Review

A Systematic Review of the Prevalence and Attribution of Human Papillomavirus Types among Cervical, Vaginal, and Vulvar Precancers and Cancers in the United States

Ralph P. Insinga,[1] Kai-Li Liaw,[2] Lisa G. Johnson,[3] and Margaret M. Madeleine[3]

Departments of [1]Health Economic Statistics and [2]Epidemiology, Merck Research Laboratories, North Wales, Pennsylvania and [3]Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington

Abstract

Objectives: **To describe prevalence and estimated attribution of human papillomavirus (HPV) types in U.S. cervical, vaginal, and vulvar precancers and cancers.**
Methods: **U.S. studies reporting HPV typing for cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN) and/or invasive cancers of those sites were gathered from the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez/). Selected studies had PCR testing data for ≥10 cases for a disease endpoint. Analytic methods augmented prior reviews of cervical disease with an updated and expanded analysis (including vulvar and vaginal disease), new selection criteria for specimens, and adjustment for histologic type, where possible, among pooled cancer cases. In addition, for analyses of estimated attribution of HPV types, we incorporated accounting methods for lesions infected with multiple HPV types.**
Results: **Data from 22 U.S. studies meeting review eligibility criteria were tabulated. Following adjustment for the presence of multiple HPV types in a single specimen, the top two HPV types contributing to disease were CIN 1 (HPV 16/66; 15.3%), CIN 2/3 (HPV 16/31; 61.9%), cervical cancer (HPV 16/18; 79.2%), VIN 1 (HPV 6/11; 41.7%), VIN 3 (HPV 16/18; 84.0%), vulvar cancer (HPV 16/33; 55.5%), VaIN 3 (HPV 16/18; 65.1%), and vaginal cancer (HPV 16/18; 72.7%).**
Conclusions: **The HPV type distribution and proportion of cases testing positive for any HPV type were observed to vary among U.S. cervical, vulvar, and vaginal neoplasias and by grade of disease. Adjustment for the presence of multitype HPV infections can have an important effect on the estimated attribution of HPV types to disease, particularly for types other than HPV 16.** (Cancer Epidemiol Biomarkers Prev 2008;17(7):1611–22)

Introduction

Cervical cancer is the second most common cancer in women worldwide (1) and is caused by human papillomavirus (HPV) infection (2). In the United States, it is estimated that there will be 11,150 women newly diagnosed with cervical cancer in 2007, with 3,670 deaths (3). Most vulvar cancers are also caused by HPV infection, particularly among younger women (4, 5). However, among older women, there is evidence of a mixed etiology for vulvar cancers. Some cases are associated with HPV infection, whereas others, especially of the less common keratinizing form of squamous cell carcinoma (SCC), are likely the result of smoking or other etiology (6-9). It is estimated that 3,490 U.S. women will be diagnosed with vulvar cancer in 2007, with 880 deaths (3).

Vaginal cancers are also of mixed etiology. Although the majority of squamous cell cancers are associated with HPV infection (10), a small proportion of vaginal cancers are clear cell adenocarcinomas that have been linked to intrauterine exposure to maternal diethylstilbestrol use (11). Chronic vaginitis, prior hysterectomy for benign disease, endometriosis, and cervical irradiation have also been cited as predisposing factors for vaginal cancers (11). Risk factors commonly associated with HPV diseases at other genital sites, such as smoking, prior history of anogenital cancer, and greater numbers of lifetime sexual partners, are also associated with squamous cell vaginal cancers (10). Approximately 1,100 U.S. women are diagnosed with vaginal cancer annually (12), with 400 deaths (13). The vast majority of precursor lesions to these cancers, cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN), are caused by HPV infection (14). Most preinvasive lesions are asymptomatic, and CIN is the most common among them, in part as a

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Requests for reprints: Ralph P. Insinga, Merck & Co., Inc., UG1C-60, P.O. Box 1000, North Wales, PA 19454-1099. Phone: 267-305-7992; Fax: 267-305-6455. E-mail: ralph_insinga@merck.com

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result of routine cervical screening, as well as the distinct anatomy of the cervical transformation zone. An estimated 400,000 cases of CIN are newly diagnosed in the United States each year (15).

With the advent of type-specific HPV vaccines (16, 17) and tests (18) for preventing and diagnosing HPV disease, policymakers are seeking to evaluate the population benefits and cost-effectiveness of these emerging technologies (2, 19, 20). Key to this evaluation is an understanding of the attribution of individual HPV types to the development of disease (the fraction of disease cases caused by a given HPV type). With respect to earlier literature reviews for cervical disease (21-25), the present study updates, expands on, and provides additional perspectives in describing the prevalence and estimated attribution of individual HPV types among cervical, vulvar, and vaginal cancers and precancers diagnosed within the United States.

Materials and Methods

Analytic Scope. We began our literature review by searching the PubMed database of the National Library of Medicine (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) for relevant studies by pairing the keyword [human papillomavirus] with each of the following terms and eliminating duplicates: [cervix, cervical, vulva, vulvar, vagina, vaginal]. The search comprised studies listed in PubMed up to July 1, 2007. Disease endpoints of interest for cervical disease were CIN 1, CIN 2/3, cervical adenocarcinoma (including adenosquamous carcinoma), and cervical SCC. For vaginal and vulvar disease, endpoints of interest were VIN 1, VIN 2/3, vulvar adenocarcinoma, vulvar SCC, VaIN 1, VaIN 2/3, vaginal adenocarcinoma, and vaginal SCC. We did not review data for other, noninvasive, HPV-related lesions of these sites such as glandular intraepithelial neoplasia.

In their worldwide reviews, Clifford et al. (21-23) and Smith et al. (25) illustrated the marked variability by geographic region in the prevalence of individual HPV types among women with cervical lesions, particularly for non-HPV 16/18 types. As the focus of the present analysis was for the U.S. population, we excluded studies conducted in other countries. Studies selected for this review were required to have been published since 1994 (as earlier HPV testing methods may have been less refined) to examine at least one additional HPV type in addition to HPV 16 and to have HPV testing data available for at least 10 cases for a given disease endpoint of interest. Analyses focusing exclusively on a clearly differentiated subset of disease within a given endpoint (e.g., clear cell adenocarcinoma of the vagina and small-cell neuroendocrine carcinoma of the cervix) were excluded, as they reflected a nonrepresentative sampling of diagnosed disease. Similar to past reviews (21-25), we also limited our review to studies conducting PCR testing of specimens and only selected the largest study when multiple studies overlapped within the same patient population. Also consistent with several prior reviews (21-23, 25), we report data for HPV 6, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, and 82; we also include HPV 11, as this type is targeted by an HPV vaccine (17).

However, in addition to the inclusion of more recently published studies, and an expanded scope of HPV diseases examined (vulvar and vaginal neoplasia), our review also differs from prior reviews in several key respects. First, we elected to exclude studies with HPV typing of exfoliated cells such as those collected via lavage, swab, or brush and focused on analyses performing HPV typing of biopsy tissue specimens. Because our goal was to specifically consider HPV types contributing to neoplastic lesions, we were concerned that exfoliated cells could also encompass HPV infections occurring elsewhere in the cervicovaginal tract, unrelated to the lesion of interest. For instance, a recent study of female adolescents found that a single HPV type was detected on cervicovaginal swab in 44% of HPV-positive women, with 56% testing positive for two to eight different HPV types at a single time (26). High- and low-risk HPV infections were often simultaneously observed. Examination of multiple areas of the cervix and vagina have confirmed that infections observed in typing of lesion tissue specimens can differ by HPV type from those observed elsewhere in normal-appearing tissue or other lesions with potentially differing histology (27-29).

