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Article

ARTICLE

US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines

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Abstract

Background: This study sought to determine the prevaccine type-specific prevalence of human papillomavirus (HPV)–associated cancers in the United States to evaluate the potential impact of the HPV types in the current and newly approved 9-valent HPV vaccines.

Methods: The Centers for Disease Control and Prevention partnered with seven US population-based cancer registries to obtain archival tissue for cancers diagnosed from 1993 to 2005. HPV testing was performed on 2670 case patients that were fairly representative of all participating cancer registry cases by age and sex. Demographic and clinical data were evaluated by anatomic site and HPV status. Current US cancer registry data and the detection of HPV types were used to estimate the number of cancers potentially preventable through vaccination.

Results: HPV DNA was detected in 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 68.8% of vulvar, 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS). A vaccine targeting HPV 16/18 potentially prevents the majority of invasive cervical (66.2%), anal (79.4%), oropharyngeal (60.2%), and vaginal (55.1%) cancers, as well as many penile (47.9%), vulvar (48.6%) cancers: 24 858 cases annually. The 9-valent vaccine also targeting HPV 31/33/45/52/58 may prevent an additional 4.2% to 18.3% of cancers: 3944 cases annually. For most cancers, younger age at diagnosis was associated with higher HPV 16/18 prevalence. With the exception of oropharyngeal cancers and CCIS, HPV 16/18 prevalence was similar across racial/ethnic groups.

Conclusions: In the United States, current vaccines will reduce most HPV-associated cancers; a smaller additional reduction would be contributed by the new 9-valent vaccine.

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Human papillomavirus (HPV) infection is causally associated with most anogenital (1) cancers, as well as oropharyngeal (OP) and possibly oral cavity (OC) and laryngeal cancers, contributing to an estimated 600 000 incident cancers worldwide and 250 000 premature deaths (2,3). A small subset of all HPV types are considered oncogenic (4,5). Internationally, the etiologic fraction of HPV-associated malignancy, based on HPV detection, varies by geography and anatomic site, but overall suggests that 70% of cervical cancers are caused by HPV 16/18, and HPV 16 is the primary oncogenic virus in other anogenital and OP cancers. The fraction of HPV detected in OP cancers ranges from 13% to 72%, with the highest in North America (2,6,7). HPV detection varies from 40% in vaginal to 90% in anal cancers (2).

Widespread uptake of HPV 16/18 vaccines has already been shown to decrease high-grade cervical lesions (8,9) and is anticipated to substantially reduce the burden of HPV-associated cancers. Clinical trials and ad hoc analyses demonstrated high efficacy of HPV 16/18 vaccines in preventing cervical, vulvar, anal, and vaginal precursor lesions (10–13). A recent secondary analysis supports efficacy of the 16/18 vaccine in preventing oral HPV 16/18 infection (14). The US Food and Drug Administration (FDA) recently approved the nonavalent (9-valent) vaccine targeting HPV 6/11/16/18 and five additional oncogenic types (15), which could extend protection to almost 90% of all cervical cancers worldwide (16,17). However, reductions in cancer incidence will take several decades to achieve given the long natural history of disease progression and low vaccine coverage in the United States (18).

Baseline and ongoing surveillance of type-specific, population-based HPV prevalence in cervical and other HPV-associated cancers will strengthen measures of the impact of HPV vaccines on cancer. Presently, these systematic surveillance efforts have not been established in the United States. Indeed, the United States has been underrepresented in international studies of HPV prevalence in tumors (19). To address this gap, the CDC used population-based cancer registries to establish the type distribution in HPV-associated malignancies prior to the public introduction of the HPV vaccine in 2006. Cancer registries provide well-annotated tissues linked to demographic and clinical data that allow determination of type-specific differences in HPV prevalence that may be important for monitoring impact and cost-effective analyses for current and future vaccines.

Methods

The CDC Cancer Registry Sentinel Surveillance System was designed and coordinated in 2006 in partnership with seven population-based cancer registries selected based on several factors, including large racial-ethnic populations or geographic areas with higher rates of cervical cancer (Florida, Hawaii, Iowa, Kentucky, Louisiana, Los Angeles County [LAC], and Michigan). All protocols were reviewed and approved by the institutional review boards of all participating organizations and CDC.

Case Recruitment and Identification

The recruitment procedures have been described elsewhere (20–24). Briefly, four cancer registries (FL, KY, LA, and MI) identified a sample of potentially eligible cancer cases diagnosed between 2004 and 2005 in their state (KY, MI, LA) or catchment area (three counties: Broward, Palm Beach, Miami-Dade). Eligibility criteria included residency within the catchment area and histologically confirmed invasive cancers from cervix, vagina, vulva, penis, anus, or oropharynx. MI also collected tissue from cervical cancer in situ (CCIS). Three cancer registries (HI, IA, LAC) that were part of the Residual Tissue Repository (RTR) were added to enhance the geographic distribution and number of available cases for each of the HPV-associated malignancies. RTR sites contributed cases from 1993 to 2004 as shown in Table 1. RTR case eligibility was expanded to capture CCIS and

