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Original Article

Evaluation of partial genotyping with HPV16/18 for triage of HPV positive, cytology negative women in the COMPACT study

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ABSTRACT

Objective: While cytology-based screening programs have significantly reduced mortality and morbidity from cervical cancer, the global consensus is that primary human papillomavirus (HPV) testing increases detection of high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer. However, the optimal triage strategy for HPV+ women to avoid over-referral to colposcopy may be setting specific. We compared absolute and relative risk (RR) of >CIN2/3 within 12 months of a negative cytologic result in women HPV16/18+ compared to those with a 12-other high-risk HPV (hrHPV) genotype to identify women at greatest risk of high-grade disease and permit less aggressive management of women with other hrHPV infections.
Methods: Participants were 14,160 women aged 25–69 years with negative cytology participating in the COMparison of HPV genotyping And Cytology Triage (COMPACT) study. Women who were HPV16/18+ were referred to colposcopy. Those with a 12-other hrHPV type underwent repeat cytology after 6 months and those with >abnormal squamous cells of undetermined significance went to colposcopy.
Results: Absolute risk of >CIN2 in HPV16/18+ women was 19.5% (95% CI=12.4%–29.4%). In women 25–29 years and HPV16+ it was 40.0% (95% CI=11.8%–76.9%). Absolute risk of >CIN3 in women HPV16/18+ was 11.0% (95% CI=5.9%–19.6%). For women 30–39 years and HPV16+ it was 23.1% (95% CI=5.0%–53.8%). Overall risk of >CIN2, >CIN3 in women with a 12-other hrHPV HPV type was 5.6% (95% CI=3.1%–10.0%) and 3.4% (95% CI=1.6%–7.2%) respectively. RR of >CIN2, >CIN3 in HPV16/18+ vs. 12-other hrHPV was 3.5 (95% CI=1.7–7.3) and 3.3 (95% CI=1.2–8.8), respectively.
Conclusion: Primary HPV screening with HPV16/18 partial genotyping is a promising strategy to identify women at current/future risk of >CIN2 in Japan without over-referral to colposcopy.

Trial Registration: UMIN Clinical Trials Registry Identifier: UMIN000013203

Keywords: Cervical Cancer; Human Papillomavirus; Cytology; Cancer Screening

Trial Registration
UMIN Clinical Trials Registry Identifier: UMIN000013203

Presentation
This manuscript has been presented in part at the IGCS Kyoto, 2018, and the IPVC Sydney, 2018.

Conflict of Interest
SK, SJBH, KK, TT, YM, AT, TS, MM, YK, HW, declare no conflict of interest. HF declares receiving grants from Roche Diagnostics and Qiagen Japan and lecture fees from Roche Diagnostics. NS declares receiving grants and lecture fees from Roche Diagnostics. MK, ST, SK declare receiving grants from Roche Diagnostics. YK declares receiving lecture fees 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 up of the study.

Author Contributions
Conceptualization: N.S.; Data curation: F.H., K.M.; Formal analysis: H.S., A.K.S.; Investigation: T.T., M.Y.; Methodology: N.S.; Project administration: F.H., N.S.; Writing - original draft: H.S.; Writing - review & editing: A.K.S.

INTRODUCTION

Cytology based screening programmes have significantly reduced incidence of and mortality from cervical cancer [1]. Discovery that persistent infection with one or more high-risk human papillomavirus (hrHPV) type was a necessary cause of cervical cancer led to 2 important developments: primary prevention with human papillomavirus (HPV) vaccination and HPV testing to either screen or manage cytology screened positive women. While most countries use HPV testing for the latter, evidence from large-scale clinical trials [2-4] has resulted in many countries transitioning to an HPV primary cervical screening programme [5].

Reasons for a shift to HPV primary screening include: increased efficacy at detecting invasive cervical cancers (ICCs) and pre-cancers; eliminating the ambiguity of equivocal Pap smears such as atypical squamous cells of undetermined significance (ASC-US) [2,3,6]; higher sensitivity which permits longer screening intervals and reduces harm from too frequent screening [7,8]; increased protection against adenocarcinoma [2]; and higher sensitivity compared to Pap smears on self-collected samples [9,10].

While the global consensus is that HPV primary screening is clinically superior, more cost-effective and less burdensome for women than Pap smears, consensus has yet to be reached on the optimal triage strategy for HPV positive women [5]. This is a critical component of an HPV-based screening program to avoid referring all HPV positive women to colposcopy due to the increased sensitivity, but decreased specificity of the test. Several potential strategies include cytology alone; cytology with partial genotyping for HPV16 and HPV18; biomarkers p16/Ki-67; and DNA methylation [11-13]. Optimal triage strategy depends on perceived risk; availability of assays; screening costs; screening infrastructure; and healthcare budget which are all likely to be setting specific. Australia has chosen a partial genotyping strategy where all HPV16 and HPV18 positive women are sent directly to colposcopy, while women positive for other hrHPV types are triaged with cytology. Those with a high-grade squamous intraepithelial lesion are sent to colposcopy and those with a low-grade squamous intraepithelial lesion or less are retested in 12 months [14,15]. The Netherlands sends all hrHPV positive women with ASC-US or worse directly to colposcopy, regardless of hrHPV genotype, and women hrHPV positive, cytology negative are retested in 12 months [5].

