Received: 4 April 2018 | Accepted: 6 April 2018

DOI: 10.1111/cas.13608

ORIGINAL ARTICLE

WILEY Cancer Science

Comparison of human papillomavirus genotyping and cytology triage, COMPACT Study: Design, methods and baseline results in 14 642 women

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Although cytology-based screening programs have significantly reduced mortality and morbidity from cervical cancer, the global consensus is that primary human papillomavirus (HPV) testing for cervical screening increases detection of high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer. However, the optimal triage strategy for HPV-positive women to avoid over-referral to colposcopy may be setting specific. As Japan requires data that have been generated domestically to modify screening guidelines, we conducted a 3-year prospective study, COMparison of HPV genotyping And Cytology Triage (COMPACT), to evaluate the potential role of HPV16/18 partial genotyping and cytology for primary HPV screening. In total, 14 642 women aged 20 to 69 years undergoing routine screening at 3 centers in Hokkaido were enrolled.

Abbreviations: AIS, adenocarcinoma in situ; ASC-US, abnormal squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; COMPACT, COMparison of HPV genotyping And Cytology Triage; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical carcinoma; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; MHLW, Ministry of Health Labour and Welfare; NILM, negative for intraepithelial lesions or malignancy; PPV, positive predictive value; RCT, randomized control trial; SCC, squamous cell carcinoma.

UMIN Clinical Trials Registry (UMIN000013203)

Conventional cytology and HPV testing were carried out. Women with abnormal cytology or HPV16/18 positivity underwent colposcopy. Those with 12 other high-risk (hr) HPV types underwent repeat cytology after 6 months. Primary study endpoints were detection of high-grade cervical disease defined as CIN2/CIN3 or greater as determined by consensus pathology. Prevalence of cytological abnormalities was 2.4%. hrHPV, HPV 16, and HPV 18 were detected in 4.6%, 0.9%, and 0.3% of women, respectively. HPV16/18 were detected in all (8/8) invasive cervical cancers and in all (2/2) adenocarcinomas in situ. Both cytological abnormalities and hrHPV positivity declined with increasing age. This is the first Japanese study to investigate the role of partial genotyping and cytology in an HPV-based screening program. Results should help policy-makers develop guidelines for future cervical screening programs and management of cervical abnormalities based on HPV genotype.

KEYWORDS
cervical cancer screening, COMPACT Study, human papillomavirus deoxyribonucleic acid testing, partial genotyping, triage

1 | INTRODUCTION

Over the past 50 years, cytology-based screening programs have significantly reduced mortality and morbidity from cervical cancer.[1] However, even in countries with organized screening programs, cervical cancer remains a significant cause of morbidity and mortality. One important limitation of cytology is the low sensitivity of a single screen. Consequently, women must attend for repeated screens to achieve acceptable sensitivity. Furthermore, in vaccinated cohorts, the prevalence of cervical abnormalities will decrease, lowering the PPV of cytology-based testing which will, in turn, affect cytotechnician training and quality assurance in a vaccinated population.[2,3]

Almost all high-grade CIN grades 2 and 3, AIS and ICC are caused by persistent infection with 1 of 14 hrHPV.[4] Increased understanding of the natural history of cervical cancer, and the essential role of HPV, has prompted many countries to move towards a screening program which uses molecular testing for hrHPV alone as the primary screening test or, less common, an HPV test combined with cytology (co-testing). The Netherlands, for example, began 5-yearly primary hrHPV screening in January 2017, Australia will follow in December 2017, and the UK and New Zealand from 2018.[5-7]

Pooled data from 4 European RCT of primary HPV screening showed that, overall, women who were randomized to HPV screening were at a significantly decreased risk of ICC than women in the cytology control arms.[8] However, compared to cytology, concerns have been expressed about the lower specificity of hrHPV testing as a primary screening tool, which may result in increased colposcopy referrals and overdiagnosis and/or overtreatment of regressive CIN2 lesions in women <30 years.[9] It is, however, also known that in hrHPV-positive women, the risk for CIN2 + lesions and ICC is not the same for all HPV types. One US study showed that women positive for HPV 16 were at the highest risk for CIN3 + in both the short and longer term and the risk was also higher for HPV 18, albeit not as high as HPV 16.[10] Similar results were also found in a Japanese longitudinal study.[11] Therefore, to investigate the possible role of HPV16/18 partial genotyping triage in primary HPV screening, 2 large clinical trials, the ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial in the USA[12] and the COMPASS (Randomized Controlled Trial of Primary HPV Testing for Cervical Screening in Australia) trial in Australia were implemented.[13]

In Japan, the overall incidence of cervical cancer decreased between 1975 and 2011. However, there was a 4.4% annual percentage increase in incidence in women aged 15-39 years between 1994 and 2011 and a 1.9% increase in mortality rates between 1994 and 2014 in the same age group.[14] One reason for this may be earlier age at sexual debut combined with low participation in cervical screening (between 20% and 40%), especially in women of reproductive age.[14] Biennial screening using cytology began in the 1960s. Although it is still used as the primary screening method, HPV testing to triage ASC-US was introduced in 2011.[15] Despite this, LBC use is not widespread and women must often be recalled to give another sample if they had an abnormal Pap smear. This, combined with the fact that there is no national call-recall system, results in many women at higher risk for cervical cancer or cervical precancers being lost to follow up. Given this situation, it is essential that when women do attend for screening, they undergo as accurate a screening test as possible so that those most at risk can be identified, triaged, and followed up as appropriate.

