Cervical cancer remains one of the most common cancers in women worldwide. The estimated age-standardised incidence rate for cervical cancer is higher in Japan than in North America and the UK. The incidence of cervical cancer is increasing, particularly in women aged 15-39 years. The mortality rate among Japanese women aged 15-39 years increased between 1994 and 2014. The high incidence...
and mortality rates of cervical cancer are important social issues in Japan. Thus, increasing human papillomavirus (HPV) vaccination rates and improving cancer screening are also important social issues. HPV vaccination rates are very low because the Ministry of Health, Labor and Welfare stopped recommending HPV vaccination in 2013.2,3 The reason why the Japanese Ministry suspended the vaccination was a series of highly publicised adverse events.3 Thus, the current focus of cancer screening is the prevention of cervical cancer in Japan. However, cytological testing, which is generally adopted for cervical cancer screening programmes financed by almost all municipalities, has a low sensitivity for the detection of pre-malignant cervical changes and early cervical cancer.1,4-6

HPV testing was introduced as a cancer screening measure and has been used extensively worldwide to improve the low sensitivity of cytology.1,4-6 The high-risk (hr) HPVs include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. hrHPV infection is responsible for most cases of cervical precancer and cancer, and some studies have demonstrated that HPV testing is more sensitive than cytology for the detection of intraepithelial neoplasia grade 2 or worse (CIN2+).1-4 In 2012, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology recommended performing co-testing with cytology and HPV testing every 5 years for women aged 30-65 years.7 However, the specificity of this co-testing strategy is remarkably lower than that of cytology.8

Stratifying patients according whether they test positive for HPV16, HPV18 (HPV16/18) or the other hrHPVs (12 other hrHPVs genotypes) has been proposed as a means of improving the low sensitivity of the co-testing strategy in the USA.9 Among the hrHPVs, HPV16/18 are the most carcinogenic viruses and are strongly associated with cervical precancer and invasive cervical cancer.10 The prevalences of HPV16/18 are extremely high in women aged 20-29 years, and these viruses are responsible for 90% of cases of invasive cervical cancer and 54% of cases of CIN2 and CIN3.9 A previous multicentre prospective cohort study of Japanese women with hrHPV demonstrated that HPV16/18 conferred a much higher risk of cervical cancer than the 12 other hrHPV genotypes. Studies comparing outcomes among patients with hrHPV infections caused by different viruses showed that the estimated risk of progression from viral infection to CIN2+ was much higher for patients with HPV16/18 than for patients with the 12 other hrHPV genotypes.11 A recent clinical trial in the USA, Addressing the Need for Advanced HPV Diagnostics (ATHENA), suggested that stratifying patients according to whether they were infected with HPV16/18 or the 12 other hrHPV genotypes may be a more effective means of improving the low specificity of the co-testing strategy.7 No clinical trials in Japan have confirmed the effectiveness of stratifying patients according to whether they are positive for HPV16/18 or the 12 other hrHPV genotypes.

The Fukui Cervical Cancer Screening (FCCS) study is the first study about cervical cancer screening in Japan. Its objectives were to determine the frequency of women with HPV16/18 in the Japanese cancer screening population and to determine whether stratifying patients according to whether they are positive for HPV16/18 or the 12 other hrHPV genotypes is an effective cancer screening strategy for Japanese patients.

2 METHODS

2.1 Study design

The FCCS study included a baseline phase and a 3-year follow-up phase. The study design is shown Figure 1. The present study assessed data from only the baseline phase because the follow-up phase is ongoing. The cobas 4800 HPV test was used as the HPV-DNA test. The end point of the study was occurrence of CIN2+, which was defined as CIN2, CIN3, adenocarcinoma in situ or invasive cervical cancer. The management of the cervical cancer screening in Japan does not have a unified national population-based cervical screening programme. However, the screening activity is financed by each municipality. We asked all women, who accepted the cervical cancer screening programme of the eight municipalities in Fukui Prefecture between May 2015 and March 2016, to participate this study. Patients aged 25-69 years who were not pregnant, had an intact uterus, were willing to undergo a colposcopy and biopsy within 6 months if required, and had not undergone treatment or a follow-up evaluation for CIN within the previous 12 months were included in the FCCS study,12 which was approved by the ethics review board of Fukui University (UMIN000025977).