In Japan, national screening guidelines are drawn up by the Japanese Advisory Committee on Cancer Screening and implemented by local governments. Current guidelines recommend biennial cervical cancer screening using the Pap smear with reflex HPV testing for ASC-US in women aged ≥20 years. Women who are ASC-US hrHPV positive are referred to colposcopy, while those who are ASC-US hrHPV negative return for retesting in 12 months [16]. In July 2020, the committee published a revised draft version of screening guidelines not yet approved by the Ministry of Health, Labour and Welfare. In these updated guidelines, biennial cytology from 20–69 years is recommended. Physician-sampled primary HPV screening every 5 years at age 30–60 years is also recommended [17]. However, no recommendations have been given for the triage test if a women tests HPV positive.

Prior cross-sectional [18,19] and longitudinal studies [20-22] have demonstrated that hrHPV status is an important predictor of current or future risk of CIN2+, even in women with negative for intraepithelial lesion or malignancy (NILM) cytology. Furthermore, the oncogenic potential of all hrHPV types is not equal [23,24] so referring all hrHPV positive women to colposcopy may results in over diagnosis and treatment of regressive lesions [2].

Since infection with HPV16 and or HPV18 has been shown to confer the greatest short and longer-term risk for CIN2+ [23,24], triaging only those women who are HPV16/18 positive to immediate colposcopy may be one strategy to safely limit hrHPV referrals in an HPV primary screening programme. One previous Japanese study reported the frequency of hrHPV genotype in Japanese women with NILM cytology, but a CIN2/3+ lesion [25]. However, absolute and relative risk (RR) of high-grade disease by age group were not reported. While the global consensus is primary HPV testing should not be used in women under 25 years, for women 25 years or older it is setting specific. In the UK and Australia, for example, primary HPV screening is recommended from the age of 25 years; in the Netherlands it is from the age of 30 years.

Given the paucity of data in Japanese women, we analysed data from 14,160 Japanese women aged 25–69 years with NILM cytology but hrHPV positive who were enrolled in the COMparison of HPV genotyping And Cytology Triage (COMPACT) study and compared absolute and RR of CIN2/3 or worse in women positive for HPV16 and or HPV18 to those positive for one or more 12 other hrHPV genotype (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

MATERIALS AND METHODS

1. Study design

An explanation of the COMPACT study has been reported elsewhere. In brief, 14,642 women 20–69 years undergoing routine screening between April 2013 and March 2017 at 3 centers in northern Japan were enrolled [26]. Conventional cytology and hrHPV testing using Cobas 4800 (Roche Molecular Systems, Pleasanton, CA, USA) were performed. Women with abnormal cytology (ASC-US or worse) or who were HPV16/18 positive, regardless of cytology results, underwent colposcopy. Those with negative for intraepithelial neoplasm or malignancy (NILM) cytology but 12 other hrHPV type positive underwent repeat cytology after 6 months and those with ASC-US or worse were sent to colposcopy. Primary endpoints are high-grade cervical disease (CIN2/3+) determined by consensus pathology. The COMPACT study was conducted in 2 phases (**Fig. 1**), a baseline phase and a 3-year follow-up phase. The present study is a sub-analysis of the baseline phase. The COMPACT 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).

2. Study population, cytology and HPV test

Participants were 14,160 women 25–69 years with NILM cytology at baseline. Inclusion criteria included: age; informed consent; not pregnant; intact uterus; and willing to undergo colposcopy and/or biopsy if required. Women with symptoms where cervical cancer had to be excluded or those undergoing treatment or follow-up for previous cervical pre/cancers were excluded.

Conventional cytology took place with a cervical brush. Sample processing and evaluation of cytology were performed 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 immediately fixed in 95% ethanol and sent for Papanicolaou staining. The final classification was made by a supervising medical cytologist. Cytology results were reported in accordance with the 2001 Bethesda system. HPV test was the Cobas 4800 System (Roche Molecular Diagnostics, Pleasanton, CA, USA), which detects HPV16, HPV18, and 12 other