As the Japanese MHLW requires data that have been generated within Japan to modify national screening guidelines, we conducted a 3-year prospective study, COMPACT, to evaluate the potential role of HPV16/18 partial genotyping and cytology for primary HPV cervical cancer screening. Here we present the study protocol and

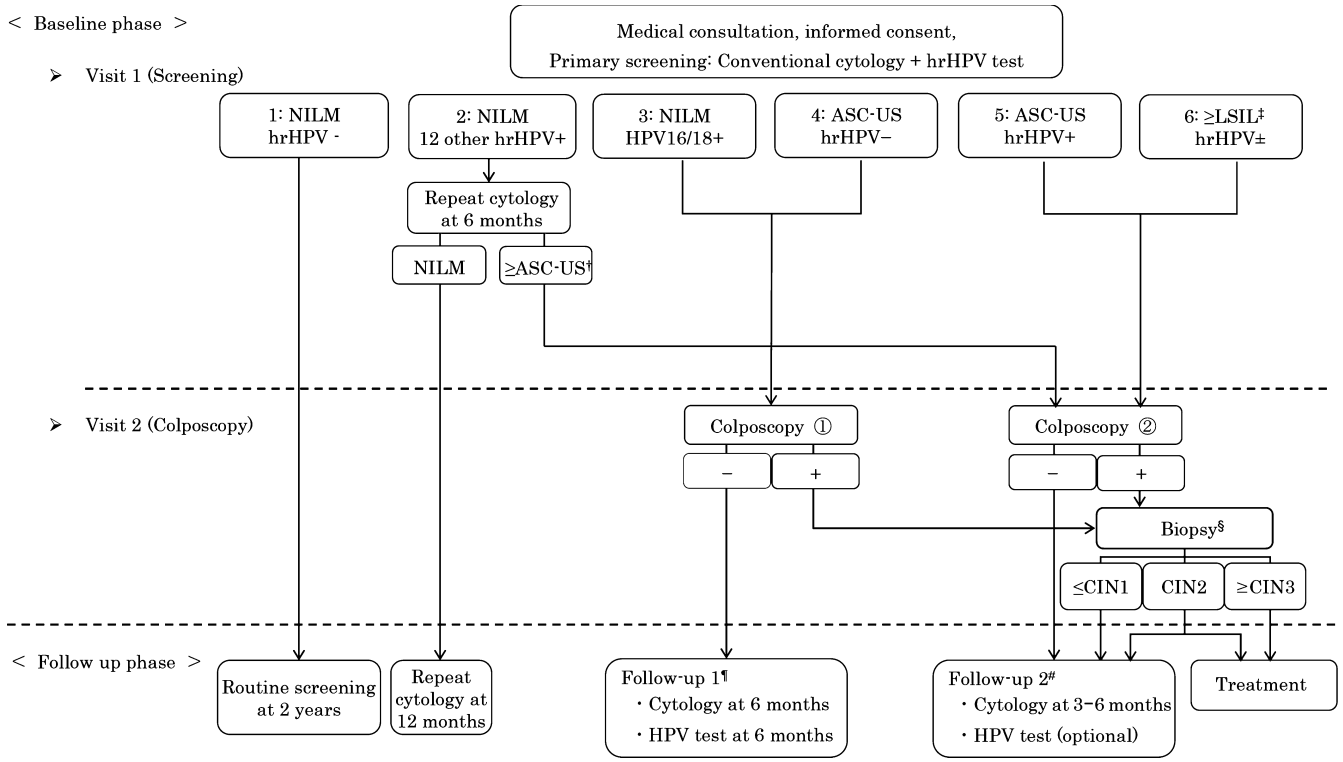

FIGURE 1 AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, cannot rule out HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; hrHPV, high risk human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancy; SCC, squamous cell carcinoma. †≥ASC-US includes: ASC-US, LSIL, ASC-H, HSIL, AGC, AIS, SCC and adenocarcinoma; ‡≥LSIL includes: LSIL, ASC-H, HSIL, AGC, AIS, SCC and adenocarcinoma; §≤CIN1 includes within normal limits and CIN1, Women with CIN2 or greater were managed according to standard CIN guidelines of the Japan Association of Obstetrics and Gynecology (JAOG) and standard of care at each clinical site taking into consideration the patient's HPV status and age, ≥CIN3 includes: CIN3, AIS, SCC and adenocarcinoma; ¶See manuscript about selection of women who proceeded to follow-up 1; #See manuscript about selection of women who proceeded to follow-up 2. In this category, during the follow-up phase, HPV testing was performed at intervals determined according to age, HPV status, and colposcopy result.

baseline characteristics of the study population, including hrHPV prevalence, cytology results and cervical disease status by age and HPV status.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was conducted in 2 phases: a baseline (cross-sectional) phase and a 3-year follow-up (longitudinal) phase. The follow-up phase was completed in March 2018. The study was approved by the institutional review board for clinical trials at Hokkaido University (ID-013-0364) and Hokkaido Cancer Society (ID-12-01-001). It is registered at UMIN Clinical Trials Registry (UMIN000013203). HPV testing (when not provided by the local government), follow-up cytology, colposcopy and pathology were provided free of charge. Women were also given a 3000-yen (US$30) gift token to help with travel fees for attending the colposcopy clinic; no other financial incentive was given for participation in the study. Data from the baseline phase, completed in March 2015, are reported here. The study protocol is shown in Figure 1.