2.2 Baseline phase

All enrolled participants took part in study visit 1. After informed consent was obtained from the participants, obstetric and gynaecological histories were taken.13 An LBC sample (PreservCyt solution: Hologic, Marlborough, MA, USA) was then collected from the transformation zone of the cervix in each participant using an endocervical brush (Cervix-Brush, Rovers Medical Devices, Netherlands), which was inserted into endocervical canal and rotated 360° in a clockwise direction more than three times. The PreservCyt solution was distributed for HPV (5 mL) and cytology testing (15 mL). An adequate sample was obtained from the transformation zone of the cervix using a cervical sampler (broom-like device). The central bristles of the broom were inserted into the endocervical canal deep enough to allow the shorter bristles to fully contact the ectocervix. The brush was pushed gently and rotated 360° in a clockwise direction three to five times. An LBC sample (PreservCyt solution: ThinPrep®, Hologic, Bedford, MA, USA) was then collected from each participant using an endocervical brush, and PreservCyt solution was distributed for HPV (5 mL) and cytology testing (15 mL). The cobas 4800 HPV test was used to test for 14 types of hrHPV (HPV16, HPV18, and the 12 other hrHPV genotypes) simultaneously.12 The cytological evaluations were conducted at only one accredited clinical laboratory in Fukui Prefecture. The cytologists were blinded to the HPV results and reported their results using the Bethesda 2001 System.
Women with abnormal cytology [atypical squamous cells of undetermined significance (ASC-US) or worse], whether HPV positive or negative; women with a positive HPV test with either normal or abnormal cytology; and women randomly selected from a group of women with normal cytology (negative for intraepithelial lesions or malignancies) and a negative HPV test were referred for colposcopy, which was performed within 6 months after visit 1, according to the study design. The procedure included biopsies of visible cervical lesions or a random biopsy at the squamocolumnar junction in women with satisfactory colposcopy results but no visible cervical lesions. Women who had CIN3 or worse were excluded from the study.

**2.3 Consensus pathology review**

The consensus pathology review panel consisted of three study pathologists blinded to all participant and laboratory information. The three pathologists separately reported the results using the three CIN grades, as well as adenocarcinoma in situ or carcinoma. In the cases of discordant diagnoses, the final diagnosis was determined by discussion among the three study pathologists.

**2.4 Statistical analysis**

In Figure 2, Spearman rank correlation coefficient was used for the analysis about the correlation between the prevalence of HPV and the age. In Table 4, verification bias-adjusted estimates for the absolute risks of CIN2+ in women with normal cytology were obtained by calculating the projected number of women if all women had undergone colposcopy and biopsy. In Table 5, the sensitivity and specificity of the cytology and HPV tests for the detection of CIN2+ were determined by statistical tests, and 95% confidence intervals (CIs) were calculated using the bootstrap method with 1000
bootstrap samples. The 2.5th and 97.5th percentiles of the bootstrap distribution for prevalence were used as the lower and upper limits of the 95% CIs, respectively.\textsuperscript{13}

3.1 | Study population

Between May 1, 2015, and March 31, 2016, 12,869 women aged 25-69 years were found to be eligible for the FCCS study (Table 1). Of these 12,869 women, 7,585 (58.9%) were enrolled in the study. The proportions of participants in each age group were 8.3% (55-59-year age group) and 15.6% (35-39-year age group).

3.2 | Frequency of women with hrHPV or HPV16/18 positivity in the Japanese cancer screening population

We analysed the prevalence of hrHPV or HPV16/18 positivity using the cobas HPV test. The prevalence of hrHPV or HPV16/18 positivity was 6.8% or 1.7% among all women. The highest hrHPV or HPV16/18 positivity rate was noted among women aged 25-29 years, while the lowest hrHPV positivity rate was noted among women aged 60-64 years and the lowest HPV16/18 positivity rate was noted among women aged 65-69 years. The prevalence of hrHPV or HPV16/18 positivity increased with decreasing age (Figure 2). The prevalence of hrHPV positivity in women aged 25-29 years was approximately eight times higher than that in women aged 60-64 years. The prevalence of HPV16/18 positivity increased with decreasing age ($r = .84$). The prevalence of HPV16/18 positivity in women aged 25-29 years was approximately 10 times higher than that in women aged 65-69 years (Figure 2).

