

## Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis

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This meta-analysis investigated human papillomavirus (HPV) prevalence in vulvar, vaginal and anal intraepithelial neoplasia (VIN, VAIN, AIN) grades 1–3 and carcinoma from 93 studies conducted in 4 continents and using PCR assays. Overall HPV prevalence was 67.8%, 85.3% and 40.4% among 90 VIN1, 1,061 VIN2/3 and 1,873 vulvar carcinomas; 100%, 90.1% and 69.9% among 107 VAIN1, 191 VAIN2/3 and 136 vaginal carcinomas; and 91.5%, 93.9% and 84.3% among 671 AIN1, 609 AIN2/3 and 955 anal carcinomas, respectively. HPV16 was found more frequently (>75%) and HPV18 less frequently (<10%) in HPV-positive vulvar, vaginal and anal carcinomas than in cervical carcinoma. HPV6 and 11 were common in VIN1 and AIN1, but not in VAIN1. HPV prevalence in vulvar carcinoma varied most by histological type (69.4% in warty-basaloid and 13.2% in keratinized type) and was also higher in women 60 years or younger and in studies carried out in North America. HPV prevalence in anal carcinoma was higher among women (90.8%) than men (74.9%), but no difference by gender emerged in North America. The majority of AIN2/3 derived from studies of HIV-positive individuals and/or men who have sex with men. Among AIN2/3, HIV infection was associated with higher HPV prevalence, more multiple-type infections and a relative under-representation of HPV16. In conclusion, ~40% of vulvar, 60% of vaginal and 80% of anal carcinoma may be avoided by prophylactic vaccines against HPV16/18. This proportion would be similar for the corresponding high-grade lesions of the vagina and anus, but higher for VIN2/3 (75%) than for vulvar carcinoma.

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**Key words:** vulva; vagina; anus; carcinoma; human papillomavirus; human immunodeficiency virus; meta-analysis

Anogenital carcinomas other than cervical carcinoma are relatively rare. Only a few areas of the United States show age-standardized incidence rates for vulvar carcinoma in women, or anal carcinoma in men, greater than 2 per 100,000, and those for vaginal cancer in all parts of the world are below 1 per 100,000.<sup>1</sup> Anogenital carcinomas share many risk factors with cervical carcinoma, namely those relating to sexual behavior and smoking,<sup>2–6</sup> and immunosuppression.<sup>7,8</sup> Increases in their incidence have been reported in the last decades in some high-resource countries, notably in women and men below age 50 years.<sup>9–13</sup>

In 2005, an expert working group convened by the International Agency for Research on Cancer established a causal role for human papillomavirus (HPV) 16 in a subset of vulvar, vaginal and anal carcinoma.<sup>14</sup> A similar role for types other than HPV16 could not be established due to the limited number and size of the reviewed studies.

Also strongly related to HPV are vulvar, vaginal and anal intraepithelial neoplasia (VIN, VAIN, AIN) grades 1–3, which are considered precursor lesions of carcinoma in the corresponding sites. However, scant data are available on the HPV types that contribute to intraepithelial neoplasia, as well as their potential to progress to carcinoma in the anogenital tract.<sup>14</sup>

Current prophylactic HPV vaccines against HPV types 16/18, or 6/11/16/18, are thus expected to offer protection against anogenital carcinomas<sup>14</sup> and their precursor lesions.<sup>15</sup> To estimate the fraction of cancerous and precancerous lesions of the anogenital tract that may be prevented by HPV vaccines, we collated all relevant data published from 4 continents on the prevalence of HPV overall, and of individual HPV types.

### Material and methods

#### Search strategy and selection criteria

MEDLINE and regional databases (MedCarib, LILACS, African Index Medicus, IndMed and IMSEAR) were used to search for articles published between January 1986 and March 2008, regardless of language of publication. Combinations of the MeSH terms: “papillomavirus,” “papillomavirus infections,” “vulva neoplasms,” “vagina neoplasms” and “anal neoplasms” were used. References cited in selected articles were also investigated. Eligibility criteria included the report of HPV DNA detection by means of PCR in a minimum of 4 cases. Studies had to provide a clear description of PCR primers and methods used for HPV typing, and DNA prevalence had to be reported for carcinoma and intraepithelial neoplasia separately. Careful checks were made to avoid including overlapping data. Where study methods suggested that additional data were available, these data were requested and provided by some investigators.<sup>2–4,16–20</sup>

A total of 63 studies on vulvar lesions, 14 on vaginal lesions and 29 on anal lesions identified from MEDLINE were included in the present meta-analysis (no additional studies were retrieved from regional databases). Detailed information on each of the 93 included studies (some dealing with more than 1 anogenital site) is listed in Tables AI–AVI.

#### Data extraction

For each study, information on country, sample size, age group, gender (when applicable), type of specimen, PCR primers used to detect the presence of HPV DNA, and overall and type-specific HPV prevalence was extracted. HIV infection status was available only for AIN as none of the identified studies on vulvar and vaginal lesions, or anal carcinoma, explicitly included HIV-positive individuals.

Where possible, HPV findings were stratified by histological type of carcinoma (e.g., warty/basaloid or keratinizing),<sup>21,22</sup> grade of intraepithelial neoplasia (grades 1, 2 and 3)<sup>21</sup> with *in situ* carcinoma included as grade 3, age group, geographical region and HIV status. Thirty reported cases of differentiated VIN, which are often associated with lichen sclerosis or other dermatoses, and 32 cases of anal warts were not included in this report.

#### Estimation of HPV prevalence

Type-specific prevalence is presented for (i) 15 high-risk HPV types, namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82; and (ii) low-risk HPV Types 6 and 11.<sup>23</sup> No other type was found in more than 0.5% of any anogenital carcinomas.

**Abbreviations:** AIN, anal intraepithelial neoplasia; CI, confidence interval; HPV, human papillomavirus; MSM, men who have sex with men; OR, odds ratio; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

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**TABLE 1** – HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE IN INTRAEPITHELIAL NEOPLASIA AND CARCINOMA OF THE VULVA, VAGINA AND ANUS, BY GEOGRAPHICAL REGION

Region	Studies (N)	Intraepithelial neoplasia		Carcinoma		Countries represented
		Subjects (N)	HPV-positive (%)	Subjects (N)	HPV-positive (%)	
<b>Vulva</b>						
Asia	9	19	78.9	186	38.2	China, Hong Kong, Japan
Europe	34	520	80.6	929	34.7	Austria, Czech Republic, Denmark, Finland, Germany, Italy, Israel, the Netherlands, Poland, Spain, Sweden, United Kingdom
North America	18	627	88.8	443	63.2	Canada, United States
Latin America	2	12	100.0	161	24.2	Brazil, Colombia, Mexico, Peru, Puerto Rico
Oceania	3	19	36.8	154	28.6	Australia, New Zealand
Total	63 <sup>1</sup>	1,197	84.0	1,873	40.4	
<b>Vagina</b>						
Asia	3	72	100.0	16	43.8	Japan, Thailand
Europe	8	74	97.3	56	76.8	Denmark, Germany, Finland, Italy, Sweden, the Netherlands, Portugal, United Kingdom
North America	4	135	89.6	64	70.3	Canada, United States
Latin America	1	17	82.4	–	–	Brazil, Colombia, Mexico, Peru, Puerto Rico
Total	14 <sup>1</sup>	298	93.6	136	69.9	
<b>Anus</b>						
Asia	2	2	100.0	27	96.3	Japan, Korea
Europe	13	235	89.8	696	84.2	Czech Republic, Denmark, France, Germany, Italy, Norway, Sweden, Switzerland, United Kingdom
North America	14	1,043	93.3	232	83.2	United States, Canada
Total	29	1,280 <sup>2</sup>	92.7	955	84.3	

<sup>1</sup>Including one multicentric study (Ref. 15) whose components have been assigned to the corresponding regions.—<sup>2</sup>Includes 805 HIV-positive individuals (mainly men who have sex with men, MSM) and 210 HIV-negative MSM.