2.2 | Study population, cytology and HPV test

Women aged 20-69 years attending for routine cervical screening at Hokkaido Cancer Society in 3 medium to large cities between April 2013 and March 2014 were eligible for the study. The screening centers were in Sapporo (center 1), which has a population of 2 million people and is the largest city in Hokkaido; Asahikawa (center 2) which has a population of 341 000 and is the second largest city in Hokkaido; and Kushiro (center 3), a port city with a population of 173 000 and the largest city in more rural Eastern Hokkaido.

Apart from age, inclusion criteria were as follows: informed consent was given, not pregnant; intact uterus; and willing to undergo colposcopy and/or biopsy within 6 months if required. Women who presented with symptoms for which cervical cancer had to be excluded, currently undergoing treatment for previous cervical precancers or cancer, and attending for follow up for previous low-grade abnormalities were excluded. Conventional cytology took place with a cervical brush. Sample processing and evaluation of cytology were carried out without computerized imaging, according to the same standard procedure at each of the 3 cytology centers of Hokkaido Cancer Society. In brief, the cervical sample was

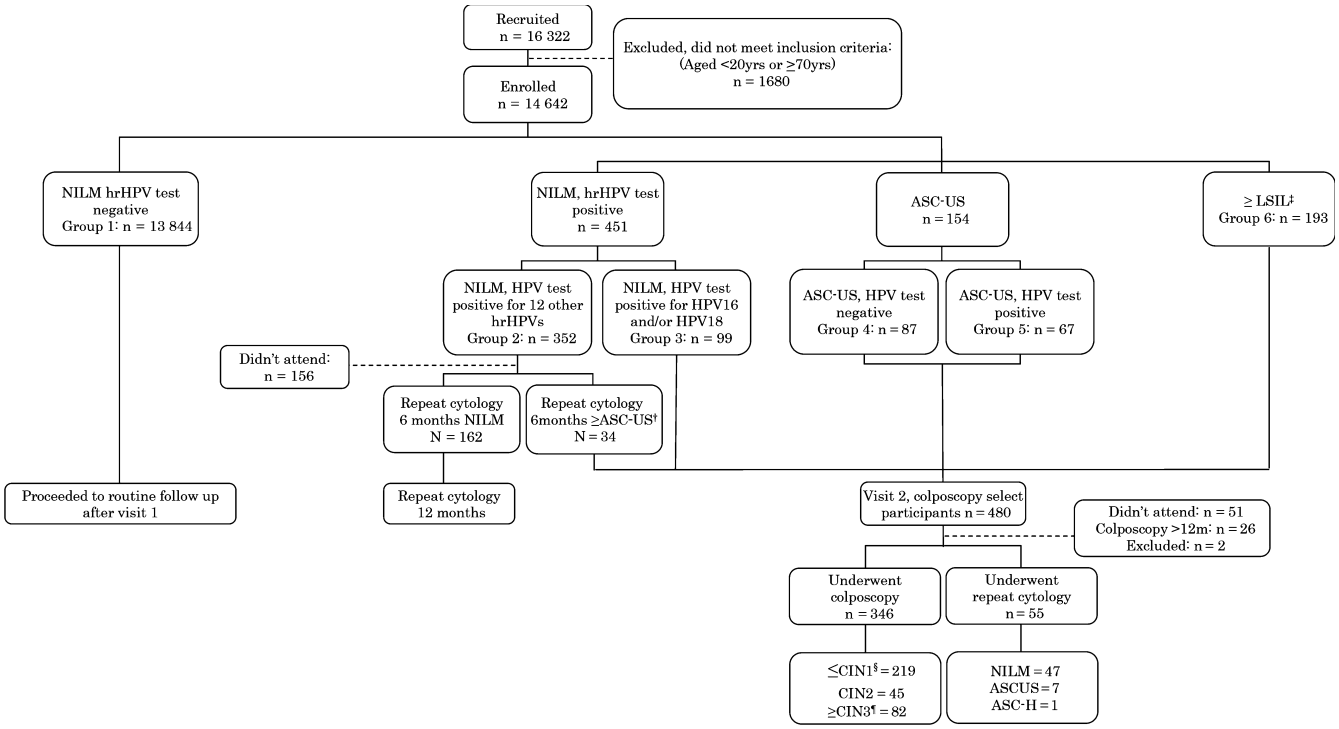

FIGURE 2 AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, cannot rule out HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; hrHPV, high risk human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancy; SCC, squamous cell carcinoma. †≥ASC-US includes: ASC-US, LSIL, ASC-H, HSIL, AGC, AIS, SCC and adenocarcinoma; ‡≥LSIL includes: LSIL, ASC-H, HSIL, AGC, AIS, SCC and adenocarcinoma; §≤CIN1 includes within normal limits and CIN1; ¶≥CIN3 includes: CIN3, AIS, SCC and adenocarcinoma

immediately fixed in 95% ethanol and sent for Papanicolaou staining. Staining and screening took place by a certified cytotechnician at each center and the final classification was made by a supervising medical cytologist. Cytology results were reported in accordance with the 2001 Bethesda system. The HPV test was the Cobas 4800 (Roche Molecular Systems, Pleasanton, CA, USA) which detects HPV16, HPV18, and 12 other pooled hrHPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Primary study endpoint was high-grade cervical disease defined as CIN2 or greater (CIN2, CIN3, AIS and ICC) as determined by 3 pathologists. Reporting of the study endpoints was based on the highest-grade lesion identified by the pathologists during the follow-up phase.