A second difference is that we elected to exclude cervical cancer studies that either did not specify histologic type (SCC versus adenocarcinoma) or failed to separately report HPV typing data by histologic type. In addition, in reporting HPV typing across all cervical cancer cases (combining mixed histologies), we adjusted HPV typing data presented in stratified form by histologic type to reflect the relative proportion of SCC versus adenocarcinomas at that site observed in the U.S. population. This adjustment was based on 1998 to 2002 data from multiple cancer registries covering 87% of the U.S. population (30). The adjustment was done to improve the external generalizability of results, as the prevalence of individual HPV types varies between cervical SCC and adenocarcinomas (31, 32), and a simple summation across individual studies may not be representative of the histologic type distribution among the general population of cancer patients. For instance, in the Smith et al. review, the proportion of cervical adenocarcinomas versus cervical SCC (including instances where histologic type was not specified) among all cancer specimens varied substantially by region from 4% for Africa to 32% for North America (25). It was unclear whether this variation was due to case selection criteria of individual studies or regional heterogeneity in histologic types resulting from differences in underlying biology or detection. For vulvar and vaginal cancers, available data were only sufficient for describing HPV typing results for squamous cell cancers; however, the occurrence of adenocarcinomas and general representativeness of the results will also be discussed.

A third difference between this and previous reviews is that we account for multitype HPV infections in estimating attribution as described below.

Accounting for Multitype HPV Infections in Estimating Attribution. Estimates of the crude prevalence of HPV types in lesion tissue samples will likely overestimate the attribution of individual HPV types, and certainly groups of HPV types (if summed), when infections with multiple types are present. Consistent

with prior reviews, we report the crude prevalence of HPV types, where the total number of type-specific infections observed is divided by the total number of study lesions with HPV typing data available. In addition, we estimate the attribution of individual HPV types to lesions adjusted for the presence of multitype HPV infections. Analyses of attribution were further restricted to studies that describe the distribution of HPV types within multitype infections when present and those reporting data for at least eight HPV types. Studies with results for fewer types were more likely to incompletely characterize the spectrum of multitype HPV-infected lesions.

The precise interrelationships among multiple HPV infection types in contributing to lesion development have not yet been fully elucidated. At one extreme, when lesions testing positive for multiple HPV types are observed, it could be surmised that each type is individually *sufficient* for lesion development (prevention of all lesion HPV types is required to prevent the lesion). Another extreme would be to assume that each HPV type is individually *necessary* for lesion development (prevention of any single lesion HPV type will prevent the lesion). Empirical data support the notion that neither extreme is likely in practice (33-35). For instance, Lai et al. observed a wide variation in the proportion of single-type infections (versus multitype HPV infections) in cervical cancer tissue specimens ranging from 84% for HPV 16 (n = 1,059) to 0% for HPV 11, 32, 55, 71, 74, and 81 (combined n = 14 multitype infections), with a wide spectrum in between for other oncogenic HPV types (34). If the HPV types found only in multitype infected lesions were truly necessary or sufficient for cervical cancer development, one would expect to observe at least some cancers with single-type HPV infections of these genotypes; yet, this was not seen.

Thus, it is likely that some HPV types play a more dominant role in lesion development than others, when multitype infections are observed. Recent data have suggested that fused lesions each containing a unique HPV type are uncommon and, in most instances where more than one HPV type is present in a cell, only a single type is transcriptionally active and pathogenic (36).

To approximate this, in analyses examining the attribution of individual HPV types to lesions, we assumed a fractional allocation for each individual HPV type with respect to the lesion of interest when studies reported a multitype infection. This was based on the relative number of instances in which each HPV infection type was observed as a single-type infection in a lesion of that grade and disease type within each individual study. For example, in deriving an apportionment for two CIN 1 lesions found to test positive for both HPV 16 and 68 in a study, if there were nine single-type HPV 16-infected CIN 1 lesions and one single-type HPV 68-infected lesion in that study, then [2 * 9 / (9 + 1)] or 1.8 of these two multitype infected lesions would be attributed to HPV 16 and [2 * 1 / (9 + 1)] or 0.2 attributed to HPV 68.

Statistical Analysis. The prevalence and relative attribution of individual HPV types to cervical, vulvar, and vaginal lesions are reported as percentages, with estimation of 95% confidence intervals (95% CI) by the score method (37). In the case of overall cervical cancer data adjusted by histologic type, 95% CI were estimated from SE derived from the formula for the sum of products of the variances of two independent random variables (histology and HPV prevalence in this instance; ref. 38). P values for differences in the distribution of HPV types across different types of lesions were estimated based on a χ^2 test for independent proportions.

Results

Overall, 23 U.S. studies met the eligibility criteria for the analyses of HPV prevalence among lesions. On inspection, one of these studies was excluded due to a high suspicion of faulty HPV testing methods or poor sample quality, which resulted in the detection of an excessive number of multitype HPV infections (>50% of all lesions tested) relative to U.S. and international norms (34, 35). The study did testing for three HPV types in CIN 2/3 specimens and detected double or triple infections in 68% (23 of 34; ref. 39) We report data from the remaining 22 eligible studies (4, 5, 10, 31, 32, 40-56). When not stated explicitly in a published article, authors of these studies were contacted regarding the specific HPV types for which testing was conducted and the availability of data on multitype HPV infections. Through this process, additional data were kindly made available for five studies (4, 10, 31, 32, 55) as referenced in the tables.

Cervical Disease. Among CIN 1 lesions (n = 224; 8 studies), HPV 16, 31, 66, 52, and 51 were the five most frequently observed HPV types, in order of decreasing prevalence (Table 1). Adjustment for multitype HPV infections, observed in 0.0% to 8.9% of lesions from each study (among studies testing for at least 8 HPV types), resulted in a lower percentage attribution of individual HPV types to CIN 1 lesions than figures reported for prevalence for 8 of the 18 HPV types for which data were available. The largest relative differences following adjustment for multitype HPV infections were observed for HPV 58 (41% lower; 4.1-2.4%) and HPV 11 (36% lower; 4.5-2.9%). No single HPV type was estimated to account for >10% of CIN 1 lesions. HPV 16 was estimated to be the largest single contributor to CIN 1 lesions (8.6%), with the top 2 (HPV 16 and 66), 4 (HPV 16, 66, 31, and 52), and 8 (HPV 16, 66, 31, 52, 51, 18, 6, and 56) reported HPV types contributing to 15.3%, 27.9%, and 46.3% of CIN 1 lesions, respectively.

