intra-epithelial lesion (LSIL); high-grade squamous

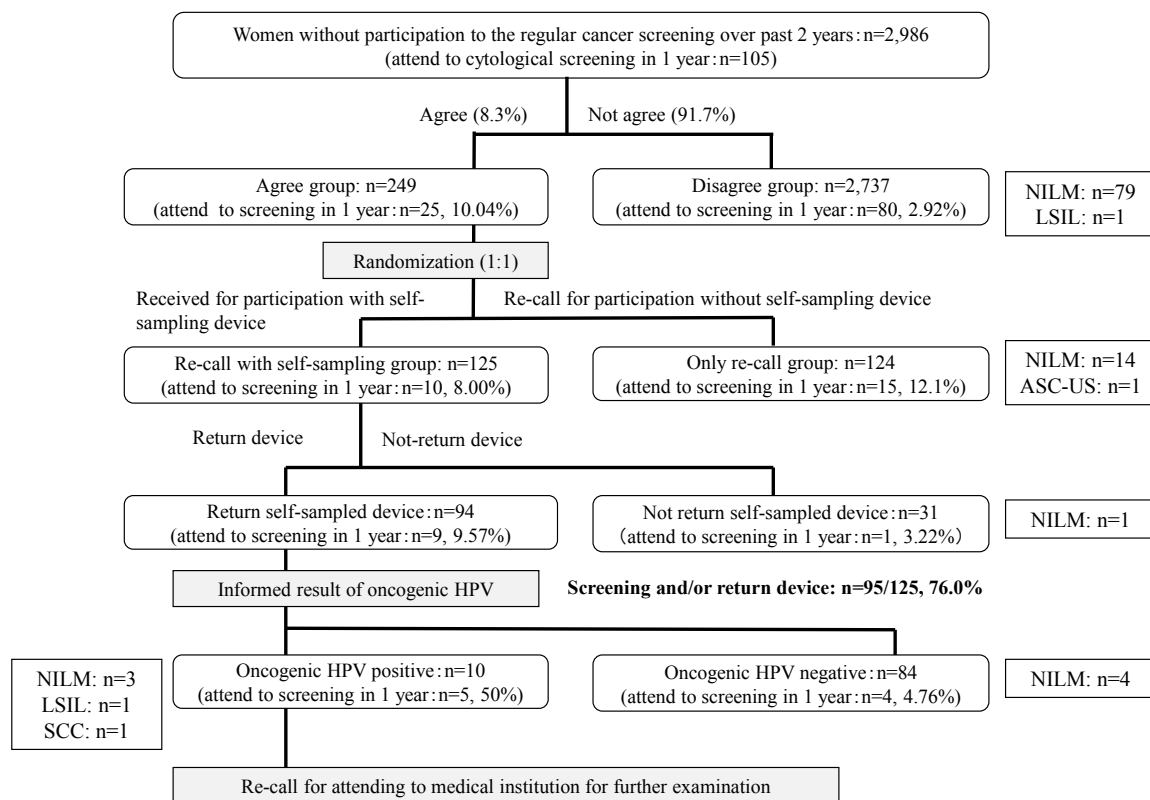


Figure 1. Flowchart of randomization in the study population

“Non-attenders” were defined as women aged 20 to 49 years in the Goto Islands who did not participate in regular cytology in the past 2 years. There were 2,986 non-attenders in Goto city. We randomly assigned the 249 women from whom we received consent by mail into the “re-call” group and the self-sampling group, using the Box–Muller method. HPV self-sampling devices were mailed to the 125 non-attenders in the self-sampling group. Each of the 124 women in the “re-call” group was invited by mail to attend a regular cytology screening.

intra-epithelial lesion (HSIL); atypical squamous cells, cannot exclude HSIL (ASC-H); atypical squamous cells of undetermined significance (ASC-US); and squamous cell carcinoma (SCC).

HPV testing results

Women in the self-sampling group received letters with the results of their HPV test and scheduled appointments with a medical institution for cytology. The women’s gynecologists were informed about the study and the individual women’s HPV results (oncogenic HPV-positive or negative in the self-sampled specimen).

Management of adverse events with the use of the HPV self-sampling device

Women were instructed in writing to call Goto City Hospital if there were adverse events while using the HPV self-sampling device.