Table 1. Patient demographics by cancer registry and cancer tissue site

Characteristic	Los Angeles No. (%)	Hawaii No. (%)	Iowa No. (%)	Kentucky No. (%)	Florida No. (%)	Louisiana No. (%)	Michigan No. (%)	Total No. (%)
Cancer tissue site								
Cervical	70 (30.8)	116 (31.5)	66 (19.2)	159 (40.5)	169 (38.9)	93 (34.4)	104 (16.4)	777 (29.1)
Vulvar	0 (0)	20 (5.4)	16 (4.7)	49 (12.5)	37 (8.5)	35 (13.0)	19 (3.0)	176 (6.6)
Vaginal	6 (2.6)	4 (1.1)	1 (0.3)	13 (3.3)	10 (2.3)	13 (4.8)	13 (2.1)	60 (2.2)
Anal	16 (7.0)	12 (3.3)	2 (0.6)	38 (9.7)	46 (10.6)	20 (7.4)	12 (1.9)	146 (5.5)
Penile	4 (1.8)	3 (0.8)	4 (1.2)	14 (3.6)	29 (6.7)	11 (4.1)	14 (2.2)	79 (3.0)
In situ cervical	57 (25.1)	0 (0)	91 (26.5)	0 (0)	0 (0)	0 (0)	333 (52.5)	481 (18.0)
In situ vulvar	14 (6.2)	41 (11.1)	13 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	68 (2.5)
Oropharyngeal	21 (9.3)	47 (12.8)	19 (5.5)	120 (30.5)	144 (33.1)	98 (36.3)	139 (21.9)	588 (22.0)
Base of tongue	4 (1.8)	14 (3.8)	1 (0.3)	49 (12.5)	56 (12.9)	38 (14.1)	58 (9.1)	220 (8.2)
Tonsillar	13 (5.7)	21 (5.7)	3 (0.9)	54 (13.7)	58 (13.3)	47 (17.4)	60 (9.5)	256 (9.6)
Other oropharyngeal	4 (1.8)	12 (3.3)	15 (4.4)	17 (4.3)	30 (6.9)	13 (4.8)	21 (3.3)	112 (4.2)
Laryngeal	22 (9.7)	48 (13.0)	78 (22.7)	0 (0)	0 (0)	0 (0)	0 (0)	148 (5.5)
Oral cavity	17 (7.5)	77 (20.9)	53 (15.5)	0 (0)	0 (0)	0 (0)	0 (0)	147 (5.5)
Oral tongue	7 (3.1)	39 (10.6)	25 (7.3)	0 (0)	0 (0)	0 (0)	0 (0)	71 (2.7)
Gum	2 (0.9)	7 (1.9)	6 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	15 (0.6)
Floor of mouth	1 (0.4)	18 (4.9)	10 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	29 (1.1)
Other oral cavity	7 (3.1)	13 (3.5)	12 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	32 (1.2)
Years contributed	1993–1999	2000–2004	1994–2004	2004–2005	2004–2005	2004–2005	2004–2005	1993–2005
Race/ethnicity								
White, non-Hispanic	105 (46.3)	102 (28.7)	307 (93.9)	345 (88.2)	211 (48.8)	174 (64.4)	466 (84.1)	1710 (66.9)
Black, non-Hispanic	14 (6.2)	3 (0.8)	9 (2.8)	42 (10.7)	73 (16.9)	90 (33.3)	66 (11.9)	297 (11.6)
Hispanic	87 (38.3)	7 (2.0)	6 (1.8)	4 (1.0)	147 (34.0)	3 (1.1)	16 (2.9)	270 (10.6)
Asian/Pacific Islander	21 (9.3)	242 (68.0)	5 (1.5)	0 (0)	0 (0)	3 (1.1)	4 (0.7)	275 (10.8)
Other	0 (0)	2 (0.6)	0 (0)	0 (0)	1 (0.2)	0 (0)	2 (0.4)	5 (0.2)

vulvar cancers in situ (VCIS) and invasive OC and larynx cancers. For all contributing registries, case patients were assigned code numbers to link demographic information, including age at diagnosis, diagnosis year, race/ethnicity, county of residence, and clinical information, including tumor grade, stage, and histology. Tissue collection was performed as part of cancer registry operations with all patient identifiers removed and no written informed consent required by the IRBs.

Pathology and Laboratory Procedures

Pathology and laboratory procedures have been described (20,25). Briefly, the diagnostic pathology laboratories or RTR selected one representative formalin-fixed paraffin-embedded tissue block from the primary site of each case patient. For oropharyngeal cancer only, a lymph node metastasis was accepted if the primary was not available (n = 15). All blocks were processed following a standardized protocol to prevent contamination and allow confirmation of the presence of tumor (20). Histology review failed to identify representative tissue in 255 of 3017 specimens submitted (8.5%) (Figure 1).

Samples passing histologic review were extracted and tested as previously described (20). Briefly, DNA extracts were tested with the Linear Array HPV Genotyping Test (LA, Roche Diagnostics, Indianapolis, IN), and those that were HPV negative were retested with the INNO-LiPA HPV Genotyping Assay (LiPA, Innogenetics, Gent, Belgium).

The 92 samples that failed to amplify control sequences in both assays were excluded (3.3% of those tested) (Figure 1).

Statistical Analysis

HPV type-specific detection percentages were determined by anatomic site and demographic characteristics. In addition to individual HPV types, categories of HPV types were examined: HPV 16/18; HPV 31, 33, 45, 52, and 58 (the five additional HR types in 9-valent vaccine); other HPV types; and HPV negative. When multiple HPV types were present, we used proportional weighting attribution to assign single-type contributions (26,27). Cases were weighted according to the distribution of single-type infections as the proportion positive for a given type divided by the sum of the proportions of each type present. For example, if HPV 16 exists in 60% of the single infection cervical specimens, and HPV 31 exists in 10% of the single infection specimens, then for a cancer that has both 16 and 31, 60/(60+10) or 0.857 would be attributed to HPV 16 and 10/(60+10) or 0.143 attributed to HPV 31. Ninety-five percent Wilson confidence limits around the HPV prevalence estimates were calculated.

Statistical testing was performed using the Pearson chi-square test or Fisher's exact test for discrete variables. Linear

