Implementation of primary HPV testing in Japan

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Abstract. Cervical cancer screening has been shifting from primary cytology to primary HPV testing worldwide as primary HPV testing is more sensitive than primary cytology. To the best of our knowledge, the current study is the first in Japan to examine the feasibility of primary HPV testing. One of the disadvantages of this shift is that hrHPV-/≧LSIL/CIN2+ (high-risk HPV negative cancers or pre-cancerous lesions with abnormal cytology results) can be missed. The objectives of the present study are to clarify in detail CIN2+ missed by this shift and to evaluate the feasibility of primary HPV testing in Japan. Data from 115,273 women who underwent co-testing with cytology and HPV testing in cancer screening were used in the current study. The cases with hrHPV-/≧LSIL ('hrHPV-/≧L-SIL' include CIN2-, in contrast, 'hrHPV-/≧L-SIL/CIN2+' doesn't include CIN2-) were analysed in detail. Women with hrHPV-/≧LSIL comprised 0.3% of the total. The prevalence of CIN2, CIN3, SCC or cervical adenocarcinomas in the lesions with HPV-/≧LSIL was 0.03% in the cancer screening group. Only one case of 14 cervical adenocarcinomas in ≧LSIL was hrHPV-. The prevalence of cancer missed by the shift in patients >50 years of age was significantly higher compared with patients younger than 49 years. In conclusion, the prevalence of CIN2+, which might be missed by the shift from primary cytology to primary HPV testing, was remarkably low in this Japanese cancer screening. The data indicated that primary HPV testing, which was more sensitive for CIN2+ than primary cytology, was a feasible method that can be used in Japan. In particular, primary HPV testing should be introduced for women <50 years old.

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Introduction

In 2018, uterine cervical cancer ranked third in both estimated new cases and deaths in females in the world (1). The estimated age-standardized incidence rate in Eastern Asia, including Japan, is higher than that in North America (2). The high incidence rate of cervical cancer is a crucial public health problem for women in Japan. The oncogenic mechanisms of cervical cancer are well known. Almost all cervical cancers are associated with a persistent infection with human papillomavirus (HPV). Therefore, the WHO states that actions such as vaccination against HPV, screening and treatment of pre-cancer, early detection and prompt treatment of early invasive cancers and palliative care must be embedded in health systems aimed at delivering universal health coverage and that now is the time for global elimination. (https://www.who.int/cancer/cervical-cancer) The preventive actions of this strategy are two-fold. One is the vaccination against HPV infection as a primary prevention. The other is cancer screening for early detection as secondary prevention. Unfortunately, in Japan, the HPV vaccination rate is only 1% because the Japanese Ministry of Health, Labor and Welfare has suspended proactive recommendations for the HPV vaccination programme (3). Thus, to prevent cervical cancer in Japanese women, cancer screening has played an important role.

Three programmes for cervical cancer screening have been recommended worldwide: Primary cytology, co-testing

with cytology and HPV test (co-testing), and primary HPV testing (4). Cancer screening has shifted from primary cytology to co-testing or primary HPV testing (5). The cancer screening environment is different in different countries. Each country has chosen the programme they feel is optimal by verifying the balance between benefit and harm in each program (5-12). In Japan, hardly any areas have introduced primary HPV testing. Therefore, we must analyse hrHPV-/CIN2+/≧LSIL (high-risk HPV negative cancerous or pre-cancerous lesions with abnormal cytology results) in detail, which are missed by primary HPV testing without cytology. The objective of the present study is to clarify the prevalence and histology of hrHPV-/CIN2+/≧LSIL from a Japanese cancer screening programme and to evaluate the feasibility of primary HPV testing in Japan. This report is the first to study hrHPV-/CIN2+/≧LSIL using big data from 115,273 women who underwent cancer screening.

Table I. The total numbers by age group in 8 regions.