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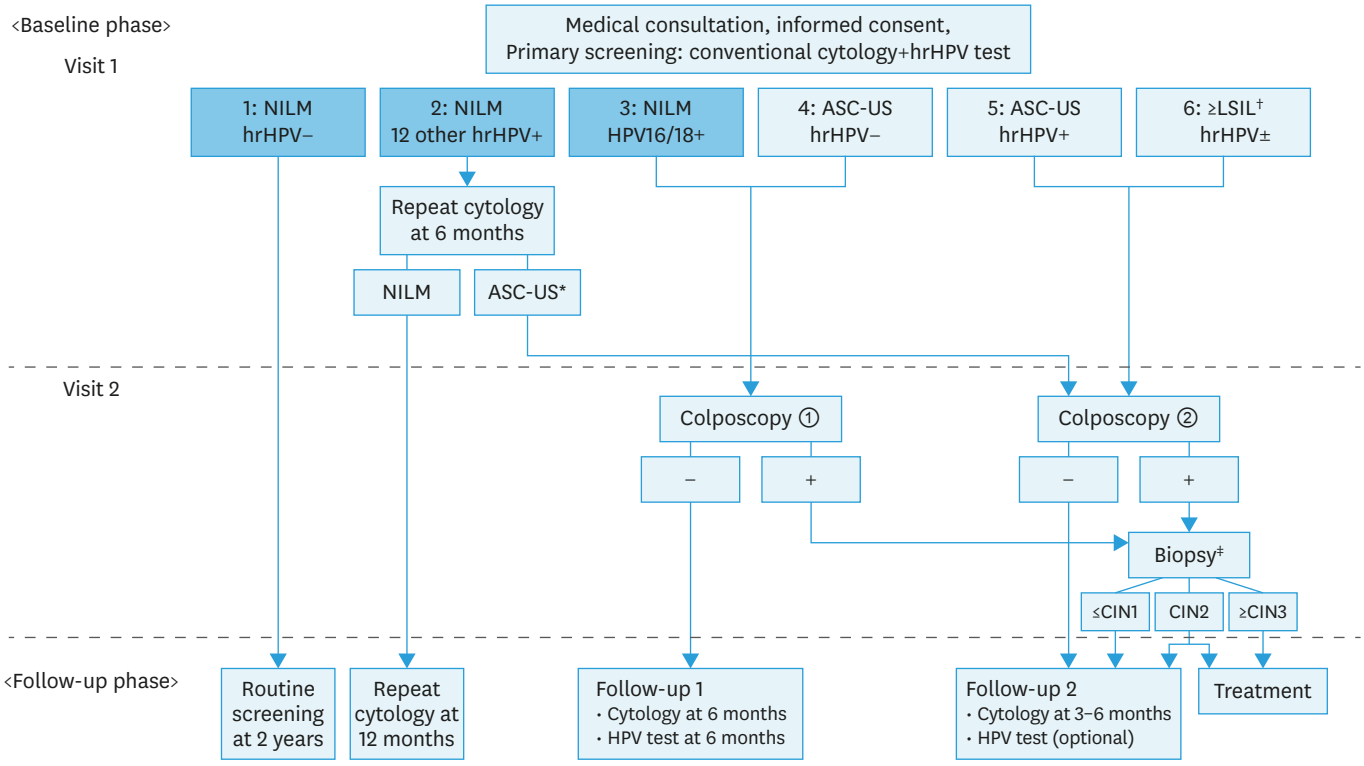

Fig. 1. Study design and protocol used to triage women with NILM cytology at baseline in the COMparison of HPV genotyping And Cytology Triage study.
ASC-US, abnormal squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancy.
*≥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 Japan Association of Obstetrics and Gynecology CIN guidelines and standard of care at each clinical site.

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+ (CIN2, CIN3, adenocarcinoma in situ and ICC) by 3 pathologists. Reporting of study endpoints was based on the highest-grade lesion identified by the pathologists during the follow-up phase.

3. Colposcopy and consensus pathology review

Colposcopy was performed according to standard protocol. Biopsy was only taken in cases with abnormal cervical findings; if colposcopy was unsatisfactory, an endocervical curettage sample was obtained. Histological diagnosis was performed 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.). A diagnosis that 2 of the 3 pathologists agreed on was used as the final diagnosis.

4. Statistical analysis

Data were analysed using IBM SPSS Statistics Version 22.0 (SPSS Inc., Chicago, IL, USA). Absolute risk and RR of high-grade cervical disease with respective 95% confidence intervals (CIs) were calculated in women with NILM cytology for different categories of hrHPV results. HPV results of genotypes 16 and 18 were analysed as individual results and as combined

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16/18 results (genotype 16 and/or 18). Genotype 16 positive results included cases positive for genotype 16 alone, with or without genotype 18, and with or without a 12 other hrHPV type present. Genotype 18 positive results included cases positive for genotype 18 alone, with or without a positive result for a 12 other hrHPV genotype, and cases negative for genotype 16. The 12 other hrHPV positive samples were positive only for these 12 hrHPV types but not HPV16 or HPV18. A p-value of <0.05 was considered statistically significant.

RESULTS

1. Enrolment and demographics

Basic characteristics of participants are shown in **Table 1**. Mean age of participants was 51.1±10.8 years. Totally, 44.6% of participants were ≤49 years and 49.6% were premenopausal. Public funding for the HPV vaccine was only available for women born after 1994. No participant in the present study was in this age group and no one had been vaccinated against HPV (data not shown).