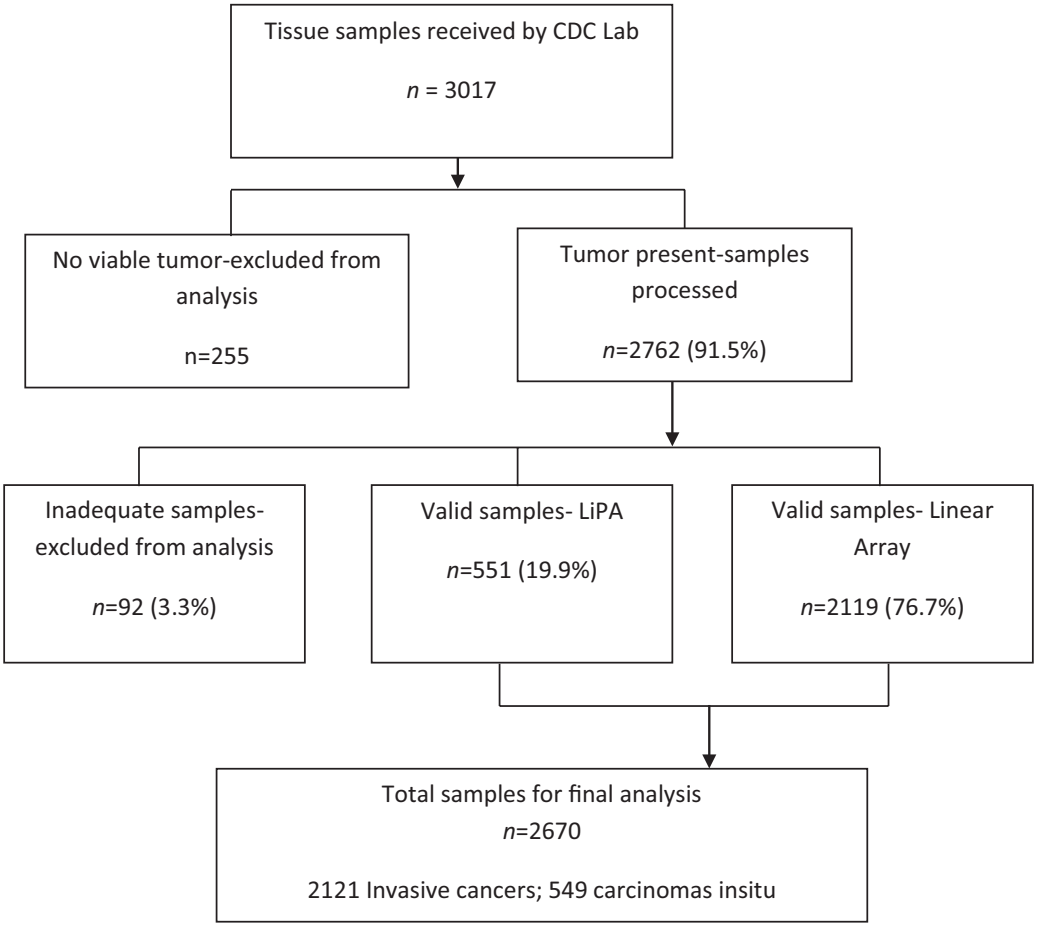

Figure 1. Flow chart of selected cases from all cancer tissues, Centers for Disease Control and Prevention Cancer Registry Sentinel Surveillance System for human papillomavirus (HPV) typing of cancers. All samples were tested by Linear Array HPV genotyping test (LA), but if the results were inadequate or negative INNO-LiPA HPV genotyping (LiPA) was performed. If LiPA detected HPV, then the HPV results were based on the LiPA test.

trends in the ordinal age groups were tested using the Mantel-Haenszel row means score test. Static estimates for the number of HPV-associated invasive and in situ cancers and the numbers of malignancies attributed to the HPV types in current and newly approved vaccines were calculated using cancer registry data from diagnosis years (2008–2010) multiplied by the observed sex-specific HPV type attribution (28,29). For ease of comparison with other studies, we also provide an estimated percentage attribution limiting the denominator to HPV-positive case patients. A *P* value of less than .05 was considered statistically significant, and all statistical tests were two-sided.

Representativeness

We conducted a comparison of HPV-typed vs nontyped case patients by age, sex, and race (see the Supplementary Methods and Supplementary Tables 3–10, available online). In general, typed case patients were representative of nontyped case patients by sex and age for all anatomic sites. Overselection of nonwhite case patients assisted with analysis of HPV prevalence by increasing the sample size in these populations.

Results

Overall, 2670 specimens were eligible for inclusion in the final analysis (Figure 1). Approximately two-thirds of the specimens were from non-Hispanic whites (66.9%), with fewer specimens from other racial ethnic groups (10.6% to 11.6%). Nearly half of the specimens were from women with invasive cervical or CCIS, while the select head and neck cancers accounted for about one-third of the total specimens, most from OP (Table 1).

HPV detection was highest in CCIS (98.8%) and VCIS (97.1%), followed by invasive cervical (90.6%) and vulvar cancers (68.8%) (Figure 2). HPV detection was also high for anal (91.1%), vaginal (75.0%), and penile (63.3%) cancers. Among the head and neck cancers, HPV detection was highest for OP cancer (70.1%), especially tonsil (82.0%), and much less common in OC (32.0%) and larynx (20.9%) cancers.

HPV 16 was the most common type found in all cancers, with highest detection in VCIS (80.9%) and lowest in larynx cancer (6.1%) (Figure 3, A and B). The attribution of HPV 16/18 was highest for VCIS (80.9%), anal cancer (79.4%), invasive cervical cancer (66.2%), OP cancer (60.2%), and the lowest for larynx cancer (7.5%) (Figure 4, A and B). HPV 16/18 attribution accounted for around half of invasive vaginal (55.1%), vulvar (48.6%), and penile cancers (47.9%). Among OP cancers, the attribution was highest among tonsillar (72.2%) and base of tongue (58.7%). The additional types in the 9-valent vaccine contributed the most for CCIS (21.4%), and invasive cervical (14.7%), vaginal (18.3%), and vulvar (14.2%) cancers, and the least for invasive oropharyngeal (5.7%).

HPV 16 or 18 was detected more frequently in invasive cervical cancer from women younger than 35 years at diagnosis (74.4%) compared with those 65 years or older (50.6%, $P_{trend} < .001$) (Table 2). A similar age trend for HPV 16/18–positive tumors was statistically significant for invasive