3.3 | Distribution of cytology results by HPV status

We examined whether HPV status is associated with the cytology results. We noted a significant difference in the prevalence of normal cytology between the negative (99.3%) and positive hrHPV (60.2%) groups. We compared the prevalences of HPV16/18 and those of the 12 other hrHPV genotypes among women with cellular findings (ASC-H, H-SIL or SCC) that were highly suspicious for cancer. We noted significant differences between the prevalences of HPV16/18 (11.7%) and those of the other 12 other hrHPV genotypes (7.0%) in this population of women. We therefore concluded that women with cellular findings that were highly suspicious for cancer were more likely to be infected with HPV16/18 than with the 12 other hrHPV genotypes (Table 2).

3.4 | Histology results in women with normal cytology

Of the 7,585 women enrolled in the study, 7,335 had normal cytology, and 309 (4%) were hrHPV positive and had normal cytology. A total of 196 (63.4%) of these women underwent colposcopy alone (5.1%) or colposcopy with biopsy (94.9%). Of these 196 women, 22.4% and 77.0% were positive for HPV16/18 or the 12 other hrHPV genotypes, respectively. Fourteen women who were hrHPV negative and had normal cytology underwent colposcopy with biopsy (Table 3). Ten women with the 12 other hrHPV genotypes and no abnormal findings underwent only colposcopy and had no lesions. We analysed the association between histology and HPV status. No woman with invasive cancer were identified in the group of women with normal cytology. Among women with CIN3, the rate (22.7%) of HPV16/18 positivity was significantly higher than the rate (6.6%) of positivity for the 12 other hrHPV genotypes. Among women with CIN1 or better, the rate (6.8%) of HPV16/18 positivity...
TABLE 2 Distribution of cytology results by HPV status

| HPV test result | NILM | ASC-US | L-SIL | ASC-H | SIL | SCC | AGC | Total |
|-----------------|------|--------|-------|-------|-----|-----|-----|-------|
| Positive hrHPV  | 57.0 | 18.8   | 12.5  | 1.6   | 10.2| 0.0 | 0.0 | 100   |
| HPV16/18        | 61.3 | 14.0   | 17.7  | 0.5   | 6.2 | 0.3 | 0.0 | 100   |
| 12 other hrHPV  | 99.3 | 0.2    | 0.2   | 0.0   | 0.0 | 0.0 | 0.0 | 100   |
| other genotypes|      |        |       |       |     |     |     |       |

NLM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; L-SIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; H-SIL, high-grade squamous intraepithelial lesion; SCC, squamous cell cancer; AGC, atypical glandular cells; hr, high-risk

was significantly lower than the rate (15.9%) of positivity for the 12 other hrHPV genotypes. Table 3 illustrates that among women with HPV16/18, the proportion (77.3%) of women with CIN1 or better who did not need colposcopy was clearly smaller than the proportion (93.4%) of women who were hrHPV positive (Table 3).

3.5 Estimated absolute risk of CIN2+ in women with normal cytology

The end point of this study was the incidence of CIN2+, as patients with CIN2+ warrant treatment. We analysed the estimated absolute risk of CIN2+ in women with normal cytology, as shown in Table 3. The estimated absolute risk of CIN2+ in women with HPV16/18 was approximately three times higher than that in women with the 12 other hrHPV genotypes. As shown in Table 4, CIN2+ was more efficiently detected in women with HPV16/18 than in women with the other 12 HPVs.