For CIN 2/3 lesions (n = 360; 8 studies), HPV 16, 31, 18, 33, and 35 were the 5 most frequently observed HPV types, in order of prevalence. Multitype HPV infections were observed in 0.0% to 14.4% of lesions in each study. The largest relative differences following adjustment for multitype HPV infections vis-à-vis crude figures for prevalence were observed for HPV70 (100% lower) and HPV 33 (36% lower). Following multitype adjustment, the highest attribution to CIN 2/3 lesions was observed for HPV 16 (53.8%), with the top 2 (HPV 16 and 31), 4 (HPV 16, 31, 18, and 35), and 8 (HPV 16, 31, 18, 35, 33, 58, 52, and either 56 or 66) reported HPV types accounting for 61.9%, 70.6%, and 79.9% of CIN 2/3 lesions, respectively. The nominal contributions of individual HPV types to CIN 2/3 lesions were higher

Table 1. Prevalence and attribution of HPV types in CIN 1 and CIN 2/3 lesions

Year	First author	*n*	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
CIN 1 (41, 42, 45-47, 49, 53, 55)																						
2007	Kong	11	0.0	9.1	0.0	27.3	0.0	18.2	9.1	9.1	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0			90.9
2007	Guo†	23	4.9			0.0	0.0	9.9	9.9	0.0		5.8		9.9		4.9							59.3
2006	Srodon	36	0.0	2.8	2.8	11.1	16.7	5.6	5.6	8.3	2.8	5.6	2.8	2.8	0.0	2.8	2.8	11.1	5.6	0.0			100.0
2005	Hu	45	8.9			8.9	2.2	6.7	0.0	2.2		2.2		13.3		11.1							87.0
2002	Evans	28	3.6	7.1	3.6	7.1	3.6	7.1	3.6	3.6	10.7	3.6	10.7	7.1	3.6	0.0	0.0	10.7	0.0				100.0
1998	Aoyama	11		0.0	0.0	27.3	9.1	9.1	9.1														54.5
1998	Quade	30	0.0	3.3	3.3	10.0	3.3	6.7	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0		73.3
1996	Isacson	40		5.0	10.0																		
Pooled prevalence		224‡	1.2	4.5	4.5	10.3	5.4	7.8	4.0	3.5	2.1	3.7	5.7	6.5	3.8	4.1	1.0	6.7	1.9	0.0	0.0		84.1
95% CI, lower				2.2	2.2	6.7	3.0	4.7	2.0	1.6	0.8	1.7	2.6	3.7	1.5	2.0	0.2	3.3	0.5	0.0	0.0		
95% CI, upper				9.0	9.0	15.6	9.7	12.5	7.8	7.4	5.7	7.6	11.9	11.2	9.4	8.2	5.2	13.1	6.7	4.8	11.4		
Multitype adjusted§		**173‡**		**4.0**	**2.9**	**8.6**	**4.9**	**6.4**	**3.3**	**3.5**	**2.3**	**3.7**	**5.7**	**6.2**	**3.8**	**2.4**	**1.0**	**6.7**	**1.9**	**0.0**	**0.0**		
95% CI, lower				**1.7**	**1.0**	**5.3**	**2.5**	**3.6**	**1.5**	**1.6**	**0.7**	**1.7**	**2.6**	**3.5**	**1.5**	**1.0**	**0.2**	**3.3**	**0.5**	**0.0**	**0.0**		
95% CI, upper				**9.3**	**7.7**	**13.7**	**9.2**	**11.1**	**7.1**	**7.4**	**7.3**	**7.6**	**11.9**	**10.8**	**9.4**	**6.0**	**5.2**	**13.1**	**6.7**	**4.8**	**11.4**		
CIN 2/3 (41, 42, 45-47, 49, 53, 55)																						
2007	Kong	14	14.3	0.0	0.0	42.9	0.0	28.6	14.3	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.1			92.9
2007	Guo†	60	10.0			36.9	0.0	8.4	5.0	8.4		0.0		5.0		5.0							72.1
2006	Srodon	116	0.0	0.0	0.0	75.0	4.3	5.2	1.7	5.2	0.0	0.0	0.0	0.9	0.9	3.4	0.9	0.9	0.0	0.0			100.0
2005	Hu	97	14.4			40.2	12.4	13.4	1.0	3.1		2.1		8.2		6.2							93.6
2002	Evans	22	0.0	0.0	0.0	68.2	4.5	9.1	4.5	0.0	0.0	4.5	0.0	0.0	4.5	4.5	0.0	0.0	0.0				100.0
1998	Aoyama	21		0.0	0.0	52.4	0.0	19.0	19.0														95.2
1998	Quade	19	0.0	0.0	0.0	52.6	5.3	0.0	15.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		78.9
1996	Isacson	11	0.0	0.0	0.0	45.5	0.0	18.2	9.1	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9.1	0.0				100.0
Pooled prevalence		360‡	6.5	0.0	0.0	54.2	5.3	10.0	4.7	4.7	0.0	0.9	0.0	3.5	1.1	4.1	0.5	1.1	0.0	0.7	0.0		92.0
95% CI, lower				0.0	0.0	49.0	3.4	7.3	3.0	3.0	0.0	0.3	0.0	2.1	0.3	2.4	0.1	0.3	0.0	0.1	0.0		
95% CI, upper				1.9	1.9	59.3	8.1	13.5	7.4	7.4	2.1	2.5	2.1	6.0	3.9	7.2	3.0	3.9	2.1	3.7	16.8		
Multitype adjusted§		**339‡**		**0.0**	**0.0**	**53.8**	**4.8**	**8.1**	**3.0**	**3.9**	**0.0**	**0.6**	**0.0**	**2.4**	**1.1**	**2.8**	**0.5**	**1.1**	**0.0**	**0.0**	**0.0**		
95% CI, lower				**0.0**	**0.0**	**48.5**	**3.0**	**5.7**	**2.0**	**2.3**	**0.0**	**0.2**	**0.0**	**1.2**	**0.3**	**1.4**	**0.1**	**0.3**	**0.0**	**0.0**	**0.0**		
95% CI, upper				**2.1**	**2.1**	**59.0**	**7.6**	**11.5**	**6.1**	**6.5**	**2.2**	**2.1**	**2.2**	**4.6**	**3.9**	**5.5**	**3.0**	**3.9**	**2.1**	**2.5**	**16.8**		

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.
† In the Guo et al. study, 4 CIN 1 lesions and 1 CIN 2 lesion that tested HPV positive based on consensus primers were not further tested for specific HPV types due to insufficient DNA. Results from the analysis have been adjusted to reflect this.
‡ *n* refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.
§Lesions in these studies containing multiple HPV types were fractionally attributed to individual HPV types as described in Materials and Methods. Based on this method, figures for the attribution of individual HPV types differing from those reported in the table for prevalence were as follows: Evans et al. CIN 1 (HPV 6, 4.5%); Guo et al. CIN 1 (HPV 31, 7.4%; HPV 33, 7.4%; HPV 58, 0.0%), CIN 2/3 (HPV 16, 36.2%; HPV 31, 3.9%; HPV 33, 3.4%; HPV 52, 3.5%; HPV 58, 3.4%); Hu et al. CIN 1 (HPV 16, 6.4%; HPV 31, 3.1%; HPV 52, 12.2%; HPV 58, 7.2%), CIN 2/3 (HPV 16, 38.9%; HPV 18, 9.6%; HPV 31, 11.6%; HPV 35, 1.2%; HPV 45, 1.1%; HPV 52, 5.0%; HPV 58, 2.6%); Kong et al. CIN 2/3 (HPV 35; 0.0%, HPV 70, 0.0%).

than for CIN 1 lesions for HPV 16, 31, 35, and 58; however, only the difference for HPV 16 was statistically significant ($P < 0.0001$).

