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Transmission and treatment of cutaneous warts in general practice

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CHAPTER 4

Cutaneous wart-associated HPV types: prevalence and relation with patient characteristics

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ABSTRACT

Background

Epidemiological data on cutaneous wart-associated HPV types are rare.

Objectives

To examine the prevalence of cutaneous wart-associated HPV types and their relation with patient characteristics.

Study design

Swabs were taken from all 744 warts of 246 consecutive immunocompetent participants and analysed by a broad spectrum HSL-PCR/MPG assay. Patient details including location, duration, and number of warts were recorded.

Results

No HPV DNA was detected in 49 (7%) swabs, a single HPV type in 577 (78%) swabs, and multiple HPV types in 118 (16%) swabs. HPV 2, 27 and 57 (alpha genus), HPV 4 (gamma genus) and HPV 1 (mu genus) were the most frequently detected HPV types, and HPV 63 (mu genus) was only frequently detected together with other HPV types. Less frequently detected HPV types were HPV 3, 7, 10 and 28 (alpha genus), 65, 88 and 95 (gamma genus) and 41 (nu genus). Warts containing HPV 1 showed the most distinct clinical profile, being related to children aged <12 years, plantar location, duration <6 months, and to patients with < 4 warts.

Conclusions

HPV 27, 57, 2 and 1 are the most prevalent HPV types in cutaneous warts in general population. Warts infected with HPV 1 have a distinct clinical profile.

BACKGROUND

Cutaneous warts are benign papillomas of the skin of which common warts (*verrucae vulgaris*) and plantar warts (*verrucae plantaris*) are the most common types. Up to one third of primary school children have cutaneous warts.¹ Although cutaneous warts have a benign natural history, they cause significant physical and psychological inconvenience. Therefore, patients with warts frequently consult physicians, mostly in primary care.^{2,3} Warts are caused by infection with human papillomaviruses (HPV). More than 120 HPV types, distributed over 5 genera and 16 species, have been described based on their DNA sequences.^{4,5} HPV 2, 7, 27 and 57 from the alpha genus, HPV 4 and 65 from the gamma genus, and HPV 1 from the mu genus have most frequently been detected in cutaneous warts.⁶⁻¹¹ However, epidemiological data on cutaneous wart-associated HPV types are rare, and available studies are conducted in selected patient groups such as patients from dermatology clinics. The prevalence of cutaneous wart-associated HPV types in the general population is largely unknown.

Specific types of infecting HPV are correlated with histological characteristics and, to a lesser extent, with morphological features of warts.¹²⁻¹⁶ Clinical characteristics other than morphological wart features may be useful to predict the prognosis and make treatment decisions. For example, the decisions of patients to consult physicians, and of physicians to start treatment, are influenced by the age of the patients as well as the location, duration, and number of warts.^{3,17,18} Little is known about the relation between these patient characteristics and associated HPV genotypes.

OBJECTIVES

This study examines the prevalence of wart-associated HPV types in a large sample of patients with cutaneous warts in primary care, and explores the relation between HPV types and patient characteristics.

STUDY DESIGN

Patients and samples

We collected our samples from the warts of the participants of the Warts Randomised Treatment Study (WARTS).¹⁷ All patients aged ≥ 4 years who attended one of the 50 participating family practices with one or more new cutaneous warts were invited to participate in this trial. We defined new warts as warts on the skin that were presented for the first

time without prior treatment from a general practitioner or dermatologist in the previous year. We excluded immune compromised patients, patients with genital warts, seborrheic warts, or mosaic warts ≥ 1 cm in diameter. Trained research nurses confirmed eligibility and obtained informed consent. Details on patient inclusion are already published.¹⁷

The protocol was approved by the medical ethical committee of the Leiden University Medical Center. The research nurses took swabs from each single wart by firmly rubbing a pre-wetted cotton-tipped stick over the surface of the wart five times. This swab technique adequately detects HPV types present in wart scab as well as wart biopsy.¹⁹ Only when warts were too close to take separate swabs, was a single swab taken from the cluster of warts. We considered multiple warts as a cluster when the distance between warts was ≤ 1 cm. All swabs were stored in 1 ml of saline solution.