Methods for estimation of type-specific HPV prevalence have been described in detail previously.<sup>24</sup> Whereas most studies did report the prevalence of HPV16, the prevalence of other types was less frequently reported. Thus, the prevalence of an individual HPV type was based only on studies testing for the genotype in question, and includes the prevalence in single- and multiple-type infections. HPV type-distribution is expressed either as a proportion of all cases tested for the given HPV type, or as a proportion of HPV-positive women.

#### Statistical analysis

Odds ratios (ORs) for HPV positivity and corresponding 95% confidence intervals (CIs) in the 2 largest groups of carcinoma (*i.e.*, vulvar and anal) were estimated by unconditional logistic regression including terms for PCR primers (MY09/11 and/or GP5+/6+, other), geographical region (North America, elsewhere), major histological types (keratinized, warty, basaloid, large-cell and unspecified) and variables that were known or suspected to be possible sources of heterogeneity in HPV prevalence, *i.e.*, age group ( $\leq 60$ ; 61–70;  $\geq 71$  years) for vulvar carcinoma, and gender for anal carcinoma. Upon review, studies of AIN2/3 in which HIV status was not reported were considered on the basis of geographical region, age distribution and case sources, as unlikely to be HIV-positive and were therefore combined with the HIV-negative subjects. Crude ORs by HIV status (negative/not reported, positive) were computed for AIN2/3.

## Results

### Prevalence of HPV

Table I shows the number and location of studies included in the present meta-analysis and overall HPV prevalence separately for intraepithelial neoplasia and carcinoma. For all 3 anatomic sites considered, the majority of studies were from Europe and North America. The vast majority of information on HPV in AIN derived from studies of HIV-positive individuals or men who have sex with men (MSM).

Overall HPV prevalence in VIN was 84.0%—with a breakdown by grade of 67.8% in 90 VIN1 and 85.3% in 1,061 VIN2/3 (87.7% in 856 VIN3)—and 40.4% in 1,873 vulvar carcinomas. Overall HPV prevalence in VAIN was 93.6%—with a breakdown by

grade of 100.0% in 107 VAIN1 and 90.1% in 191 VAIN2/3 (88.2% in 110 VAIN3)—and 69.9% in 136 vaginal carcinomas. Finally, overall HPV prevalence in AIN was 92.7%—with a breakdown by grade of 91.5% in 671 AIN1, 93.9% in 609 AIN2/3 (94.0% in 234 AIN3)—and 84.3% in 955 anal carcinomas.

### HPV type-specific prevalence

Figure 1 shows the distribution of HPV types by site and lesion severity in studies that reported on individual HPV types (see also Tables AI–AVI).

The most common HPV types in VIN1 were HPV6 (22.4%), 16 (9.8%) and 11 (9.0%). In contrast, the most common HPV types in VIN2/3 and vulvar carcinoma were HPV16 (71.9% and 32.2%, respectively), 33 (8.0% and 4.5%) and 18 (5.0% and 4.4%) (Fig. 1). The prevalence of infections with multiple HPV types decreased from 13.4% in VIN1 to 2.8% in vulvar carcinoma (data not shown).

In VAIN1 HPV16 predominated (23.4%), but a broad range of other HPV types was detected, notably HPV56 (11.0%) and 51 (8.8%). In VAIN2/3, the most common HPV types were HPV16 (57.6%), 18 (6.9%) and 58 (5.9%). In vaginal carcinoma, the most common HPV types were HPV16 (53.7%), 18 (7.6%) and 31 (5.6%) (Fig. 1). The prevalence of multiple-type HPV infections decreased from 10.3% in VAIN1 to 3.4% in vaginal carcinoma (data not shown).

The most frequently detected types for AIN1 were HPV16 (37.2%), 6 (36.2%), 18 (21.3%) and 11 (18.1%). HPV16 (59.8%), 18 (17.4%), 33 (13.6%) and 58 (13.1%) were the types most frequently detected in AIN2/3. In anal carcinoma HPV16 (73.4%) predominated, followed by HPV18 (5.2%), and 33 (4.8%) (Fig. 1). The prevalence of multiple-type infections decreased from 54.4% in AIN1 to 6.8% in anal carcinoma (data not shown).

### Sources of heterogeneity in HPV prevalence

Table II describes the main sources of heterogeneity in HPV prevalence in vulvar carcinoma, both overall and stratified by geographical region. The HPV prevalence was significantly higher in North American studies than studies from elsewhere (OR = 2.87, 95% CI: 2.25–3.66) and in warty-basaloid (69.4%) compared to keratinized (13.2%) carcinomas (OR = 13.47, 95% CI: 9.36–