Outcomes measurement and statistical analysis

We defined participation as either returning a self-sampling device within 1 month of receiving it and/or having a conventional cervical cytology conducted by a physician within 3 months of being invited to do so, from April 2015, when non-attenders were identified, to the end of March 2016. We analyzed participation in cervical cancer screening, returning self-sampling devices, and the results of cytology and HPV testing.

Results

Rate of participation in cervical cancer screening and/or returning the self-sampling device

Of the 249 women who agreed to participate in the study, 25 underwent cytological screening. Eighty of the 2,737 women who did not agree to participate underwent cytological

screening. There was a statistically significant difference in participation rate in cervical cancer screening between the group that agreed to participate (10.04%) and the group that did not agree to participate (2.92%) ($P < 0.001$, chi-square test; Table 1). There were 10 cytological screening attendees in the “re-call” with self-sampling group ($n = 125$) and 15 in the “re-call” group ($n = 124$). There were no statistically significant differences in the participation rate in cervical cancer screening between the self-sampling group (8.00%) and the “re-call” group (12.10%).

A total of 95 of the 125 cases in the self-sampling group participated in cervical cancer screening and/or returned the self-sampling device. The overall rate of participation in cervical cancer screening and/or returning the self-sampling device was 76.00%. A total of 15 of the 124 cases in the “re-call” group participated in cervical cancer screening. The overall cervical cancer screening participation rate was higher in the self-sampling group than in the “re-call” group (12.1%). There was a statistically significant difference between the self-sampling group and the “re-call” group ($P < 0.01$, chi-square test; Table 2).

The details of the 94 cases in which the self-sampling device was returned are as follows: A total of 85 women returned the self-sampling devices without attending a cervical cancer screening, and nine women returned the self-sampling devices and also attended a screening. The details of the 31 cases in which the self-sampling device was not returned are as follows: One woman made an appointment for a

screening without returning the device, and 30 women never participated in a cervical cancer screening or returned the self-sampling device. Oncogenic HPV was detected in 10 of the 94 cases in which the self-sampling device was returned. In 5 of these 10 cases, the women attended a cytological screening within 1 year.

Follow-up of abnormal cytology

The cytological findings are shown in Figure 1 and Table 3. In the group that did not agree to participate in the study, cytological findings showed that 79 women had NILM and one woman had LSIL. In the group that agreed to participate in the study, three women had abnormal cytology results that required follow-up. In the group of re-call for participation without self-sampling device, 14 women were diagnosed with NILM and one woman was diagnosed with ASC-US. In the self-sampling group, eight women were diagnosed with NILM, one with LSIL, and one with SCC. The woman with SCC was introduced to another institution for further examination. After receiving cervical conization, the histological diagnosis was CIS. This woman has not had a recurrence of abnormal cytological findings after conization.

Adverse events in the self-sampling group

In the self-sampling group, there were no adverse events among the 94 non-attenders who returned their devices according to the simple instructions.

Table 1. Participation of the study population

Age (years)	Intervention group (participation rate (n/N))	Control group (participation rate (n/N))	Chi-squared test (P-value)
20-29	38.46% (10/26)	2.71% (12/442)	<0.01*
30-39	47.25% (43/91)	3.52% (29/825)	<0.01**
40-49	43.18% (32/57)	2.65% (39/1,470)	<0.01***
Total	44.18% (110/249)	2.92% (80/2,737)	<0.01****

Participation was defined as returning a self-sampling device and/or attending a conventional cervical cancer cytology screening conducted by a physician at a medical institution.

n: number of enrolled non-attenders.

N: overall number of non-attenders

* 2.7686E-19

** 1.5391E-43

*** 5.4535E-79

**** 8.4985E-144

Table 2. Participation of the intervention group

Age (years)	Re-call with self-sampling group (participation rate (n/N))	Only re-call group (participation rate (n/N))	Chi-squared test (P-value)
20-29	76.92% (10/13)	0.00% (0/13)	<0.01*
30-39	78.24% (36/46)	15.56% (7/45)	<0.01**
40-49	74.24% (49/66)	12.12% (8/66)	<0.01***
Total	76.00% (95/125)	12.10% (15/124)	<0.01****

Participation was defined as returning a self-sampling device and/or attending a conventional cervical cancer cytology screening conducted by a physician at a medical institution.

There was a significant difference between the self-sampling group and the “re-call” group.

n: number of enrolled non-attenders.

