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Specificity of the Linear Array HPV Genotyping Test for detecting human papillomavirus genotype 52 (HPV-52)

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Abstract

Introduction: HPV-52 is one of the most frequent human papillomavirus (HPV) genotypes causing significant cervical pathology. The most widely used HPV genotyping assay, the Roche Linear Array HPV Genotyping Test (Linear Array), is unable to identify HPV-52 status in samples containing HPV-33, HPV-35, and/or HPV-58.
Methods: Linear Array HPV-52 analytical specificity was established by testing 100 specimens reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but not with the HPV-33, HPV-35, and/or HPV-58 individual probes, using an HPV-52–specific real-time PCR assay with a detection level of 3.9 DNA copies/reaction. In addition, we established the prevalence of HPV-52 in 49 samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but containing either HPV-33, HPV-35, and/or HPV-58 using the same approach.
Results: The HPV-52–specific assay detected HPV-52 in all 100 samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but not with the HPV-33, HPV-35, and/or HPV-58 probes. The presence of up to six other HPV genotypes did not influence the HPV-52 analytical performance of Linear Array. Only 6/49 (12.2%) samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but containing either HPV-33, HPV-35 or/and HPV-58, were HPV-52 positive.
Conclusions: Linear Array is a highly reliable test for detecting HPV-52 in the absence of genotypes HPV-33, HPV-35, and HPV-58. Additional testing using an HPV-52–specific test is necessary when HPV-33, HPV-35, and/or HPV-58 are present in the sample.

Keywords: HPV, human papillomaviruses, Linear Array, HPV genotype 52, HPV-52

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Introduction

Cervical cancer affects 530,000 women annually and is still one of the three leading cancers in 90% of countries worldwide (1, 2). It has been widely demonstrated that persistent infection with human papillomaviruses (HPV) is etiologically linked with cervical cancer (2). In 2009, the International Agency for Research on Cancer (IARC) classified 12 HPV genotypes (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, and HPV-59) as high-risk HPV (hrHPV) genotypes (3). HPV-16 is the major causative agent of cervical cancer worldwide and also the HPV genotype most commonly found in women with normal cervical cytological findings, followed by HPV-18, HPV-52, HPV-31, and HPV-58 (4).

HPV-52 is one of the most frequent hrHPV genotypes causing significant cervical pathology. It was first characterized by Wayne Lancaster in May 1987 (5) and is classified taxonomically in the genus *Alphapapillomavirus* (*Alpha*-PV) as species Alpha-9. In a recent meta-analysis on HPV genotype distribution across the complete spectrum of cervical disease, HPV-52 ranked second in women with a cytological finding of atypical squamous cells of undetermined significance, third in women with high-grade squamous intraepithelial lesions, and third in women with histologically confirmed cervical intraepithelial neoplasia grade 3 (CIN3) (6). However, the relative etiological importance of HPV-52 significantly dropped between CIN3 and invasive cervical cancers (cancer:CIN3 ratio 0.35), a pattern that was also seen for all other hrHPV genotypes except HPV-16, HPV-18, and HPV-45 (6). Similarly, in Slovenia HPV-52 is the fourth most frequently identified hrHPV genotype in women with normal cytology (7), sixth among women with CIN3 (8), but ranked only tenth in women with invasive cervical cancer (9).

In a recent review of commercially available HPV tests, at least 125 distinct tests for detecting *Alpha*-PVs were identified with at least 84 variants, but unfortunately no single publication in peer-reviewed literature could be found for more than 75% of HPV tests (10). HPV DNA full genotyping tests, which allow individual determination of several *Alpha*-PV genotypes, including all 12 officially recognized hrHPV genotypes, are the largest group of currently available commercial HPV tests. Currently, these tests are indispensable as research tools, but their clinical value has not been finally determined (10). As the use of prophylactic HPV vaccines becomes more widespread, surveillance for population-levels of effectiveness is becoming an increasingly important activity, which requires the use of standardized HPV genotyping tests with analytical performance different from tests with clinically validated cutoffs; for example, tests with higher analytical sensitivity and absolute analytical specificity (10).

