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Human papillomavirus genotype contribution to cervical cancer and precancer: Implications for screening and vaccination in Japan

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Abstract

To obtain baseline data for cervical cancer prevention in Japan, we analyzed human papillomavirus (HPV) data from 5045 Japanese women aged less than 40 years and diagnosed with cervical abnormalities at 21 hospitals during 2012-2017. These included cervical intraepithelial neoplasia grade 1 (CIN1, n = 573), CIN2-3 (n = 3219), adenocarcinoma in situ (AIS, n = 123), and invasive cervical cancer (ICC, n = 1130). The Roche Linear Array was used for HPV genotyping. The HPV type-specific relative contributions (RCs) were estimated by adding multiple infections to single types in accordance with proportional weighting attributions. Based on the comparison of type-specific RCs between CIN1 and CIN2-3/AIS/ICC (CIN2+), RC ratios were calculated to estimate type-specific risks for progression to CIN2+. Human papillomavirus DNA was detected in 85.5% of CIN1, 95.7% of CIN2-3/AIS, and 91.2% of ICC. Multiple infections decreased with disease severity: 42.9% in CIN1, 40.4% in CIN2-3/AIS, and 23.7% in ICC ($P < .0001$). The relative risk for progression to CIN2+ was highest for HPV16 (RC ratio 3.78, 95% confidence interval [CI] 3.01-4.98), followed by HPV31 (2.51, 1.54-5.24), HPV18 (2.43, 1.59-4.32), HPV35 (1.56, 0.43-8.36), HPV33 (1.01, 0.49-3.31), HPV52 (0.99, 0.76-1.33), and HPV58 (0.97, 0.75-1.32). The relative risk of disease progression was 1.87 (95% CI, 1.71-2.05) for HPV16/18/31/33/35/45/52/58, but only 0.17 (95% CI, 0.14-0.22) for HPV39/51/56/59/66/68. Human papillomavirus 16/18/31/33/45/52/58/6/11 included in a 9-valent vaccine contributed to 89.7% (95% CI, 88.7-90.7) of CIN2-3/AIS and 93.8% (95% CI, 92.4-95.3) of ICC. In conclusion, our data support the Japanese guidelines that recommend discriminating HPV16/18/31/33/35/45/52/58 genotypes for CIN management. The 9-valent vaccine is estimated to provide over 90% protection against ICC in young Japanese women.

KEYWORDS

adenocarcinoma in situ, cervical intraepithelial neoplasia, human papillomavirus, invasive cervical cancer, vaccine

1 | INTRODUCTION

The WHO reported 570 000 new cases of cervical cancer worldwide in 2018, making it the fourth most common cancer for women after breast, colon, and lung cancer.[1,2] This disease claims the lives of more than 300 000 women annually, mostly in lower income countries. Two approaches for cervical cancer prevention, human papillomavirus (HPV) vaccines and the use of methods to detect carcinogenic HPV infections, have been introduced in the last 2 decades. Bivalent HPV16/18 and quadrivalent HPV16/18/6/11 vaccines have the potential to prevent approximately 70% of cervical cancer cases attributable to HPV16 or HPV18 worldwide.[3] Furthermore, the next-generation 9-valent vaccine extends coverage to HPV31, 33, 45, 52, and 58,[4] which, together, are the second most common types associated with cervical cancer globally.[5,6] In addition to vaccination, effective screening is also needed because these vaccines cannot treat preexisting infections or related cervical abnormalities.[7] Human papillomavirus testing as a primary screening tool for cervical cancer has been shown to have greater sensitivity and reproducibility for detecting cervical cancer and precancer than standard cytological examination.[8,9] In the United States, cotesting with the HPV test and cytology was recommended for cervical cancer screening in 2003,[10] and the Netherlands and Australia changed their national cervical cancer screening programs from Pap test to primary HPV screening in 2017.[11,12] Recent models have suggested that successful elimination of cervical cancer will be possible by the end of this century if 2 major primary prevention strategies, HPV-based screening and HPV vaccination programs, are scaled up to 80%–100% coverage over the next 50 years.[13]

In Japan, cervical cancer rates have risen in recent years because of a low cancer-screening rate and changes in sexual lifestyle.[14,15] Cytology-based screening programs are still ongoing, with HPV-based screening not yet recommended in the Japanese guidelines.[16] Although the bivalent and quadrivalent vaccines are available, the 9-valent vaccine has not yet been licensed. In contrast, Japan is the first country to incorporate full HPV genotyping into cervical intraepithelial neoplasia (CIN) management.[16] The Japanese clinical guidelines recommend discriminating HPV16/18/31/33/35/45/52/58 as more carcinogenic HPV types in clinical management of women with histologically proven CIN grade 1 (CIN1) or CIN2.

Baseline data on HPV genotype attributes in cervical cancer and precancer are needed to predict how HPV vaccination, HPV-based screening, and type-specific CIN management will influence cervical cancer prevention. Although global data are available, HPV genotype distributions in cervical cancer and precancer vary by geographical region and race/ethnicity.[3,5] In Japan, limited data are available that describe HPV genotype distributions for this disease, especially in a reproductive-age population that are mainly targeted by HPV vaccination and screening. To address this lack of data, we analyzed HPV type-specific data from 5045 Japanese women aged less than 40 years and diagnosed with cervical cancer and its precursors at 21 hospitals during 2012-2017. To our knowledge, this is the largest nationwide study of HPV genotype distribution in women with cervical abnormalities in Japan. The aim of this study was to provide baseline data for cervical cancer prevention in Japan. In the present study, we provide a description of the relative risks for progression to CIN2 or worse (CIN2+) by individual HPV genotypes and estimate the potential impact of current and new HPV vaccines on cervical cancer and precancer among young Japanese women of reproductive age.

2 | MATERIALS AND METHODS

2.1 | Study design

We prospectively undertook a collaborative hospital-based study to monitor the long-term population-level impact of HPV vaccination in Japan (the MINT Study). Details of the design and methods have been provided elsewhere.[17,18] In this study, participants consisted of women aged 16-39 years (age at registration) newly diagnosed with invasive cervical cancer (ICC), CIN, or adenocarcinoma in situ (AIS), without a previous history of treatment for cervical diseases, at 21 participating institutions during 2012-2017. All participants entered the study only after voluntarily providing signed informed consent and were registered together with their vaccine history, each year commencing on January 1 and ending on December 31. We did not review histological specimens because of the relevance to clinical practice. Based on local histological diagnoses, the study participants were divided into the following three groups: (i) Category A, women newly diagnosed with ICC at participating facilities each year (registration and HPV genotyping test were necessary for all women diagnosed with ICC); (ii) Category B, women newly diagnosed with CIN2-3 or AIS (registration was necessary for all women diagnosed with CIN2-3 or AIS, however, HPV genotyping tests were carried out until the total number of participants tested reached 600); and (iii) Category C, women newly diagnosed with CIN1 (each year, registration and HPV genotyping were carried out until the total number of subjects tested at all facilities reached 100).