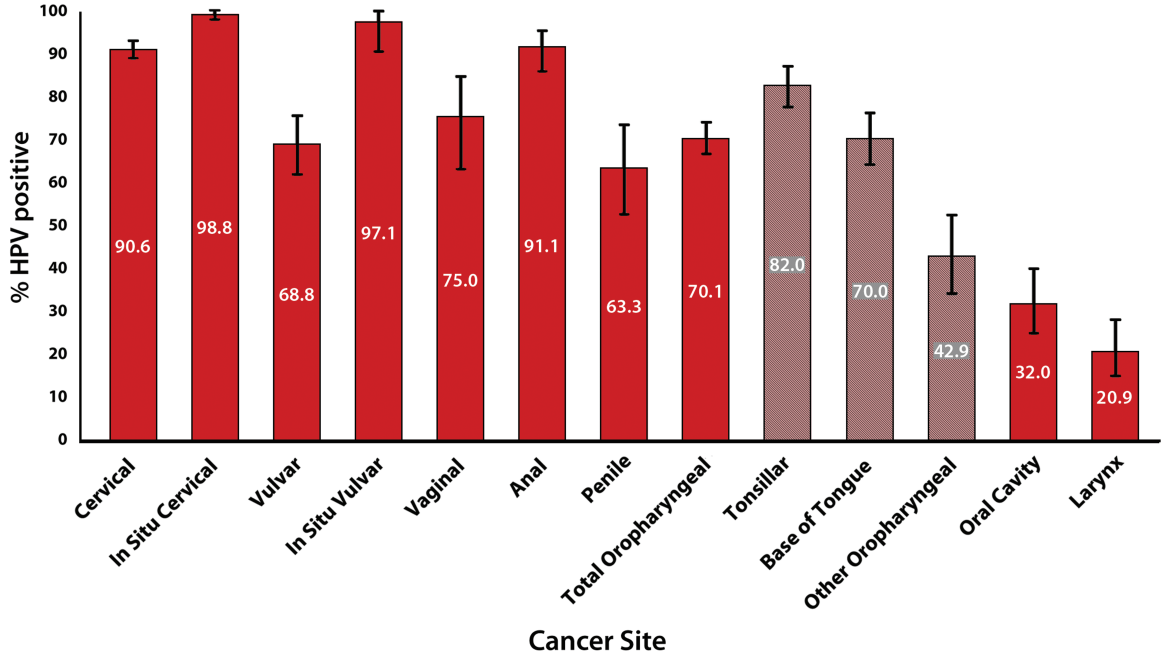

Figure 2. Human papillomavirus (HPV) detection by cancer site. The percent HPV-positive cancers was determined using all cancers for that anatomic site as denominator. Ninety-five percent Wilson confidence limits around the prevalence estimates are presented. These percentages reflect the HPV DNA that was detected. Finding HPV in a cancer tissue does not necessarily indicate a causal relationship. International Agency for Research on Cancer defined some cancers to have strong evidence for causal etiology such as cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers. Oral cavity and laryngeal cancers are considered to have less evidence for causal etiology (larynx) and/or inconsistent correlation with HPV DNA detection and percent causal (oral cavity and larynx). Cancer sites were determined using the following ICD-O-3 morphology codes: C53 (cervix), C51 (vulva), C52 (vagina), C21 (anus), C60 (penis), and C01.9, C02.4, C02.8, C05.1, C05.2, C05.9, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8 (oropharynx), C02.0, C02.1, C02.2, C02.3 C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0, C06.1, C06.2, C06.8, C06.9 (oral tongue and oral cavity), C32.0, C32.1, C32.2, C32.3, C32.8, C32.9 (larynx). ICD-O-3 morphology codes: 9590–9729, 9827 (lymphoma), 8800–8991 (sarcoma), and 8720–8790 (melanoma) were not included.

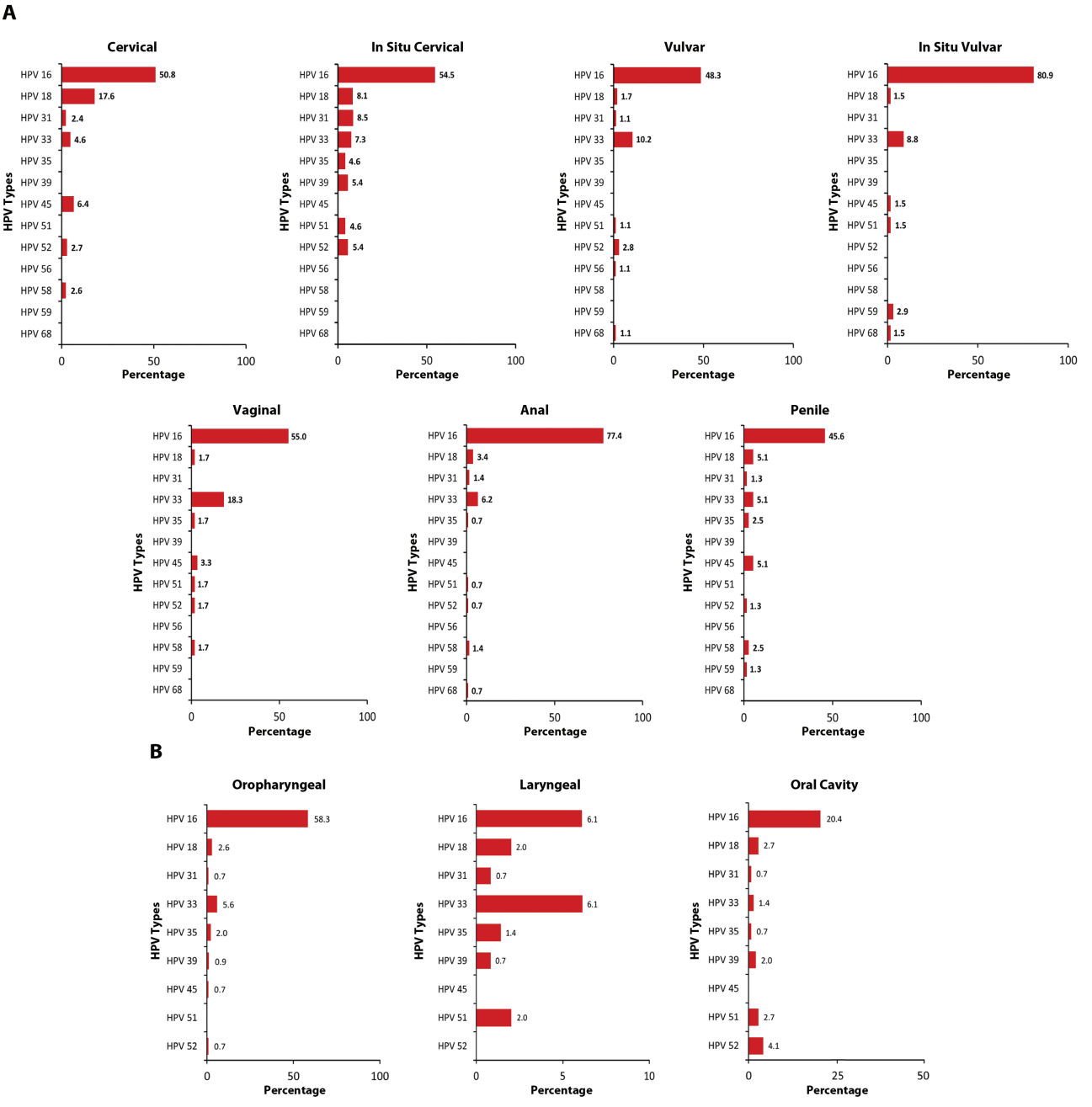

Figure 3. The seven most common oncogenic human papillomavirus (HPV) genotypes detected in select anogenital and head and neck cancers. **A)** Anogenital cancers incude cervical, vaginal, vulvar, anal, and penile cancers. **B)** Head and neck cancers include oropharyngeal, laryngeal, and oral cavity cancers. Number of types may add up to more than seven in instances where we found ties in the percentages.

vulvar, vaginal, and OP cancer, and CCIS, but not for invasive anal, penile, larynx, or OC, or VCIS. For many anatomic sites, the percentage of HPV-negative cases increased with age at diagnosis. No statistically significant age trends were observed in the prevalence of the five additional types in the 9-valent vaccine for most cancers, with the exception of CCIS, in which detection was higher with increasing age at diagnosis ($P_{trend} < .001$).