2.3 | Baseline (cross-sectional) phase

2.3.1 | Visit 1 (Enrolment: All participants)

Because this was a study that took place within regular community-based screening, available demographics on the participants were limited. Information used for screening such as age, menopausal status, previous history of cervical disease and HPV vaccination status was obtained. Smoking history could only be ascertained for those participants also undergoing lung cancer screening and was not reliable, as younger women were less likely to be included. Furthermore, these data were available from only 1 of the 3 screening centers. Consequently, smoking status is not reported in the present study. Therefore, after obtaining written informed consent, a speculum examination was carried out and 2 cervical samples were collected using a cervical brush according to the manufacturer's instructions; 1 for conventional cytology and the other for hrHPV testing.

Based on cytology and HPV test results, all eligible women were then classified into 6 groups as shown in Figures 1 and 2. In brief, group 1 (n = 13 844) included women with NILM cervical cytology and a negative HPV test; group 2 (n = 352) included women with NILM cervical cytology but positive for 1 or more of the 12 other pooled hrHPV types; group 3 (n = 99) included women with NILM cervical cytology but HPV 16 and/or 18 positive; group 4 (n = 87) included women with ASC-US cervical cytology and a negative HPV test; group 5 (n = 67) included women with ASC-US cervical cytology and a positive HPV test; and group 6 (n = 193) included women with LSIL or greater cervical cytology, irrespective of the HPV test result.

Women with NILM cervical cytology and a negative hrHPV result (group 1) were assigned to routine screening in 2 years. Those who had NILM cervical cytology, but were positive for 1 or more of the other pooled hrHPV types (group 2) underwent repeat cytology after 6 months. Of these women, those who were cytology positive after 6 months were assigned to either group 5 or group 6 depending on the cytology results.

2.3.2 | Visit 2 (Colposcopy: Select participants)

Women with NILM cervical cytology and a positive HPV 16 and/or 18 test result (group 3) or women with a positive cytology result (ASC-US or greater), irrespective of HPV test result (groups 4, 5 and 6) were referred for a 2nd-visit colposcopy. Biopsies were taken only in women with abnormal colposcopy findings. For ethical reasons, a subset of women who were cytology negative, HPV negative was not randomly sent to colposcopy. Women whose biopsy results did not reach the study endpoint of CIN3 or greater, as well as those without biopsy, were eligible for the follow-up phase of the study. Women with histologically confirmed CIN3 or greater were excluded from the follow-up phase of the study. They were managed according to standard CIN guidelines of the Japan Association of Obstetrics and Gynecology (JAOG) and standard of care at each clinical site taking into consideration the patient's HPV status and age. In Japan, it is standard practice to follow up CIN2 lesions; treatment for CIN2 under specific conditions is optional.

2.4 | Follow-up phase (3-year longitudinal follow up)

Women who underwent colposcopy but did not meet the primary endpoint of CIN3 or greater were enrolled in the 3-year follow-up phase of the study. In follow-up 1, participants underwent repeat cytology and HPV testing every 6 months. Follow-up 1 included those in groups 3 and 4 with negative colposcopy results.

In follow-up 2, participants underwent repeat cytology every 3-6 months and optional HPV testing at given intervals according to age and HPV status. Follow-up 2 included those in group 2 with ASC-US cytology at repeat cytology and those with a negative colposcopy result. It also included those in groups 5 and 6 with a negative colposcopy result, and those who had CIN1 or less confirmed by biopsy regardless of group at the 1st visit. Those who had CIN2 confirmed by biopsy proceeded to follow-up 2 or treatment according to age and HPV status.

Women reaching the primary endpoint of CIN3 or greater were also managed according to standard CIN guidelines of the Japan Association of Obstetrics and Gynecology (JAOG) and standard of care at each clinical site taking into consideration the patient's HPV status and age. The main outcome of the longitudinal phase was cumulative incidence of CIN2/CIN3 or greater in each group.

2.5 | Colposcopy and consensus pathology review

Colposcopy was carried out in women at the 2nd visit according to standard protocol. Of those women who underwent colposcopy, biopsy was taken only in cases with abnormal cervical findings and, if colposcopy was unsatisfactory, a cervical curettage sample was obtained. Histological diagnosis was carried out by 3 pathologists (K.K., T.T. and Y.M.) blinded to all subjects and laboratory information and using standard criteria and CIN terminology. If the diagnosis was concordant between K.K. and T.T., it was recorded as the central pathology review panel diagnosis; if discordant, the biopsy was reviewed by the third study pathologist (Y.M.), and a diagnosis upon which 2 of the 3 pathologists agreed was used as the final diagnosis.

2.6 | Statistical analysis

Prevalence estimates of cytology and HPV were calculated based on all eligible women with valid cytology or HPV test results. The Cochran-Armitage test for trend was carried out to investigate any linear trend in hrHPV prevalence and age, as well as for HPV 16 and HPV 18. *P*-value $<.05$ was considered statistically significant. For cervical disease, screen-detected (verification bias unadjusted) CIN2/3 prevalence was calculated.

3 | RESULTS

3.1 | Baseline characteristics of participants

Baseline characteristics are shown in Table 1. In total, 14 642 women with valid cytology or HPV results consented to participate in the study. Mean age of participants (years) was 50.6 ± 11.1 SD and only 14.5% of participants were 39 years or younger. As public funding for the HPV vaccine was available for women born after 1994 and only 1 participant in the COMPACT study was in this age group, almost all of the participants in the present study had not been vaccinated against HPV (data not shown). Close to half of the participants (47.2%) had reached menopause.