Age group	Number	Rate % (95% CI)
20-24	2,823	2.4
25-29	9,121	7.9
30-34	14,216	12.3
35-39	14,799	12.8
40-44	17,473	15.2
45-49	12,949	11.2
50-54	7,501	6.5
55-59	8,189	7.1
60-	28,202	24.5
Total	115,273	100

CI, confidence interval.

Materials and methods

Population. Data from 115,273 women who underwent cervical cancer screening in eight areas (Hokkaido 16,322; Tochigi 21,338; Chiba 17,292; Fukui 7,573; Tottori 19,664; Saga 3,064; Miyazaki 19,858; Shimane 10,162) in Japan were used for this study. The data of Hokkaido were from 2013. The data of Tochigi and Chiba were from 2012-2014. The data of Fukui were from 2015. The data of Tottori were from 2013-2017. The data of Saga were from 2013. The data of Miyazaki and Shimane were from 2014-2016. We obtained consent from all participants using the opt-out system. All women underwent both cytology and HPV testing. All women were older than 20 years of age. This study was approved by the Ethics Review Board of Fukui University (approval no. 20190094).

Cytology. In cytological samples, 25.6% were analysed using conventional cytology, and 74.4% were analysed using liquid-based cytology. The cytologists were blinded to the HPV results and reported their results using the Bethesda 2001 System (13). In this study, LSIL (low-grade squamous intraepithelial lesion) or worse, which indicated the need to undergo colposcopy, were defined as abnormal cytology results.

HPV testing. In the HPV test, 59.6% used Hybrid Capture 2 (HC2; Qiagen Inc.), and 40.4% used Cobas HPV (Roche). HC2 can detect 13 different oncogenic HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (14). Cobas HPV can be detected in three separate channels: HPV16 individually, HPV18 individually, and a pool of 12 other HPV genotypes: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (14). Negative results for the HC2 test or Cobas HPV test were treated as hrHPV-(negative high-risk HPV) in this study.

Data analysis. The data collected by co-testing were simulated as a model for the primary HPV test. The confidence interval was calculated at 95%. The difference in the prevalence of cancer with hrHPV-/≧LSIL between less than 49 and more than 50 was analysed using the Fisher's test. In the discussion, the difference between other studies and our study was also analysed using the Fisher's test. P-values <0.01 were considered to indicate a statistically significant difference. We used Bell Curve for Excel (v3.20) for all analyses.

Results

Results by age group in 8 regions. We analysed the 115,273 women who underwent cervical cancer screening by the government programme in 8 regions. The highest rate was 24.5%, which was observed in women older than 60 years. The lowest rate was 2.4% in women 20-24 years old. Overall, a mountain-shaped curve was observed, with a peak in women 40-44 years old. There was no significant difference in the population ratio among age groups (Table I).

The distribution of cytology results by HPV status. We found that the percentage of women with hrHPV+ (positive high-risk HPV) was 7.4%, whereas the percentage of women with hrHPV- was 92.6%. Table II shows the women with hrHPV-/≧LSIL were found in only 0.3%. Moreover, in the women with ≧LSIL, the prevalence of hrHPV- was 12.0% (298/2,491). Table II indicates that the number of women with hrHPV-/≧LSIL who were missed by the primary HPV test was extremely low (Table II).

The distribution of pathological results in women with hrHPV-/≧LSIL. In 298 cases, 255 cases could be analysed and 43 cases could be not analysed (36 cases of no biopsy and seven cases of inadequate biopsy). Approximately half of the women with hrHPV-/≧LSIL had no lesions according to the pathological results. No lesions or CIN1, which did not require treatment or additional examination, were found in 81.17% (207/255) of women. CIN2, CIN3 or SCC were found in 14.90% (38/255). Cervical adenocarcinoma was found in 0.39% (1/255). Only one case of 14 cervical adenocarcinomas with ≧LSIL was hrHPV-. Nine cases of endometrial adenocarcinomas were found. Although we were concerned regarding the difficulty of detecting cervical adenocarcinoma by primary HPV test, our results suggested that the frequency of cervical adenocarcinoma missed by the primary HPV test was much lower than expected (Table III).