There were few racial or sex differences in HPV detection, with the exception of CCIS and OP cancers (Tables 2 and 3). Total HPV (and HPV 16/18) prevalence was lower in OP cancers from non-Hispanic blacks compared with other racial-ethnic groups ($P < .001$). For CCIS, the frequency of HPV 16/18 was lower among non-Hispanic blacks compared with non-Hispanic whites, as was the frequency of all seven oncogenic types in the vaccine (data not shown, 64% vs 83%, $P < .01$).

The distribution of HPV 16/18 was similar among men and women for anal, OC, and laryngeal cancers, with a slightly higher HPV 16/18 prevalence for OP cancer in men compared with women. For anal cancer, detection of the five additional types in the vaccine was more frequent in women than men, but the difference was not statistically significant. Men had a higher frequency of HPV-positive OP cancer than women (72.4% vs 63.3%, $P = .04$), largely a reflection of the higher percentage of HPV 16– and/or 18–positive cancers (63.4% vs 50.8%, $P = .01$) (Table 3).

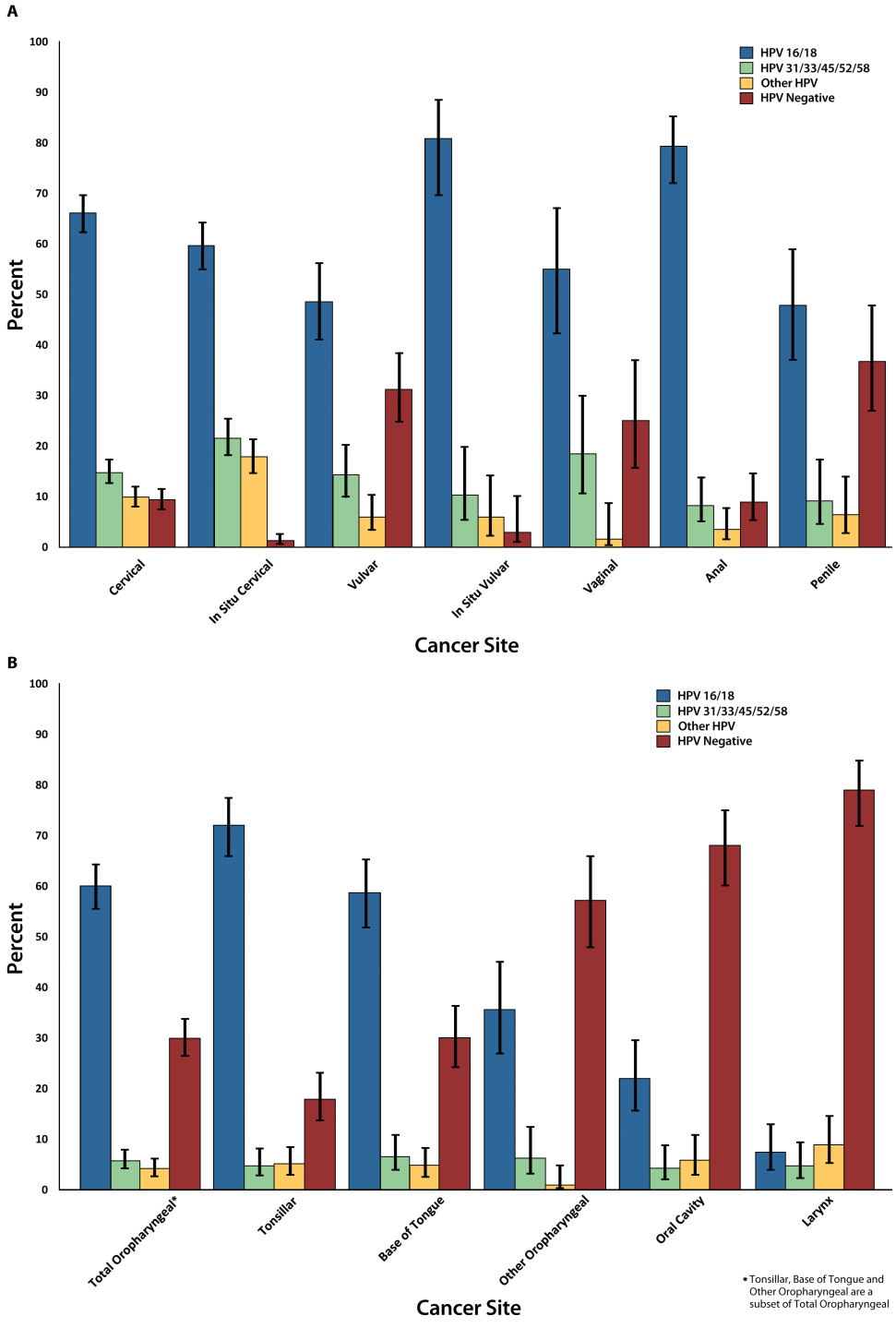

Figure 4. Population attribution of human papillomavirus (HPV) in select anogenital and head and neck cancers. **A)** Anogenital cancers include cervical, vaginal, vulvar, anal, and penile cancers. It should be noted that the International Agency for Research on Cancer (IARC) has defined some cancers to have strong evidence for a causal association of HPV 16 and 18 with cervical, vaginal, vulvar, anal, and penile. Percent multiple infections ranged by type of anogenital cancer: cervical 8.2%; in situ cervical 21.4%; vulvar 6.3%, in situ vulvar 7.4%, vaginal 15%, anal 11.0%, penile 11.4%. Ninety-five percent Wilson confidence limits around the prevalence estimates are presented. **B)** Select head and neck cancers include oropharyngeal (OP), laryngeal, and oral cavity (OC) cancers. According to IARC, there is strong evidence for a causal role of HPV 16 and 18 in oropharyngeal cancer. The oral cavity is considered to have evidence for a causal association with HPV, but some of the HPV DNA detected in tissues may not represent the true causal agent. Laryngeal cancer has limited evidence for a causal etiology with HPV; and the correlation of HPV DNA detected does not reflect the percentage that is causal. **C)** Percent multiple infections were similar across cancer types for OP, OC, and laryngeal cancers (4.1%). Ninety-five percent Wilson confidence limits around the prevalence estimates are presented.