Among invasive squamous cell cervical cancer specimens (n = 1,090; 8 studies), HPV 16, 18, 33, 6, and 31 were the 5 most frequently observed HPV types, in order of decreasing prevalence, compared with HPV 16, 18, 45, 33, and 31 for cervical adenocarcinomas (Table 2). Multitype HPV infections were observed in 0.0% to 9.7% of lesions from each study. The proportion of all cancer specimens with HPV typing data that were adenocarcinomas or adenosquamous carcinomas versus squamous cell cancers varied by HPV type examined (due to heterogeneity across studies in reporting of data for specific HPV types) from 23.6% to 27.6%. These figures were generally similar to those estimated based

Table 2. Prevalence and attribution of HPV types in cervical cancers

Year	First author	*n*	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
SCC (31, 32, 41, 44, 45, 53, 54, 56)																						
2007	Guo	29	6.9			69.0	3.4	3.4	3.4	10.3		0.0		0.0		6.9							96.6
2001	Schwartz †	579	9.5	6.9	0.0	68.4	14.9	3.0	4.4	0.3	0.0	1.6	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.2	0.0	90.7
2000	Sebbelov	53				77.4	3.8	20.8	30.2	0.0		0.0											98.2
1998	Aoyama,	19		0.0	0.0	63.2	15.8	0.0	5.3														84.2
1998	Quade	12	0.0	0.0	0.0	58.3	8.3	0.0	8.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		75.0
1997	Wistuba	20				60.0	20.0	5.0	5.0														90.0
1996	Burger ‡	312		0.6	0.3	61.9	9.9	3.2	1.3	0.0	0.0	1.9	0.0	1.3	0.0	0.3	0.0	0.0	0.3	0.6	0.3	0.0	87.2
1994	Gregoire	66		0.0	0.0	56.1	10.6																87.9
Pooled prevalence		1,090§	9.1	4.3	0.1	65.9	12.4	4.1	4.9	0.5	0.0	1.6	0.0	0.5	0.0	0.6	0.0	0.0	0.1	0.3	0.3	0.0	89.6
95% CI, lower				3.2	0.0	63.0	10.6	3.0	3.7	0.2	0.0	0.9	0.0	0.2	0.0	0.3	0.0	0.0	0.0	0.1	0.1	0.0	
95% CI, upper				5.7	0.6	68.6	14.5	5.6	6.5	1.2	0.5	2.6	0.5	1.3	0.5	1.5	0.5	0.5	0.7	1.0	1.0	0.5	
Multitype adjusted‖		**472§**		**2.5**	**0.0**	**67.8**	**10.5**	**2.8**	**2.8**	**0.4**	**0.0**	**1.3**	**0.0**	**0.0**	**0.0**	**0.4**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, lower				**1.4**	**0.0**	**63.4**	**8.1**	**1.6**	**1.6**	**0.1**	**0.0**	**0.6**	**0.0**	**0.0**	**0.0**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper				**4.5**	**0.9**	**71.8**	**13.6**	**4.7**	**4.7**	**1.6**	**0.9**	**2.8**	**0.9**	**0.8**	**0.9**	**1.5**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	
Adenocarcinomas (31, 32, 40, 43, 50)																						
2003	Kuzmin	53				43.4	28.3					1.9											77.4
2001	Schwartz †	196	9.7	0.5	0.0	45.4	41.3	1.2	1.8	0.5	0.6	1.2	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	86.7
1998	Ferguson	27				25.9	25.9					7.4											
1997	Anciaux	28				32.1	21.4																
1996	Burger ‡	109		0.0	0.0	29.4	45.9	0.0	0.0	0.0	0.0	3.7	0.0	0.0	0.0	0.9	0.0	0.0	0.0	0.0	0.0	0.0	81.7
Pooled prevalence		413§	9.7	0.3	0.0	38.7	38.5	0.7	1.1	0.3	0.4	2.5	0.0	0.0	0.0	0.4	0.0	0.4	0.0	0.0	0.0	0.0	83.5
95% CI, lower				0.1	0.0	34.2	33.9	0.2	0.4	0.1	0.1	1.3	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	
95% CI, upper				1.8	1.2	43.5	43.3	2.6	3.2	1.8	2.0	4.8	1.4	1.4	1.4	2.0	1.4	2.0	1.4	1.4	1.4	1.4	
Multitype adjusted§		**165§**		**0.6**	**0.0**	**41.6**	**40.8**	**1.2**	**1.2**	**0.0**	**0.0**	**1.2**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.6**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, lower				**0.1**	**0.0**	**34.3**	**33.6**	**0.3**	**0.3**	**0.1**	**0.0**	**0.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper				**3.4**	**2.3**	**49.2**	**48.5**	**4.3**	**4.3**	**1.6**	**2.3**	**4.3**	**2.3**	**2.3**	**2.3**	**2.3**	**2.3**	**3.4**	**2.3**	**2.3**	**2.3**	**2.3**	
All cervical cancers¶																						
Pooled prevalence		1,503§	9.2	3.3	0.1	59.4	18.6	3.3	4.0	0.5	0.1	1.8	0.0	0.4	0.0	0.6	0.0	0.1	0.1	0.2	0.2	0.0	88.1
95% CI, lower				2.7	0.0	57.6	17.3	2.6	3.3	0.2	0.0	1.3	0.0	0.1	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	
95% CI, upper				3.9	0.2	61.3	19.9	4.0	4.7	0.7	0.2	2.3	0.4	0.6	0.4	0.9	0.4	0.2	0.2	0.4	0.4	0.4	
Multitype adjusted§		**637§**		**2.1**	**0.0**	**61.5**	**17.7**	**2.4**	**2.4**	**0.3**	**0.0**	**1.3**	**0.0**	**0.0**	**0.0**	**0.3**	**0.0**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, lower				**1.4**	**0.0**	**58.8**	**15.8**	**1.6**	**1.6**	**0.0**	**0.0**	**0.7**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper**				**2.8**	**0.6**	**64.2**	**19.7**	**3.1**	**3.2**	**0.6**	**0.6**	**1.8**	**0.6**	**0.6**	**0.6**	**0.6**	**0.6**	**0.3**	**0.6**	**0.6**	**0.6**	**0.6**	

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.

† Data for additional cases and HPV typing provided by the authors. In the study, HPV testing methods changed over time. Early testing of squamous cell and adenocarcinoma specimens ($n = 179$) was conducted for individual HPV types 6, 11, 16, 18, and 35 (HPV testing for types 31 and 33 was combined in a single cocktail). Later testing was conducted for a much broader spectrum of individual HPV types ($n = 596$). In the table, prevalence data are reported across all specimens for HPV types 6, 11, 16, 18, and 35, whereas only specimens tested during the latter period are included in results for the remaining HPV types as earlier testing for these types individually was not conducted. Only specimens tested during the latter period are included in the multitype adjusted HPV data, as the earlier testing covered <8 HPV types.

‡ Data for additional cases and HPV typing provided by the authors. Two small-cell (neuroendocrine) carcinomas are included among data for SCC.

§ *n* refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.

‖Lesions in these studies containing multiple HPV types were fractionally attributed to individual HPV types as described in Materials and Methods. Based on this method, figures for the attribution of individual HPV types differing from those reported in the table for prevalence were as follows: Guo et al. SCC (HPV 16, 68.6%; HPV 33, 0.0%; HPV 35, 7.2%); Schwartz et al. SCC (HPV 6, 2.6%; HPV 16, 68.0%; HPV 18, 11.1%; HPV 31, 2.8%; HPV 33, 2.8%; HPV 35, 0.0%; HPV 45, 1.4%; HPV 58, 0.0%; HPV 73, 0.0%), adenocarcinomas (HPV 6, 0.6%; HPV 16, 41.6%; HPV 18, 40.8%; HPV 33, 1.2%; HPV 35, 0.0%; HPV 39, 0.0%).

¶Prevalence across all cervical cancer cases adjusted for the relative proportion of cervical SCC versus adenocarcinomas (including adenosquamous carcinomas) observed in the U.S. population (30).