Table II. The distribution of cytology results by HPV status.

	HPV-positive		HPV-negative	
Cytology result	Number	Rate % (95% CI)	Number	Rate % (95% CI)
NILM	5,232	4.54 (4.42-4.66)	105,590	91.60 (91.44-91.76)
ASC-US	1,085	0.94 (0.89-1.00)	875	0.76 (0.71-0.81)
≧L-SI	2,193	1.90 (1.82-1.98)	298	0.26 (0.23-0.29)
Total	8,510	7.38 (7.23-7.53)	106,763	92.62 (92.47-92.77)

CI, confidence interval; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undermined significance; L-SIL, low grade-squamous intraepithelial lesion.

Table III. The distribution of pathological results in the women with hrHPV-/≧L-SIL.

Feature	hrHPV-/≧L-SIL	Rate (%) (95% CI)
No lesion	127	49.80 (43.71-55.90)
CIN1[a]	80	31.37 (25.71-37.04)
CIN2[b]	21	8.24 (4.77-11.70)
CIN3[c]	16	6.27 (3.18-9.37)
SCC	1	0.39 (-0.89-1.68)
Cervical adenocarcinoma	1	0.39 (-0.89-1.68)
Endometrial adenocarcinoma	9	3.53 (1.08-5.98)
Total	255	100.0

CI, confidence interval; CIN1[a], cervical intraepithelial neoplasia, Grade 1; CIN2[b], cervical intraepithelial neoplasia, Grade 2; CIN3[c], cervical intraepithelial neoplasia, Grade 3; SCC, squamous cell carcinoma; L-SIL, low grade-squamous intraepithelial lesion.

The prevalence of carcinomas by age group in women with hrHPV-/≧L-SIL. Table IV reveals that the prevalence of SCC, cervical adenocarcinoma or endometrial carcinoma in the women with hrHPV-/≧LSIL was 0.0095% (11/115,273) in this study. 9 women had hrHPV-/≧LSIL carcinomas in women 50 years or older and the remaining 2 women had hrHPV-/≧LSIL carcinomas in women younger than 49 years old. The detection rate for carcinomas in women older than 50 years old (0.0205%: 9/43,892) was significantly higher than that in women younger than 49 years old (0.0028%: 2/71,381; P<0.01). However, the reason of the difference is to discover endometrial carcinomas which is advantage as unexpected for cervical cancer screening. 72.7% (8/11) of cancers detected by primary cytology in Japanese cervical cancer screening were endometrial adenocarcinomas of women older than 50 years old (Table IV).

Discussion

Cervical cancer screening has shifted from primary cytology to primary HPV testing in the world (5). In Japan, the Cervical Cancer Screening Program organized by almost all municipalities currently requires primary cytology screening every 2 years for all women over 20 years old (15). The disadvantage of cytology is its low sensitivity for CIN2+. From our data, the sensitivity of this method is 70% (16). No municipalities in Japan have introduced the primary HPV testing because of a lack of Japanese data. This is the first study in Japan to examine the feasibility of the primary HPV testing. Studies on hrHPV-/CIN2+, which cannot be detected by the primary HPV test, are essential to introduce primary HPV testing in Japan. In the Belgian cancer register, the prevalence in hrHPV negative cancers was 14.7% (17). In some literatures, the percentage of hrHPV negative cancers ranges from 7 to 11% (17-19). A previous report from Japan suggested that 1.5% of cervical cancers and 3.8% of CIN2-3 were hrHPV- (20). The prevalence range was wide because the population of each study varied. From this prevalence, we cannot determine whether primary HPV testing is an optimal strategy in Japan. We focused on hrHPV-/≧LSIL /CIN2+, which can be detected by primary cytology and missed by primary HPV testing. We conducted the present study to clarify hrHPV-/≧LSIL/CIN2+ in detail and then evaluate the feasibility of the primary HPV testing in Japan.