Projections for the impact of HPV vaccines were made based on the type-specific attribution of HPV for cancers in this study. Data shown in Table 4 only included cancers recognized as causally and highly associated with HPV detection. Assuming full vaccine coverage and 100% vaccine efficacy, an estimated 24 858 HPV-associated cancers in the United States could be

Table 2. HPV detection by age, race, and cancer tissue site (% by category)

	Age, y							Race				
Cancer tissue site	<35	35–44	45–54	<55	55–64	65+	P*	White NH	Black NH	Hispanic	Other	P
Cervical	(n = 123)	(n = 217)	(n = 177)		(n = 113)	(n = 147)	<.001	(n = 409)	(n = 129)	(n = 124)	(n = 110)	.62
HPV 16/18	74.4	76.1	68.1		55.4	50.6		67.3	67.9	63.6	61.6	
HPV 31/33/45/52/58	15.6	13.3	10.3		20.5	16.7		11.5	14.9	17.8	23.0	
Other HPV	5.9	5.5	15.4		6.4	15.0		9.4	12.6	10.5	7.3	
HPV Negative	4.1	5.1	6.2		17.7	17.7		11.7	4.7	8.1	8.2	
In situ cervical	(n = 328)	(n = 83)	(n = 30)		(n = 24)	(n = 16)	<.001	(n = 309)	(n = 39)	(n = 38)	(n = 8)	<.001
HPV 16/18	64.7	53.6	56.7		45.2	18.8		66.7	27.0	49.9		
HPV 31/33/45/52/58	17.2	27.0	26.7		37.5	43.8		16.3	36.8	26.3		
Other HPV	16.8	19.4	13.3		13.1	37.5		16.0	31.1	23.8		
HPV negative	1.2	0.0	3.3		4.2	0.0		1.0	5.1	0.0		
Vulvar				(n = 55)	(n = 22)	(n = 99)	.01	(n = 136)	(n = 13)	(n = 11)	(n = 15)	.87
HPV 16/18				61.8	58.9	39.1		48.4	52.6	54.5	39.6	
HPV 31/33/45/52/58				21.8	9.1	11.1		11.6	39.7	18.2	13.3	
Other HPV				3.7	0.2	8.4		5.4	7.7	0.0	13.7	
HPV negative				12.7	31.8	41.4		34.6	0.0	27.3	33.3	
In situ vulvar				(n = 43)	(n = 12)	(n = 12)	.70	(n = 37)	(n = 0)	(n = 5)	(n = 14)	.23
HPV 16/18				79.1	83.3	83.3		78.4			92.9	
HPV 31/33/45/52/58				9.3	16.7	8.3		13.5			0.0	
Other HPV				9.3	0.0	0.0		5.4			7.1	
HPV negative				2.3	0.0	8.3		2.7			0.0	
Vaginal				(n = 13)	(n = 16)	(n = 31)	.01	(n = 45)	(n = 4)	(n = 8)	(n = 2)	-
HPV 16/18				73.9	73.8	37.5		49.0				
HPV 31/33/45/52/58				26.1	7.5	20.6		17.7				
Other HPV				0.0	0.0	3.2		2.2				
HPV negative				0.0	18.8	38.7		31.1	0.0	12.5	0.0	
Penile				(n = 21)	(n = 10)	(n = 48)	.59	(n = 44)	(n = 17)	(n = 13)	(n = 3)	.65
HPV 16/18				42.4	50.0	49.9		45.3	58.2	46.2		
HPV 31/33/45/52/58				14.6	10.0	6.4		11.5	6.3	0.0		
Other HPV				14.4	0.0	4.2		4.5	6.1	15.4		
HPV negative				28.6	40.0	39.6		38.6	29.4	38.5		

* P value tests for differences among HPV 16/18–positive cancers compared with HPV 16/18–negative cancers.

Data are suppressed and excluded from statistical testing when sample sizes are under 10 case patients. HPV = human papillomavirus.

Table 3. HPV detection by age, race, sex, and cancer tissue site (% by group)

	Age, y				Race					Sex		
Cancer tissue site	<55	55–64	65+	*P*	White NH	Black NH	Hispanic	Other	*P*	Male	Female	*P**
Anal	(n = 52)	(n = 37)	(n = 57)	.63	(n = 105)	(n = 15)	(n = 21)	(n = 5)	.99	(n = 53)	(n = 93)	.95
HPV 16/18	76.8	81.1	80.6		80.0	79.7	80.9			79.1	79.5	
HPV 31/33/45/52/58	13.5	2.7	7.0		6.7	6.7	9.6			3.8	10.8	
Other HPV	3.9	5.4	1.8		2.9	6.9	4.8			5.8	2.2	
HPV negative	5.8	10.8	10.5		10.5	6.7	4.8			11.3	7.5	
Oropharyngeal	(n = 200)	(n = 198)	(n = 190)	<.01	(n = 443)	(n = 74)	(n = 40)	(n = 29)	<.001	(n = 438)	(n = 150)	.01
HPV 16/18	64.4	66.6	49.1		64.0	29.1	70.0	69.0		63.4	50.8	
HPV 31/33/45/52/58	5.6	2.6	9.0		5.3	10.8	5.0	0.0		4.4	9.5	
Other HPV	4.6	6.1	1.9		3.9	10.1	0.0	0.0		4.6	3.1	
HPV negative	25.5	24.7	40.0		26.9	50.0	25.0	31.0		27.6	36.7	
Oral cavity	(n = 49)	(n = 24)	(n = 73)	.21	(n = 80)	(n = 1)	(n = 6)	(n = 57)	.20	(n = 76)	(n = 71)	.98
HPV 16/18	15.7	25.0	25.6		17.0			25.9		21.9	22.1	
HPV 31/33/45/52/58	6.1	0.0	4.3		5.0			3.7		3.9	4.4	
Other HPV	6.8	8.3	4.4		4.3			5.4		7.0	4.5	
HPV negative	71.4	66.7	65.8		73.8			64.9		67.1	69.0	
Larynx	(n = 27)	(n = 32)	(n = 89)	.45	(n = 102)	(n = 5)	(n = 4)	(n = 37)	.20	(n = 121)	(n = 27)	.41
HPV 16/18	9.9	9.4	6.1		5.6			12.0		8.4	3.7	
HPV 31/33/45/52/58	8.6	3.1	4.0		4.2			6.9		3.2	11.1	
Other HPV	11.1	12.5	6.7		10.8			2.7		6.6	18.5	
HPV negative	70.4	75.0	83.1		79.4			78.4		81.8	66.7	

* *P* value tests for differences among HPV 16/18–positive cancers compared with HPV 16/18–negative cancers. HPV = human papillomavirus.
Data are suppressed and excluded from statistical testing when sample sizes are under 10 case patients.