Of the 14,160 women aged 25–69 years, 441 (3.1%) had NILM cytology with a hrHPV infection at baseline (**Fig. 2**). Among these women, 97 (22.0%) were HPV16/18 positive and 344 (78.0%) women were positive for a 12 other hrHPV type that did not include a co-infection with HPV16 and/or HPV18. In the HPV16/18 group, 82 (84.5%) underwent colposcopy and one participant (1%) had repeat cytology performed. In the 12 other group, 192 (55.8%) attended for repeat cytology after 6 months and of these, 33 (17.2%) women had ASC-US cytology. In women with ASC-US cytology, 19 (57.6%) underwent colposcopy, 7 (21.2%) had repeat cytology performed and 7 (21.2%) didn't attend.

2. Prevalence of hrHPV by age

Among the 14,160 women aged 25–69 years with NILM cytology, prevalence of HPV16, HPV18 and 12 other hrHPV types was 0.5%, 0.2%, and 2.4%, respectively. For all categories, overall prevalence of hrHPV decreased with increasing age, except for women aged 60–69 years where a small increase was observed. Prevalence of hrHPV (14 types) was 10.8% in women aged 25–29 years, but 1.9% in women aged 50–59 years and 2.3% in women aged 60–69 years. In the same age groups, for HPV16, it was 2.6%, 0.3%, and 0.4% and for HPV18, it was 1.5%,

Table 1. Basic characteristics of participants with NILM cytology

Characteristics (n=14,160)	Value
Age (yrs)	51.1±10.8
25–29	268 (1.9)
30–39	1,617 (11.4)
40–49	4,438 (31.3)
50–59	3,825 (27.0)
60–69	4,012 (28.3)
Screening center	
Center 1	7,583 (53.6)
Center 2	4,709 (33.3)
Center 3	1,868 (13.2)
Menopausal status	
Premenopausal	7,024 (49.6)
Postmenopausal	6,866 (48.5)
Unknown	270 (1.9)

Data are shown as mean±standard deviation or number (%).
NILM, negative for intraepithelial lesions or malignancy.

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Table 2. Prevalence of hrHPV in women 25 years or older with NILM cytology

Age group (yrs)	HPV test result*					
	Total	hrHPV+	12 other† hrHPV+	HPV16/18+	HPV16+	HPV18+
25–29	268	29 (10.8)	18 (6.7)	11 (4.1)	7 (2.6)	4 (1.5)
30–39	1,617	97 (6.0)	69 (4.3)	28 (1.7)	17 (1.1)	11 (0.7)
40–49	4,438	149 (3.4)	123 (2.8)	26 (0.6)	21 (0.5)	5 (0.1)
50–59	3,825	74 (1.9)	63 (1.6)	11 (0.3)	11 (0.3)	0 (0.0)
60–69	4,012	92 (2.3)	71 (1.8)	21 (0.5)	16 (0.4)	5 (0.1)
Overall	14,160	441 (3.1)	344 (2.4)	97 (0.7)	72 (0.5)	25 (0.2)

Values are presented as number (%).
HPV, human papilloma virus; hrHPV, high-risk human papilloma virus; NILM, negative for intraepithelial lesions or malignancy.
*HPV16+ includes HPV16+, with or without HPV18+, and with or without 12 other hrHPV+ types; HPV18+ includes HPV16−, HPV18+, with or without 12 other hrHPV+ types; 12 other hrHPV+ includes HPV16−, HPV18−, 12 other hrHPV+ types; †12 other hrHPV includes infection with one or more of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

0.0%, and 0.1%, respectively. For women ≥40 years, the prevalence of HPV16/18 was 0.5%, compared to 4.1% in women 25–29 years (**Table 2**).

3. Absolute risk of CIN by hrHPV test result

For ethical reasons, women with NILM cytology and HPV negative were not referred to colposcopy. Therefore, screen-detected (verification bias-unadjusted) prevalence of CIN2/3 was measured. For women with NILM cytology who were hrHPV positive (14 types), estimated overall absolute risk of CIN2+ was 10.0% (95% CI=6.9–14.3) and for CIN3+ it was 5.8% (95% CI=3.1–10.0) (**Fig. 2**).

Overall absolute risk for CIN2+ in women HPV16/18 positive was 19.5% (95% CI=12.4–29.4) versus 5.6% (95% CI=3.1–10.0) in women with a 12 other hrHPV genotype. Having an HPV16 infection conferred the highest absolute risk of CIN2 at 20.0% (95% CI=11.8–31.8). By age group, absolute risk for CIN2+ was highest in women 25–29 years at 40.0% (95% CI=11.8–76.9) with an HPV16 infection. For the 3 categories hrHPV overall, HPV16/18 and 12 other hrHPV type, absolute risk of CIN2+ decreased with age, until the age 60–69 years where the risk began to rise again in women being positive for HPV16 or 18 (**Fig. 2** and **Table 3**).