**Upper confidence interval width estimated using score interval (37) where undefined from Barnett et al. (38) (for $P = 0.0$).

Table 3. Prevalence of HPV types in VIN 1, VIN 2/3, and VIN 3 lesions

Year	First author	*n*	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
VIN 1 (51, 55)																						
2006	Srodon	33	21.2	27.3	15.2	6.1	0.0	3.0	3.0	0.0	0.0	0.0	6.1	3.0	0.0	6.1	6.1	3.0	9.1	3.0			90.9
2003	Logani	11	9.1	36.4	9.1	9.1	0.0	9.1	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	9.1	0.0			100.0
Pooled prevalence		44	18.2	29.5	13.6	6.8	0.0	4.5	2.3	0.0	0.0	0.0	6.8	2.3	0.0	4.5	4.5	2.3	9.1	2.3			93.2
95% CI, lower				18.2	6.4	2.3	0.0	1.3	0.4	0.0	0.0	0.0	2.3	0.4	0.0	1.3	1.3	0.4	3.6	0.4			
95% CI, upper				44.2	26.7	18.2	8.0	15.1	11.8	8.0	8.0	8.0	18.2	11.8	8.0	15.1	15.1	11.8	21.2	11.8			
Multitype adjusted †		**44**		**29.2**	**12.5**	**5.1**	**0.0**	**2.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**4.5**	**2.8**	**2.3**	**9.1**	**0.0**			
95% CI, lower				**17.9**	**5.7**	**1.5**	**0.0**	**0.4**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**1.3**	**0.6**	**0.4**	**3.6**	**0.0**			
95% CI, upper				**43.9**	**25.4**	**15.9**	**8.0**	**11.8**	**8.0**	**8.0**	**8.0**	**8.0**	**8.0**	**8.0**	**8.0**	**15.1**	**12.7**	**11.8**	**21.2**	**8.0**			
VIN 3																						
2006	Srodon	34	11.8	0.0	2.9	91.2	5.9	0.0	2.9	5.9	0.0	0.0	2.9	2.9	0.0	0.0	0.0	0.0	2.9	0.0			100.0
2001	Carter ‡	469	9.5	3.1	0.0	77.0	9.0	1.0	8.7	0.2	0.0	1.8	0.0	0.8	0.0	0.3	0.0	0.0	0.0	0.0	0.3	0.0	91.5
Pooled prevalence		503 ‡	9.7	2.8	0.2	77.9	8.7	0.9	8.3	0.6	0.0	1.7	0.2	0.9	0.0	0.2	0.0	0.0	0.2	0.0	0.3	0.0	92.2
95% CI, lower				1.6	0.0	74.1	6.4	0.4	6.0	0.2	0.0	0.8	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
95% CI, upper				4.9	1.3	81.3	11.8	2.4	11.3	1.7	0.9	3.4	1.3	2.4	0.9	1.3	0.9	0.9	.3	0.9	1.4	1.0	
Multitype adjusted †		**424** §		**0.0**	**0.0**	**77.7**	**6.3**	**0.2**	**6.3**	**0.5**	**0.0**	**0.7**	**0.0**	**0.2**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, lower				**0.0**	**0.0**	**73.5**	**4.3**	**0.0**	**4.4**	**0.1**	**0.0**	**0.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper				**0.9**	**0.9**	**81.4**	**9.0**	**1.3**	**9.0**	**1.7**	**0.9**	**2.1**	**0.9**	**1.3**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**1.0**	**1.0**	

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.

† Additional data on the type distribution within multitype HPV infections were kindly referred to us for the Srodon et al. study (36). Lesions in these studies containing multiple HPV types were fractionally attributed to individual HPV types as described in Materials and Methods. Based on this method, figures for the attribution of individual HPV types differing from those reported in the table for prevalence were as follows: Srodon et al. VIN 1 (HPV 6, 26.8%; HPV 11, 13.6%; HPV 16, 3.8%; HPV 31, 0.0%; HPV 33, 0.0%; HPV 51, 0.0%; HPV 52, 0.0%; HPV 59, 3.8%; HPV 70, 0.0%), VIN 3 (as reported here); Logani et al. VIN 1 (HPV 51, 0.0%); Carter et al. VIN 3 (HPV 6, 0.0%; HPV 16, 76.5%; HPV 18, 6.8%; HPV 31, 0.3%; HPV 33, 6.6%; HPV 35, 0.0%; HPV 45, 0.8%; HPV 52, 0.3%; HPV 58, 0.0%; HPV 73, 0.0%).

‡ Data for additional cases and HPV typing provided by the authors. In the study, HPV testing methods changed over time. Early testing of specimens (n = 79) was conducted for individual HPV types 16 and 35 (HPV testing for types 6/11, 18/45, and 31/33 were combined in single cocktails). Later testing (n = 390) was conducted for a much broader spectrum of individual HPV types. In the table, prevalence data are reported across all specimens for HPV types 16 and 35, whereas only specimens tested during the latter period are included in results for the remaining HPV types as earlier testing for these types individually was not conducted. Only specimens tested during the latter period are included in the multitype adjusted HPV data, as the earlier testing covered <8 HPV types.

§ *n* refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.

on pooled data from U.S. cervical cancer registries (23.8%; ref. 30). Following multitype adjustment, the highest attribution to cervical cancers was observed for HPV 16 (61.5%), with the 2 two (HPV 16 and 18), 4 (HPV 16, 18, 31, and 33), and 8 (HPV 16, 18, 31, 33, 6, 45, 58, and 35) reported HPV types estimated to account for 79.2%, 84.0%, and 88.0% of cervical cancers, respectively.

Vulvar Disease. Among VIN 1 lesions (*n* = 44; 2 studies), HPV 6, 11, 68, 16, and 51 were the 5 most frequently observed HPV types, in order of prevalence (Table 3). Multitype infections were detected in 18.2% of VIN 1 lesions when studies were pooled. After multitype adjustment, HPV 6 was estimated to contribute to the largest fraction (29.5%) of VIN 1 lesions, with the top 2 (HPV 6 and 11), 4 (HPV 6, 11, 68, and 16), and 8 (HPV 6, 11, 68, 16, 58, 59, 31, and 66) reported HPV types accounting for 41.7%, 55.9%, and 67.8% of VIN 1 lesions, respectively. The attribution of HPV 6 and 11 to VIN 1 lesions (41.7%) was greater than that estimated for CIN 1 (6.9%; $P < 0.0001$).

No studies meeting the review eligibility criteria reported data for VIN 2/3 lesions. We therefore report available U.S. data for VIN 3 lesions (*n* = 503; 2 studies) in Table 3. No studies were found reporting data exclusively for VIN 2 lesions. Following multitype adjustment, HPV 16 was estimated to contribute to more than three-fourths (77.7%) of VIN 3 lesions, with the top 2 (HPV 16 and 18 or 33), 4 (HPV 16, 18, 33, and 45), and 8 (HPV 16, 18, 33, 45, 35, 31, and 52; 0% attribution for remaining types) reported HPV types accounting for 84.0%, 91.0%, and 91.9% of VIN 1 lesions, respectively.

Among vulvar cancers (n = 197; 4 studies), only data for squamous cell cancers were available. HPV 16, 33, 6, 18, and 31 were the five most frequent HPV types detected, in order of prevalence, and multitype infections were observed in 5.8% of cases. The proportion of cancers testing positive for any HPV type was 65.3%. Following multitype adjustment, HPV 16 contributed to ~50% of cases overall and >75% of HPV-positive cases. One study by Monk et al. (5) additionally reported HPV prevalence by age group, with 6 of 6 (100%) of patients ages <45 years with vulvar cancers positive for HPV infection compared with 12 of 17 (71%) of patients ages 45 to 69 years and 47% of patients ages ≥70 years (Table 4).