3.2 | Prevalence of cytological abnormalities and hrHPV by age at enrolment

In total, 97.6% of cytology results were classified as NILM at baseline (Table 2). Overall prevalence of ASC-US, LSIL, and HSIL was

TABLE 1 Basic characteristics of participants in the present study

Characteristic (N = 14 642)	Mean ± SD	n (%)
Age (y)	50.6 ± 11.1	
20-29		439 (3.0)
30-39		1690 (11.5)
40-49		4594 (31.4)
50-59		3879 (26.5)
60-69		4040 (27.6)
Screening center		
Center 1		7927 (54.1)
Center 2		4803 (32.8)
Center 3		1912 (13.1)
Menopausal status		
Premenopausal		7371 (50.3)
Postmenopausal		6917 (47.2)
Unknown		354 (2.4)

TABLE 2 Distribution of cytology results by age group

Cytology	Total (n = 14 642) n (%)	Age group (y)				
		20-29 (n = 439) n (%)	30-39 (n = 1690) n (%)	40-49 (n = 4594) n (%)	50-59 (n = 3879) n (%)	60-69 (n = 4040) n (%)
NILM	14 295 (97.6)	403 (91.8)	1617 (95.7)	4438 (96.6)	3825 (98.6)	4012 (99.3)
ASC-US	154 (1.1)	19 (4.3)	23 (1.4)	66 (1.4)	33 (0.9)	13 (0.3)
ASC-H	25 (0.2)	2 (0.5)	5 (0.3)	10 (0.2)	4 (0.1)	4 (0.1)
LSIL	93 (0.6)	11 (2.5)	24 (1.4)	50 (1.1)	5 (0.1)	3 (0.1)
HSIL	66 (0.5)	4 (0.9)	18 (1.1)	28 (0.6)	11 (0.3)	5 (0.1)
AGC	6 (0.0)	0 (0.0)	2 (0.1)	2 (0.0)	0 (0.0)	2 (0.0)
AGC favor neoplastic	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
SCC	2 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot rule out HSIL; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancies; SCC, squamous cell carcinoma.
AGC includes: AGC endocervical, AGC endometrial, and AGC not otherwise specified.
AGC favor neoplastic includes: AGC endocervical, favor neoplastic, and AGC favor neoplastic.

1.1%, 0.6%, and 0.5%, respectively. Prevalence of cytological abnormalities, particularly low-grade lesions, decreased with increasing age. ASC-US or worse cytology was highest at 8.2% for women in their twenties compared to 3.4% for women in their forties and 0.7% for women in their sixties. Prevalence of hrHPV (14 types) by institution is shown in Table 3. As with abnormal cytology, the prevalence of hrHPV infection also decreased significantly with increasing age. At enrolment, hrHPV was detected in 16.2% of women 20-29 years of age, but by age 40-49 years, the prevalence of hrHPV had decreased to only 5.2%, and for women aged 60-69 years it was 2.7% (P for trend = .003). Similar reductions in prevalence with increasing age were also observed for both HPV 16 and HPV 18. For HPV 16, prevalence was 4.6%, 0.9% and 0.5% (P for trend = .003) for women aged 20-29 years, 40-49 years and 60-69 years, respectively; for HPV 18, it was 1.4%, 0.3% and 0.1% (P for trend <.001), respectively.

3.3 | Confirmed cervical disease at baseline

Of the 480 women referred for colposcopy at baseline, 346 (72.1%) underwent colposcopy and 55 (11.5%) underwent repeat cytology. Of those women who underwent colposcopy, 133 (38.4%) were within normal limits (WNL). Biopsy-confirmed cervical disease (consensus pathology) at baseline decreased with increasing age, 78.1% in women aged 20-29 years compared to 45.5% for women in their sixties (Table 4). Prevalence of moderate to high-grade disease (CIN2 +) in women who underwent colposcopy was highest in women of reproductive age, at 43.8% and 44.8% in women aged 20-29 years and 30-39 years, respectively. However, high-grade disease CIN3 + was highest (29.0%) in women aged 40-49 years. Overall crude population prevalence of CIN is shown in Table 5. It was highest in the 20-29-year age group at 2.3% but decreased from 0.8% in women aged 30-39 years to 0.1% in women aged 50 years and over.

3.4 | Cervical disease by age and hrHPV test results

Cervical disease by age and hrHPV test results (hrHPV positive, HPV 16 positive, HPV 18 positive, HPV 16 and/or 18 positive) are shown in Table 6. Proportion of women positive for hrHPV (1 or more of 14 types) increased with severity of cervical lesions. HrHPV was identified in 82.6% of women with CIN1, in 88.9% of women with CIN2, and in 90.3% of women with CIN3. In addition, all women (100%) with a diagnosis of AIS or invasive cervical cancer were hrHPV positive. Of these, all cases (100%) of AIS and invasive cervical cancer were either HPV 16 and/or 18 positive. Although there were no invasive cervical cancers in women aged 20-29 years, HPV 16 was also detected in 3 out of 4 (75%) cases of CIN3. Together, HPV 16 and 18 contributed to 44.7% and 45.8% of overall CIN2 and CIN3 cases, respectively.