The currently most frequently used HPV full genotyping tests utilize the principle of reverse hybridization. In these tests, a fragment of the HPV genome is first PCR-amplified with biotin-labeled primers, and the resulting amplicons are then denatured and detected using HPV genotype-specific probes immobilized on a strip, filter (DNA microarray chip), or microtiter well. The Linear Array HPV Genotyping Test (Linear Array; Roche Molecular Diagnostics, Pleasanton, CA) currently has the most abundant data in peer-reviewed literature among commercially available genotyping tests (10). Linear Array combines PCR-amplification and reverse-line blot hybridization for simultaneously detecting 36 individual HPV genotypes (HPV-6, HPV-11, HPV-16, HPV-18, HPV-26, HPV-31, HPV-33, HPV-35, HPV-39, HPV-40, HPV-42, HPV-44, HPV-45, HPV-51, HPV-52, HPV-53, HPV-54, HPV-56, HPV-58, HPV-59,

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HPV-61, HPV-62, HPV-64, HPV-66, HPV-67, HPV-68, HPV-69, HPV-70, HPV-71, HPV-72, HPV-73, HPV-81, HPV-82, HPV-83, HPV-84, and HPV-89), and one HPV subtype (subHPV-82 or IS39), including all 12 hrHPV genotypes. Additional primer pairs targeting the human β-globin gene provide a control for cell adequacy, extraction, and amplification. Because directly detecting HPV-52 in Linear Array is prohibited due to intellectual property rights, HPV-52 is identified using a probe that cross-reacts with HPV-33, HPV-35, and HPV-58 (11–13). Therefore Linear Array is unable to correctly determine HPV-52 status in women co-infected with either HPV-33, HPV-35, and/or HPV-58 (10, 11). Because the manufacturer of Linear Array does not provide any supplementary test to resolve the final HPV-52 status in specimens containing HPV-33, HPV-35, and/or HPV-58, correctly detecting HPV-52 DNA in these samples currently relies merely on different in-house HPV-52–specific assays (11–14), including Universal ProbeLibrary-based HPV 52-specific real-time PCR, developed in our laboratory (12).

In the first part of this study, the analytical specificity of Linear Array for detecting HPV-52 was established by testing 100 routine specimens reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but not with the HPV-33, HPV-35, and/or HPV-58 genotype-specific individual probes, using a rapid and reproducible HPV-52–specific real-time PCR assay with a detection level of 3.9 DNA copies/reaction (12). Using the same approach, in the second part of the study we established the prevalence of HPV-52 infection in samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but also containing either HPV-33, HPV-35, and/or HPV-58.

Methods

For the first part of the study, 100 consecutive routine cervical smears obtained from the same number of Slovenian women, which tested reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but not with the individual HPV-33, HPV-35, and/or HPV-58 genotype-specific probes (defined for the purpose of this study as "Linear Array true HPV-52–positive") were selected from cervical smear archives at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia (Table 1). For the second part of the study, 49 consecutive samples defined for the purpose of this study as "Linear Array possible HPV-52–positive" – samples which reacted positively with an HPV-33/35/52/58 cross-reactive hybridization probe and in addition also with probe(s) specific for either HPV-33 (eight samples), HPV-35 (12 samples), and/or HPV-58 (31 samples) were selected from the same archives (Table 2).

All samples included in the study were tested initially for the presence of 13 and 14 hrHPV with either of two clinically validated HPV assays: the Hybrid Capture 2 HPV DNA Test (Qiagen, Hilden, Germany) and/or the RealTi*m*e High Risk HPV test (Abbott, Wiesbaden, Germany), respectively, according to the manufacturer's instructions and as previously described (15). Linear Array was performed according to the manufacturer's instructions (11).

An HPV-52–specific real-time PCR assay with a detection level of 3.9 HPV-52 DNA copies/reaction was performed as previously described (12). Briefly, the assay was performed on a LightCycler 1.5 Real-time PCR instrument (Roche Diagnostics) in a 20 µl reaction mixture containing water, 5 µl of template DNA, 5 µl of 5× LightCycler TaqMan Master Mix (Roche Diagnostics), 0.8 µM of each of the primers, and 0.2 µM of TaqMan probe (12).