Table 4. Estimated annual number of HPV 16/18- and HPV 16/18/31/33/45/52/58–attributable invasive cancer cases in the United States

Invasive cancer tissue site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)			Cancers attributable to any HPV						Cancers attributable to HPV 16/18						Cancers attributable to HPV 31, 33, 45, 52, 58					
				%		Number			% among HPV+	%		Number			% among HPV+	%		Number			% among HPV+
	M	F	Both sexes	M	F	M	F	Both sexes	Both sexes	M	F	M	F	Both sexes	Both sexes	M	F	M	F	Both sexes	Both sexes
Cervix	0	12 114	12 114		90.6	0	10 976	10 976	100		66.2	0	8018	8018	73.1		14.7	0	1775	1775	16.2
Vulva	0	4131	4131		68.8	0	2840	2840	100		48.6	0	2009	2009	70.8		14.2	0	587	587	20.7
Vagina	0	1106	1106		75.0	0	830	830	100		55.1	0	609	609	73.4		18.3	0	202	202	24.4
Anus	2161	3554	5715	88.7	92.5	1916	3286	5203	100	79.1	79.5	1710	2827	4537	87.2	3.8	10.8	82	382	464	8.9
Penis	1183	0	1183	63.3		749	0	749	100	47.9		567	0	567	75.7	9.0		107	0	107	14.3
Oropharynx	12 002	2970	14 972	72.4	63.3	8686	1881	10 567	100	63.4	50.8	7610	1508	9118	86.3	4.4	9.5	527	282	809	7.7
Total	15 346	23 875	39 221			11 351	19 813	31 164				9886	14 972	24 858				716	3228	3944	

Data on numbers of cancers are from 2008–2010 diagnosis years from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program. HPV-associated cancers are defined as cancers at specific anatomic sites and with specific cellular types in which HPV DNA frequently is found. Presence of viable tumor tissue in polymerase chain reaction samples was confirmed by review of hematoxlyin and eosin slides before and after sections tested. These estimates do not take into account future changes in incidence, population structure, or the percentage of cancers that are HPV positive. The number of cancers attributable to specific human papillomavirus (HPV) types was derived by multiplying the site-specific average annual number of incident cancers by the percent from this study found to be HPV positive.

prevented annually with the current 16/18 vaccines (63.4%), with around 3944 (10.1%) additional cancers preventable through the 9-valent vaccine. The percent of preventable cancers based on HPV-positive cancers would be nearly 80% through uptake of the current HPV vaccine, with an additional 13% of cancers preventable through the 9-valent vaccine, representing over a 90% reduction of HPV-positive cancers (given anticipated 31 164 HPV-positive cancers annually).

The population attributions for the vaccine and the individual types for each of the cancers are shown in Supplementary Tables 1 and 2 (available online). Case patients in this study are fairly representative of all participating cancer registry case patients by age and sex, strengthening the population-based interpretations (Supplementary Tables 3–10, available online). However, age at diagnosis was somewhat younger in the typed vs nontyped OP case patients. Nonwhites were overrepresented in cervical, vulvar, penile, larynx, and OC cancer cases. No statistically significant temporal trends in HPV positivity were observed for any anatomic site over the time periods (Supplementary Table 11, available online).

Discussion

This large study of HPV-associated cancers in the United States establishes the prevaccine type-specific attribution and is in agreement with findings from international studies on cervical cancer (17,19,30). Furthermore, the study provides additional insights into the contribution of HPV to noncervical cancers. HPV 16/18 predominates, and there are no racial/ethnic differences in HPV distribution other than for OP cancer.

The combined attribution of all HR types in the 9-valent vaccine was 81.2% for CCIS and 80.8% for invasive cervical cancers, consistent with a recent meta-analysis of data from two worldwide HPV distribution studies (17). The addition of HPV31/33/45/52/58 to the prophylactic vaccine could increase protection against invasive cervical cancer by 14.7%. Globally, HPV 16/18 comprised an estimated 71% (range 68% to 82%) of HPV-positive invasive cervical cancers (our percentage is 73.3% if we limit our denominator to HPV-positive cases) (19,31).

The finding that nearly 10% of all cervical cancers tested negative for HPV and that the proportion of cervical tissue testing negative for HPV increased with age is consistent with findings other studies (32,33). While we have no definitive explanation for these patterns, it is recognized that clinical differentiation between endometrial primaries in the lower uterine segment and endocervical primaries can be difficult because of similarities in their presentation and histology. The rate of endometrial cancer increases with age, offering a potential explanation for the age-related trends in HPV-negative tumors. While we do not believe that our study results contradict the notion that HPV is a necessary agent in cervical carcinogenesis (34), from a population-based surveillance perspective, we believe that the HPV-negative cervical cancer cases represent a combination of true HPV-negative cancers (presumed to be rare) (35), misclassification of lower uterine-segment endometrial as endocervical primaries, and assay failure because of preservation, inhibitors, or unique viral features. For monitoring purposes, these cancers should not be considered preventable through HPV vaccination.

Importantly, this study demonstrates that the estimated protection of current and 9-valent vaccines for invasive cervical cancer does not differ by race/ethnicity. The proportion of HPV 16/18 CCIS was lower among non-Hispanic black and Hispanic

women, compared with non-Hispanic whites. This observation is consistent with another US study of preinvasive cervical disease (36). One implication of this difference is that the incidence of cervical screening abnormalities will be less influenced by HPV vaccines in black and Hispanic women compared with non-Hispanic whites. It is not clear why the racial differences in HPV-associated CCIS were not also found in invasive cervical cancer, but it is recognized that not all CCIS will progress to invasive disease. These data highlight the importance of monitoring changes in the incidence of invasive cancer in association with population patterns of vaccine uptake (37).