4 | DISCUSSION

One important limitation of a cytology-based screening program is the low sensitivity of a single screen. Japan has no national, population-based cervical call-recall screening program and secondary prevention has not been given high priority in the National Cancer Control Plan. Screening activities are financed by each municipality (within each of the 47 prefectures) and screening programs are poorly developed because municipalities have allocated relatively small budgets for disease prevention. Although the central government, through the Ministry of Finance, controls fund allocation for health, large discrepancies exist in cancer control activities between prefectures and between municipalities within the same prefecture.[14] These discrepancies include, among other things, the establishment of a call-recall system, reflected in the fact that only 5% of local governments have organized call-recall cervical cancer screening programs and the use of LBC within the screening program

TABLE 3 Distribution of hrHPV type by age group

	Overall				Center 1				Center 2				Center 3			
		No. women HPV positive, n (%)				No. women HPV positive, n (%)				No. women HPV positive, n (%)				No. women HPV positive, n (%)		
	N	hrHPV[a] n (%)	HPV16 n (%)	HPV18 n (%)	N	hrHPV n (%)	HPV16 n (%)	HPV18 n (%)	N	hrHPV n (%)	HPV16 n (%)	HPV18 n (%)	N	hrHPV n (%)	HPV16 n (%)	HPV18 n (%)
20-29	439	71 (16.2)	20 (4.6)	6 (1.4)	246	46 (18.7)	13 (5.3)	4 (1.6)	112	16 (14.3)	5 (4.5)	2 (1.8)	81	9 (11.1)	2 (2.5)	0 (0.0)
30-39	1690	149 (8.8)	36 (2.1)	13 (0.8)	946	98 (10.4)	25 (2.6)	7 (0.7)	423	27 (6.4)	7 (1.7)	4 (0.9)	321	24 (7.5)	4 (1.2)	2 (0.6)
40-49	4594	239 (5.2)	43 (0.9)	13 (0.3)	2698	150 (5.6)	23 (0.9)	9 (0.3)	1245	54 (4.3)	12 (1.0)	2 (0.2)	651	35 (5.4)	8 (1.2)	2 (0.3)
50-59	3879	101 (2.6)	15 (0.4)	2 (0.1)	2044	63 (3.1)	7 (0.3)	1 (0.0)	1387	26 (1.9)	7 (0.5)	1 (0.1)	448	12 (2.7)	1 (0.2)	0 (0.0)
60-69	4040	110 (2.7)	21 (0.5)	6 (0.1)	1993	57 (2.9)	13 (0.7)	5 (0.3)	1636	34 (2.1)	7 (0.4)	0 (0.0)	411	19 (4.6)	1 (0.2)	1 (0.2)
Overall	14 642	670 (4.6)	135 (0.9)	40 (0.3)	7927	414 (5.2)	81 (1.0)	26 (0.3)	4803	157 (3.3)	38 (0.8)	9 (0.2)	1912	99 (5.2)	16 (0.8)	5 (0.3)
P for trend		.003	.003	<.001		.003	<.001	<.001		<.001	<.001	<.001		.002	.01	.40

[a]Positive for 1 or more of 14 high-risk HPV genotypes.
hrHPV, high-risk human papillomavirus.

varies widely. Screening coverage is also poor, particularly in women of reproductive age. The reasons for this are complex and include: no education about cervical cancer in school or university; no general practitioner system where women can be advised on health interventions according to their life stage; and the fact that screening is done at a gynecologist's clinic. As most women see a gynecologist only when they are pregnant, stigma can be attached to a young single woman going there, particularly in more rural areas. Given this situation, when women do attend for screening, it is essential that they undergo as accurate a screening test as possible so that those most at risk can be identified, triaged and followed up as appropriate. To try and identify the best strategy to achieve this, combined with the fact that the MHLW requires data that have been generated within Japan to modify national screening guidelines, we carried out a 3-year prospective study, COMPACT, to compare HPV16/18 partial genotyping and cytology for primary HPV cervical cancer screening. Here we present the baseline characteristics of the study population.

Mean age of women in the present study is considerably higher than in the ATHENA study[12] (50.6 ± 11.1 years vs 39.8 ± 12.3 years); however, it is only slightly higher than an ongoing Japanese population-based screening trial, CITRUS, which is comparing cytology alone with HPV and cytology co-testing.[16] The latter used both a hospital-based and local government-run screening program and the mean age was 44.3 ± 3.7 years. This higher mean age is representative of women undergoing cervical screening in Japan as there is no cut-off age for cervical screening. Furthermore, women who attend local government screening programs tend to be those who do not qualify for workplace screening programs and therefore may either be retired or women who have gone back to work part-time once their children reach a certain age.

The overall rate of cytological abnormalities (ASC-US or worse) was 2.4%; of these, 1.1% was ASC-US. These results are similar to the CITRUS study where 2.2% were ASC-US or more and, of these, 1.3% were ASC-US.[16] Our results are also comparable with cytology results for the Japanese local government population-based screening programs reported by the Regional Public Health Services and Health Promotion Services.[17]

As a result of the older mean age of participants, the overall prevalence of hrHPV was also considerably lower (4.8%) in the present study compared to the ATHENA study (12.6%) and in CITRUS (11.7%). However, it is similar to a further 2 Japanese studies on co-testing, 1 conducted in the Oyama region of Japan with 11 554 women aged 20-69 years, and the other in Fukui prefecture with 7584 women aged 25-69 years, where the hrHPV prevalence was 5.2% and 6.8%, respectively.[18,19] Recruitment for both the Oyama study and the Fukui study took place at local hospitals and within local government-run programs organized by the Japan Cancer Society. As with the present study, the Fukui study used COBAS 4800 as their HPV test and when they stratified their data by institution, hospital vs Japan Cancer society, hrHPV prevalence was 8.3% and 4.5%, respectively (pers. comm., Dr Tetsuji Kurokawa). Therefore, we believe our results can be generalized to other regions of Japan that