Results

As shown in Table 1, among 100 samples used to evaluate Linear Array HPV-52 analytical specificity, 34 samples contained HPV-52 only, 21 samples contained one additional HPV genotype, 18 samples contained two additional HPV genotypes, and 27 samples contained three to six additional HPV genotypes. A clearly detectable fluorescence signal using an HPV-52–specific real-time PCR assay was obtained in all 100 "Linear Array true HPV-52–positive" samples, resulting in 100% analytical specificity of the Linear Array for detecting HPV-52. The presence of several other HPV genotypes (for details, see Table 1) did not influence the analytical performance of either Linear Array or an HPV-52–specific real-time PCR assay for detecting HPV-52.

Of the 49 samples labelled as "Linear Array possible HPV-52–positive", only six samples tested positive with an HPV-52–specific real-time PCR assay (samples 144–149, Table 2), giving 12.2% prevalence of HPV-52 infection in samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but containing HPV-33 and/or HPV-35 and/or HPV-58. As shown in Table 2, among 43 "Linear Array possible HPV-52–positive" samples that tested HPV-52-negative using an HPV-52–specific real-time PCR assay (samples 101–143, Table 2), 26 (60.5%) samples contained HPV-58, 11 (25.6%) samples contained HPV-35, five (11.6%) samples contained HPV-33, and one sample (2.3%) contained HPV-33 and HPV-58 (sample 132, Table 2). Among six "Linear Array possible HPV-52–positive" samples that tested HPV-52–positive using an HPV-52–specific real-time PCR assay (samples 144–149, Table 2), three samples contained HPV-58, one sample contained HPV-35, one sample contained HPV-33, and one sample contained HPV-33 and HPV-58.

Discussion

In the past two decades, various tests for detecting and genotyping a broad spectrum of HPV genotypes have been developed, validated, and introduced into clinical laboratories (10). In addition to recently introduced HPV tests that can discriminate HPV-16 and HPV-18 (both account for 73% of all cervical cancer worldwide) from other hrHPV genotypes (15–17), there is increased interest in sensitive and specific genotyping tests that will be necessary to evaluate real-life clinical efficacy of prophylactic HPV vaccines and will impact current and future HPV vaccination programs (18).

In this study, we evaluated the analytical specificity of Linear Array, the most commonly used HPV genotyping assay (10, 18), to detect HPV-52 in the absence/presence of genotypes HPV-33, HPV-35, and HPV-58. HPV-52 is a hrHPV genotype that is highly prevalent in various Asian and African countries and accounts for a larger fraction of cervical cancers in these regions (6). Knowledge of the exact prevalence and geographical distribution of HPV-52 is thus important for designing and implementing next-generation HPV vaccines with a broader spectrum of protection than current HPV vaccines and for designing the next generation of clinically useful HPV tests. Due to the inability of Linear Array to resolve the HPV-52 status in specimens containing HPV-33, HPV-35, and/or HPV-58, correctly detecting HPV-52 DNA in these samples mainly relies on in-house HPV-52–specific assays. Several different in-house HPV-52–specific real-time PCR-based assays have been developed in the past years (11–14, 19). Sensitivity and specificity of HPV-52–specific real-time PCR developed by Coutlee et al. in 2007 were evaluated on 265 anogenital samples obtained from

Table 1 | Distribution of HPV genotypes in 100 samples that tested positive with the HPV-33/35/52/58 cross-reactive probe, but not with the HPV-33, HPV-35, or HPV-58 genotype-specific individual probes with HPV Linear Array ("Linear Array true HPV-52–positive" samples), assessed by using an HPV-52–specific real-time PCR assay.