For CIN3+, absolute risk was 11.0% (95% CI=5.9–19.6) for women HPV16/18 positive compared to only 3.4% (95% CI=1.6–7.2) for women with a 12 other hrHPV genotype. Overall, having an HPV16 infection conferred the highest absolute risk for CIN3+ at 11.7% (95% CI=5.8–22.2). By age group, absolute risk for CIN3+ was highest in women 25–29 years with a 12 other hrHPV genotype at 33% (95% CI=6.2–79.2). In women 30–39 years and 40–49 years, absolute risk was 23.1% (95% CI=5.0–53.8) and 22.2% (95% CI=9.0–45.2), respectively. For women 60–69 years it was 20% (95% CI=3.6–62.5). The correlation between age and absolute risk of CIN3+ in women with NILM cytology who were hrHPV positive was less pronounced compared to CIN2+. The pattern was bimodal, increased risk between the age of 30–49 years, where CIN3 rates peak in Japan, followed by a decrease then a further increase in women >60 years (**Fig. 2** and **Table 3**).

4. RRs of CIN by hrHPV test result

Estimated RR of CIN2+ and CIN3+ by hrHPV status in women 25-69 years with NILM cytology are shown in **Table 4**. RR for CIN2+ was highest in women with an HPV16 infection compared to the 12 other hrHPV genotypes at 3.6 (95% CI=1.6–7.8). For CIN3+ RR was highest in women with an HPV16 infection compared to women infected with the 12 other hrHPV genotypes at 3.5 (95% CI=1.2–9.9). For HPV18, the risk of CIN3 was 2.7 times higher