TABLE 4 Biopsy-confirmed cervical disease by consensus pathology in women undergoing colposcopy

		Age group (y)				
Pathology	Overall N (%)	20-29 n (%)	30-39 n (%)	40-49 n (%)	50-59 n (%)	60-69 n (%)
WNL	133 (38.4)	7 (21.9)	24 (30.8)	49 (33.8)	29 (61.7)	24 (54.5)
CIN1	86 (24.9)	11 (34.4)	19 (24.4)	43 (29.7)	7 (14.9)	6 (13.6)
CIN2	45 (13.0)	10 (31.3)	14 (17.9)	11 (7.6)	5 (10.6)	5 (11.4)
CIN3	72 (20.8)	4 (12.5)	20 (25.6)	38 (26.2)	5 (10.6)	5 (11.4)
AIS	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.3)
SCC	4 (1.2)	0 (0.0)	1 (1.3)	2 (1.4)	0 (0.0)	1 (2.3)
Adenocarcinoma	4 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.1)	2 (4.5)
Overall	346	32	78	145	47	44

AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; WNL, within normal limits.

TABLE 5 Overall screened detected prevalence of CIN

	Prevalence, % (95% CI)		
Age group (y)	CIN1	CIN2	≥CIN3[a]
20-29	2.5 (1.0-4.0)	2.3 (0.9-3.7)	0.9 (0.0-1.8)
30-39	1.1 (0.6-1.6)	0.8 (0.4-1.3)	1.2 (0.7-1.8)
40-49	0.9 (0.7-1.2)	0.2 (0.1-0.4)	0.9 (0.6-1.2)
50-59	0.2 (0.0-0.3)	0.1 (0.0-0.2)	0.2 (0.0-0.3)
60-69	0.1 (0.0-0.3)	0.1 (0.0-0.2)	0.2 (0.0-0.4)
Overall	0.5 (0.4-0.7)	0.3 (0.2-0.4)	0.6 (0.4-0.7)

[a]≥CIN3 includes CIN3, adenocarcinoma in situ, squamous cell carcinoma, and adenocarcinoma.
CI, confidence interval; CIN, cervical intraepithelial neoplasia.

use local government-run programs. Although some studies, both in Japan and globally, have shown a bimodal age distribution in HPV prevalence,[20] in line with the ATHENA study we found an age-related linear decrease in hrHPV prevalence. However, around 2.7% of women between 50 and 69 years were still infected with a hrHPV. Given Japan's rapidly aging society, this rate should not be taken lightly.

HPV16/18 was detected in all invasive cancers in the present study, as well as in the 2 (100%) cases of AIS. Except for 1 invasive cancer case, which had 12 other hrHPV coinfections, all these cases had a single HPV16 or HPV18 infection, suggesting a causal role. In women aged 20-29 years, 3 out of 4 cases of CIN3 were positive for HPV 16, and 2 of these were also single infections. These results suggest that the HPV vaccines which protect against hrHPV types 16 and 18 could play a significant role in reducing invasive cervical cancers and precancers in Japan. However, Japanese women have been put at an avoidable future risk of cervical cancer because these vaccines are no longer proactively recommended.[21]

In Japan, cytology remains the primary screening method, with HPV testing for ASC-US triage. Two studies, 1 population based, open-labeled, randomized controlled study, CITRUS,[16] and a nationwide study sponsored by the MHLW[22] are being undertaken to investigate the efficacy of concurrent LBC and HPV-DNA testing (co-testing) vs LBC alone for primary cervical cancer screening. A third study with MHLW funding, the JCHO-HPV study enrolling 20 000 women >20 years and using the Hybrid Capture 2 HPV test (Qiagen, Germantown, MD, USA), which does not allow for partial genotyping, and comparing cytology to HPV co-testing, is also about to start.[23] However, the global consensus is that there is strong and uniform evidence for the efficacy of HPV-based screening, as it allows earlier detection of cervical precancers and is more effective than cytology-based screening because it permits an extension of screening intervals at equal or better safety while reducing harm from too frequent screening.[24,25] Most national and international organizations also agree there is little evidence for the usefulness of adding cytology to primary HPV screening in the form of co-testing. This was reinforced recently by a draft from the US Preventative Task Force (USPTF) also withdrawing its recommendations for HPV and cytology co-testing.[26] What has not been agreed on is, to a lesser extent, screening interval, and the optimal triage strategy for HPV-positive women, a critical component of an HPV-based screening program to avoid referring all HPV-positive women to colposcopy. Several potential options include: cytology, cytology with partial genotyping, biomarkers p16/Ki-67, and DNA methylation.[27-29] However, the screening interval and optimal triage method will depend on perceived risk (among others), screening costs (both of the HPV assays and colposcopy), screening infrastructure and health-care budget. As this is likely to be setting specific, we carried out a 3-year prospective study, COMPACT, to compare the potential role of HPV16/18 partial genotyping and cytology in primary HPV cervical cancer screening in Japan and present the design, method and cross-sectional baseline results.