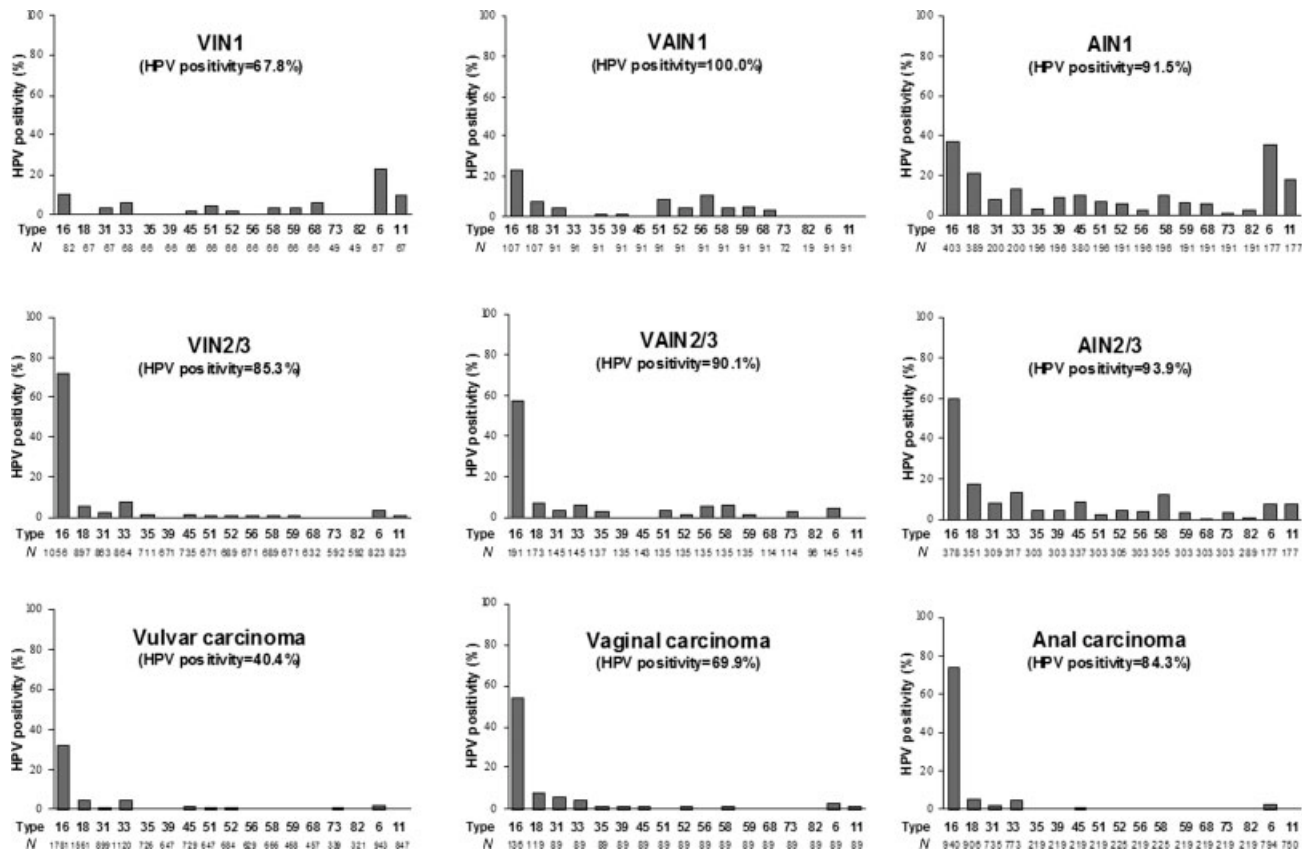


FIGURE 1 – Prevalence of human papillomavirus (HPV) types in vulvar intraepithelial neoplasia (VIN) grades 1 and 2/3, vulvar carcinoma, vaginal intraepithelial neoplasia (VAIN) 1 and 2/3, vaginal carcinoma, anal intraepithelial neoplasia (AIN) 1 and 2/3, and carcinoma of the anus. Only studies reporting individual HPV types were included. N, number tested for a given HPV type.

TABLE II – SOURCES OF HETEROGENEITY IN HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE IN 1,873 VULVAR CARCINOMAS

	North America		Elsewhere		Overall		
	N	HPV-positive (%)	N	HPV-positive (%)	N	HPV-positive (%)	OR <sup>1</sup> (95% CI)
Histological type							
Keratinized	68	25.0	508	11.6	576	13.2	1
Warty-basaloid	80	85.0	178	62.4	258	69.4	13.47 (9.36–19.39)
Unspecified	295	66.1	744	41.3	1,039	48.2	5.53 (4.18–7.32)
Age group (years)							
≥71	126	54.0	163	24.5	289	37.4	1
61–70	80	72.5	48	39.6	128	60.2	2.19 (1.41–3.40)
≤60	113	79.7	69	56.5	182	70.9	3.63 (2.40–5.47)
Unknown	124	51.6	1,150	32.5	1,274	34.4	1.30 (0.97–1.73)
PCR primers							
MY09/11 or GP5+/6+	312	66.7	682	33.3	994	43.8	1
Other	131	55.0	748	33.3	879	36.5	1.09 (0.88–1.35)
Geographical region	443	63.2	1,430	33.3	–	–	–
OR <sup>1</sup> (95% CI)	2.87 (2.25–3.66)		1		–		

<sup>1</sup>ORs adjusted for geographical region, histological type and PCR primers, except the OR for age group, which could be adjusted for geographical region and PCR primers only.

OR, odds ratio; CI, confidence intervals.

19.39). Young age at diagnosis was also associated with HPV prevalence (OR for women aged ≤60 versus women aged ≥71 years = 3.63, 95% CI: 2.40–5.47), whereas the type of PCR primers used had no influence. Consistent differences in HPV prevalence by histological type and age group were observed both in North America and elsewhere (Table II). HPV16 predominance was also consistent in all strata (data not shown). The type of specimen used (exfoliated cells or tissue samples) did not significantly affect HPV prevalence and was not included in the model (data not shown).

Table III shows the main sources of heterogeneity in HPV prevalence in anal carcinoma overall and stratified by geographical region. Large-cell carcinoma represented the most common histological type, but HPV prevalence was similar in large-cell and basaloid carcinoma. HPV-positive anal carcinoma was more frequent in women than men (OR = 3.46, 95% CI: 2.25–5.31), but equally frequent among the 2 genders in North American studies. PCR primers other than MY09/11 or GP5+/6+ detected fewer HPV infections (OR = 0.44, 95% CI: 0.27–0.73).

TABLE III – SOURCES OF HETEROGENEITY IN HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE IN 955 ANAL CARCINOMAS

	North America		Elsewhere		Overall		
	N	HPV-positive (%)	N	HPV-positive (%)	N	HPV-positive (%)	OR <sup>1</sup> (95% CI)
Histological type							
Large-cell	116	89.7	35	71.4	151	85.4	1
Basaloid	44	97.7	24	70.8	68	88.2	1.11 (0.45–2.73)
Unspecified	72	63.9	664	85.8	736	83.7	0.87 (0.47–1.61)
Gender							
Male	57	91.2	150	68.7	207	74.9	1
Female	114	90.4	475	90.9	589	90.8	3.46 (2.25–5.31)
Both	61	62.3	98	78.6	159	72.3	1.76 (0.92–3.37)
PCR primers							
MY09/11 or GP5+/6+	171	90.6	478	87.7	649	88.4	1
Other	61	62.3	245	78.8	306	75.5	0.44 (0.27–0.73)
Geographical region	232	83.2	723	84.6	–	–	–
OR <sup>1</sup> (95% CI)	0.90 (0.53–1.50)		1				

<sup>1</sup>ORs adjusted for geographical region, histological type, gender and PCR primers. OR, odds ratio; CI, confidence intervals.

#### Impact of HIV and lesion severity on HPV type distribution

Table IV shows HPV prevalence in AIN2/3 according to HIV status. HIV-positive individuals had a significantly higher prevalence of HPV infection (96.7%) than HIV-negative ones (90.1%) ( $\chi^2_1$ : 7.16;  $p = 0.0075$ ). A comparison of HPV type distribution by HIV status was also done, restricted to HPV-positive samples. Multiple-type infections were more frequently detected in HIV-positive individuals (OR = 12.60, 95% CI: 7.05–22.51), and the distribution of individual high-risk types also differed. HPV16 (OR = 0.38, 95% CI: 0.24–0.61) was significantly under-represented and most other types were significantly over-represented in AIN2/3 among HIV-positive, compared to HIV-negative individuals. Moreover, many HPV types were only detected in HIV-positive individuals.