Institutional ethical and research review boards of the participating institutions approved the study protocol. This study was registered in the UMIN Clinical Trials Registry as UMIN000008891.

2.2 | Human papillomavirus detection and genotyping procedures

The presence of HPV DNA in cervical samples was determined using the Linear Array (LA) assay (Roche Molecular Systems), a commercialized L1 consensus primer-based PCR method that uses a primer set designated PGMY09/11. The LA test was carried out according to the manufacturer's recommended protocol. Briefly, exfoliated ecto- and endocervical cells were stored in ThinPrep PreservCyt solution (Hologic) until DNA extraction. Total cellular DNA was extracted using a QIAamp MinElute Media kit (Qiagen). Amplicons were subjected to reverse line blot hybridization for detection of 37 individual HPV genotypes (HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51 to 56, 58, 59, 61, 62, 64, 66 to 73, 81 to 84, and 89). Detection and genotyping of HPV were undertaken at a clinical testing laboratory (SRL, Tokyo, Japan). All of the HPV DNA assays were carried out by individuals who were blinded to the results of the clinical profile for each subject.

2.3 | Statistical methods

To add multiple infections to HPV type-specific analyses, we calculated relative contributions (RCs) of each HPV type among HPV-positive women by category.[5,6] Multiple infections were added to single types in accordance with a proportional weighting attribution. For example, if an ICC lesion is positive for both HPV16 and HPV52 (multiple infection) and there are 8 cases infected by HPV16 alone (single infection) and 2 cases infected by HPV52 alone (single infection) in an ICC category, then 0.8 [8/(8 + 2)] of the multitype infected ICC lesion was attributed to HPV16 and 0.2 [2/(8 + 2)] attributed to HPV52 in Category A.

To estimate HPV genotype-specific risks for progression from CIN1 to CIN2 or worse, RC ratios and 95% confidence intervals (CIs) were calculated using JMP 10.0J software (SAS Institute). The HPV types detected only among a small number of women (fewer than 50) were excluded from this analysis. In addition, to estimate the impact of current HPV vaccines among young Japanese women, combined RCs of HPV16/18 (carcinogenic types included in bivalent and quadrivalent vaccines) and HPV16/18/31/33/45/52/58 (carcinogenic types included in a 9-valent vaccine) were calculated according to disease severity, histology, and age group (20-24, 25-29, 30-34, and 35-39 years), using HPV type-specific data from unvaccinated cases. The χ^2 test for trend was used to analyze the prevalence of multiple infections according to disease severity. Two-sided P values were obtained in all tests and considered significant when P was less than .05.

TABLE 1 Human papillomavirus (HPV) type distribution among young Japanese women by histology

			Precancer						Invasive cancer					
	CIN1 (N = 573)		All (N = 3342)		CIN2-3 (N = 3219)		AIS (N = 123)		All (N = 1130)		SCC (N = 720)		Non-SCC (N = 410)	
HPV type	n	%	n	%	n	%	n	%	n	%	n	%	n	%
HPV positive	490	85.5	3195	95.6	3081	95.7	114	92.7	1030	91.2	672	93.3	358	87.3
Single infection	327	57.1	1993	59.6	1903	59.1	90	73.2	862	76.3	544	75.6	318	77.6
6	6	1.0	4	0.1	4	0.1	0	0.0	2	0.2	2	0.3	0	0.0
11	2	0.3	2	0.1	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
16	27	4.7	723	21.6	695	21.6	28	22.8	475	42.0	368	51.1	107	26.1
18	9	1.6	104	3.1	57	1.8	47	38.2	173	15.3	46	6.4	127	31.0
26	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
31	9	1.6	149	4.5	149	4.6	0	0.0	19	1.7	18	2.5	1	0.2
33	5	0.9	46	1.4	46	1.4	0	0.0	4	0.4	4	0.6	0	0.0
35	1	0.2	13	0.4	13	0.4	0	0.0	1	0.1	1	0.1	0	0.0
39	9	1.6	14	0.4	14	0.4	0	0.0	7	0.6	4	0.6	3	0.7
40	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
42	4	0.7	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	2	0.5
43	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
44	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
45	3	0.5	8	0.2	7	0.2	1	0.8	6	0.5	2	0.3	4	1.0
51	21	3.7	52	1.6	52	1.6	0	0.0	5	0.4	3	0.4	2	0.5
52	29	5.1	318	9.5	316	9.8	2	1.6	10	0.9	8	1.1	2	0.5
53	9	1.6	5	0.1	5	0.2	0	0.0	1	0.1	0	0.0	1	0.2
54	2	0.3	2	0.1	2	0.1	0	0.0	1	0.1	0	0.0	1	0.2
55	1	0.2	1	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
56	21	3.7	13	0.4	13	0.4	0	0.0	4	0.4	4	0.6	0	0.0
58	34	5.9	301	9.0	300	9.3	1	0.8	25	2.2	22	3.1	3	0.7
59	5	0.9	6	0.2	6	0.2	0	0.0	11	1.0	8	1.1	3	0.7
61	2	0.3	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1	0	0.0
62	4	0.7	4	0.1	4	0.1	0	0.0	4	0.4	2	0.3	2	0.5
64	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
66	13	2.3	10	0.3	10	0.3	0	0.0	2	0.2	1	0.1	1	0.2
67	2	0.3	4	0.1	4	0.1	0	0.0	1	0.1	0	0.0	1	0.2
68	8	1.4	6	0.2	6	0.2	0	0.0	1	0.1	1	0.1	0	0.0
69	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
70	2	0.3	2	0.1	2	0.1	0	0.0	2	0.2	0	0.0	2	0.5
71	2	0.3	3	0.1	3	0.1	0	0.0	3	0.3	1	0.1	2	0.5
72	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
73	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
81	1	0.2	1	0.0	1	0.0	0	0.0	1	0.1	0	0.0	1	0.2
82	7	1.2	45	1.3	45	1.4	0	0.0	0	0.0	0	0.0	0	0.0
83	0	0.0	1	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
84	3	0.5	2	0.1	1	0.0	1	0.8	0	0.0	0	0.0	0	0.0
89	1	0.2	2	0.1	1	0.0	1	0.8	1	0.1	0	0.0	1	0.2
Undetermined	0	0.0	5	0.1	5	0.2	0	0.0	0	0.0	0	0.0	0	0.0

(Continues)

TABLE 1 (Continued)