HPV identification

We used a newly developed broad spectrum PCR/MPG assay for genotyping all known wart-associated HPV types from the alpha- (HPV 2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 77, 91 and 94), gamma- (HPV 4, 65, 95, 48, 50, 60 and 88), mu- (HPV 1 and 63) and nu-genus (HPV 41) to determine HPV distribution. This sensitive and specific assay (HSL-PCR/MPG assay; Labo Biomedical Products BV, Rijswijk, the Netherlands) has been described and evaluated by de Koning et al.²⁰ In short, 10 μ l of the saline solution was used in the single-step HSL-PCR, generating a biotinylated amplicon of 76-84 bp from the L1 region. Subsequently, simultaneous identification of the 23 HPV genotypes was performed with bead-based xMAP suspension array technology. Negative samples were not analysed any further. All PCR reactions were carried out with all precautions to avoid contamination described by the manufacturer. Negative PCR and genotyping controls were incorporated and remained negative upon analysis with the HSL-PCR/MPG assay.

Patient characteristics

We recorded the following characteristics: sex (male vs. female); age (4-11 years vs. 12-20 years vs. 21 years and older); location of warts (plantar warts [warts on the soles of the feet] vs. common warts [warts on other locations than soles of the feet, mostly hand warts]); duration of warts at the time of investigation (≤ 6 months vs. > 6 months); number of warts per patient (< 4 vs. ≥ 4 warts); part of cluster of warts (yes vs. no); inconvenience caused by warts (pain, irritation, or cosmetic inconvenience; yes vs. no). For statistical purposes and clear presentation of results, the characteristics were dichotomised with cut-off values closest to the median.

Statistical analysis

Prevalence with 95% confidence interval (CI) was calculated for warts associated with a single HPV type and for warts associated with multiple HPV types. We used warts with a single HPV type in our primary analysis. All HPV types were stratified according to dichotomised patient characteristics. We considered a number of <30 warts per HPV type too small to reliably investigate their relation with patient characteristics. For the most prevalent HPV types, proportions of warts per characteristic were compared using 95% CI. In the sensitivity analyses, prevalence and clinical profiles were calculated with a proportional weighting attribution, which includes information about warts with multiple types.²¹⁻²³ For example, in a wart with multiple types consisting of HPV 2 and HPV 4 where prevalence in single types is 22% and 5%, respectively, using the proportional attribution, the case would be split between the two types with the prevalence in single types used as reference: 22/27 for HPV 2 and 5/27 for HPV 4.

To explore the different types involved in warts with multiple HPV types, we compared observed numbers of specific 2-type combinations with expected numbers, which were obtained by multiplying the prevalence of both HPV types in warts with a single type, multiplied by the total number of warts. We also repeated analyses of prevalence and clinical profiles with patients instead of warts as unit of analysis, and assessed concordance of HPV types within patients with multiple warts calculating the proportions of patients sharing one HPV type in all warts.

RESULTS

Patients and samples

Of the 250 included patients, 246 provided wart swabs for HPV testing. The swabs of 4 patients were lost in transport to the laboratory. Median age was 13 (range 4-73) years and 59% of the participants were female (Table 4.1). At study entry, 91 patients (37%) had one wart, 117 (58%) had 2-5 warts, and 38 (15%) had 6 or more warts. Sixty patients (24%) had at least one cluster of warts. Furthermore, 103 patients (42%) had plantar warts only, 108 (44%) had common warts only, and 35 (14%) had both plantar and common warts. All 744 warts from these 246 patients were analysed: 373 plantar warts (50%) located on the soles of the feet, and 371 common warts (50%) of which 75% was located on hands and 25% on the rest of the body.