N: overall number of non-attenders

* 0.000056

** 2.0933E-9

*** 5.8265E-13

**** 3.2209E-24

Table 3. Results of the cytological findings

Bethesda classification	Agree group		Disagree group (n)
	Re-call with self-sampling group (n)	Only re-call group (n)	
NILM	8	14	79
ASC-US	0	1	0
LSIL	1	0	1
SCC	1	0	0

There are 105 cytological findings in this study. We were able to detect squamous cell carcinoma in non-attenders by offering HPV self-sampling devices.

n: number of women

Discussion

This study has contributed to the knowledge about HPV self-sampling among women in a remote area of Japan. In most previous studies, the participation rate was significantly increased by offering an HPV self-sampling device, compared with only a re-call inviting women to attend a gynecological cytology screening. Although all non-attenders had the opportunity to participate in a cervical cancer screening over the course of a year, participation in a cervical cancer screening

was improved from 2.92% to 44.18% when non-attenders received self-sampling devices or a re-call for participation. The participation rate was 12.1% in the “re-call” group and 76.0% in the self-sampling group. This participation rate in the self-sampling group (76.0%) is similar to cancer screening participation rates observed in the West.^{6,7} However, it is possible that women with higher knowledge of cancer screening were targeted because they agreed to participate in the study before receiving a self-sampling HPV device.

Cervical cancer screening participation rates are low in

Japan. Especially because the recommendation for the HPV vaccine was discontinued in Japan, an effective method of screening for non-attenders is necessary. To improve the participation of non-attenders, a high-risk group for cervical cancer, several barriers to cancer screening should be considered. In general, anticipation of pain, forgetting to make an appointment, lack of time, and embarrassment are reasons for non-attenders to avoid cervical cancer screening.¹³ There is usually more than one reason for non-attenders to avoid participation in cervical cancer screening programs. Low levels of understanding about cervical cancer and HPV, low education, insufficient income, difficulty obtaining time off, and the lack of someone to accompany them to the cervical cancer screening and gynecological examination can all play a role.¹⁴ In a study in the United States, non-attenders of cervical cancer screening were found to have low levels of HPV-related knowledge and awareness of the risk of cervical cancer.¹⁵ Education on cervical cancer and HPV before self-sampling improves the acceptability of the method.¹⁶

In the self-sampling group, five HPV-positive women participated in screening cytology (50%), and abnormal cytology was detected in two of these women. There is a possibility that women in the self-sampling group did not participate in cervical cancer screening because they had returned the self-sampling device instead. Therefore, HPV self-sampling devices should be efficiently introduced in cervical cancer screening programs already using oncogenic HPV testing as the primary screening test. Sending simple pictorial instructions on how to obtain the self-sampled specimen and return the self-sampling device proved sufficient for HPV testing in all 94 cases where the HPV self-sampling devices were returned, and there were no adverse events. Japanese women need to be further educated about the accuracy of cervical cancer screening, and our results have shown that cancer screening coverage could be effectively and safely increased by offering HPV self-sampling devices.

In this study, CIS was detected in one case. HPV self-sampling devices returned by non-attenders showed higher rates of cervical intraepithelial lesion grade 2 or worse (CIN2+), compared with regular cytology-based screening. Cervical cancer screening based on cytological diagnosis is common in Japan. It is well recognized that the clinical sensitivity of oncogenic HPV testing is higher than that of cytology, leading to the higher detection of CIN2+.^{17,18} Among non-attenders, the detection rate of CIN2+ is higher among those returning HPV self-sampling tests than among those undergoing cytological testing during regular screening.¹⁹ These results emphasize the importance of HPV self-sampling for non-attenders in cervical cancer screening. Because it is

important for municipalities to consider cost performance, the effectiveness of self-sampling should be carefully considered. Screening methods that include HPV self-sampling as an option have the potential to increase the population covered by cancer screening. Several countries have switched to HPV testing for cervical cancer screening, and HPV self-sampling devices have been used as part of the national screening program in the Netherlands.²⁰ This study has suggested that it is conceivable that HPV self-sampling might become the primary method of screening for cervical cancer in remote areas. Cervical cancer screening programs that incorporate HPV self-sampling tests and re-calls for participation are feasible and may significantly improve the uptake of cervical cancer screening in remote areas.²¹

In conclusion, offering HPV self-sampling devices to non-attenders may improve screening coverage and acceptability in remote areas where there is a lack of medical services. In this study, we were able to identify CIS patients among non-attenders by offering HPV self-sampling devices.

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Disclosure

There are no conflicts of interest to disclose.

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