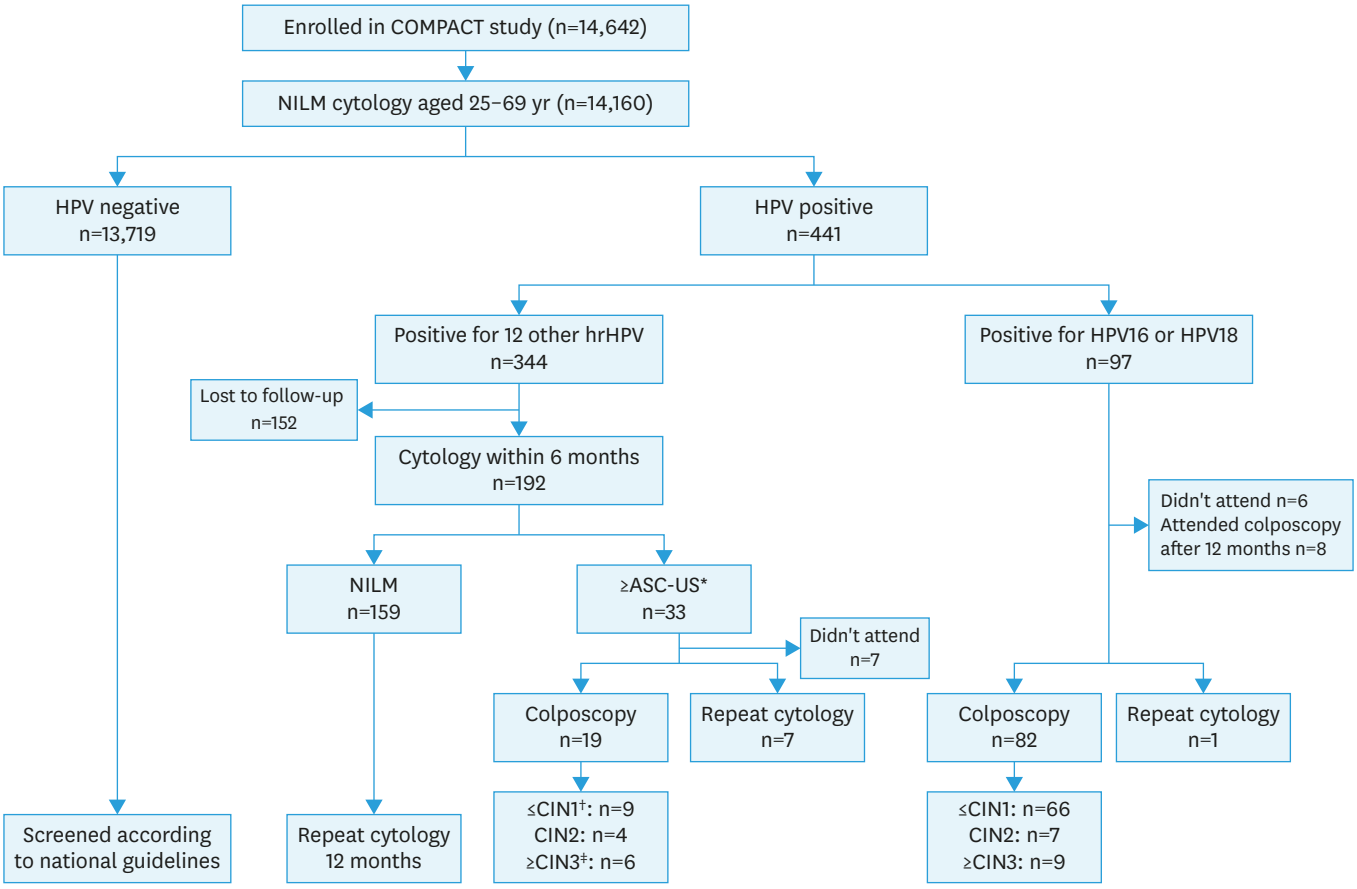

Fig. 2. Flow of evaluable women aged 25–69 years with NILM cytology through the baseline phase of the study.
AIS, adenocarcinoma in situ; ASC-US, abnormal squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; COMPACT, COMparison of HPV genotyping And Cytology Triage; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancy.
*≥ASC-US includes: ASC-US, LSIL, ASC-H, HSIL, AGC, AIS, SCC and adenocarcinoma; †≤CIN1 includes within normal limits and CIN1; ‡≥CIN3 includes: CIN3, AIS, SCC and adenocarcinoma.

(95% CI=0.6–12.6) than for an infection with a 12 other hrHPV type, however, due to the small number of cases, it was not statistically significant (p=0.21).

DISCUSSION

High-risk HPV status is an important predictor of current or future risk of CIN2+, even in women with NILM cytology. However, referring all hrHPV positive women to colposcopy may results in over diagnosis and treatment of transient lesions. To investigate an effective triage strategy for HPV positive women in a Japanese cervical screening programme, we analysed data from 14,160 Japanese women aged 25–69 years with NILM cytology but hrHPV positive and compared absolute and RR of CIN2/3 or worse in women HPV16 and or HPV18 positive to those positive for one or more of 12 other hrHPV types. We found that women with NILM cytology and an HPV16/18 infection had a 3.5-fold risk of a CIN2+ lesion compared to those with a 12 other hrHPV type. However, absolute risk of a CIN2+ in women with NILM cytology was highest in those 25-29 years who were HPV16 positive at 40.0%.

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Table 3. Impact of hrHPV genotype on absolute risk of high-grade cervical lesion in women with negative for intraepithelial lesions or malignancy cytology

Pathology results*	Age group																	
	Overall			25–29 yrs			30–39 yrs			40–49 yrs			50–59 yrs			60–69 yrs		
	No.	No. (%)	95% CI	No.	No. (%)	95% CI	No.	No. (%)	95% CI	No.	No. (%)	95% CI	No.	No. (%)	95% CI	No.	No. (%)	95% CI
CIN2 or worse																		
hrHPV	260	26 (10.0)	6.9–14.3	12	4 (33.3)	13.8–60.9	50	8 (16.0)	6.1–25.4	82	8 (9.8)	5.0–18.1	43	2 (4.7)	1.3–15.5	73	4 (5.5)	2.2–13.3
12 others†	178	10 (5.6)	3.1–10.0	3	1 (33.3)	6.2–79.2	28	3 (10.7)	1.8–22.5	60	4 (6.7)	2.6–15.9	34	1 (2.9)	0.1–14.9	53	1 (1.9)	0.0–9.9
HPV16/18	82	16 (19.5)	12.4–29.4	9	3 (33.3)	12.1–64.6	22	5 (22.7)	7.8–45.4	22	4 (18.2)	7.3–38.5	9	1 (11.1)	0.3–48.3	20	3 (15.0)	5.2–36.0
HPV16	60	12 (20.0)	11.8–31.8	5	2 (40.0)	11.8–76.9	13	3 (23.1)	5.0–53.8	18	4 (22.2)	9.0–45.2	9	1 (11.1)	2.0–43.5	15	2 (13.3)	1.7–40.5
HPV18	22	4 (18.2)	7.3–38.5	4	1 (25.0)	0.5–69.9	9	2 (22.2)	2.8–60.0	4	0 (0.0)	0.0–49.9	0	0 (0.0)	-	5	1 (20.0)	3.6–62.5
CIN3 or worse																		
hrHPV	260	15 (5.8)	3.5–9.3	12	1 (8.3)	1.5–35.4	50	4 (8.0)	1.9–16.7	82	8 (9.8)	5.0–18.1	43	0 (0.0)	0.0–10.2	73	2 (2.7)	0.8–9.5
12 others	178	6 (3.4)	1.6–7.2	3	1 (33.3)	6.2–79.2	28	0 (0.0)	0.0–8.0	60	4 (6.7)	2.6–15.9	34	0 (0.0)	0.0–7.2	53	1 (1.9)	0.0–9.9
HPV16/18	82	9 (11.0)	5.9–19.6	9	0 (0.0)	0.0–29.9	22	4 (18.2)	5.2–40.3	22	4 (18.2)	7.3–38.5	9	0 (0.0)	0.0–29.9	20	1 (5.0)	0.1–23.6
HPV16	60	7 (11.7)	5.8–22.2	5	0 (0.0)	0.0–43.4	13	3 (23.1)	5.0–53.8	18	4 (22.2)	9.0–45.2	9	0 (0.0)	0.0–29.9	15	0 (0.0)	0.0–18.1
HPV18	22	2 (9.1)	2.5–27.8	4	0 (0.0)	0.0–49.0	9	1 (11.1)	0.3–48.3	4	0 (0.0)	0.0–49.9	0	0 (0.0)	-	5	1 (20.0)	3.6–62.5