Table 4.1. Patient characteristics of the study population (n=246)

Sex	
Female	150 (58.9)
Male	96 (41.1)
Age	
4-11 years	107 (43.5)
12-21 years	45 (18.3)
21+ years	94 (38.2)
Location of warts	
Plantar warts only	103 (41.9)
Common warts only	108 (43.9)
Plantar as well as common warts	35 (14.2)
Duration of oldest wart	
< 6 months	100 (40.7)
≥ 6 months	146 (59.3)
Number of warts	
1	91 (37.0)
2	47 (19.1)
3	33 (13.4)
4	24 (9.8)
5	13 (5.3)
6 or more	38 (15.4)
Presence of wart cluster	60 (24.4)
Warts cause inconvenience*	184 (74.8)

Data are numbers of patients (%)

* Pain, irritation, or cosmetic inconvenience

HPV type prevalence

From the 744 swabs, 49 (7%) were negative for HPV DNA, 577 (78%) were positive for a single HPV genotype, and 118 (16%) swabs contained DNA of multiple HPV types. In total, 217 warts (29%) were part of a cluster, of which 27 clusters providing 69 warts had been swabbed with a single swab because warts were too close to take separate swabs. In these swabs, the proportion of swabs with multiple HPV types was equal to the proportion in all swabs (also 16%).

Table 4.2 presents the prevalence of HPV types in all HPV-positive warts. Most prevalent HPV types in warts with a single HPV type were HPV 27 (24%), HPV 57 (22%), HPV 2 (22%), and HPV 1 (19%). Their combined relative contribution was 86% (95% confidence interval (CI) 83-88%). Furthermore, HPV 4, HPV 65, HPV 28, HPV 3 and HPV 10 were each present in 1-5% of swabs, and HPV 7, HPV 63, HPV 41 and HPV 95 in <1%. The prevalence

Table 4.2. Human papillomavirus (HPV) types in all HPV-positive warts, according to a single or multiple HPV type present (n=695).

HPV type*	Warts with single HPV type			Warts with multiple HPV types					All warts			
	number of warts with single type (n=577)	%	95%CI	number of warts with two types (n=94)	number of warts with three types (n=20)	number of warts with four types (n=4)	number all warts with multiple types (n=118)	%	95%CI	proportional weighting attribution (n=695)†	%‡	95%CI
27	137	23.7	20.5-27.4	35	7	3	45	38.1	29.9-47.1	162	23.3	20.3-26.6
57	126	21.8	18.7-25.4	26	3	-	29	24.6	17.7-33.1	145	20.9	18.0-24.0
2	125	21.7	18.5-25.2	45	10	3	58	49.2	40.3-58.1	166	23.9	20.9-27.2
1	107	18.5	15.6-21.9	29	9	2	40	33.9	26.0-42.8	130	18.7	16.0-21.8
4	29	5.0	3.5-7.1	27	10	1	38	32.2	24.4-41.1	36	5.2	3.8-7.1
65	14	2.4	1.5-4.0	5	5	-	10	8.5	4.7-14.9	15	2.2	1.3-3.6
28	13	2.3	1.3-3.8	2	1	-	3	2.5	0.9-7.2	14	2.0	1.2-3.3
3	10	1.9	0.9-3.2	-	-	-	-	-	-	10	1.4	0.8-2.6
10	8	1.4	0.7-2.7	5	-	-	5	4.2	1.8-9.5	8	1.2	0.6-2.3
7	3	0.5	0.2-1.5	-	-	-	-	-	-	3	0.4	0.1-1.3
63	2	0.3	0.1-1.3	10	10	4	24	20.3	14.1-28.5	2	0.3	0.1-1.1
41	2	0.3	0.1-1.3	2	3	3	8	6.8	3.5-12.8	2	0.3	0.1-1.1
95	1	0.2	0.0-1.0	1	-	-	1	0.9	0.1-4.6	1	0.1	0.0-0.8
88	-	-	-	1	2	-	3	2.5	0.9-7.2	0	0.0	0.0-0.5

HPV types 29,77,94, 40,43,91,48,50,60 were tested, but not identified in wart swabs

* One of multiple HPV types involved in warts with multiple types

† The mean number of HPV types per wart is 2.2 (264/118) for warts with multiple HPV types, and 1.2 (841/695) for all warts

‡ Rounded off in whole numbers

§ Sum of percentages ≠ 100% due to rounding off

of HPV types in all warts according to the proportional attribution was comparable to the prevalence in warts with a single HPV type (Table 4.2).