Vaginal Disease. Among VaIN 1 lesions (n = 36; 2 studies), the 5 most prevalent HPV types were HPV 18, 56, 16, 51 and 66, each of which were observed in 10% to 20% of cases. Multitype HPV infections were observed in 28.6% of cases. Only 19 cases had complete data available for performing multitype adjustment, so these results are not presented for VaIN 1.

No studies were identified meeting review eligibility criteria that described VaIN 2/3 or VaIN 2 lesions. Instead, we report data for two studies of VaIN 3 lesions (n = 97; 2 studies). HPV 16, 18, 6, 58, and 73 were the 5 most common HPV types detected in order of prevalence. Following adjustment for multitype HPV infections, which were observed in 11.4% of lesions, HPV 16 was estimated to have the highest attribution to VaIN 3 (64.6% of cases). In order of attribution, the top 2 HPV types were HPV 16 and 18, top 4 types were HPV 16, 18, 73, and 33, and top 8 types were HPV 16, 18, 73, 33, 6, 56, 58, 59, and 66 (four-way tie among the last four types) accounting for 69.6%, 77.7%, and 84.2% of VaIN 3 lesions, respectively (Tables 5 and 6).

Data for squamous cell vaginal cancers were sparse (n = 50; 1 study) compared with corresponding data for invasive cervical or vulvar disease, and no eligible studies for vaginal adenocarcinoma were identified. Following multitype adjustment, HPV 16 contributed to the largest proportion of cases (63.2%), with a similar representation of this type as seen among cervical cancers. The study reported that HPV-negative vaginal cancer cases tended to be of older age than HPV-positive cases (10).

Discussion

This review of the prevalence and attribution of individual HPV types among U.S. female genital cancers builds on the work of prior reviews (21-25) through the incorporation of updated references, adjustments for histologic type and presence of multitype HPV infections where feasible, and inclusion of vulvar and vaginal neoplasias in addition to cervical disease. We now discuss findings based on each of these study features in addition to the broader implications of the HPV typing results.

Among prior published reviews of the prevalence of HPV types in invasive and preinvasive cervical disease, the worldwide meta-analysis of Smith et al. is the most recent, covering studies published through January 2006 (25). However, several studies, particularly among those

Table 4. Prevalence and attribution of HPV types in vulvar cancers

Year	First author	n	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
Vulvar squamous cell cancers (4, 5, 48, 52)																						
2001	Carter †	110	8.1	8.1	0.0	59.1	5.8	2.3	9.3	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	75.6
1999	Pinto	16	0.0	0.0	0.0	37.5	0.0	0.0	6.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		50.0
1996	Kim	18	0.0	5.6	0.0	27.8	5.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0				38.9
1995	Monk	53		1.9		50.9	5.7																60.0
Pooled prevalence		197 ‡	5.8	5.2	0.0	52.3	5.2	1.7	7.5	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	65.3
95% CI, lower				2.8	0.0	45.3	2.8	0.5	4.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
95% CI, upper				9.6	3.1	59.1	9.6	5.9	13.6	2.6	3.1	3.1	3.1	4.6	3.1	3.1	3.1	3.1	3.1	3.6	3.6	4.3	
Multitype adjusted		**120** ‡		**3.6**	**0.0**	**49.5**	**4.2**	**1.7**	**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**	
95% CI, lower				**1.4**	**0.0**	**40.7**	**1.8**	**0.5**	**3.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper				**8.6**	**3.1**	**58.3**	**9.5**	**5.9**	**11.8**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.1**	**3.6**	**3.6**	**4.3**	

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.

† Data for additional cases and HPV typing provided by the authors. In the study, HPV testing methods changed over time. Early testing of specimens (n = 24) was conducted for individual HPV types 16 and 35 (HPV testing for types 6/11, 18/45, and 31/33 were combined in single cocktails). Later testing was conducted for a much broader spectrum of individual HPV types (n = 86). In the table, prevalence data are reported across all specimens for HPV types 16 and 35, whereas only specimens tested during the latter period are included in results for the remaining HPV types as earlier testing for these types individually was not conducted. Only specimens tested during the latter period are included in the multitype adjusted HPV data, as the earlier testing covered <8 individually evaluable HPV types.

‡ n refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.

Table 5. Prevalence of HPV types in VaIN 1 and VaIN 3 lesions

Year	First author	*n*	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
VaIN 1 (51, 55)																							
2006	Srodon	17	29.4	0.0	0.0	5.9	23.5	0.0	0.0	0.0	5.9	0.0	23.5	5.9	11.8	5.9	0.0	11.8	0.0	0.0			100.0
2003	Logani	19	26.3	0.0	0.0	21.1	15.8	5.3	0.0	5.3	0.0	0.0	0.0	0.0	21.1	0.0	5.3	10.5	10.5	0.0			100.0
Pooled prevalence		36†	28.6	0.0	0.0	13.9	19.4	2.8	0.0	2.8	2.8	0.0	11.1	2.8	16.7	2.8	2.8	11.1	5.6	0.0			100.0
95% CI, lower				0.0	0.0	6.1	9.8	0.5	0.0	0.5	0.5	0.0	4.4	0.5	7.9	0.5	0.5	4.4	1.5	0.0			
95% CI, upper				9.6	9.6	28.7	35.0	14.2	9.6	14.2	14.2	0.0	25.3	14.2	31.9	14.2	14.2	25.3	18.1	9.6			
VaIN 3 (10, 55)																							
2006	Srodon	16	12.5	0.0	0.0	50.0	0.0	12.5	0.0	6.3	0.0	0.0	6.3	6.3	0.0	18.8	0.0	6.3	0.0	0.0			93.8
2002	Daling‡	81	11.1	6.3	0.0	60.5	7.9	0.0	4.8	0.0	0.0	0.0	0.0	0.0	1.6	1.6	1.6	3.2	0.0	0.0	4.8	0.0	87.3
Pooled prevalence		97†	11.4	5.1	0.0	58.8	6.3	2.5	3.8	1.0	0.0	0.0	1.3	1.3	1.3	5.1	1.3	3.8	0.0	0.0	4.8	0.0	88.6
95% CI, lower				2.0	0.0	48.8	2.7	0.7	1.3	0.2	0.0	0.0	0.2	0.2	0.2	2.0	0.2	1.3	0.0	0.0	1.6	0.0	
95% CI, upper				12.3	4.6	68.0	14.0	8.8	10.6	5.6	4.6	4.6	6.8	6.8	6.8	12.3	6.8	10.6	4.6	4.6	13.1	5.7	
Multitype adjusted		**63**†		**1.7**	**0.0**	**64.6**	**5.0**	**0.0**	**3.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**1.6**	**1.6**	**1.6**	**1.6**	**0.0**	**0.0**	**4.8**	**0.0**	
95% CI, lower				**0.3**	**0.0**	**52.2**	**1.8**	**0.0**	**0.9**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.3**	**0.3**	**0.3**	**0.3**	**0.0**	**0.0**	**1.6**	**0.0**	
95% CI, upper				**8.7**	**5.7**	**75.2**	**13.4**	**5.7**	**11.0**	**5.7**	**5.7**	**5.7**	**5.7**	**5.7**	**8.5**	**8.5**	**8.5**	**8.5**	**5.7**	**5.7**	**13.1**	**5.7**	

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.