Sample no.	Linear Array result	HPV-52 real-time PCR assay result	Frequency
1–34	**52**	Positive	34
35–38	16, **52**	Positive	4
39, 40	18, **52**	Positive	2
41, 42	31, **52**	Positive	2
43	42, **52**	Positive	1
44	45, **52**	Positive	1
45	**52**, 54	Positive	1
46	**52**, 56	Positive	1
47	**52**, 59	Positive	1
48	**52**, 61	Positive	1
49, 50	**52**, 62	Positive	2
51–53	**52**, 66	Positive	3
54	**52**, 83	Positive	1
55	**52**, 89	Positive	1
56	16, 42, **52**	Positive	1
57	16, **52**, 59	Positive	1
58	16, **52**, 89	Positive	1
59	18, 39, **52**	Positive	1
60	18, **52**, 59	Positive	1
61	18, **52**, 82	Positive	1
62	31, 45, **52**	Positive	1
63	31, **52**, 54	Positive	1
64	39, 51, **52**	Positive	1
65	39, **52**, 54	Positive	1
66	42, **52**, 56	Positive	1
67	42, **52**, 66	Positive	1
68	45, **52**, 89	Positive	1
69	51, **52**, 58	Positive	1
70	**52**, 59, 73	Positive	1
71	**52**, 61, 73	Positive	1
72	**52**, 62, 89	Positive	1
73	**52**, 66, 89	Positive	1
74	6, 16, **52**, 66	Positive	1
75	6, 39, **52**, 67	Positive	1
76	16, 18, 35, **52**	Positive	1
77	16, 42, **52**, 83	Positive	1
78	16, 45, 51, **52**	Positive	1
79	16, **52**, 59, 66	Positive	1
80	16, **52**, 61, 84	Positive	1
81	18, 51, **52**, 53	Positive	1
82	18, **52**, 56, 62	Positive	1
83	18, **52**, 66, 84	Positive	1
84	18, **52**, 73, 89	Positive	1
85	31, **52**, 53, 70	Positive	1
86	39, 42, **52**, 55	Positive	1
87	39, 42, **52**, 83	Positive	1
88	42, **52**, 56, 68	Positive	1
89	42, **52**, 58, 59	Positive	1
90	45, **52**, 58, 62	Positive	1
91	**52**, 53, 54, 62	Positive	1
92	52, 53, 62, 89	Positive	1
93	16, 51, **52**, 59, 82	Positive	1
94	31, 39, 45, **52**, 66	Positive	1
95	51, **52**, 61, 82, 84	Positive	1
96	**52**, 53, 59, 73, 84	Positive	1
97	16, **52**, 53, 59, 66, 84	Positive	1
98	16, **52**, 54, 61, 66, 73	Positive	1
99	39, 45, **52**, 53, 61, 62, 68	Positive	1
100	6, 11, 40, 51, **52**, 59, 84	Positive	1

Table 2 | Distribution of HPV genotypes in 49 samples that tested positive with the HPV-33/35/52/58 cross-reactive probe and with at least one of the HPV genotype-specific probes for HPV-33, HPV-35, or HPV-58 with HPV Linear Array ("Linear Array possible HPV-52–positive" samples), assessed by using an HPV-52–specific real-time PCR assay.