Figure 2 shows a comparison of HPV6, 11, 16 and 18 prevalence by lesion severity among HPV-positive lesions. Because of the strong influence of HIV infection on HPV type distribution, HIV-positive AIN were not included. The HPV16 fraction increased markedly in all 3 sites with increasing lesion severity (Fig. 2). The HPV18 fraction also increased by lesion severity in the vulva, but not in the vagina or anus. HPV6 and 11 were far more common among HPV-positive VIN1 (29.4% and 11.8%) than in VIN2/3 (3.7% and 0.7%) or vulvar carcinoma (4.4% and 0.3%), whereas no clear trend in HPV6 or 11 was detectable in the corresponding vaginal lesions. Only 7 AIN1 in HIV-negative individuals were tested for HPV6 and 11, and hence, they were not used for comparison purposes (Fig. 2).

#### Discussion

In our present meta-analysis of anogenital cancerous and precancerous lesions, the first to our knowledge to systematically include all published information on the topic worldwide, the highest HPV prevalence was found in anal carcinoma (84.3%), improving on the precision of the previous consensus estimation of >50% for the proportion of anal carcinoma attributed to HPV infection.<sup>14</sup> The prevalence of HPV infection in our present meta-analysis on anal carcinoma approaches, therefore, that reported in a similar worldwide meta-analysis of cervical carcinoma (87.3%),<sup>25</sup> for which HPV infection is considered a necessary cause.<sup>14</sup> Also analogous with the cervix uteri, the majority of AIN and anal carcinoma are detected in a squamocolumnar junction (*i.e.*, the dentate line, between the anal canal and the rectum).<sup>26</sup>

HPV prevalence was lower in vaginal carcinoma (69.9%) and lower still in vulvar carcinoma (40.4%). Among high-grade lesions in the vulva (85.3%) and vagina (90.1%), however, HPV prevalence was as high as that in the corresponding precursor lesions of the cervix (cervical intraepithelial neoplasia grades 2/3, 84.9%).<sup>25</sup> Our present findings strongly support, therefore, the hypothesis raised in the early 1990s<sup>27,28</sup> that 2 distinct subsets of car-

cinoma in the vulva and vagina exist, one that is strongly associated with HPV and that may be preceded by high-grade lesions as in cervical carcinoma, and another, which arises independently of HPV infection and is of greater relative importance in the vulva than the vagina. It is conceivable that the presence of HPV in these cancer subsets may be accompanied by different gene expression profiles or genetic alterations as already shown in cancer of the oral cavity and pharynx, where HPV presence is accompanied by a lack of TP53 mutations.<sup>29</sup>

Whereas a broad range of high-risk and low-risk HPV types was detected in all grades of intraepithelial neoplasia, HPV16 was found in over three-quarters of HPV-positive anogenital carcinoma at all 3 sites. By comparison, HPV16 accounts for only approximately half of cervical carcinoma.<sup>25</sup> A stronger predominance of HPV16 than in cervical carcinoma has also been reported in HPV-related head and neck carcinoma.<sup>30</sup> In agreement with what has been found in cervical carcinoma, however, the relative importance of HPV16 infection in anogenital lesions increases substantially with their severity, highlighting the greater potential of HPV16 to progress to carcinoma in comparison to other types.

HPV18 seems to be rarer in noncervical anogenital carcinoma than in cervical carcinoma. In studies of cervical carcinoma, however, HPV18 has been shown to have a strong tropism for glandular epithelia, and hence adenocarcinoma.<sup>31</sup> Adenocarcinoma is rare in the vulva and vagina<sup>32</sup> and is excluded, by definition, from anal carcinoma in order to avoid misclassification with rectal adenocarcinoma. However, HPV18 is still under-represented in anogenital carcinoma, even if the comparison is restricted to squamous cell carcinoma of the cervix.<sup>31</sup> HPV6 was slightly more frequent in vulvar (2.0%) and anal (2.9%) carcinoma than in cervical carcinoma (0.5%),<sup>25</sup> but it was most often accompanied, among cases where this information was available, by multiple infections with high-risk types.

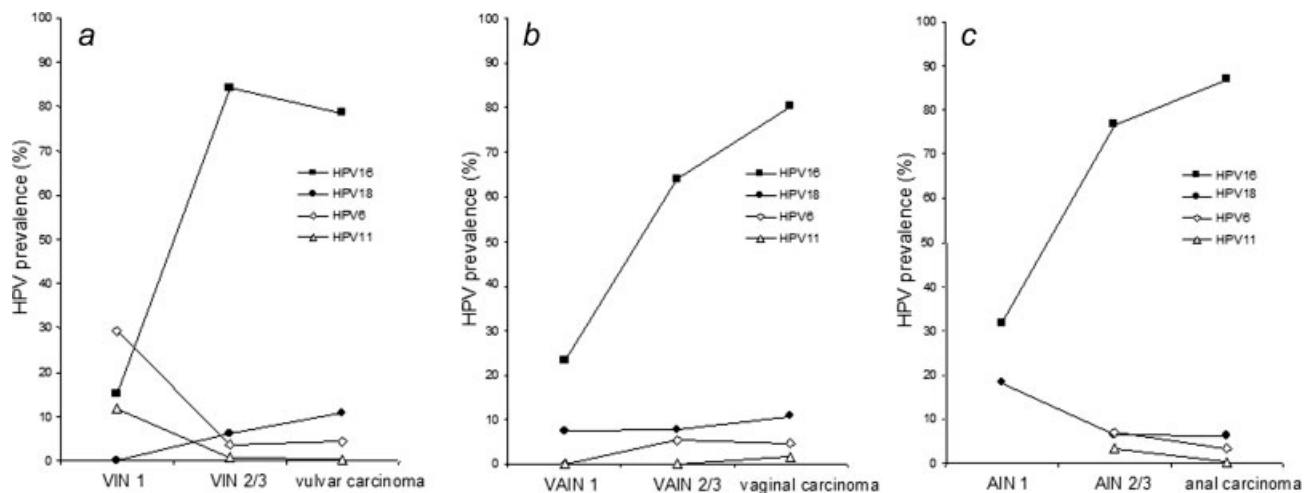
Strong sources of heterogeneity in HPV prevalence were found in our present meta-analysis, and they varied by anatomical site and type of population studied. In vulvar carcinoma, the clearest variation in HPV prevalence was found by histopathological type: HPV prevalence was 69.4% in warty-basaloid carcinoma, but only 13.2% in keratinized carcinoma. Histopathological type of vulvar carcinoma is known to be correlated with age at diagnosis, with warty-basaloid carcinoma being diagnosed more often among younger women than the keratinized type. This meta-analysis was not able to disentangle the independent effects of histological type and age, but carcinoma diagnosed at a younger age was indeed more likely to be HPV-positive. Many studies reported that the mean age at vulvar carcinoma diagnosis was significantly lower in HPV-positive than HPV-negative cases,<sup>33–35</sup> although this was not the case in the largest North American study.<sup>36</sup>