HPV type and patient characteristics

Table 4.3 presents data on the relation between patient characteristics and the detected HPV types in warts associated with a single HPV type. The four most prevalent HPV types were related to specific clinical profiles (Figure 4.1). Warts with HPV 1 showed the most distinct clinical profile, being related to children aged <12 years, plantar location, duration <6 months at the time of investigation, and to patients with < 4 warts. For these characteristics, the 95% CI for HPV 1 did not overlap the 95% CI of all warts, nor the CI of the other most prevalent HPV types. Warts with HPV 27 and warts with HPV 57 had a similar clinical profile which slightly differed from warts with HPV 2: HPV 27/57 were related to patients aged ≥ 12 years, especially to patients aged 21+; HPV 2 was related to location on the hands (Table 4.3). Less frequently detected HPV types were found in warts with short as well as long duration.

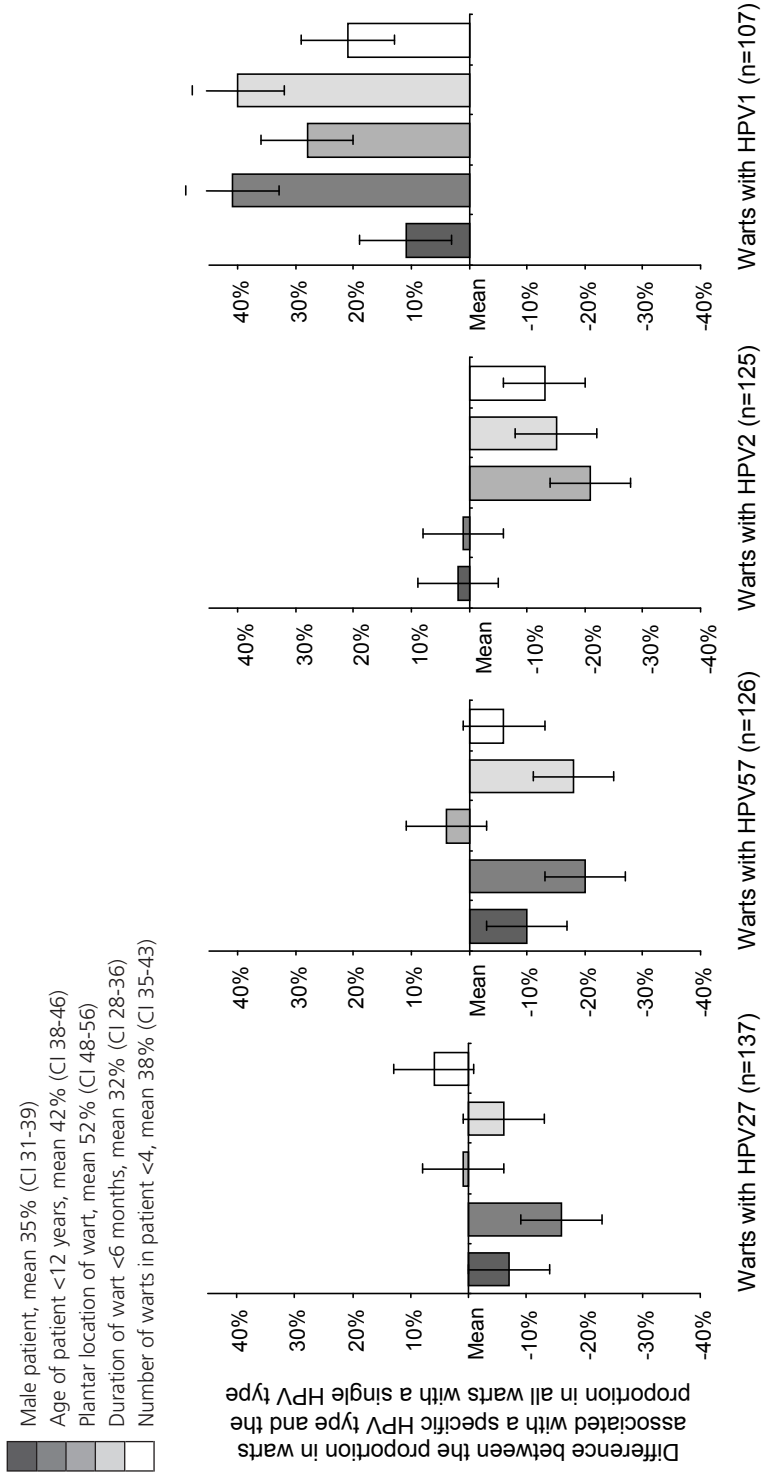
Warts with multiple HPV types

In warts associated with multiple HPV types ($n=118$), HPV 4 and HPV 63 were also involved in >20% in addition to the highly prevalent HPV 27, 57, 2 and 1 (Table 4.2). Warts with double HPV types ($n=94$) were observed less frequently than expected (Appendix 4.1). The combination of HPV 2 and 4 ($n=18$), and the combination of HPV 1 and 27 ($n=18$) were the most prevalent. In all observed combinations, one of the four most prevalent HPV types was present, with the exception of the combination HPV 65 and 28 ($n=1$). Remarkably, the combination of HPV 1 and 57, and the combination of HPV 1 and 2 were not observed, while combinations with HPV 63 ($n=10$) were more prevalent than expected. Patient characteristics of warts with combinations of multiple types did not reveal significant profiles (data not shown).

Patients with multiple warts

When patients were used as unit of analysis, HPV prevalence (Appendix 4.2) and clinical profiles (data not shown) were in line with the results in warts. In 74% of patients with multiple warts ($n=150$), all warts shared one HPV type. In a further 23% of patients with multiple warts some but not all warts shared one HPV type. As an example for this, a 6 year old boy had a plantar wart associated with HPV 65 and two hand warts, of which one was also associated with HPV 65 but the other with HPV 57. Within all clusters of warts ($n=82$), the HPV positive warts shared one HPV type, with the exception of one plantar cluster of 3 warts, where in one wart HPV 27 was detected and in the other two warts HPV 57 was detected.