In this study, the prevalence of hrHPV-/≧LSIL was 0.26% in the total age groups. We compared the prevalence of hrHPV-/≧LSIL between the ARTISTIC study, which was a large study from the U.K. in the cancer screening population, and our study (20-24). The prevalence in our study (0.26%: 298/115,273) was significantly lower (P<0.01) than that in the ARTISTIC study (1.14%: 209/18386) (23). However, we must consider the possibility that the difference in prevalence was due to age differences (ARTISTIC 20-64 years old vs. Our study 20+ years) (23). Our study was also compared with the ATHENA study, which was a large study from the U.S. in cancer screening population (25-30). In the 30-39-year-old group, the prevalence of negative high-risk HPV with ASC-US+ (ASC-US or worse) in our study (1.15%: 333/29,015) was statistically lower than that in the ATHENA study (4.59%: 562/12,248). (Data

Table IV. The prevalence of carcinomas by age group in the women with hrHPV-/≧L-SIL.

Age	Cervical Ca or adenoca	Endometrial Ca	Total number	Prevalence (%) (95% CI)
20-49	1	1	71,381	0.0028 (-0.0026-0.0082)[a]
50-	1	8	43,892	0.0205 (0.0058-0.0353)
Total	2	9	115,273	0.0095 (0.0034-0.0157)

[a]P<0.01 vs. 50-. HPV, human papillomavirus; CI, confidence interval; L-SIL, low grade-squamous intraepithelial lesion; cervical ca or adenoca, cervical cancer or cervical adenocarcinoma; endometrial Ca, endometrial adenocarcinoma.

not shown) (27). It is necessary to consider the possibility that the difference in the prevalence was due to differences in the distribution by age group. Our results suggested the possibility that the prevalence of hrHPV-/≧LSIL in Japan was extremely lower than that in the U.K. or U.S..

Before we introduce the primary HPV testing in Japan, we need to estimate the proportion of women with hrHPV-/≧LSIL /CIN2+. The prevalence of CIN2, CIN3, SCC or cervical adenocarcinoma in all women was 0.03% (39/115,273) in this study and 0.10% (25/24510) in the ARTISTIC study. The prevalence in Japan was significantly lower than that in the U.K.. The prevalence of CIN2, CIN3, SCC or cervical adenocarcinoma in women with hrHPV-/≧LSIL was 15.3% (39/255) in this study and 8.0% (25/311) in the ARTISTIC study (23). The prevalence in Japan was the same as that in the U.K. (P=0.073). Therefore, our data suggest that primary HPV testing may have the same efficacy in both the U.K. and Japan.

We were concerned with missed hrHPV negative cervical adenocarcinoma by introducing the primary HPV testing because cervical adenocarcinomas increase and has more hrHPV negative cancer than SCC. Cervical adenocarcinomas account for 15-20% of cervical cancers (31). Cervical adenocarcinoma can be divided into nine histological groups (17). The highest prevalent histology (75%) is usual type, and almost all (80-100%) are hrHPV+. The secondary high prevalent histology (8%) is the intestinal type, and almost all (80-100%) are hrHPV+. Other histology (villoglandular, signet ring cell, endometrioid from the squamous columnar junction zone, serous, clear cell, gastric type, mesonephric) accounted for 7% or less. Villoglandular, signet ring cell, endometrioid from the squamous columnar junction zone are hrHPV+. Serous and clear cells comprise approximately 30% of the total. Gastric type and mesonephric are almost all hrHPV negative cancers (17). The prevalence of cervical adenocarcinomas out of the usual type that is missed by the primary HPV testing is quite low. Our data verified that hrHPV negative cervical adenocarcinomas were only one gastric type in cancer screening. We think that concerns over missed cervical adenocarcinoma by primary HPV testing may not be warranted.