In addition, HPV prevalence among North American vulvar carcinoma was approximately twice that among those diagnosed

**TABLE IV** – ODDS RATIOS (ORS) OF HUMAN PAPILLOMAVIRUS (HPV) POSITIVITY FOR DIFFERENT TYPES AND CORRESPONDING 95% CONFIDENCE INTERVALS (CIS) AMONG INDIVIDUALS WITH ANAL INTRAEPITHELIAL NEOPLASIA 2/3 BY HIV STATUS

	HIV-positive		HIV-negative/not reported		OR (95% CI)
	Positive/tested (N) <sup>1</sup>	%	Positive/tested (N) <sup>1</sup>	%	
Any HPV type	208/215	96.7	145/161	90.1	$\chi^2_1: 7.16; p = 0.0075$
Within HPV-positive samples					
Multiple infections	137/208	65.9	17/128	13.3	12.60 (7.05–22.51)
High-risk type					
HPV16	115/208	55.3	111/145	76.6	0.38 (0.24–0.61)
HPV18	53/208	25.5	8/127	6.3	5.09 (2.36–10.92)
HPV31	24/182	13.2	3/113	2.7	5.57 (1.74–17.77)
HPV33	35/182	19.2	8/119	6.7	3.30 (1.50–7.27)
HPV35	13/182	7.1	0/109	0.0	$\infty$ (2.16– $\infty$ )
HPV39	14/182	7.7	0/109	0.0	$\infty$ (2.34– $\infty$ )
HPV45	29/208	13.9	1/117	0.9	18.79 (3.19– $\infty$ )
HPV51	7/182	3.8	0/109	0.0	$\infty$ (1.12– $\infty$ )
HPV52	14/182	7.7	0/111	0.0	$\infty$ (2.39– $\infty$ )
HPV56	11/182	6.0	0/109	0.0	$\infty$ (1.81– $\infty$ )
HPV58	39/182	21.4	1/111	0.9	30.00 (5.12– $\infty$ )
HPV59	10/182	5.5	0/109	0.0	$\infty$ (1.63– $\infty$ )
HPV68	2/182	1.1	0/109	0.0	$\infty$ (0.31– $\infty$ )
HPV73	9/182	4.9	1/109	0.9	5.62 (0.90– $\infty$ )
HPV82	3/168	1.8	0/109	0.0	$\infty$ (0.51– $\infty$ )
Low-risk type					
HPV6	11/110	10.0	8/117	6.8	1.51 (0.60–3.81)
HPV11	15/110	13.6	4/117	3.4	4.46 (1.50–13.21)

<sup>1</sup>Only studies testing for a particular HPV type contribute to the analysis for that type, therefore sample size varies between the type-specific analyses.



**FIGURE 2** – Prevalence of human papillomavirus (HPV) types 6, 11, 16 and 18 in HPV-positive intraepithelial neoplasias and carcinomas of the (a) vulva, (b) vagina and (c) anus, restricted to HIV-negative subjects. HPV types 6 and 11 not shown for AIN1, due to the low number tested ( $N = 7$ ). VIN, vulvar intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia.

in other geographical regions. Higher HPV prevalence in North America did not appear to be an artefact of HPV detection methods (see also Insinga *et al.*<sup>37</sup>) and was observed across all age groups and histopathological types of vulvar carcinoma. Enhanced surveillance of the vulva during cervical cancer screening, combined with some misclassification of VIN3 as microinvasive vulvar carcinoma, may partly explain the higher HPV positivity found in vulvar carcinoma diagnosed in North American studies.

This meta-analysis identified 14-fold more published data on vulvar carcinoma than on vaginal carcinoma, despite an only 2- to 3-fold reported difference in their estimated incidence around the world.<sup>1</sup> Vaginal lesions are less amenable to discovery during gynecological examination than vulvar lesions, as they can be hidden by the speculum. Thus, information on vaginal lesions and carcinoma was limited and did not allow the assessment of source of heterogeneity in HPV prevalence.

In respect to anal carcinoma, we did not find a significant difference in HPV prevalence between basaloid and other subtypes,<sup>3</sup> and an excess of HPV positivity in women compared to men was limited to studies outside North America. As discussed for vulvar carcinoma in women, higher HPV prevalence in men in the United States than elsewhere may be related to early efforts at surveillance of MSM.<sup>38</sup>

Most studies of AIN to-date derived from populations of MSM living in North America, many of whom were HIV-positive, a characteristic that we and others<sup>14</sup> showed to be significantly associated with increased prevalence of HPV and multiple-type infections. We showed for the first time that HPV16 was significantly under-represented, and other types over-represented, among HIV-positive AIN2/3 (*i.e.*, the only group where data were adequate to compare HPV type distribution by HIV status). Our present findings agree, therefore, with previously reported differences in HPV

type distribution between HIV-positive and HIV-negative women with high-grade precancerous lesions of the cervix.<sup>39</sup> Indeed, HIV-related immune suppression seems to affect the course of cervical HPV16 infection less than for other HPV types,<sup>40</sup> allowing a broader range of HPV types to develop into high-grade disease. The high prevalence of multiple-type infections in HIV-positive individuals, however, complicates the issue, and differences in HPV type distribution by HIV status have not been confirmed for cervical carcinoma<sup>41</sup> and have never been reported for anal carcinoma.

We were able to retrieve much fewer information on low-grade than high-grade lesions, and confirmed<sup>37</sup> that HPV6 and 11 are frequently detected in VIN1 and AIN1 (as in anogenital warts), but not in VAIN1. Distinction of low-grade lesions by presence of wart-like characteristics was, however, impossible from publications, and VIN1 has been abolished from the revised classification of VIN.<sup>42</sup>

This meta-analysis has certain limitations. The vast majority of data on anogenital carcinoma and intraepithelial lesions originated from Europe and the United States, and none from Africa. Detailed information on age, histological subtype, copresence of multiple HPV types, HIV status and, when applicable, gender were often missing. However, HPV findings were consistent across the many studies examined, thus providing reassurance on the possibility of estimating pooled prevalence. In addition, our present HPV findings broadly agree with a recent meta-analysis of female genital carcinoma in the United States<sup>37</sup> that was smaller than our study, but applied much stricter inclusion criteria (*i.e.*, only biopsy-based studies; specified histological types; and >7 HPV types tested) and attempted to account for multiple-type infections. Publication bias is impossible to rule out completely, but seems unlikely due to the tendency of the largest and most recent studies to show some of the highest HPV prevalence (Tables AI–AVI).

It is obviously worth bearing in mind that detection of HPV DNA does not necessarily mean that the infection is causally related to the concurrent lesion. However, a vast amount of epide-

miological and mechanistic evidence shows that certain HPV types act as a potent carcinogen in the anogenital mucosae.<sup>14</sup>

In conclusion, our present meta-analysis suggests that ~40% of vulvar carcinoma, 60% of vaginal carcinoma and 80% of anal carcinoma may be avoided by prophylactic vaccines against HPV16/18. This proportion would be similar for the corresponding high-grade intraepithelial lesions of the vagina and anus, but higher for VIN2/3 (75%) than for vulvar carcinoma. An accurate estimate of the fraction of low-grade lesions avoidable using a vaccine that also includes HPV6 and 11 or other additional types is hampered by the difficulty in distinguishing these lesions from anogenital warts and by high prevalence of multiple-type infections, particularly in high-risk populations.