Values are presented as number (%).

AIS, adenocarcinoma in situ; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ICC, invasive cervical cancer.

*CIN2 or worse includes CIN2, CIN3, AIS, ICC, and adenocarcinoma, CIN3 or worse includes CIN3, AIS, ICC, and adenocarcinoma; †12 other hrHPV includes infection with one or more of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

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Table 4. Relative risk of high-grade cervical lesion* by hrHPV genotype in women with negative for intraepithelial lesions or malignancy cytology

HPV test result	CIN2 or worse					CIN3 or worse				
	No.	No. (%)	RR	95% CI	p-value	No.	No. (%)	RR	95% CI	p-value
12 other hrHPV†	178	10 (5.6)	1			178	6 (3.4)	1		
HPV16	60	12 (20.0)	3.6	1.6–7.8	0.021	60	7 (11.7)	3.5	1.2–9.9	0.021
12 other hrHPV	178	10 (5.6)	1			178	6 (3.4)	1		
HPV18	22	4 (18.2)	3.2	1.1–9.5	0.032	22	2 (9.1)	2.7	0.6–12.6	0.206
12 other hrHPV	178	10 (5.6)	1			178	6 (3.4)	1		
HPV16/18	82	16 (19.5)	3.5	1.7–7.3	<0.001	82	9 (11.0)	3.3	1.2–8.8	0.018

Values are presented as number (%). No. represents the number of women with a 12 other hrHPV, while n represents the number with this group with a CIN2 or CIN3 or worse lesion.

AIS, adenocarcinoma in situ; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ICC, invasive cervical cancer; RR, relative risk.

*CIN2 or worse includes CIN2, CIN3, AIS, ICC, and adenocarcinoma, CIN3 or worse includes CIN3, AIS, ICC, and adenocarcinoma; †12 other hrHPV includes infection with one or more of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

Compared to women >30 years, younger women are more likely to have a prevalent transient HPV infection, clear the infection and acquire new infections [27,28] Furthermore, many CIN2 lesions do not progress to ICC [28]. However, one large prospective cohort study of 11,088 women aged 20–29 years in Denmark found that HPV16 had both the greatest tendency to persist and highest probability for progression when it did persist. Absolute risk of developing CIN3 or ICC within the first 12 years of follow-up in women with normal cytology, but HPV16 positive at baseline was 26.7% (95% CI=21.1–31.8). With HPV18 absolute risk was 19.1% (95% CI=10.4–27.3). The authors also reported that among women with normal cytology, but a persistent HPV16 infection, estimated absolute risk for CIN3 or cervical cancer within 12 years was 47.4% (95% CI=34.9–57.5) [22]. Similarly, a population-based cohort study of 8,545 sexually active women in Costa Rico found that in women <30 years with a persistent HPV16 infection, 3-year and 5-year cumulative incidence rate of CIN2+ was 65.9 (95% CI=40.3–91.5). For CIN3 it was 40.3 (95% CI=11.4–69.3). For other nonHPV16/18 hrHPV types, the 3-year cumulative incidence rate of CIN2 and CIN3 was 7.1 (95% CI=0.4–13.8) and 3.8 (95% CI=1.4–16.1), respectively [29]. Both studies concluded that partial genotyping with HPV16/18 might be a better triage strategy in younger women at risk for developing high grade cervical lesions, than a strategy not distinguishing between pooled hrHPV genotypes. In the latter, the authors suggested monitoring HPV16 and HPV18 positive women from age 25 years, but waiting for evidence of persistence in women aged 25–30 years rather acting on the first HPV16 or HPV18 positive test [27].