The present study has several limitations that need to be addressed. First, only screen-detected (verification bias-unadjusted) prevalence estimates of cervical disease were calculated based on women who underwent colposcopy/biopsy. This may have resulted in bias as a sample of women with a negative result

TABLE 6 Grade of cervical disease according to age and hrHPV[a] status

Pathology	Overall	Age group (y)				
		20-29	30-39	40-49	50-59	60-69
hrHPV positive, % (n/N)						
CIN1	82.6 (71/86)	81.8 (9/11)	89.5 (17/19)	79.1 (34/43)	85.7 (6/7)	83.3 (5/6)
CIN2	88.9 (40/45)	90.0 (9/10)	85.7 (12/14)	81.8 (9/11)	100.0 (5/5)	100.0 (5/5)
CIN3	90.3 (65/72)	100.0 (4/4)	100.0 (20/20)	84.2 (32/38)	80.0 (4/5)	100.0 (5/5)
AIS	100.0 (2/2)	0.0 (0/0)	0.0 (0/0)	100.0 (1/1)	0.0 (0/0)	100.0 (1/1)
SCC/adenocarcinoma	100.0 (8/8)	0.0 (0/0)	100.0 (1/1)	100.0 (3/3)	100.0 (1/1)	100.0 (3/3)
HPV16 positive, % (n/N)						
CIN1	19.8 (17/86)	18.2 (2/11)	26.3 (5/19)	16.3 (7/43)	14.3 (1/7)	33.3 (2/6)
CIN2	35.6 (16/45)	40.0 (4/10)	14.3 (2/14)	45.5 (5/11)	20.0 (1/5)	80.0 (4/5)
CIN3	43.1 (31/72)	75.0 (3/4)	60.0 (12/20)	34.2 (13/38)	60.0 (3/5)	0.0 (0/5)
AIS	50.0 (1/2)	0.0 (0/0)	0.0 (0/0)	0.0 (0/1)	0.0 (0/0)	100.0 (1/1)
SCC/adenocarcinoma	50.0 (4/8)	0.0 (0/0)	100.0 (1/1)	33.3 (1/3)	0.0 (0/1)	66.7 (2/3)
HPV18 positive, % (n/N)						
CIN1	10.5 (9/86)	9.0 (1/11)	15.8 (3/19)	9.3 (4/43)	0.0 (0/7)	16.7 (1/6)
CIN2	11.1 (5/45)	20.0 (2/10)	7.1 (1/14)	9.1 (1/11)	20.0 (1/5)	0.0 (0/5)
CIN3	2.8 (2/72)	0.0 (0/4)	10.0 (2/20)	0.0 (0/38)	0.0 (0/5)	0.0 (0/5)
AIS	50.0 (1/2)	0.0 (0/0)	0.0 (0/0)	100.0 (1/1)	0.0 (0/0)	0.0 (0/1)
SCC/adenocarcinoma	50.0 (4/8)	0.0 (0/0)	0.0 (0/1)	66.7 (2/3)	100.0 (1/1)	33.3 (1/3)
HPV16/18 positive, % (n/N)						
CIN1	30.2 (26/86)	27.3 (3/11)	42.1 (8/19)	25.6 (11/43)	14.3 (1/7)	50.0 (3/6)
CIN2	46.7 (21/45)	60.0 (6/10)	21.4 (3/14)	45.5 (5[b]/11)	40.0 (2/5)	80.0 (4/5)
CIN3	45.8 (33/72)	75.0 (3/4)	70.0 (14/20)	34.2 (13/38)	60.0 (3/5)	0.0 (0/5)
AIS	100.0 (2/2)	0.0 (0/0)	0.0 (0/0)	100.0 (1/1)	0.0 (0/0)	100.0 (1/1)
SCC/adenocarcinoma	100.0 (8/8)	0.0 (0/0)	100.0 (1/1)	100.0 (3/3)	100.0 (1/1)	100.0 (3/3)

[a]hrHPV, positive for 1 or more of 14 high-risk HPV genotypes.
[b]One case positive for both HPV16 and HPV18.
AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

were not referred to colposcopy and, of those referred to colposcopy, biopsy was taken only in cases with abnormal findings. However, there is considerable controversy regarding the merits of adjusting for verification bias.[12,30] Not only is it unethical to send low-risk women for an invasive procedure that has the potential to be both mentally and physically traumatic, it has been shown that the proportion of women with a double-negative result (cytology negative, HPV negative) who willingly attend for colposcopy is low and these women are also likely to represent a biased sample.[13] A further limitation of the current study is that almost no women in this study were vaccinated against HPV; therefore, the results of this study will only apply to a non-vaccinated population. Finally, the high mean age of participants meant that the overall hrHPV prevalence was low. However, the rate of reported cytological abnormalities was similar to national Japanese data, suggesting the women in this study were quite representative of Japanese women undergoing cervical screening. Despite these limitations, this is the first Japanese study to investigate the role of HPV partial genotyping and cytology in an HPV-based screening program. The results obtained should be invaluable for Japanese policy-makers and academic organizations developing guidelines for both cervical screening and the management of women with or without cervical abnormalities based on HPV genotype.

ACKNOWLEDGMENTS

The authors would like to thank all the women who participated in the present study.

CONFLICTS OF INTEREST

S.K., S.J.B.H., K.K., T.T., Y.M., A.T., T.S., M.M., Y.K., D.P., and H.W. declare no conflicts of interest. H.F. declares receiving grants from Roche Diagnostics and Qiagen Japan. N.S., M.K., S.T., and S.K. declare receiving grants from Roche Diagnostics. Roche Diagnostics provided the HPV assays, funding for colposcopy when it was not covered by national health insurance and travel compensation for colposcopy. Roche Diagnostics had no role in the data analysis or writing of the study.

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How to cite this article: Aoyama-Kikawa S, Fujita H, Hanley SJB, et al. Comparison of human papillomavirus genotyping and cytology triage, COMPACT Study: Design, methods and baseline results in 14 642 women. *Cancer Sci*. 2018;109:2003–2012. https://doi.org/10.1111/cas.13608