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Appendix

First author	Reference	Country	PCR primers	N	HPV type <sup>1</sup>												
					VIN1/VIN2/VIN3/ VIN2-3/unspec	Any	6	11	16	18	31	33	45				
Gao X	Dermatol Surg (1997)	China	HPV6/11, 16/18 only	8	8/0/0/0/0	100.0	—	—	—	—	—	—	—	—	—	—	—
Xin Y	Chinese med Science J (2002)	China	HPV6/11,16/18 only	5	0/0/5/0/0	20.0	—	—	—	—	—	—	—	—	—	—	—
Nagano H	J Obstet Gynecol Res (1996)	Japan	L1C1/C2	6	0/0/6/0/0	100.0	—	—	—	—	—	—	—	—	—	—	—
Kohlberger PD	Cancer (1998)	Austria	GP5+/6+	28	0/0/0/0/28	92.9	—	—	—	—	—	—	—	—	—	—	—
Skapa P	Am J Surg Pathol (2007)	Czech Rep.	GP5+/6+	46	4/9/33/0/0	100.0	2.2	2.2	2.2	76.1	6.5	0.0	0.0	17.4	6.5	—	—
Hording U	Gynecol Oncol (1991)	Denmark	TS only	19	0/0/19/0/0	78.9	—	—	—	78.9	—	—	—	—	—	—	—
Junge J	APMIS (1995)	Denmark	TS only	58	0/3/55/0/0	81.8	0.0	0.0	0.0	77.6	0.0	0.0	0.0	10.3	0.0	0.0	0.0
Bryndorf T	Cytogenet Gen Res (2004)	Denmark	SPF10	11	1/1/9/0/0	100.0	0.0	0.0	0.0	63.6	0.0	0.0	0.0	18.2	0.0	—	—
Tervahauta AI	Anticancer Res (1993)	Finland	MY09/11	2	1/0/1/0/0	100.0	0.0	0.0	50.0	0.0	—	—	—	—	—	—	—
Petry KU	Gynecol Oncol (1996)	Germany	TS only	10	1/1/8/0/0	90.0	—	—	—	70.0	—	—	—	10.0	10.0	—	—
Hampl M	Journal of Cancer Res Clin Oncol (2007)	Germany	GP5+/6+; MY09/11	49	3/11/35/0/0	91.8	2.0	2.0	2.0	67.3	0.0	0.0	8.2	8.2	0.0	—	—
Della Torre G	Diagn Mol Pathol (1992)	Italy	TS only	7	0/0/7/0/0	100.0	0.0	0.0	0.0	100.0	0.0	—	—	—	—	—	—
Pliotti S	Diagn Mol Pathol (1995)	Italy	TS only	5	0/0/5/0/0	100.0	—	—	—	100.0	0.0	—	—	—	—	—	—
Bonvicini F	J Med Virol (2005)	Italy	MY09/11	18	0/5/13/0/0	61.1	—	—	—	50.0	0.0	0.0	0.0	5.6	0.0	—	—
Beurden M	Cancer (1995)	Netherlands	Cp1/IG	46	0/0/46/0/0	95.7	0.0	0.0	0.0	89.1	0.0	0.0	0.0	2.2	2.2	—	—
Avoort IA	Int J Gynecol Pathol (2005)	Netherlands	SPF10	29	5/7/17/0/0	65.5	13.8	0.0	0.0	41.4	0.0	0.0	6.9	3.4	0.0	0.0	0.0
Van Seters M	J Clin Pathol (2007)	Netherlands	GP5+/6+	26	9/11/6/0/0	30.8	0.0	0.0	0.0	26.9	0.0	0.0	0.0	0.0	0.0	—	—
Van Seters M	New Engl J Med (2008)	Netherlands	GP5+/6+	52	0/0/0/52/0	96.2	0.0	0.0	0.0	78.8	1.9	0.0	0.0	15.4	0.0	—	—
Lerma E	Int J Gynecol Pathol (1999)	Spain	L1+VPHFast	12	0/0/0/12/0	41.7	—	—	—	41.7	0.0	—	—	—	—	—	—
Abdel-Hady ES	Cancer Res (2001)	UK	GP5+/GP6+; TS	29	0/0/0/29/0	62.1	—	—	—	44.8	0.0	—	—	0.0	0.0	—	—
Gasco M	Oncogene (2002)	UK	MY09/11; Cp1/IG	32	4/6/22/0/0	37.5	—	—	—	37.5	—	—	—	—	—	—	—

TABLE A1 – TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN VULVAR INTRAEPITHELIAL NEOPLASIA (VIN), BY STUDY

TABLE AI – TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN VULVAR INTRAEPITHELIAL NEOPLASIA (VIN), BY STUDY (CONTINUED)

First author	Reference	Country	PCR primers	N	VIN1/VIN2/VIN3/ VIN2-3/unspec	HPV type <sup>1</sup>									
						Any	6	11	16	18	31	33	33	45	
Baldwin PI	Clin Cancer Res (2003)	UK	GP5+/6+	11	0/0/11/0/0	100.0	0.0	0.0	90.9	0.0	0.0	0.0	9.1	0.0	
Todd RW	Gynecol Oncol (2004)	UK	GP5/6	10	0/0/10/0/0	90.0	—	—	50.0	0.0	0.0	0.0	20.0	—	
Woo YL	J Virol Methods (2007)	UK	GP5+/6+; MY09/11	8	0/0/0/0/8	62.5	—	—	50.0	—	—	—	—	—	
Aziz DC	J Gynecol Surg (1993)	Canada	TS only	10	0/0/0/0/10	90.0	0.0	0.0	90.0	0.0	0.0	0.0	0.0	—	
Nuovo GJ	Gynecol Oncol (1991)	US	MY09/11	22	0/0/0/22/0	59.1	0.0	0.0	40.9	0.0	0.0	4.5	0.0	—	
Madeleine M	J Natl Cancer Inst (1997) part 1 <sup>2</sup>	US	MY09/11	390	0/0/390/0/0	91.5	3.1	0.0	76.9	9.0	1.0	8.7	1.8	—	
Madeleine M	J Natl Cancer Inst (1997) part 2 <sup>2</sup>	US	MY09/11	79	0/0/79/0/0	87.3	—	—	77.2	—	—	—	—	—	
Logani S	Mod Pathol (2003)	US	SPF10	17	11/0/6/0/0	100.0	29.4	5.9	29.4	5.9	5.9	0.0	0.0	0.0	
Ruffomy J	J Lower Genit Tract Dis (2005)	US	TS only	34	10/3/21/0/0	58.8	—	—	58.8	—	—	—	—	—	
Srodon M	Am J Surg Pathol (2006)	US	PGMY09/11; SPF10	67	33/0/34/0/0	95.5	13.4	9.0	49.3	3.0	1.5	3.0	0.0	—	
Park JS	Cancer (1991)	New Zealand	MY09/11; TS	18	0/0/18/0/0	33.3	0.0	0.0	33.3	0.0	—	—	—	—	
Joura EA	Lancet (2007)	Multicentric	MY09/11	33	0/0/0/33/0	87.9	24.2	6.1	63.6	3.0	18.2	3.0	0.0	0.0	
Total				1,197	905/7856/148/46	84.0	4.4	1.2	67.5	4.6	2.1	7.7	1.4	—	

<sup>1</sup>Percent of all subjects tested for the specific type.—<sup>2</sup>This study was expanded since original publication, with a change in the HPV genotyping protocol. TS, type-specific.