Figure 4.1: Patient characteristics of warts in relation to the four most prevalent HPV types (n=577). X-axis represents the mean proportion in all warts. Differences between proportions are considered significant when 95% CIs of proportions do not overlap.



Difference between the proportion in warts associated with a specific HPV type and the proportion in all warts with a single HPV type

Table 4.3. Clinical profiles of all identified HPV types in warts with single HPV type (n=577).

Patient characteristic	Alpha										Gamma		Mu		All warts (n=577)
	Species 2		Species 4		Species 8		Species 1		Species 1		Species 2		Species 1		
	HPV3 (n=10)	HPV10 (n=8)	HPV28 (n=13)	HPV2 (n=125)	HPV27 (n=137)	HPV57 (n=126)	HPV7 (n=3)	HPV4 (n=29)	HPV65 (n=14)	HPV95 (n=1)	HPV1 (n=107)	HPV63 (n=2)	HPV41 (n=2)	Species 1 (n=2)	
Male	3 (30)	0 (0)	4 (31)	46 (37)	39 (28)	32 (25)	3 (100)	19 (66)	7 (50)	1 (100)	49 (46)	0 (0)	0 (0)	0 (0)	203 (35)
Age	3 (30)	0 (0)	4 (31)	54 (43)	36 (26)	28 (22)	0 (0)	19 (66)	10 (71)	0 (0)	89 (83)	0 (0)	0 (0)	0 (0)	243 (42)
12-20 years	0 (0)	0 (0)	0 (0)	51 (41)	44 (32)	38 (30)	0 (0)	1 (3)	1 (7)	0 (0)	8 (7)	2 (100)	0 (0)	0 (0)	145 (25)
21+ years	7 (70)	8 (100)	9 (69)	20 (16)	57 (42)	60(48)	3 (100)	9 (31)	3 (21)	1 (100)	10 (9)	0 (0)	2 (100)	2 (100)	189 (33)
Plantar location	0 (0)	0 (0)	0 (0)	39 (31)	72 (53)	70 (56)	0 (0)	18 (62)	10 (71)	0 (0)	86 (80)	2 (100)	2 (100)	2 (100)	299 (52)
<6 months duration	0 (0)	0 (0)	0 (0)	21 (17)	35 (26)	18 (14)	3 (100)	21 (72)	5 (36)	1 (100)	77 (72)	2 (100)	0 (0)	0 (0)	183 (32)
<4 warts in patient	0 (0)	0 (0)	0 (0)	31 (25)	60 (44)	40 (32)	3 (100)	9 (31)	12 (86)	1 (100)	63 (59)	1 (50)	2 (100)	2 (100)	222 (38)
Part of cluster	2 (20)	5 (63)	7 (54)	47 (38)	26 (19)	55 (44)	2 (67)	11 (38)	0 (0)	0 (0)	20 (19)	0 (0)	0 (0)	0 (0)	175 (30)
Inconvenience*	7 (70)	8 (100)	11 (85)	101 (81)	112 (82)	91 (72)	3 (100)	27 (93)	7 (50)	1 (100)	89 (83)	1 (50)	2 (100)	2 (100)	260 (80)