	Precancer								Invasive cancer							
	CIN1		All		CIN2-3		AIS		All		SCC		Non-SCC			
	(N = 573)		(N = 3342)		(N = 3219)		(N = 123)		(N = 1130)		(N = 720)		(N = 410)			
HPV type	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Multiple infections	246	42.9	1349	40.4	1316	40.9	33	26.8	268	23.7	176	24.4	92	22.4		
HPV negative	83	14.5	147	4.4	138	4.3	9	7.3	100	8.8	48	6.7	52	12.7		

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

3 | RESULTS

3.1 | Detection and genotyping of HPV

A total of 7709 women aged less than 40 years, who were newly diagnosed with CIN1 (n = 589), CIN2-3/AIS (n = 5828), or ICC (n = 1292) at 21 participating institutions, were registered between 2012 and 2017. In the present study, HPV-genotyping assays were undertaken for CIN1 and CIN2-3/AIS until the total number of samples tested reached 100 and 600 each year, respectively. Although all ICC cases were to be tested for HPV genotype, HPV typing results were lacking among 162 early-stage ICC cases, because of an ICC diagnosis after conization. Thus, we obtained HPV type-specific data from 5045 women (CIN1, n = 573; CIN2-3/AIS, n = 3342; ICC, n = 1130). The mean age ± SD of these women was 32.4 ± 4.6 years at the registration date: 30.6 ± 5.3 years in CIN1, 32.2 ± 4.6 years in CIN2-3/AIS, and 34.0 ± 3.8 years in ICC.

Human papillomavirus type-specific data from 5045 women are shown in Table 1. Human papillomavirus DNA was detected in 93.5% (4715/5045) of the study subjects: 85.5% in CIN1, 95.7% in CIN2-3/AIS, and 91.2% in ICC. Although 38 cases with mixed AIS/CIN2-3 lesions were classified into AIS, HPV type-specific data were similar between pure AIS and mixed AIS/CIN2-3 (data not shown). Among single infections, a total of 31 HPV types were detected in CIN1, 28 types in CIN2-3/AIS, and 25 types in ICC. Infections from multiple types were found in 36.9% (1863/5045) of the study subjects. Multiple infections decreased with disease severity: 42.9% in CIN1, 40.4% in CIN2-3/AIS, and 23.7% in ICC ($P < .0001$).

3.2 | Human papillomavirus type-specific risk for cervical cancer and precancer

Using data from HPV-positive women, including multiple infections, HPV type-specific RCs among young Japanese women diagnosed with CIN1, CIN2-3/AIS, or ICC between 2012 and 2017 were calculated (Table 2). For ICC, the most common HPV types were, in order of decreasing RC, HPV16 (62.3%), HPV18 (22.7%), HPV58 (3.2%), HPV31 (2.9%), HPV52 (1.6%), HPV59 (1.3%), and HPV39 (0.9%) (Figure 1A). For CIN2-3/AIS, HPV16 was also most prevalent (40.0%), followed by HPV52 (17.2%), HPV58 (16.3%), HPV31 (8.3%), HPV18 (4.9%), HPV51 (3.2%), and HPV82 (2.4%) (Figure 1B). The 5 most common HPV types were HPV16, HPV18, HPV31, HPV52, and HPV58 in ICC as well as in CIN2-3/AIS. These 5 types contributed to 86.7% of CIN2-3/AIS and 92.7% of ICC. A remarkable contribution of HPV18 was observed in AIS (51.6%; 95% CI, 42.1-59.9) and nonsquamous cell carcinomas (non-SCC) (47.8%; 95% CI, 42.8-52.9). In CIN1, HPV52 (13.6%) was the most common genotype, followed by HPV58 (13.5%), HPV16 (12.0%), HPV56 (8.6%), HPV51 (8.1%), HPV66 (5.6%), and HPV53 (4.4%).

Based on the comparison of type-specific RCs between CIN1 and CIN2-3/AIS/ICC, the estimated risks for progression to CIN2+ was highest in HPV16 (RC ratio 3.78; 95% CI, 3.01-4.98), followed by HPV31 (2.51; 95% CI, 1.54-5.24), HPV18 (2.43; 95% CI, 1.59-4.32), HPV35 (1.56; 95% CI, 0.43-8.36), HPV33 (1.01; 95% CI, 0.49-3.31), HPV52 (0.99; 95% CI, 0.76-1.33), HPV58 (0.97; 95% CI, 0.75-1.32), HPV82 (0.74; 95% CI, 0.39-1.76), and HPV45 (0.43; 95% CI, 0.13-2.91) (Figure 2). The estimated risk of disease progression was statistically significant for HPV16, HPV18, and HPV31 ($P < .05$).

The combined RCs of HPV16/18/31/33/35/45/52/58, carcinogenic types regarded as higher-risk types in the Japanese clinical guidelines, increased according to disease severity (CIN1, 48.7%; CIN2-3/AIS, 89.9%; ICC, 93.8%). Conversely, the combined RCs of the other carcinogenic types, HPV39/51/56/59/66/68, decreased with disease severity (CIN1, 30.8%; CIN2-3/AIS, 5.9%; ICC, 3.6%). A similar trend was observed for nononcogenic types (CIN1, 20.5%; CIN2-3/AIS, 4.2%; ICC, 2.6%). Accordingly, the relative risk for progression to CIN2+ was 1.87 (95% CI, 1.71-2.05) for HPV16/18/31/33/35/45/52/58, but only 0.17 (95% CI, 0.14-0.22) for HPV39/51/56/59/66/68 and 0.19 (95% CI, 0.14-0.25) for non-carcinogenic types.

3.3 | Estimating the impact of HPV vaccines on cervical cancer and precancer in Japan

Clinical studies of HPV vaccines have reported close to 100% protection against vaccine type-related infections and diseases. Therefore, the combined RCs of HPV types included in current HPV vaccines were specifically analyzed to estimate the potential impact of bivalent, quadrivalent and 9-valent vaccines. Of 5045 study participants tested for HPV genotype, 3.1% (157/5045) previously received HPV

TABLE 2 Human papillomavirus (HPV) type-specific relative contribution among HPV-positive cases in Japan by histology