TABLE AII – TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN CARCINOMA OF THE VULVA, BY STUDY

First Author	Reference	Country	PCR primers	N	Warty-basoid/ keratinised/unspec	HPV type <sup>1</sup>									
						Any	6	11	16	18	31	33	45		
Guo L	Chinese J Obstet and Gyn (1996)	China	TS only	33	12/21/0	30.3	—	—	21.2	0.0	—	—	—	—	
Gao X	Dermatol Surg (1997)	China	HPV6/11, 16/18 only	13	0/0/13	23.1	—	—	—	—	—	—	—	—	
Ngan HY	Eur J Cancer (1999)	Hong Kong	TS only	48	0/0/48	47.9	—	—	37.5	14.6	—	—	—	—	
Huang FY	Cancer Genet Cytogenet (2005)	Hong Kong	TS only	8	0/0/8	75.0	—	—	37.5	37.5	—	—	—	—	
Toki T	Int J Gynecol Pathol (1991)	Japan	TS only	21	9/0/12	57.1	0.0	0.0	47.6	14.3	—	—	—	—	
Niagano H	J Obstet Gynecol Res (1996)	Japan	L1C1/C2	11	0/0/11	72.7	9.1	0.0	36.4	9.1	0.0	0.0	0.0	0.0	
Koyamatsu Y	Gynecol Oncol (2003)	Japan	L1C1/C2	31	0/0/31	12.9	—	—	6.5	6.5	—	—	—	—	
Osakabe M	Pathol Int (2007)	Japan	L1C1/C2	21	4/13/4	23.8	4.8	0.0	14.3	0.0	0.0	0.0	0.0	—	
Skapa P	Am J Surg Pathol (2007)	Czech Rep.	GP5+/6+	46	0/0/46	39.1	2.2	0.0	23.9	0.0	0.0	0.0	8.7	2.2	
Hording U	Gynecol Oncol (1991)	Denmark	TS only	24	0/0/24	58.3	—	—	58.3	—	—	—	—	—	
Hording U	Int J Cancer (1993)	Denmark	TS only	62	0/0/62	30.6	0.0	0.0	21.0	4.8	—	4.8	—	—	
Hording U	Gynecol Oncol (1994)	Denmark	TS only	78	27/51/0	30.8	0.0	0.0	28.2	0.0	—	3.8	—	—	
Bryndorf T	Cytogenet Gen Res (2004)	Denmark	SPF10	10	0/0/10	60.0	0.0	0.0	40.0	0.0	0.0	20.0	0.0	0.0	
Madsen BS	Int J Cancer (2008)	Denmark	GP5+/6+	60	0/0/60	51.7	0.0	0.0	36.7	0.0	0.0	11.7	0.0	0.0	
Iwasawa A	Obstet Gynecol (1997)	Finland	MY09/11	74	0/0/74	36.5	0.0	0.0	25.7	12.2	—	1.4	—	—	
Tervahauta AI	Anticancer Res (1993)	Finland	MY09/11	7	0/0/7	85.7	14.3	14.3	14.3	0.0	—	14.3	—	—	
Milde-Langosch K	Int J Cancer (1995)	Germany	MY09/11	40	6/0/34	27.5	0.0	0.0	25.0	0.0	0.0	0.0	0.0	—	
Hampf M	Obstet Gynecol (2006)	Germany	GP5+/6+	48	0/0/48	60.4	—	—	39.6	2.1	4.2	8.3	—	—	
Petry KU	Gynecol Oncol (1996)	Germany	TS only	3	3/0/0	100.0	—	—	100.0	—	—	0.0	—	—	
Menczer J	Eur J Gynaecol Oncol (2000)	Israel	TS only	14	0/14/0	64.3	—	—	57.1	7.1	—	—	—	—	
Bonvicini F	J Med Virol (2005)	Italy	MY09/11	16	0/16/0	0.0	—	—	0.0	0.0	0.0	0.0	0.0	0.0	
Piotti S	Diagn Mol Pathol (1995)	Italy	TS only	23	1/0/22	47.8	—	—	43.5	4.3	—	—	—	—	
Della Torre G	Diagn Mol Pathol (1992)	Italy	TS only	10	0/0/10	50.0	0.0	0.0	40.0	10.0	—	—	—	—	

TABLE AII - TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN CARCINOMA OF THE VULVA, BY STUDY (CONTINUED)