Japan has no organized population based cervical cancer screening programme and less than 5% of local governments have a call-recall system. Screening is mostly opportunistic, and coverage is low (between 30%–40%) [30]. Screening does not take place within a primary healthcare setting where women might be in regular connect with a primary healthcare physician [31]. Pap smears are done by a gynaecologist and women tend to see a gynaecologist only if they have specific symptoms that need treating or if they are pregnant. In the current approved Japanese screening algorithm, women only undergo HPV testing when they have ASC-US cytology [16]. It is therefore possible that some women with normal cytology who are HPV16/18 positive may believe their current or future risk of cervical cancer is low and not have another screen until they have symptoms or a condition that warrants a visit to a gynaecologist. Japan has no national screening registry and call-recall programs are limited so sending all women who are known to be positive for HPV16/18 straight to colposcopy may be a safer strategy than asking women aged 25–29 years to return within a given period for a repeat HPV test, since compliance with screening in this age-group is poor (<30%).

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Unlike CIN2, the risk of a CIN3 lesion progressing to ICC is substantial if left untreated [32]. In the current study, absolute risk for a CIN3+ lesion in women with NILM cytology and positive HPV16/18 was 11.0% (95% CI=5.9–19.6). For women with a 12 other hrHPV type it was 3.4% (95% CI=1.6–7.2). As with CIN2+, women with an HPV16/18 infection also had a significantly elevated risk of CIN3+ compared to women positive for one or more of the 12 other hrHPV types (RR=3.3, 95% CI=1.1–8.8, p=0.02). Incidence of CIN3 starts to rise in women in their late twenties in Japan and peak in women in their thirties. In the present study, absolute risk of a CIN3 lesion in women aged 30-39 years with NILM cytology but HPV16 positive was 23.1% (95% CI=5.0–53.8) compared to 0.0% (95% CI=0.0–0.8) in women with a 12 other infection. In the 25–29-year age group, 33% (1 out of 3) of women with a 12 other infection had a CIN3 lesion, however loss to follow-up was high at 83% (15 out of 18), making it difficult to accurately interpret this result.

In the 60–69-year age group there was one HPV18 positive adenocarcinoma. The patient had normal cytology and no significant findings at colposcopy; she was only diagnosed after endocervical sampling. While HPV18 causes between 10-15% of squamous cell cervical carcinomas, it is responsible for >35% of adenocarcinomas [33]. Incidence of adenocarcinoma is increasing in Japan. In 2005, it accounted for 16.9% of all cervical carcinomas, but in 2014 this figure rose to 20.1% [34]. In the baseline data of all women eligible for the COMPACT study [26] HPV18 was responsible for 50% of ACIS and 50% of ICC (of which 50% were adenocarcinoma). Since adenocarcinomas tend to occur further up the cervical canal, they are often missed in cytology-based screening programmes [35], which have been successful in reducing incidence of and mortality from squamous cell cervical carcinomas but ineffective in reducing the burden of adenocarcinomas [36].

While HPV vaccination will have the greatest impact in reducing incidence of adenocarcinomas, data from Australia has predicted that in non-vaccinated women, HPV-based screening will further reduce incidence of adenocarcinoma by between 19% and 43% [37]. More modelling data from the same group, reported that in countries with high HPV vaccine uptake in younger screened cohorts but a considerable proportion of the older screened population still unvaccinated, primary HPV screening with HPV16/18 partial genotyping starting at the age of 25 years is the most beneficial screening strategy for both vaccinated and unvaccinated women.

This study has considerable strengths. It is the first Japanese study to investigate absolute and relative absolute risk for high grade cervical disease in women with NILM cytology and infection with one of more 12 pooled hrHPV types compared to an infection with HPV16/18. It is also one of few studies to look at risks in women 25–29 years. Other strengths include large sample size, and all participants underwent both cytology and HPV testing at baseline. This study also has several limitations. Firstly, 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 since a sample of women with double negative results were not referred to colposcopy and of those referred to colposcopy, biopsy was only taken in cases with abnormal findings. A further limitation is that participants were not vaccinated against HPV, therefore, the results will only apply to a non-vaccinated population. A third limitation is the high mean age and 50% loss-to-follow-up in the 12 others group, making it difficult to assess absolute risk of high-grade disease in women 25-29 years. This and the small sample after age-stratification, suggest pooling of national may be necessary. Despite high mean age, results from this study, with regards to absolute and RR of high-grade

disease by HPV genotype, are similar to the ATHENA study which had a higher baseline hrHPV prevalence [38]. Finally, a fourth limitation is cytologists, colposcopists and pathologists were not completely blinded to HPV typing results, which may have influenced their decision.

In conclusion, this study showed that the risk of high-grade cervical disease in women with NILM cytology is significantly increased with an HPV16/18 positive result, compared to testing positive for one or more of the 12 other hrHPV genotypes. Women who were HPV16/18 positive, even with NILM cytology, had an 11.0% absolute risk of CIN3+ and should be sent for immediate colposcopy. Our data suggest that an HPV primary screening programme with HPV16 and HPV18 partial genotyping might be an effective triage strategy to identify women at particularly high-risk (current and future) of cervical cancer or its immediate precursor CIN3, without over-referral to colposcopy. It might also be more effective in identifying women at risk for adenocarcinoma, who are often missed in the current Japanese cytology-based screening programme.

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