Data are numbers (percentages)

* Pain, irritation, or cosmetic inconvenience

DISCUSSION

Main findings

In the present study, HPV 27, 57, 2 and 1 were the most prevalent HPV types. In only 14% of warts other HPV types were detected. The clinical profile of warts associated with HPV 1 from the mu genus differed from those associated with HPV 27, 57 and 2 from the alpha genus. Warts with HPV 1 usually occurred in children, preferentially on a plantar surface, and had a short duration before presentation to the physician. In 74% of patients with multiple warts, one HPV type was shared in all warts of that patient.

Comparison with literature

Three other large HPV prevalence studies analysing cutaneous wart-associated HPV types have been conducted, all in selected dermatology populations.^{6,8,9} In these studies, different HPV type prevalences were reported. For example, the prevalence of HPV 1 was reported to be 44% by Hagiwara et al., 27% by Iftner et al., and 4% by Rubben et al., compared to 19% in the present study. These differences may be due (in part) to regional differences, or to patient selection. Our study was conducted in primary care, in which patient selection is less likely to have occurred than, for example, in a dermatology department. Alternatively, this discrepancy may be explained by the use of different HPV detection and typing methods in each study.

The observation that HPV 1 is related to young patients, plantar location, and short duration is in line with others.^{9,16} Furthermore, in the prevalence studies, the higher the proportion of plantar warts, the higher the reported prevalence of HPV 1.^{6,8,9} However, Hagiwara et al., Chen et al., and Tomson et al. found no relation with age.^{6,7,11} The reasons for this are not clear, but may be influenced by their study population with a very low prevalence of HPV 2/27/57^{6,7} or HPV 1.¹¹

In the current study, the presence of multiple HPV types was detected in 16% of all swabs, which is more than reported in other studies;^{6,9,20,24,25} this is probably due to our HSL-PCR/MPG method which is specifically capable of detecting multiple HPV types per sample.²⁰ These warts with multiple HPV types were analysed separately from the warts with a single HPV type, since combining them would dilute associations with patient characteristics and reduce the clarity of interpretation. In addition to the highly prevalent HPV 27, 57, 2 and 1 in warts with a single type, HPV 4 and 63 were also frequently detected in warts with multiple types. We hypothesise that in a wart in which multiple HPV types are detected, usually only one HPV type will be responsible for the development of the wart. This is supported by evidence on the clonal origin of warts,²⁶ and by a recent study which found that within a defined cervical intraepithelial neoplastic lesion, only one HPV type is present.²⁷ In the latter

study, analysis was done on dissected lesional cells for which biopsies were needed. For the present primary care population, however, non-invasive swabs of the lesion were used and the sensitive HSL-PCR/MPG could have picked up a passenger HPV type present on the skin.^{28,29} We could not use the relative abundance of HPV types, because the HSL-PCR/MPG technology is not a quantitative method. Results presented by De Koning et al. support that HPV types identified in wart swabs are representative for the HPV type present in the wart biopsy by showing a very high concordance (96%) between the HPV type detected in the wart swabs and wart biopsies: comparing HPV types on different sites, 24/25 wart swabs, 19/25 perilesional swabs and 9/25 normal epithelium swabs were identical to the wart biopsy. In the perilesional and normal epithelium swabs 3 and 2 multiple infections were detected and 2/25 and 11/25 were HPV negative, respectively.¹⁹ Alternatively, a co-infection of single cells with multiple HPV types could be responsible for the development of some warts with multiple types;²⁴ for completeness, the results of sensitivity analysis including the warts with multiple types were comparable.