† *n* refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.

‡ Data for additional cases and HPV typing provided by the authors. In the study, HPV testing methods changed over time. Early testing of specimens ($n = 18$) was conducted for individual HPV types 16 and 35 (HPV testing for types 6/11, 18/45, and 31/33 were combined in single cocktails). Later testing was conducted for a much broader spectrum of individual HPV types ($n = 63$). In the table, prevalence data are reported across all specimens for HPV types 16 and 35, whereas only specimens tested during the latter period are included in results for the remaining HPV types as earlier testing for these types individually was not conducted. Only specimens tested during the latter period are included in the multitype adjusted HPV data, as the earlier testing covered <8 individually evaluable HPV types.

fully documenting multitype HPV infections, have been published since. Five of 8 studies of CIN 2/3 lesions included in the present review were not part of this earlier study, representing 61% of all included CIN 2/3 cases. The same was true for 5 of 11 cervical cancer studies included here.

There were also studies included in these earlier reviews, which we chose to exclude because the samples were based on exfoliated cervical cells, Pap smears, or cervicovaginal lavage (21-25). The decision to exclude these studies was not taken lightly, as it ultimately meant a reduction in sample size and statistical precision. However, in the early stages of our review, an examination of two U.S. studies using exfoliated cervical cells to report HPV PCR typing for CIN 2/3 lesions revealed a very high rate of multitype HPV infections. Adam et al. (57) reported multitype HPV infections among 21.0% of women inclusive of high-risk HPV type infections alone. MacLehose et al. (58) observed 39 high- or low-risk HPV infections among 21 women with HPV-positive lesions (an 86% overage if all women had tested positive for a single HPV type). Similarly, lavage PCR data for U.S. women with CIN 2/3 reported by Ho et al. revealed multitype HPV infections among 40% of study participants (59). Unlike the biopsy-based study excluded from this review (39), where multitype infections with the same few types were consistently observed in multiple samples, HPV infections spanned a broad array of types in these nonbiopsy studies, with no clear pattern for multitype HPV infections reported. For comparison, across CIN 2/3 biopsy specimens included in the present review, where reporting of multiple HPV types was available, just 6.5% tested positive for multiple types, representing a total average of 7% among HPV-positive cases. On this basis, we concluded that although imperfect in their own right, limiting the review to biopsy specimens would produce results that were less likely to be biased by concomitant HPV infections distinct from the lesion of interest occurring elsewhere in the cervicovaginal tract as ascertained by these other testing methods.

Even so, the proportion of multitype HPV infections among biopsied specimens reported in this study was 7.2% among cervical lesions, 9.5% among vulvar lesions, and 13.7% among vaginal lesions. To avoid multiple counting when evaluating attribution among multitype infected lesions, we introduced a multitype adjustment method to estimate the proportion of cases accounted for by individual HPV types or groups of HPV types. HPV 16 and 18 are well known to be the two HPV types with

the highest attribution to cervical cancers worldwide (24). Among female genital cancers and high-grade cervical precancers, adjustment for multitype HPV infections produced a relatively small effect on the estimated attribution of these types to disease. However, other HPV types less commonly observed in high-grade or invasive female genital neoplasias were disproportionately or exclusively observed in combination with HPV 16, HPV 18, or each other. For instance, among studies of squamous cell cervical cancers where the presence of multitype infections could be assessed, HPV 16 was observed as a single-type infection in 88% of HPV 16-positive specimens (284 of 324), whereas the same was true for HPV 58 in just 25% (1 of 4) of cases ($P = 0.004$). As a result, the elimination of multiple counting of multitype infections had a more pronounced effect on the estimated attribution of non-HPV 16/18 type infections than for HPV 16 and 18. For example, crudely summing prevalence figures for the remaining 17 HPV types other than HPV 16 or 18 among squamous cell cervical cancers yields a figure of 17.4%, which is 71% higher than the estimated attribution of these types after adjusting for multitype HPV infections (10.2%). Thus, adjustment for multitype HPV infections could potentially have implications for the estimation of the incremental cost-benefit associated with expanding HPV tests and vaccines to cover additional HPV types (60). Among prior international reviews, only Muñoz et al. adjusted crude prevalence figures for multitype infections to estimate attributable fractions (24). However, unlike in the present study, all HPV types observed within multitype infections were presumed to contribute equally to disease. In addition, the study scope was limited to IARC studies. For the present analysis, we felt it was helpful to differentially weight HPV types in multitype infections according to their frequency in diagnosed disease. Thus, a HPV 6 and 16 coinfected cervical cancer was perceived to have more likely resulted from infection with HPV 16. It is interesting to note that there was a range in the proportion of lesions testing positive for multiple HPV types within a given grade and type of disease, which could be the result of purely statistical variation but also potential variation in HPV typing methods.

In this study, HPV 18 was estimated to account for a much larger proportion (4 times) of U.S. cervical adenocarcinomas than squamous cell cancers, a finding also highlighted in earlier reviews (24, 25). The adjustment of HPV prevalence and attribution data across all cervical cancers to the proportion of adenocarcinomas versus SCC estimated for the U.S. population produced a very modest effect on results relative to no adjustment (data not shown) because the proportions were similar between U.S. population data (23.8%) and studies included in this review (23.6-27.6%). Depending on the available data, though, this may not always be the case in analyses for the U.S. or other countries. For instance, Smith et al. reviewed North American studies (U.S./Canada) in which a higher proportion (32%) of cervical cancer cases were adenocarcinomas and reported a higher prevalence of HPV 18 (22.2%) than that estimated in the present review (17.6%; ref. 25).

Unfortunately, data were insufficient for describing HPV typing results for vulvar or vaginal adenocarcinomas. Thus, our review focused on squamous cell disease for these cancers and we were not able to report pooled data adjusted by histologic type for these cases. Based on data from the Surveillance, Epidemiology and End Results Program for 2000 to 2002, adenocarcinomas are estimated to comprise a very small proportion of vulvar

Table 6. Prevalence and attribution of HPV types in vaginal cancers

Year	First author	*n*	Multitype infections (%)	Percentage of specimens testing positive for individual HPV types																		Any HPV type*
				6	11	16	18	31	33	35	39	45	51	52	56	58	59	66	68	70	73	82	
Vaginal squamous cell cancers (10)																							
2002	Daling †	50	3.0	0.0	0.0	60.0	12.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	72.7
Pooled prevalence		50 ‡	3.0	0.0	0.0	60.0	12.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	72.7
95% CI, lower				0.0	0.0	46.2	4.8	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	
95% CI, upper				10.4	10.4	72.4	27.3	10.4	10.4	7.1	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	
Multitype adjusted		**33** ‡		**0.0**	**0.0**	**63.2**	**9.5**	**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**	
95% CI, lower				**0.0**	**0.0**	**46.2**	**3.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	
95% CI, upper				**10.4**	**10.4**	**77.5**	**24.1**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	**10.4**	

*As determined by consensus PCR primers sensitive to positivity for at least 15 HPV types.

† Data for additional cases and HPV typing provided by the authors. In the study, HPV testing methods changed over time. Early testing of specimens ($n = 17$) was conducted for individual HPV types 16 and 35 (HPV testing for types 6/11, 18/45, and 31/33 were combined in single cocktails). Later testing was conducted for a much broader spectrum of individual HPV types ($n = 33$). In the table, prevalence data are reported across all specimens for HPV types 16 and 35, whereas only specimens tested during the latter period are included in results for the remaining HPV types as earlier testing for these types individually was not conducted. Only specimens tested during the latter period are included in the multitype adjusted HPV data, as the earlier testing covered <8 individually evaluable HPV types.