	Precancer								Invasive cancer					
	CIN1		All		CIN2-3		AIS		All		SCC		Non-SCC	
	(N = 490)		(N = 3195)		(N = 3081)		(N = 114)		(N = 1004)		(N = 672)		(N = 358)	
HPV type	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
14 Carcinogenic types[a]	79.5	(76.4-82.5)	95.8	(95.1-96.4)	95.7	(95.1-96.3)	97.6	(95.1-100)	97.4	(96.5-98.4)	98.3	(97.4-99.2)	95.7	(93.7-97.8)
HPV16/18/31/33/35/45/52/58	48.7	(88.7-90.7)	89.9	(88.9-90.9)	89.7	(88.7-90.7)	96.4	(93.3-99.4)	93.8	(92.4-95.3)	94.3	(92.6-96.0)	92.9	(90.3-95.5)
HPV39/51/56/59/66/68	30.8	(27.2-34.4)	5.9	(5.2-6.6)	6.1	(5.3-6.8)	1.3	(0.0-2.7)	3.6	(2.5-4.7)	4.0	(2.6-5.4)	2.9	(1.2-4.5)
Non-carcinogenic types	20.5	(17.5-23.6)	4.2	(3.6-4.9)	4.3	(3.6-4.9)	13.6	(0.0-4.9)	2.6	(1.6-3.5)	1.7	(0.8-2.6)	4.3	(2.2-6.3)
6	1.5	(0.5-2.5)	0.2	(0.0-0.3)	0.2	(0.0-0.3)	0.0	(0.0-0.1)	0.2	(0.0-0.5)	0.3	(0.0-0.7)	0.0	(0.0-0.0)
11	0.5	(0.0-1.1)	0.1	(0.0-0.2)	0.1	(0.0-0.2)	0.0	(0.0-0.2)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
16	12.0	(9.4-14.6)	40.0	(38.4-41.6)	40.2	(38.6-41.9)	34.2	(25.7-42.7)	62.3	(59.3-65.2)	73.4	(70.1-76.7)	41.4	(36.4-46.4)
18	3.8	(2.3-5.3)	4.9	(4.2-5.5)	3.1	(2.6-3.7)	51.0	(42.1-59.9)	22.7	(20.2-25.2)	9.4	(7.21-11.5)	47.8	(42.8-52.9)
26	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
31	2.8	(1.5-4.1)	8.3	(7.4-9.2)	8.6	(7.7-9.5)	0.6	(0.0-1.7)	2.9	(1.9-3.9)	4.1	(2.7-5.6)	0.5	(0.0-1.3)
33	1.7	(0.6-2.8)	2.1	(1.7-2.6)	2.2	(1.7-2.7)	0.0	(0.0-0.0)	0.4	(0.0-0.8)	0.6	(0.0-1.2)	0.0	(0.0-0.0)
35	0.3	(0.0-0.7)	0.7	(0.0-1.0)	0.7	(0.4-1.0)	0.0	(0.0-0.0)	0.1	(0.0-0.3)	0.2	(0.0-0.5)	0.0	(0.0-0.0)
39	3.8	(2.4-5.3)	0.8	(0.6-1.1)	0.9	(0.6-1.2)	0.0	(0.0-0.0)	0.9	(0.4-1.5)	0.9	(0.4-1.6)	0.9	(0.0-1.9)
40	0.2	(0.0-0.6)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
42	1.7	(0.8-2.7)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.2	(0.0-0.5)	0.0	(0.0-0.0)	0.6	(0.0-1.3)
43	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
44	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
45	1.0	(0.2-1.8)	0.3	(0.2-0.5)	0.3	(0.1-0.5)	0.9	(0.0-2.7)	0.7	(0.2-1.1)	0.4	(0.0-0.9)	1.1	(0.0-2.2)
51	8.1	(5.9-10.3)	3.2	(2.7-3.8)	3.3	(2.8-3.9)	0.4	(0.0-0.9)	0.6	(0.2-1.0)	0.6	(0.0-1.1)	0.6	(0.0-1.4)
52	13.6	(10.8-16.3)	17.2	(16.0-18.4)	17.6	(16.3-18.9)	6.4	(2.5-10.4)	1.6	(0.9-2.3)	1.9	(0.9-2.9)	0.9	(0.1-1.8)
53	4.4	(2.9-5.9)	0.3	(0.2-0.5)	0.3	(0.2-0.5)	0.0	(0.0-0.0)	0.1	(0.0-0.3)	0.0	(0.0-0.0)	0.3	(0.0-0.8)
54	0.8	(0.1-1.4)	0.1	(0.0-0.2)	0.1	(0.0-0.2)	0.0	(0.0-0.1)	0.2	(0.0-0.4)	0.1	(0.0-0.2)	0.4	(0.0-1.0)
55	0.5	(0.0-1.0)	0.1	(0.0-0.1)	0.1	(0.0-0.1)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
56	8.6	(6.4-10.9)	0.7	(0.5-1.0)	0.7	(0.5-1.0)	0.8	(0.0-2.1)	0.4	(0.0-0.8)	0.6	(0.0-1.2)	0.0	(0.0-0.0)
58	13.5	(10.7-16.3)	16.3	(15.1-17.6)	16.8	(15.6-18.1)	3.1	(2.8-5.8)	3.2	(2.1-4.2)	4.3	(2.8-5.8)	1.0	(0.1-2.0)
59	1.5	(0.6-2.5)	0.2	(0.0-0.4)	0.2	(0.1-0.4)	0.0	(0.0-0.0)	1.3	(0.6-1.9)	1.4	(0.6-2.3)	1.0	(0.0-2.0)
61	1.2	(0.4-2.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.2	(0.0-0.4)	0.3	(0.0-0.6)	0.0	(0.0-0.0)
62	2.3	(1.4-3.3)	0.3	(0.1-0.4)	0.3	(0.1-0.4)	0.2	(0.0-0.6)	0.4	(0.1-0.9)	0.5	(0.0-0.9)	0.6	(0.0-1.4)

(Continues)

TABLE 2 (Continued)

			Precancer						Invasive cancer					
	CIN1		All		CIN2-3		AIS		All		SCC		Non-SCC	
	(N = 490)		(N = 3195)		(N = 3081)		(N = 114)		(N = 1004)		(N = 672)		(N = 358)	
HPV type	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
64	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
66	5.6	(3.8-7.3)	0.5	(0.3-0.7)	0.5	(0.3-0.7)	0.0	(0.0-0.0)	0.2	(0.0-0.5)	0.2	(0.0-0.5)	0.3	(0.0-0.8)
67	0.6	(0.0-1.2)	0.2	(0.0-0.4)	0.2	(0.0-0.3)	0.0	(0.0-0.0)	0.1	(0.0-0.4)	0.1	(0.0-0.2)	0.3	(0.0-0.8)
68	3.1	(1.8-4.3)	0.4	(0.2-0.6)	0.4	(0.2-0.6)	0.1	(0.0-0.3)	0.2	(0.0-0.4)	0.3	(0.0-0.6)	0.0	(0.0-0.0)
69	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
70	0.8	(0.2-1.5)	0.1	(0.0-0.2)	0.1	(0.0-0.2)	0.0	(0.0-0.0)	0.3	(0.0-0.6)	0.1	(0.0-0.4)	0.6	(0.0-1.3)
71	0.8	(0.2-1.4)	0.1	(0.0-0.3)	0.2	(0.0-03)	0.0	(0.0-0.1)	0.4	(0.0-0.8)	0.3	(0.0-0.7)	0.6	(0.0-1.3)
72	0.2	(0.0-0.6)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
73	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
81	0.7	(0.2-1.2)	0.0	(0.0-0.1)	0.0	(0.0-0.1)	0.0	(0.0-0.0)	0.2	(0.0-0.5)	0.0	(0.0-0.1)	0.6	(0.0-1.5)
82	2.5	(1.3-3.7)	2.4	(1.9-2.9)	2.5	(2.0-3.0)	0.3	(0.0-0.8)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
83	0.0	(0.0-0.0)	0.0	(0.0-0.1)	0.0	(0.0-0.1)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
84	1.2	(0.4-2.0)	0.1	(0.0-0.2)	0.1	(0.0-0.1)	0.9	(0.0-2.6)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)
89	0.6	(0.0-1.1)	0.1	(0.0-0.2)	0.1	(0.0-0.1)	0.9	(0.0-2.6)	0.1	(0.0-0.3)	0.0	(0.0-0.0)	0.4	(0.0-1.0)
Undetermined	0.0	(0.0-0.0)	0.2	(0.0-0.3)	0.2	(0.0-0.3)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)	0.0	(0.0-0.0)