Strengths and limitations

The present study population was a large non-selected sample of patients with first presentation of single or multiple warts in primary care. However, HPV type prevalence could be different in the general population since HPV types causing warts with little inconvenience are underrepresented in primary care. Only 7% of all swabs were negative for HPV DNA. The HSL-PCR/MPG was designed to amplify all HPV types previously found in cutaneous warts as well as related types from the same viral species.⁴ Viral loads below the detection limit of the assay, other or unknown HPV types, or not yet described variants of the types included in the assay may be involved in these negative swabs. Also, lesions (e.g. callus) could have been misdiagnosed as warts or residual hyperkeratotic lesions following HPV clearance could have been sampled; however, no histological investigation of the warts was made. Also, no data on mosaic warts were collected, since this was one of the exclusion criteria.

Implications

This is the first large study combining a comprehensive genotyping assay analysing all known cutaneous wart-associated HPV types and simple non-invasive swabs to collect viral DNA. This could be of special interest if specific HPV infections prove to be associated with clearance or response to specific treatments. In that case, HPV genotyping or HPV type assessment based on clinical profiles may become relevant for daily practice.

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Appendix 4.1. Specific combinations of HPV types in warts with two types (n=94)

HPV types*	27	57	2	1	4	65	Total
27							130 - 35
57	37 - 6						124 - 26
2	37 - 8	34 - 10					124 - 45
1	32 - 18	29 - 0	29 - 0				108 - 29
4	8 - 2	8 - 1	8 - 18	7 - 6			34 - 27
65	4 - 0	4 - 0	4 - 2	3 - 2	1 - 0		16 - 5
28	4 - 0	4 - 0	4 - 1	3 - 0	1 - 0	0 - 1	16 - 2
3	3 - 0	3 - 0	3 - 0	2 - 0	1 - 0	0 - 0	12 - 0
10	2 - 0	2 - 3	2 - 1	2 - 1	0 - 0	0 - 0	8 - 0
7	1 - 0	1 - 0	1 - 0	1 - 0	0 - 0	0 - 0	4 - 0
63	1 - 1	1 - 4	1 - 3	0 - 2	0 - 0	0 - 0	3 - 10
41	1 - 0	1 - 1	1 - 1	0 - 0	0 - 0	0 - 0	3 - 2
95	0 - 0	0 - 1	0 - 0	0 - 0	0 - 0	0 - 0	0 - 1
88	0 - 0	0 - 0	0 - 1	0 - 0	0 - 0	0 - 0	0 - 1

Data are numbers of combinations Expected (multiplying prevalences of both HPV types in warts with a single type multiplied by the total number of warts) – Observed.

* HPV types are ordered according to prevalence in warts with a single type.

Appendix 4.2. Human papillomavirus (HPV) types in 236 patients* with single or multiple warts, with a single or multiple HPV type present.

HPV type	Patients with single wart		Patients with multiple warts		All patients		
	patients with warts with a single type (n=79)	patients with warts with multiple types (n=7)	patients with warts with a single type (n=76)	patients with warts with multiple types (n=74)†	total (n=236)	%	95%CI
27	23	3	19	35	80	33.9	28.2-40.2
57	12	1	14	35	62	26.3	21.1-32.2
2	11	2	18	33	64	27.1	21.8-33.1
1	25	6	18	24	73	30.9	25.4-37.1
4	5	3	2	17	27	11.4	8.0-16.1
65	2	-	2	11	15	6.4	3.9-10.2
28	-	-	1	3	4	1.7	0.7-4.3
3	-	-	1	1	2	0.8	0.2-3.0
10	-	-	-	3	3	1.3	0.4-3.7
7	-	-	1	-	1	0.4	0.1-2.4
63	-	1	-	12	13	5.5	3.2-9.2
41	-	-	-	3	3	1.3	0.4-3.7
95	1	-	-	1	2	0.8	0.2-3.0
88	-	-	-	2	2	0.8	0.2-3.0
Mean number per patient	1 (79/79)	2.3 (16/7)	1 (76/76)	2.4 (180/74)	1.5 (361/236)		

HPV types 29,77,94, 40,43,91,48,50,60 were tested, but not identified in wart swabs

* In 10 of 246 patients (4%), all swabs were negative for HPV DNA.

† Due to different HPV types in warts with a single type, or due to multiple HPV types in a single wart.