First Author	Reference	Country	PCR primers	N	Warty-basaloid/ keratinised/unspecc	Any	HPV type <sup>1</sup>									
							6	11	16	18	31	33	45			
Ansink AC	Gynecol Oncol (1994)	Netherlands	GP5/6	60	0/0/60	31.7	-	-	-	-	-	-	-	-	-	-
Kagie MJ	Gynecol Oncol (1997)	Netherlands	CpI/HIG	66	24/42/0	19.7	-	-	16.7	-	-	-	-	0.0	1.5	-
Avoort IA	Int J Gynecol Pathol (2005)	Netherlands	SPF10	16	0/0/16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Liss J	Ginekol Pol (1998)	Poland	MY09/11	18	0/0/18	16.7	-	-	16.7	-	-	-	-	-	-	-
Lerma E	Int J Gynecol Pathol (1999)	Spain	L1 + VPHFast	57	7/50/0	12.3	-	-	12.3	0.0	-	-	-	-	-	-
Santos M	Am J Surg Pathol (2006)	Spain	GP5+/6+, SPF10	92	17/75/0	17.4	2.2	0.0	14.1	0.0	1.1	2.2	0.0	0.0	0.0	0.0
Ogunbiyi OA	Obstet Gynecol (1994)	UK	TS only	33	0/0/33	75.8	-	-	75.8	-	-	-	-	-	-	-
Brooks LA	Cancer Res (2000)	UK	Other	36	0/0/36	36.1	-	-	36.1	-	-	-	-	-	-	-
Gasco M	Oncogene (2002)	UK	MY09/11; CpI/HIG	36	0/0/36	36.1	-	-	36.1	-	-	-	-	-	-	-
Al-Ghamdi A	Gynecol Oncol (2002)	Canada	MY09/11; GP5/6	20	0/0/20	85.0	-	-	55.0	30.0	-	-	-	-	-	-
Tate JE	Gynecol Oncol (1994)	US	MY09/11	13	0/0/13	53.8	0.0	0.0	46.2	0.0	0.0	7.7	0.0	0.0	0.0	0.0
Sagerman PM	Gynecol Oncol (1996)	US	MY09/11; TS	19	0/0/19	15.8	0.0	0.0	15.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Nruovo G	Gynecol Oncol (1991)	US	MY09/11	23	0/16/7	30.4	0.0	0.0	17.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Lee YV	Oncogene (1994)	US	TS only	21	0/0/21	57.1	0.0	-	47.6	4.8	-	-	-	-	-	-
Bloss JD	Human Pathol (1991)	US	TS only	20	10/10/0	50.0	10.0	-	40.0	0.0	-	-	-	-	-	-
Kim YT	Human Pathol (1996)	US	MY09/11	18	4/11/3	38.9	0.0	0.0	27.8	5.6	0.0	0.0	0.0	0.0	0.0	0.0
Ruffomy I	J Lower Genit Tract Dis (2005)	US	TS only	4	0/0/4	100.0	-	-	100.0	-	-	-	-	-	-	-
Madeleine M	J Natl Cancer Inst (1997) part 1 <sup>2</sup>	US	MY09/11	24	0/0/24	83.3	-	-	66.7	0.0	-	-	-	-	-	-
Madeleine M	J Natl Cancer Inst (1997) part 2 <sup>2</sup>	US	MY09/11	86	0/0/86	75.6	8.1	0.0	57.0	5.8	2.3	9.3	0.0	0.0	0.0	0.0
Kiyabu MT	Amer J Surg Pathol (1989)	US	TS only	8	0/0/8	75.0	-	-	75.0	12.5	-	-	-	-	-	-
Monk BI	Obstet Gynecol (1995)	US	TS only	55	21/31/3	60.0	1.8	-	49.1	5.5	-	-	-	-	-	-
Sutton BC	Mod Pathol (2008)	US	MY09/11	116	45/0/71	69.8	2.6	0.0	56.0	1.7	0.0	10.3	3.4	0.6	0.6	0.6
Pinto AP	Gynecol Oncol (2004)	Brazil	GP5+/6+; TS	177	36/122/3	26.6	-	-	18.1	8.5	0.0	0.6	0.6	0.6	0.6	0.6
Scurry J	Int J Gynecol Cancer (1998)	Australia	GP5/6	130	26/104/0	22.3	-	-	18.5	1.5	-	-	-	-	-	-
Allen DG	Br J Cancer (2002)	Australia	MY09/11; TS	18	0/0/18	55.6	0.0	0.0	55.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Park JS	Cancer (1991)	New Zealand	MY09/11; TS	6	6/0/0	83.3	0.0	0.0	83.3	0.0	-	-	-	-	-	-
Total				1,873	258/576/1,039	40.4	2.0	0.1	32.2	4.4	0.6	4.5	1.0	1.0	1.0	1.0

<sup>1</sup>Percent of all subjects tested for the specific type.-<sup>2</sup>This study was expanded since original publication, with a change in the HPV genotyping protocol. TS, type-specific.

TABLE AIII – TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN), BY STUDY

First author	Reference	Country	PCR primers	N	VAIN1/VAIN2/ VAIN3/VAIN2-3		HPV type <sup>1</sup>						
					Any	6	11	16	18	31	33	45	
Sugase M	Int J Cancer (1997)	Japan	TS only	71	53/15/3/0	100.0	0.0	0.0	9.9	1.4	4.2	0.0	0.0
Hampf M	J Cancer Res Clin Oncol (2007)	Germany	GP5+/6+; MY09/11	18	2/11/5/0	94.4	11.1	0.0	61.1	0.0	5.6	11.1	0.0
Frega A	Cancer Lett (2007)	Italy	TS only	44	16/23/5/0	100.0	–	–	90.9	9.1	–	–	–
Beurden M	Int J Gynecol Pathol (1998)	Netherlands	Cp1/IIIG	8	0/0/0/8	100.0	0.0	0.0	75.0	0.0	0.0	12.5	0.0
Baldwin PJ	Clin Cancer Res (2003)	UK	GP5+/6+	1	0/1/0/0	100.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
Daling JR	Gynecol Oncol(2002) part 1 <sup>2</sup>	US	MY09/11	63	0/0/63/0	87.3	6.3	0.0	65.1	7.9	0.0	4.8	0.0
Daling JR	Gynecol Oncol (2002) part 2 <sup>2</sup>	US	MY09/11	18	0/0/18/0	77.8	–	–	38.9	–	–	–	–
Logani S	Mod Pathol (2003)	US	SPF10	19	19/0/0/0	100.0	0.0	0.0	21.1	15.8	5.3	0.0	0.0
Snodon M	Amer J Surg Pathol (2006)	US	PGMY09/11; SPF10	33	17/0/16/0	97.0	0.0	0.0	27.3	12.1	6.1	0.0	0.0
Aziz DC	J Gynecol Surg (1993)	Canada	TS only	2	0/0/0/2	50.0	0.0	0.0	0.0	50.0	0.0	0.0	–
Joura EA	Lancet (2007)	Multicentric	MY09/11	21	0/0/0/21	81.0	4.8	0.0	42.9	9.5	9.5	9.5	0.0
Total				298	107/50/110/31	93.6	3.0	0.0	45.3	7.1	3.8	3.4	0.0

<sup>1</sup>Percent of all subjects tested for the specific type.<sup>2</sup>This study was expanded since original publication, with a change in the HPV genotyping protocol. TS, type-specific.

TABLE AIV – TYPE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN CARCINOMA OF THE VAGINA, BY STUDY

First author	Reference	Country	PCR primers	N	VAIN1/VAIN2/ VAIN3/VAIN2-3		HPV type <sup>1</sup>						
					Any	6	11	16	18	31	33	45	
Koyamatsu Y	Gynecol Oncol (2003)	Japan	L1C1/C2	16	43.8	–	–	37.5	6.3	–	–	–	–
Madsen BS	Int J Cancer (2008)	Denmark	GP5+/6+	27	88.9	3.7	0.0	77.8	3.7	0.0	7.4	3.7	
Ferreira M	Mod Pathol (2008)	Portugal	SPF10	21	81.0	9.5	4.8	33.3	9.5	28.6	9.5	0.0	
Habermann JK	Cancer Genet Cytogenet (2004)	Sweden	PGMY09/11	8	25.0	0.0	0.0	12.5	0.0	0.0	0.0	0.0	
Kiyabu MT	Am J Surg Pathol (1989)	US	TS only	14	64.3	–	–	57.1	7.1	–	–	–	
Daling JR	Gynecol Oncol (2002) part 1 <sup>2</sup>	US	MY09/11	33	72.7	0.0	0.0	63.6	12.1	0.0	0.0	0.0	
Daling JR	Gynecol Oncol (2002) part 2 <sup>2</sup>	US	MY09/11	17	70.6	–	–	52.9	–	–	–	–	
Total				136	69.9	3.4	1.1	53.7	7.6	5.6	4.5	1.1	

<sup>1</sup>Percent of all subjects tested for the specific type.<sup>2</sup>This study was expanded since original publication, with a change in the HPV genotyping protocol. TS, type-specific.