The ability to detect endometrial adenocarcinoma has been discovered as an unexpected, major advantage for cervical cancer screening. Although endometrial adenocarcinoma can be missed by primary HPV testing, primary cytology can detect endometrial adenocarcinomas (32). From our data, 3% of women with hrHPV-/≧LSIL were diagnosed with endometrial adenocarcinomas. Moreover, eight of the nine cases of endometrial adenocarcinoma were discovered in women older than 50 years. Therefore, the prevalence (0.0205%: 9/43,892) of hrHPV-/≧LSIL carcinomas in women 50 years or older was significantly higher than that (0.0028%: 2/71,381) in women younger than 49 years old. In Japan, the age range of cervical cancer screening is over 20 years-old without the upper limitation. The results of our study showed that the merit in old age group on cervical cancer screening was the discovery for endometrial adenocarcinoma, which wasn't the primary purpose of cervical cancer screening. Therefore, we recommend the cytology for women older than 50 years old. Our data suggest that primary HPV testing had better be introduced in screenings for women younger than 50 years old.

This study has three limitations. First, we did not consider the vaccination rate. Thus, we are concerned that the introduction of primary HPV testing will increase unnecessary colposcopies because the rate of vaccination in Japan is extremely low. Previous reports have verified that the number of colposcopy procedures increased in unvaccinated individuals compared with vaccinated individuals (33,34). In our next study, we will analyse this issue further. Second, HPV testing was not uniform across all regions. The other, we failed to compare the sensitivity and specificity among primary HPV testing, cytology and co-testing because we didn't have the data about hrHPV+/NILM (Negative for intraepithelial lesion or malignancy). However, some manuscripts have indicate the balance between the sensitivity and the specificity in the primary HPV testing is better than the primary cytology (5,9).

In conclusion, hrHPV-/≧LSIL/CIN2+, which can be detected by primary cytology and are missed by primary HPV testing, were clarified in this study and the prevalence was found to be remarkably low in the cancer screening population in Japan. As in other countries using primary HPV testing, it was speculated that the merits were greater than the disadvantages caused by the shift from primary cytology to primary HPV testing. Therefore, our data indicated that primary HPV testing, which was more sensitive for CIN2+ than primary cytology (5), was the feasible method in Japan. Our suggestion was extremely similar with the suggestion in the previous manuscript, which suggested that the fact that there are HPV negative cancers should not undermine all ideas regarding primary HPV screening (17). The difference between primary HPV testing and co-testing in detecting CIN2+ is remarkably small and both of modalities would be effective as a cervical cancer screening program. However, in the setting where medical resource is limited, primary HPV screening should be preferable from the viewpoint of cost-effectiveness. In Japan, Minister of Health, Labour and Welfare announce the guidelines for cervical cancer screening, but actual screening

program is decided and performed by each municipality. We might recommend to each municipality that primary HPV testing would be chosen according to their financial status. In particular, our result in Table IV showed that women younger than 50 years old had little disadvantage by the shift from primary cytology to primary HPV testing because the number of the women with carcinoma missed by the shift was extremely small. However, our study, which focused on the number of the women with carcinoma missed by the shift, failure to evaluate the lower limit of age range because the number of the women younger than 50 years old, who had carcinoma missed by the shift, was extremely small. Therefore we our result suggested primary HPV testing should be recommended in women younger than 50 years old. A randomized trial should be conducted in the future to compare primary cytology and primary HPV testing and to suggest an adequate algorism and the follow-up system in Japan.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TK and MS were responsible for the organization and coordination of the study. TK was the chief investigator and also responsible for the data analysis. YY, OI, TO, TK, MH, HFujit, HFujiw, MY, NS, JK and MS developed the study design. All authors contributed to the writing of the final manuscript. All members of the study contributed to the management or administration of the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current study was approved by the Ethics Review Board of Fukui University (approval no. 20190094).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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