3.6 Comparison of screening strategies for the detection of CIN2+

We compared three methods to determine the ideal strategies for cancer screening in Japan. One (option 1: Cytology) method involves the performance of colposcopy in women with abnormal cytology. This method is generally recommended in Japan. The second (option 2: co-testing hrHPV type) involves the performance of colposcopy in women with abnormal cytology or hrHPV positivity. The third (option 3: co-testing HPV16/18) method involves the performance of colposcopy in women with abnormal cytology or HPV16/18 positivity. We analysed the sensitivity and specificity of each strategy and found that the sensitivities of options 1, 2 and 3 were 70.9%, 100% and 85.5%, respectively. Utilising HPV testing (options 2 and 3) improved the low sensitivity of cytology (option 1) (Table 5). However, the specificity of option 2 was much lower than that of option 1. The data presented in Table 5 indicate that the sensitivity of option 3 was much higher than that of option 1 and that the specificity of option 3 was not inferior to that of option 1.

4 DISCUSSION

The FCCS study, which was conducted as part of the routine government screening programme in Fukui Prefecture, is the first large-scale, population-based study of cervical cancer screening in Japan. To the best of our knowledge, this study is eighth trial (ARTISTIC: UK,14 ATHENA: USA,13 CCaST: Canada,15 HERMES: Greece,16 NTCC: Italy,17 POBASCAM: The Netherlands,18 SWEDESCREEN: Sweden19) in the world to determine whether the stratification of HPV16/18 and the 12 other hrHPV genotypes is beneficial for cervical cancer screening. This study had five main characteristics. First, all the samples included in the study were LBC samples. Second, the cobas 4800 HPV test, which can detect HPV16, HPV18 and the 12 other hrHPV genotypes separately, was used for HPV testing. The HPV test is a high quality.20 Third, the bias that may have affected the cytological diagnostic results was limited, as the cytology samples were evaluated by five cytotechnologists from a single institution. Fourth, women with abnormal cytology, whether HPV positive or negative; women with either normal or abnormal cytology results and positive HPV test results; and women randomly selected from a group of women with normal cytology and negative HPV test results were referred for colposcopy and biopsy. Fifth, a central pathology review panel determined the histological diagnoses of the samples, as the diagnostic criteria for CIN can vary among pathologists. Furthermore, the Fukui Prefecture, which we selected as the research area, has high-quality cancer registries, which are indispensable for clinical studies on cancer screening.21 The FCCS study is not a randomised controlled study. However, this study will provide data that
are extremely useful for the preparation of guidelines for cervical cancer screening in Japan.

The prevalence of hrHPV positivity among women aged 25-69 years was 6.8% in the FCCS study (Table 1). The overall prevalence of hrHPV positivity among women aged 25-69 years was 10.5% in the recent ATHENA study from the USA. That study used the same cobas HPV test as this study. The prevalence of hrHPV positivity in the FCCS study was significantly lower than that in the ATHENA study in all age groups. The age of the study population ranged from 25 to 55 years. We compared the prevalence of hrHPV positivity between our study and the HERMES study, which also used the cobas HPV test. The prevalence of hrHPV positivity in the FCCS study was significantly lower than that in the HERMES study. However, no significant difference in hrHPV positivity in patients aged 40-55 years was observed between our study and the HERMES study. In all three studies, the prevalence of hrHPV gradually increased as age fell (Figures 1 and 2). These results suggest that the infection rate in young women in Japan is low.

Some cohort studies have demonstrated that HPV16 and HPV18 are more dangerous than the 12 other hrHPV genotypes. The prevalence of HPV16/18 among patients with invasive cervical cancer was 65% in Japan and 60%-70% in the USA. The overall prevalences of HPV16 and HPV18 among women aged 25-69 years in the FCCS study were 1.2% and 0.5%, respectively. There were no significant differences in the prevalences of HPV16/18 in almost all age groups between the FCCS study and the ATHENA study. In both studies, the prevalence of HPV16/18 gradually decreased with increasing age in women aged between 25 and 69 years (Figure 2). Based on our results, the prevalence of hrHPV positivity in Japan may be lower than that in the USA, whereas the prevalence of HPV16/18 in Japan may be similar to that in the USA. We expect that the difference in the frequency of cervical cancer between the USA and Japan will be larger in the future than in the present because the frequency of HPV vaccination will increase in the USA but not in Japan.