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

[a]Carcinogenic HPV types include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

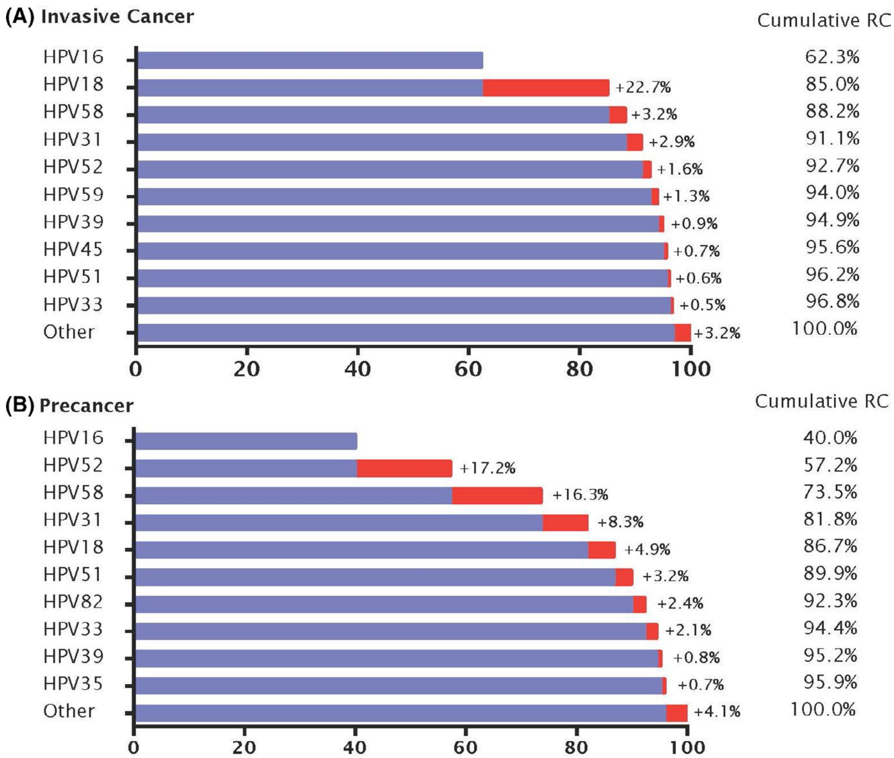

FIGURE 1 Cumulative proportion of cervical cancer and precancer cases attributed to the most frequent human papillomavirus (HPV) types in Japan. Cumulative relative contributions (RCs) of the 10 most frequent HPV types in invasive cervical cancer (A) and precancer (B) are shown

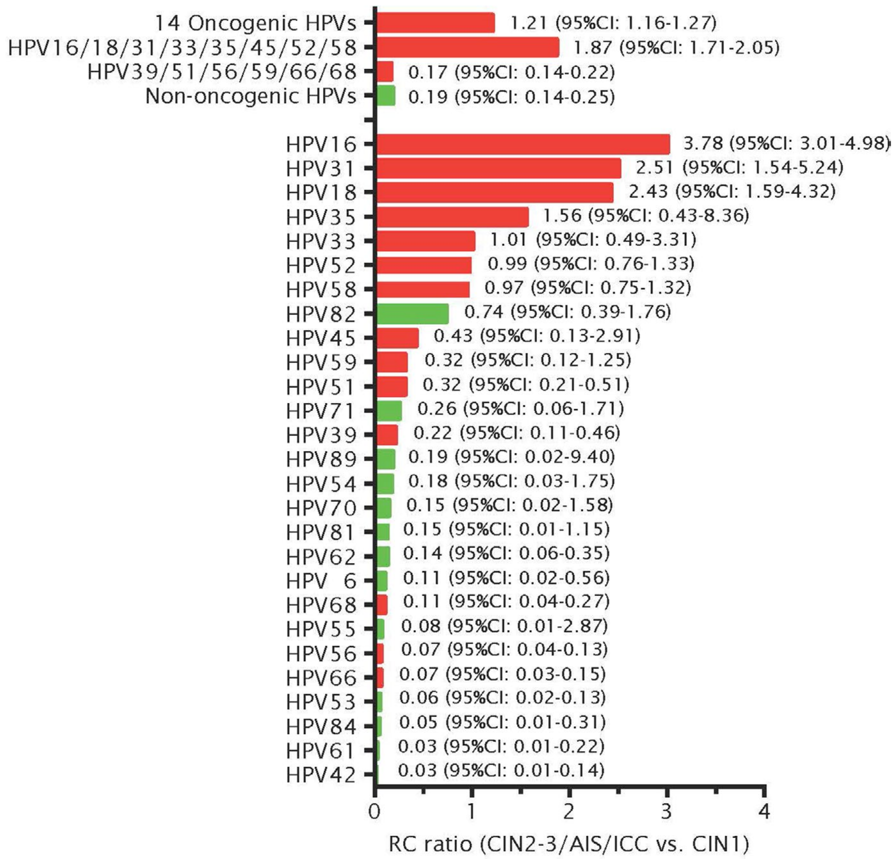

FIGURE 2 Estimates of human papillomavirus (HPV) type-specific relative risks for progression to cervical intraepithelial lesion grade 2 (CIN2) or worse. To estimate type-specific relative risks for progression to CIN2-3, adenocarcinoma in situ (AIS) or invasive cervical cancer (ICC), relative contribution (RC) ratios (CIN2-3/AIS/ICC vs CIN1) were calculated for each HPV type. Red bars represent oncogenic HPV types; green bars indicate nononcogenic HPV types. CI, confidence interval

vaccination. Prevalence of HPV16/18 was significantly reduced among vaccinated women compared with unvaccinated women (33.0% [35/106] vs 47.7% [1535/3213], *P* = .003). Thus, vaccinated women (n = 157) were excluded from this analysis.