‡ *n* refers to total number of lesions with any HPV typing data. By individual HPV type, number of observations varies depending on the number of types for which data were available within each study.

cancers (2.4%; ref. 12). However, the fraction of adenocarcinomas is larger for vaginal cancers (16.4%) and investigation of HPV typing for these tumors represents an area for further research (12).

Most of the general findings of this study such as that HPV 16 and 18 are the primary types observed in cervical and vaginal cancers (22, 25, 61), HPV 16 is the most common type among vulvar cancers (61), and that HPV 31 is the next most frequent type among U.S. cervical cancers (22, 25) have been reported by other authors previously. Also, similar to prior reviews (21-23, 25), we found that HPV prevalence varied by grade of disease. For instance, HPV 16, 18, 31, 51, 52, and 66 were each prevalent in >5% of CIN 1 cases compared with only HPV 16 and 18 observed in excess of 5% among invasive cervical cancers. However, for policy decisions, such as estimating the cost-effectiveness of expanding HPV vaccines and tests to include coverage of additional HPV types or understanding the benefits conferred by HPV vaccine cross-type protection (62, 63), accurate estimation of the absolute attribution of individual HPV types to these precancers and cancers is essential. To this end, this article has featured several methodologic adaptations that have yielded some results that differ from earlier reviews.

First, after adjustment for multitype HPV infections and the limitation of studies to only those based on cervical tissue specimens, the attribution of ''high-risk'' HPV types other than HPV 16 and 18 (types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, and 82) to cervical cancers was observed to be quite low (6.8%). This figure is much lower than what would be obtained were one to simply sum prevalence figures for these types from earlier studies for North America/Australia by Clifford et al. (12.4%; ref. 22) for North America by Smith et al. (15.0%; ref. 25) or from the data on HPV type attribution for Europe and North America reported by Muñoz et al. (>16%; ref. 24). Although these types may have a relatively smaller attribution to cervical cancer incidence in the United States, in some other regions of the world such as Asia, they may account for a much larger fraction of disease (34). For instance, in an international analysis of IARC studies, Muñoz et al. observed a pooled prevalence of single-type infected squamous cell cancers associated with these types of 19.7% and a corresponding prevalence among adenocarcinomas of 11.7% (24). In addition, these types accounted for a much larger proportion of CIN 2/3 (23.5%) and CIN 1 (46.9%) lesions. An understanding of the relative merits of alternative coverage strategies for these types in vaccines and diagnostic tests requires formal cost-effectiveness analyses.

Conversely, the proportion of U.S. cervical cancer cases estimated to be attributable to HPV 16 and 18 infections (79.2%) is higher than the 70% attribution for these types that is typically referenced as a worldwide standard (64, 65). Thus, although a 70% attributable fraction for these types could reflect a worldwide average, modest deviations may be observable for some countries and regions.

Second, although generally differentiated from these other HPV types as ''low risk,'' HPV 6 was estimated to contribute to ~2.1% of U.S. invasive cervical cancers and 3.6% of vulvar cancers. Although low, these figures were above those estimated for HPV types such as 45, 52, and 58, which are commonly regarded as ''high-risk types.'' However, a causal role of HPV 6 in cervical cancers has been regarded previously as unlikely based on its low malignant potential as shown in laboratory studies (66), and the potential role of HPV 6 in these cancers merits further evaluation.

Third, HPV appears to be present in 65% to 75% of vulvar and vaginal squamous cell cancers. HPV 16 and 18 were estimated to account for >50% of vulvar cancers and >70% of vaginal cancers in the studies reviewed, with other types found in a minority of cases. Whereas VIN 1 lesions bore some resemblance to anogenital warts in that HPV 6 and 11 were the predominant types detected (33, 67), other HPV types such as HPV 68 and 16 seemed to play a more important role in these lesions than generally observed in anogenital warts. The representation of individual HPV types among VaIN 1 lesions was somewhat more similar to that of CIN 1 than VIN 1 in that a larger proportion of lesions tested positive for HPV 16 or 18 than HPV 6 or 11.

Our study has several limitations. First, the HPV testing in the studies reviewed may have had imperfect sensitivity and specificity for the HPV types reported and variation in the detection of specific types may exist across typing methods used (68). Newer assays detect a broader range of HPV types than older methods and some studies, regardless of publication year, elected to conduct and report typing data for particular subgroups of potentially evaluable HPV types. The effect of including studies that assayed their samples for relatively fewer types would likely be to bias our results toward showing greater attribution to commonly assayed types, as the ability to detect and adjust downward for the presence of multitype infections would be limited to a relatively smaller group of types. We attempted to minimize this potential bias by restricting our analysis of attribution to studies reporting typing results for a minimum of 8 HPV types; in fact, only 2 of the 13 studies evaluated in the analyses of attribution conducted typing for <15 HPV types.

Second, because HPV infections are prevalent in the genital tracts of women without clinically evident disease, it is possible that a proportion of cases could have a given HPV type detected in a biopsy specimen by chance, without causal attribution to the lesion. Third, although our multitype adjustment method may serve as a reasonable proxy for HPV type-specific attribution when multiple types are observed in a single specimen, and mitigate concerns regarding double counting of lesions, it is not an exact method for identifying which HPV type(s) are responsible for a given lesion(s). The method implicitly assumes that if a given HPV type is rarely observed in single-type infected lesions, it is also rarely a causal type in multitype infected lesions. Further studies using laboratory methods (e.g., *in situ* hybridization and assessment of integration or transcriptional activity) to isolate the causal HPV in multitype infected lesions would be helpful. Fourth, the studies included in this and prior reviews do not constitute a truly representative random statistical sample of disease diagnosed within the general U.S. population. For instance, in some studies, there could have potentially been underrepresentation of tumor specimens from women with late-stage disease who were unable to participate or died before being contacted for participation. The effect of this potential

limitation is not known. Finally, additional studies of HPV typing would be particularly helpful for vaginal precancers and cancers (both squamous cell and adenocarcinomas) given the limited numbers of U.S. specimens, HPV types, and assessments of multitype infections reported to date for these lesions. Even for cervical cancers, where total sample sizes were much larger, the number of available studies cataloging the distribution of multitype infections to date has been relatively limited and the external validity of our results depends on the accuracy and generalizability of these studies.

In conclusion, this study has described the prevalence and attribution of HPV types to cervical, vaginal, and vulvar precancers and cancers in the United States. For instance, among the findings, a slightly higher fraction of cervical cancers (79%) in the United States may be attributable to HPV 16 and 18 infection vis-à-vis pooled international data (71%; ref. 24). The analysis has built on the work of prior reviews of cervical disease with an updated and expanded analysis, incorporation of new selection criteria for specimens, adjustment for histologic type among cervical cancers, and accounting methods for multitype HPV infections. To date, only a portion of U.S. studies of these precancers and cancers have specifically reported all HPV types for which testing was conducted, a complete characterization of single and multitype infections and HPV typing by lesion histologic type. Consistent reporting of this information in future studies will enhance the value of the data for researchers and policymakers wishing to better understand the burden of HPV disease in the population and the potential health and economic effect of technologies for preventing, diagnosing, and treating HPV infection and disease.

Disclosure of Potential Conflicts of Interest

R.P. Insinga and Kai-Li Liaw: Merck & Co., Inc. employees.

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