We also examined the sensitivity and specificity of cytology and co-testing with cytology and HPV testing in Japan for the first time. We surmised that the introduction of co-testing with cytology and HPV testing would improve the sensitivity of cytology because the quality of Japanese cytopathologists is extremely high. Few publications discussing the issue of cervical cancer screening in Japan are available in the literature. Therefore, we conducted the FCCS study to assess the effectiveness of Japanese cervical cancer screening. The FCCS study was compared with two studies [the Canadian Cervical Cancer Screening Trial (CCCaST) and the HPV in Addition to Routine Testing (HART) study in the UK] that recently assessed the effectiveness of cancer screening. The sensitivities of cytology were 71%, 56% and 77% in the FCCS study, CCCaST and HART study, respectively. Our data suggest that the sensitivity of cytology for the detection of Japanese cancer is not sufficiently high. In contrast, some reports indicated that co-testing with HPV test and cytology had a high sensitivity for the detection of cancer. Our data also suggested that the number of CIN2+ detected by option 1, which almost all municipalities adopt today, is 1.4 times higher than that by option 2. However, three studies, including the FCCS study, indicated that co-testing had a low specificity for the detection of cancer. Our results suggest that colposcopy (potential harm) was performed unnecessarily in some cases when all women with hrHPV positivity or abnormal cytology underwent colposcopy.

We used the baseline data from the FCCS study to determine the ideal cervical cancer screening strategy, which should feature a good balance between benefits and potential harm. The benefit is the detection of CIN2+, as CIN2 is a cervical cancer precursor lesion that warrants treatment. The potential harm is that women with CIN1 or better undergo unnecessary colposcopy. When a woman with HPV16/18 positivity or abnormal cytology underwent colposcopy, the sensitivity (86%) of this strategy was remarkably higher than that of cytology, and the specificity was approximately same as that of cytology (Table 4).

In conclusion, the baseline data from the FCCS study clearly show the prevalences of hrHPV and HPV16/18 positivity in the Japan cancer screening population. We believe that these data will play an extremely important role in the development of new Japanese guidelines for cervical cancer screening. Additionally, the data may drive the government to recommend vaccination for HPV. Furthermore, the baseline data from the FCCS study demonstrated that the cervical cancer screening strategy in which only women with abnormal cytology or HPV16/18 positivity undergo colposcopy may offer a good balance between benefits and potential harm. Another of the important factors evaluating a strategy of the cancer screening is cost-effectiveness. From these baseline data, we cannot appreciate the cost-effectiveness. However, when a study is completed in 3 years, we can suggest the appropriate interval of the screening and are able to analyse cost-effectiveness. The limitations of this study were that it was not a randomised clinical trial and that it did

### TABLE 5 Adjusted performance of screening for the detection of CIN2+

| Target for colposcopy | Sensitivity | Specificity |
|-----------------------|-------------|-------------|
| Option 1 Cytology     | Abnormal cytology (95% CI) | 70.9 (83/117) (62.8-78.0) | 97.8 (7301/7468) (97.6-97.9) |
| Option 2 Co-testing: hrHPV type | Abnormal cytology or hrHPV positive (95% CI) | 100 (117/117) (96.8-100.0) | 94.1 (7026/7468) (94.0-94.1) |
| Option 3 Co-testing: HPV16/18 type | Abnormal cytology or HPV16/18 positive (95% CI) | 85.5 (100/117) (78.1-90.7) | 97.0 (7245/7468) (96.9-97.1) |

Option 1: women with abnormal cytology undergo colposcopy with or without biopsy.
Option 2: women with abnormal cytology or high-risk (hr) HPV positive undergo colposcopy with or without biopsy.
Option 3: women with abnormal cytology or HPV16/18 positivity undergo colposcopy with or without biopsy.
not discuss primary HPV testing. Nevertheless, we believe that our work may serve as a springboard for improvements in cervical cancer screening in Japan. We will be able to recommend the best strategy for cancer screening in Japan when the FCCS study is completed after 3 years.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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