In agreement with other studies (38), we found that women with HPV 16/18–associated invasive cervical cancer tended to be diagnosed at a younger age than women with other or no HPV types detected, supporting the strong oncogenic potential of HPV 16 and suggesting that the HPV vaccine may have a particularly strong impact on cancer in young women. Our finding, combined with the natural history of HPV, supports delaying cervical cancer screening to age 25 years among fully vaccinated women in the United States (32,38).

In anogenital malignancies with a more modest association with HPV, such as vulvar and penile cancers, HPV prevalence was higher in squamous cell tumors and in younger age groups (20,22). A majority of the penile cancers in this study were classified as "squamous cell carcinoma (SCC) not otherwise specified." As reported, reclassification by pathologists using the digital slide scans of the sample tested did not identify the reported association of increased HPV prevalence with warty and basaloid subtypes of SCC, perhaps because of the limited number of these subtypes in our series of penile cancers (22,39). In the United States, the majority of anal and vaginal cancers, as well as a subset of vulvar and penile cancers, is potentially preventable through the HPV 16/18 vaccine. Moreover, the impact of removing HPV 16/18 from the population may be greatest in early-onset vulvar and vaginal cancers in which the HPV 16/18–attributable fraction is highest. Keeping in mind that the other anogenital cancers have a lower absolute burden and most have high HPV 16 attribution, the impact of the additional types in reducing the incidence of other anogenital cancers was more modest.

We found a 70.1% prevalence of HPV in oropharyngeal tumor tissue, a much higher fraction than observed in international settings (40) but consistent with other US studies (6,7). Although we did not note a statistically significant positive time trend in oropharyngeal tissue HPV prevalence during the 12-year surveillance period covered by this study (Supplementary Table 11, available online), the number of oropharyngeal cases in our study was small from the earlier time periods, and this may have contributed to the lack of a statistically significant trend in HPV prevalence. An increased HPV prevalence over time has been noted by other investigators (6), perhaps attributable to increased oral sex and consequent oral HPV exposure, a reduced fraction of OP cancers associated with tobacco use, and more sensitive assays (6). Furthermore, because OPC HPV prevalence was already comparatively high in our study, likely because of changes in risk factor profiles that had occurred earlier in the United States than in other geographic areas, rising trends in prevalence were more difficult to detect. We do not have supporting data on E6/E7 mRNA expression in these tumors, so the HPV-attributable fraction may be less than the 70.1% detected on the basis of HPV DNA detection.

We observed a higher prevalence of HPV in the OC (32.0%) and a lower prevalence of HPV in the larynx (20.9%) than reported in a large meta-analysis of head and neck squamous cell cancers (24% in OC cancer and 24% in laryngeal cancer). For both OC and laryngeal cancers, recent international studies suggest that despite a slightly higher HPV DNA prevalence HPV rarely plays a driving role in oncogenesis, because mRNA or p16 are detected in as few as 3% to 5% of oral cavity cancers and 4% to 7% of laryngeal cancers (41,42).

While a recent publication provides evidence that the HPV 16/18 vaccine prevents oral HPV infection (14), efficacy against any oral or OP disease endpoints remains unproven. It is reasonable to anticipate efficacy against all HPV-associated malignancies, in which case the data in our study indicate that 60.2% of OP cancers in the United States could be prevented by HPV 16/18 vaccines, with an additional 5.7% covered with the additional types in the 9-valent vaccine (65.9% total).

Women and non-Hispanic blacks were more likely than men and other racial-ethnic groups to have HPV-negative OP cancer. This finding may be explained by differences in sexual behavior, such as oral sex practices (43,44). Our results are consistent with the prevalence found in more recent cancer registry–based studies in the United States (6) and indicate that the current vaccines target the most frequent types in all HPV-positive OP malignancies regardless of race/ethnicity (45).

Our data suggest that close to 25 000 malignancies in the United States are potentially preventable with the current 16/18 vaccines, with just under 4000 additional cancers preventable through the 9-valent vaccine. This is an optimistic (upper bound) estimate, given the uncertainties in vaccine uptake and effectiveness in oropharyngeal cancer and lack of information regarding the impact of cervical cancer screening and tobacco control on the incidence of cervical and oropharyngeal cancer.

The strengths of the study include the population-based approach for each of the registries, inclusion of a wide geographical area of the United States, accurate annotation of tissues, and central review with standardized molecular methods. The cancers tested were representative of all state or county cases by age with slight underrepresentation of non-Hispanic whites.

Challenges to population-based cancer tissue collection and limitations in interpreting the data must be acknowledged. Identifying and selecting representative blocks can be a substantial burden to pathology laboratories. Detection of HPV DNA in a cross-section study is insufficient to indicate a causal relation with the tumor. Sensitive molecular methods may detect low copy-number HPV that is latent or infecting surrounding normal tissue. Additional markers, such as p16, E6/E7 mRNA, or in situ hybridization to document cellular localization of HPV, have been used to enhance evidence for causation. However, each of these methods has technical limitations, particularly in archival tissues, and does not eliminate uncertainty in the estimates.

This study demonstrates the feasibility of using cancer registries to measure the population impact of HPV vaccines on US cancers. The established protocol provides opportunities for further cancer registry–based studies to allow comparisons of vaccine impact by age, race/ethnicity, geographic area, and anatomic site to identify disparities in coverage or effectiveness. Our approach, using methods similar to those used in large international studies, provides estimates for the United States that are interpretable in the international context. We used static methods to estimate the impact of HPV vaccination: sophisticated statistical projections were beyond the scope of this study.

An essential component to determining the public health benefit and cost-effectiveness of HPV vaccination in the United States is the implementation of population-based surveillance activities (46). Unlike other countries with health registry

infrastructure that allows for active follow-up on those who have been vaccinated, defining vaccine-exposed cohorts and following them prospectively poses major challenges in the United States. At this time, there is no systematic effort to track the vaccine-specific impact on HPV-associated cancers in the United States, with the exception of New Mexico whose focus is on cervical cancer (32). The national system of cancer registries can monitor cancer incidence but does not routinely capture HPV genotype information. We implemented surveillance to determine the type-specific HPV prevalence in anogenital and head and neck cancers in the United States before HPV vaccine introduction. In the United States, current vaccines will reduce most HPV-associated cancers; a smaller but additional reduction would be contributed by the 9-valent vaccine.

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Notes

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