The combined RCs of HPV16/18/31/33/45/52/58/6/11, all 9 types included in the 9-valent vaccine, were 89.7% (95% CI, 88.7-90.7) in CIN2-3/AIS and 93.8% (95% CI, 92.4-95.3) in ICC, with HPV31/33/45/52/58 contributing to 44.3% (95% CI, 42.7-45.9) and

8.7% (95% CI, 7.1-10.4), respectively. Thus, the inclusion of the additional 5 types provides more protection against CIN2-3/AIS than ICC. Human papillomavirus 6/11 rarely contributed to cervical cancer or precancer (additional RCs of HPV6/11 were very small [less than 0.3%]). Hereafter, only the RCs of carcinogenic HPV types included in HPV vaccines were evaluated to estimate the possible impact of current HPV vaccines.

The combined RCs of HPV16/18/31/33/45/52/58 were 93.6% (95% CI, 92.1-95.1) for ICC, with 8.7% (95% CI, 7.1-10.4) of ICC cases positive for HPV31/33/45/52/58 (Figure 2). The RCs of HPV16/18/31/33/45/52/58 were similar between SCC and Non-SCC (94.1% [95% CI, 92.3-95.9] vs 92.6% [95% CI, 89.9-95.4]). The RCs of HPV31/33/45/52/58 newly added to the 9-valent HPV vaccine were greater in SCC than in non-SCC (11.4% [95% CI, 9.0-13.8] vs 3.7% [95% CI, 1.9-5.6]).

The combined RCs of HPV16/18/31/33/45/52/58 were 89.5% (95% CI, 88.5-90.5]) in CIN2-3/AIS, with HPV31/33/45/52/58 contributing to 44.3% (95% CI, 42.7-45.9) (Figure 3). Although the RCs of HPV31/33/45/52/58 were, by far, greater in CIN2-3 than in AIS (45.5% [95% CI, 43.9-47.2] vs 11.6% [95% CI, 6.3-16.8]), the RCs of HPV16/18/31/33/45/52/58 were higher in AIS than in CIN2-3 (97.4% [95% CI, 94.8-100] vs 89.2% [95% CI, 88.1-90.2]) due to a greater contribution of HPV16/18 in AIS.

The RCs of HPV16/18/31/33/45/52/58 in ICC were similar between age groups (94.0% for 20-24 years, 95.5% for 25-29 years, 94.2% for 30-34 years, and 92.8% for 35-39 years) (Figure 4A). As previously reported, the RCs of HPV16/18 were greater in younger age groups. By contrast, the RCs of HPV31/33/45/52/58 altogether increased with age, to compensate for the decrease of HPV16/18 in RCs. A similar finding was observed for CIN2-3/AIS (Figure 4B).

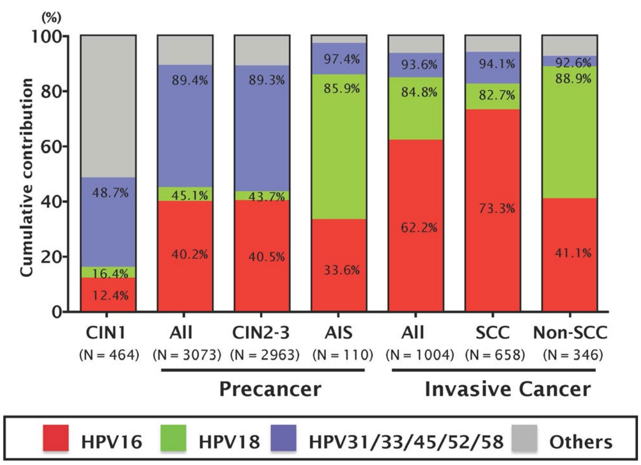

FIGURE 3 Cumulative relative contribution of the oncogenic types included in a 9-valent human papillomavirus (HPV) vaccine in cervical cancer and precancer that are positive for HPV DNA, by histology. Invasive cancer includes squamous cell carcinoma (SCC) and others (Non-SCC). Cervical precancer includes cervical intraepithelial neoplasia grade 2-3 (CIN2-3) and adenocarcinoma in situ (AIS). A 9-valent HPV vaccine covers HPV16 (red), HPV18 (green), and HPV31/33/45/52/58 (blue). Other HPV types are indicated in gray

These observations suggest that the 9-valent vaccine would provide approximately 90% protection against cervical cancer and precancer in Japan, regardless of histology (squamous cell histology vsglandular cell histology) or age.

4 | DISCUSSION

The present study provided representative data for HPV type contributions to cervical cancer and precancer in Japan. We focused on young Japanese women of reproductive age, because these women are the major target population of cervical cancer screening and vaccination. In addition, the large dataset enabled us to evaluate the oncogenic potential of individual HPV genotypes and to estimate the population-based impact of bivalent, quadrivalent, or 9-valent HPV vaccines.

Based on a comparison of type-specific RCs between CIN1 and CIN2-3/AIS/ICC, our data indicated that the relative risks of progression to CIN2+ vary considerably by HPV genotype. The relative risk was highest in HPV16, followed by HPV31, HPV18, HPV35, HPV33, HPV52, HPV58, HPV82, and HPV45 (Figure 2). The relatively high progression risk for HPV31 was consistent with that of our previous study.[19] We also confirmed that the 8 carcinogenic types of HPV16/18/31/33/35/45/52/58 confer far higher risks for progression to CIN2+ compared with the other carcinogenic and noncarcinogenic types. This supports the Japanese clinical guidelines that recommend discriminating these 8 types from other carcinogenic types in CIN management to assist in making a treatment decision for women with CIN2 or determine follow-up intervals according to risk stratification of progression to CIN3+.[16]

Of the 8 higher-risk types mentioned above, the most important HPV types are HPV16, 18, 31, 52, and 58 because they were the 5 most common types in both CIN2-3/AIS and ICC. Both HPV52 and HPV58 were lower in the estimated risk of progression (Figure 2), but much higher in the proportional contribution to cervical cancer and precancer (Figure 1), compared with HPV33 and HPV35. The 5 HPV types (HPV16, 18, 31, 52, and 58) contributed to 86.7% of CIN2-3/AIS and 92.7% of ICC, while incorporating 9 more carcinogenic types adds only an additional 5.1% and 3.7%, respectively. Human papillomavirus 16, 18, 31, 52, and 58 were also the top 5 genotypes contributing to cervical cancer in recent HPV studies in Japan.[19-21]