Sample	Linear Array result	HPV-52–specific real-time PCR assay results	HPV genotype(s)	Frequency
101, 102	33, **52***	Negative	33	2
103–105	35, **52***	Negative	35	3
106–114	**52***, 58	Negative	58	9
115	16, 35, **52***	Negative	16, 35	1
116–118	16, **52***, 58	Negative	16, 58	3
119	18, 33, **52***	Negative	18, 33	1
120	18, 35, **52***	Negative	18, 35	1
121	31, 35, **52***	Negative	31, 35	1
122	35, 51, **52***	Negative	35, 51	1
123	35, **52***, 89	Negative	35, 89	1
124	**52***, 53, 58	Negative	53, 58	1
125	**52***, 58, 59	Negative	58, 59	1
126	**52***, 58, 66	Negative	58, 66	1
127, 128	**52***, 58, 84	Negative	58, 84	2
129	6, 51, **52***, 58	Negative	6, 51, 58	1
130	16, 35, **52***, 59	Negative	16, 35, 59	1
131	16, 35, **52***, 89	Negative	16, 35, 89	1
132	33, 42, **52***, 58	Negative	33, 42, 58	1
133	**52***, 53, 56, 58	Negative	53, 56, 58	1
134	**52***, 58, 82, 89	Negative	58, 82, 89	1
135	16, 51, **52***, 58, 84	Negative	16, 51, 58, 84	1
136	16, **52***, 53, 58, 61	Negative	16, 53, 58, 61	1
137, 138	51, **52***, 58, 61, 83	Negative	51, 58, 61, 83	2
139	**52***, 53, 58, 66, 89	Negative	53, 58, 66, 89	1
140	16, 18, 33, 39, **52***, 68	Negative	16, 18, 33, 39, 68	1
141	31, 45, 51, **52***, 53, 58	Negative	31, 45, 51, 53, 58	1
142	16, 35, 51, **52***, 53, 55, 56, 84	Negative	16, 35, 51, 53, 55, 56, 84	1
143	16, 18, 31, 33, 51, **52***, 53, 84, 89	Negative	16, 18, 31, 33, 51, 53, 84, 89	1
144	33, **52***	Positive	33, **52**	1
145	33, **52***, 58	Positive	33, **52**, 58	1
146	42, 51, **52***, 58	Positive	42, 51, **52**, 58	1
147	**52***, 54, 58, 81, 89	Positive	**52**, 54, 58, 81, 89	1
148	35, **52***, 62, 83, 84	Positive	35, **52**, 62, 83, 84	1
149	51, **52***, 53, 56, 58, 61, 62, 84	Positive	51, **52**, 53, 56, 58, 61, 62, 84	1

*Co-infection with HPV-52 cannot be ruled out.

Canadian women, and tests showed excellent agreement with conventional HPV-52 typing methods (14). Stevens et al. developed the Roche Light Cycler 480-based HPV-52 highly specific real-time PCR assay in 2008, with sensitivity equivalent to Linear Array, which was successfully evaluated on a panel of Australian samples containing both single and multiple HPV genotypes (13). In the following years, two additional HPV-52–specific real-time PCRs were developed based on TaqMan chemistry (11, 12). More recently, a new HPV-52–specific real-time TaqMan-based assay targeting the E6/E7 region was developed, which can be used as a duplex assay (simultaneously detecting beta-globin) or as a single-target detection assay (19).

For determining HPV-52 status in this study, we used an HPV-52–specific real-time PCR assay with a detection level of 3.9 DNA

copies/reaction developed in our laboratory in 2010 (12). In the initial evaluation, the test proved to be highly specific, sensitive, and reproducible for detecting HPV-52 infection in clinical samples and confirming the presence/absence of HPV-52 in clinical samples tested Linear Array–positive for HPV-52 in the presence of HPV-33, HPV-35, and/or HPV-58 (12). Because our test targets the E6 gene of HPV-52, which is always retained after potential viral integration into the host-cell chromosome and is actively expressed in cervical carcinoma, it could significantly diminish the problems of detecting integrated forms of HPV-52 that may lack larger parts of the viral genome.

In this study, using an HPV-52–specific in-house real-time PCR assay we further confirmed the exceptional analytical specificity of Linear Array for detecting HPV-52. The presence of several other HPV genotypes (up to seven different HPV genotypes) did not influence the analytical performance of Linear Array. Based on our results, the confirmation of HPV-52 status in samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but not with the HPV-33, HPV-35, and/or HPV-58 genotype-specific individual probes ("Linear Array true HPV-52–positive"), using supplementary test(s) is not necessary and is not recommended. In contrast, the second part of this study showed a relatively low prevalence of HPV-52 infection in samples reactive with the Linear Array HPV-33/35/52/58 cross-reactive probe, but containing HPV-33, and/or HPV-35 and/or HPV-58 ("Linear Array possible HPV-52–positive" samples). In such samples, however, the confirmation of HPV-52 status using HPV-52–specific tests, such as HPV-52 real-time PCRs, is obligatory and highly recommended.

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