Current HPV tests for cervical cancer screening include as many as 13-14 carcinogenic types, which lead to a high sensitivity for detecting CIN2+, but substantial loss in specificity.[8] Therefore, HPV tests require additional triage to stratify screen-positive women according to risks for CIN2+ or CIN3+.[22] Of the 14 carcinogenic types, progression risk and disease contribution varied considerably by individual HPV genotype.[3,5,19-21,23] Thus, HPV genotyping could serve as triage to characterize an HPV-positive woman's risk more accurately. Currently, HPV tests discriminating HPV16 and 18 (Cobas; Roche Molecular Systems) and HPV16, 18, 31, 45, 51, and 52 (Oncoclarity; Becton Dickinson) are available. In

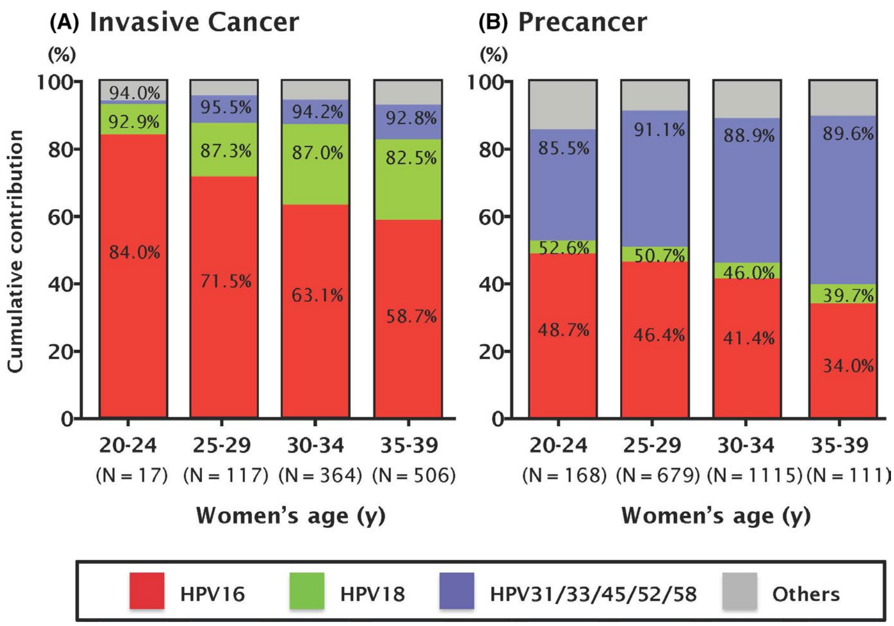

FIGURE 4 Cumulative relative contribution of the oncogenic types included in a 9-valent human papillomavirus (HPV) vaccine in cervical cancer and precancer that are positive for HPV DNA, by age group. A 9-valent HPV vaccine covers HPV16 (red), HPV18 (green), and HPV31/33/45/52/58 (blue). Other HPV types are indicated in gray. Relative contributions (RCs) of these types in cervical cancer (A) and precancer (B) are shown for 4 age groups (20-24, 25-29, 30-34 and 35-39 years)

Japan, however, HPV16, 18, 31, 52, and 58 should be considered when a new HPV test is developed for stratifying Japanese women according to risks for CIN2+ or CIN3+, although further studies are needed.

Human papillomavirus 82 was unexpectedly estimated to represent a higher risk type compared with HPV45. Although HPV82 contributed to 2.3% of CIN2-3/AIS, there was no ICC case positive for HPV82. Recent HPV studies in Japan also reported no association between HPV82 and ICC.[20,21] Global metaanalyses have suggested that HPV82 could be carcinogenic, accounting for less than 0.1% of ICC globally.[5]

The combined contribution of all carcinogenic types (HPV16, 18, 31, 33, 45, 52, and 58) in the 9-valent vaccine was 89.4% for CIN2-3/AIS and 93.6% for ICC among unvaccinated women, suggesting that the 9-valent vaccine would provide approximately 90% protection against cervical cancer and precancer in young Japanese women. The estimated impact of the 9-valent vaccine was approximately 10% higher than global estimates from metaanalyses of worldwide HPV distribution studies.[5,6] This could be explained by a relatively younger age in our study subjects and/or a higher contribution of HPV52 and HPV58 in Japan. The addition of HPV31, 33, 45, 52, and 58 to the prophylactic HPV vaccine would increase protection against ICC by only 8.8%, but against CIN2-3/AIS by 44.3%. Furthermore, the addition of these 5 types would increase protection against AIS by only 11.5%, but against CIN2-3 by 45.6%. These observations suggest that a shift from bivalent or quadrivalent vaccines to a 9-valent vaccine could provide greater protection against CIN2-3 compared with ICC and AIS in Japan. Also, the combined RCs of all carcinogenic HPV types in the 9-valent vaccine were 48.7% for CIN1. Given that most screen-positive women are diagnosed with CIN1, the number of colposcopy referrals could be reduced to half in the era of the 9-valent vaccine.

Human papillomavirustype distributions in ICC also vary greatly by age.[19,24,25] For instance, HPV16/18 prevalence in ICC in the present study was much higher than previously reported across a wide age range (85.0% vs 65.4-71.2%).[20,21] This is explained by a younger age of our study subjects, in keeping with previous reports.[19,24,25] In our previous study, HPV16/18 prevalence in ICC was highest in women aged 20-29 years (90.0%), followed by a gradual decline, and lowest in women aged 60 years or older (56.3%).[19] In the present study, even among women aged 20-39 years, HPV16/18 prevalence in ICC peaked in women aged 20-24 years (92.9%), decreased with age thereafter, and was found to be lowest in women aged 35-39 years (82.5%). Therefore, the current HPV16/18 vaccines have been estimated to provide greater protection against ICC among younger women.[19] However, the estimated protection of the 9-valent vaccine did not differ by age, because the additional RCs of HPV31/33/45/52/58 increased with age (Figure 4B). A similar trend for HPV type contribution was observed for CIN2-3/AIS (Figure 4A). Accordingly, the 9-valent vaccine would provide approximately 90% protection against both cervical cancer and precancer, regardless of a woman's age.

The existence of multiple infections complicates the estimates of type-specific contributions in such cases. In cases with multiple infections, a conservative hierarchical approach attributes each lesion to the most oncogenic HPV type among all HPV types detected. However, this method tends to overestimate the contribution of HPV16 and HPV18 that are considered to have the greatest oncogenic potential. In the present study, we used another method, in which multiple infections were added to single types in accordance with a proportional weighting attribution in women with single infections. Although this method might overestimate the contribution of less oncogenic types, recent studies of HPV type distributions have used this method.[3,5,26]

The present study has several potential limitations. First, the histology of our cervical specimens was not reviewed by central pathologists. Therefore, misclassification of histology might have affected our results. However, the good agreement with previous reports in Japan suggests the correctness and representativeness of our data to a considerable extent.[19-21] Our findings depended on local diagnoses by participating institutions that could reflect clinical practice in Japan. Second, the Roche LA assay cannot directly detect HPV52. Specimens that tested negative for HPV33, 35, and 58 individually, but were positive for the HPVmix (a combined probe for HPV33, 35, 52, and 58), were considered to be HPV52 positive. Thus, LA cannot discriminate HPV52 infection when it is coinfected with HPV33, 35, and 58, suggesting that HPV52 prevalence might be underestimated in the present study. Finally, we identified 8.8% (100/1130) of HPV-negative ICC cases, particularly among women with adenocarcinoma (12.7% [52/410]). Unfortunately, we cannot assess the quality of these HPV-negative specimens because DNA samples were not collected from the commercial laboratory. However, this proportion of HPV-negative ICC was similar to that of recent reports using fresh cervical samples in Japan.[19-21] As previously suggested,[5,27,28] HPV negativity in ICC was most likely to be attributable to technical artifacts, although we cannot completely ignore the possibility that a small fraction of ICC cases might arise independently of HPV exposure. In the present study, data from HPV-positive cases were analyzed in detail.

In conclusion, we updated HPV type-specific risks of and contributions to cervical cancer and precancer in Japan, using a large dataset from young Japanese women with cervical abnormalities. Our findings support the Japanese guidelines that recommend discriminating HPV16, 18, 31, 33, 35, 45, 52, and 58 in the clinical management of women with CIN1 or CIN2.[16] Our data and previous reports suggest that type-specific HPV-based screening tests and protocols should focus on HPV16, 18, 31, 52, and 58.[19-21] We also evaluated the likely impact of current and 9-valent vaccines on cervical cancer and precancer. The 9-valent vaccine would reduce most HPV-related cervical cancer and precancer among Japanese women up to an age of 40 years, with a greater reduction of HPV31, 33, 45, 52, and 58 for CIN2-3.

4.1 | Participating institutions

The institutions that participated in this study are as follows: Hokkaido University Graduate School of Medicine and Faculty of Medicine; Tohoku University Graduate School of Medicine; Jichi Medical University; University of Tsukuba; Saitama Cancer Center; Saitama Medical University International Medical Center; National Cancer Center Hospital; Cancer Institute Hospital; Keio University School of Medicine; Kanagawa Cancer Center; Kyoto University Graduate School of Medicine; Kindai University Faculty of Medicine; Osaka International Cancer Institute; Hyogo Cancer Center; Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; National Hospital Organization Shikoku Cancer Center; Kyusyu University; NHO Kyusyu Cancer Center; Kurume University School of Medicine; Kumamoto University; and University of the Ryukyus.

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The authors have no conflict of interest relevant to this article.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8:e191-203.
3. Muñoz N, Bosch FX, Castellsagué X, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer*. 2004;111:278-285.
4. Joura EA, Giuliano AR, Iversen OE, et al. Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;19(372):711-723.
5. de Sanjose S, Quint WG, Alemany L, et al. Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 2010;11:1048-1056.
6. Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. *Infect Agent Cancer*. 2012;7:38.
7. Hildesheim A, Herrero R, Wacholder S, et al. Costa Rican HPV Vaccine Trial Group. Effect of human papillomavirus 16/18 L1 virus-like particle vaccine among young women with preexisting infection: a randomized trial. *JAMA*. 2007;298:743-753.
8. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 2007;357:1579-1588.
9. Ronco G, Dillner J, Elfström KM, et al. International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383:524-532.
10. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol*. 2004;103:304-309.
11. Aitken CA, van Agt HME, Siebers AG, et al. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Med*. 2019;17:228.
12. Sultana F, Roeske L, Malloy MJ, et al. Implementation of Australia's renewed cervical screening program: Preparedness of general practitioners and nurses. *PLoS ONE*. 2020;15:e0228042.
13. Simms KT, Steinberg J, Caruana M, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *Lancet Oncol*. 2019;20:394-407.

14. Yagi A, Ueda Y, Kakuda M, et al. Epidemiologic and clinical analysis of cervical cancer using data from the population-based osaka cancer registry. *Cancer Res*. 2019;79:1252-1259.
15. Utada M, Chernyavskiy P, Lee WJ, et al. Increasing risk of uterine cervical cancer among young Japanese women: Comparison of incidence trends in Japan, South Korea and Japanese-Americans between 1985 and 2012. *Int J Cancer*. 2019;144:2144-2152.
16. Kawaguchi R, Matsumoto K, Akira S, et al. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2017 edition. *J Obstet Gynaecol Res*. 2019; 45: 766-786.
17. Matsumoto K, Yaegashi N, Iwata T, et al. Monitoring the impact of a national HPV vaccination program in Japan (MINT Study): rationale, design and methods. *Jpn J Clin Oncol*. 2014; 44: 1000-1003.
18. Matsumoto K, Yaegashi N, Iwata T, et al. Study Group. Reduction in HPV16/18 prevalence among young women with high-grade cervical lesions following the Japanese HPV vaccination program. *Cancer Sci*. 2019;110:3811-3820.
19. Onuki M, Matsumoto K, Satoh T, et al. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. *Cancer Sci*. 2009;100:1312-1316.
20. Sakamoto J, Kamiura S, Okayama K, et al. Single type infection of human papillomavirus as a cause for high-grade cervical intraepithelial neoplasia and invasive cancer in Japan. *Papillomavirus Res*. 2018;6:46-51.
21. Azuma Y, Kusumoto-Matsuo R, Takeuchi F, et al. Human papillomavirus genotype distribution in cervical intraepithelial neoplasia grade 2/3 and invasive cervical cancer in Japanese women. *Jpn J Clin Oncol*. 2014;44:910-917.
22. Wentzensen N, Schiffman M, Palmer T, Arbyn M. Triage of HPV positive women in cervical cancer screening. *J Clin Virol*. 2016;76(Suppl 1):S49-S55.
23. Matsumoto K, Oki A, Furuta R, et al. Japan HPV And Cervical Cancer Study Group. Predicting the progression of cervical precursor lesions by human papillomavirus genotyping: a prospective cohort study. *Int J Cancer*. 2011;128:2898-2910.
24. Nakagawa S, Yoshikawa H, Onda T, Kawana T, Iwamoto A, Taketani Y. Type of human papillomavirus is related to clinical features of cervical carcinoma. *Cancer*. 1996;78:1935-1941.
25. Hammer A, Rositch A, Qeadan F, Gravitt PE, Blaakaer J. Age-specific prevalence of HPV16/18 genotypes in cervical cancer: A systematic review and meta-analysis. *Int J Cancer*. 2016;138: 2795-2803.
26. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. 2015; 107: djv086.
27. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189:12-19.
28. Arroyo Mühr LS, Lagheden C, Eklund C, et al. Sequencing detects human papillomavirus in some apparently HPV-negative invasive cervical cancers. *J Gen Virol*. 2020;101:265–270. https://doi.org/10.1099/jgv.0.001374.

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