Assessing the Burden of HPV-Associated Cancers in the United States

Supplement to ***Cancer***

HPV Prophylactic Vaccines and the Potential Prevention of Noncervical Cancers in Both Men and Women

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Human papillomavirus (HPV) is a necessary cause of cervical cancer. In addition, on the basis of the fulfillment of a combination of viral as well as epidemiological criteria, it is currently accepted that a proportion of anal, oropharyngeal, vulvar, and vaginal cancers among women and anal, oropharyngeal, and penile cancers among men are etiologically related to HPV. At these noncervical sites with etiologic heterogeneity, HPV-associated cancers represent a distinct clinicopathological entity, which is generally characterized by a younger age at onset, basaloid or warty histopathology, association with sexual behavior, and better prognosis, when compared with their HPV-negative counterparts. Currently available estimates indicate that the number of HPV-associated noncervical cancers diagnosed annually in the US roughly approximates the number of cervical cancers, with an equal number of noncervical cancers among men and women. Furthermore, whereas the incidence of cervical cancers has been decreasing over time, the incidence of anal and oropharyngeal cancers, for which there are no effective or widely used screening programs, has been increasing in the US. The efficacy of HPV vaccines in preventing infection at sites other than the cervix, vagina, and vulva should, therefore, be assessed (eg, oral and anal). Given that a substantial proportion of cervical cancers (approximately 70%) and an even greater proportion of HPV-associated noncervical cancers (approximately 86% to 95%) are caused by HPV16 and 18 (HPV types that are targeted by the currently available vaccines), current HPV vaccines may hold great promise (provided equivalent efficacy at all relevant anatomic sites) in reducing the burden of HPV-associated noncervical cancers, in addition to cervical cancers. ***Cancer*** **2008;113(10 suppl):3036–46.** *Published 2008 by the American Cancer Society.**

KEYWORDS: human papillomavirus, screening, noncervical cancer, HPV vaccine.

Commentary

This monograph is focused on estimating the burden of human papillomavirus (HPV)-associated cervical and noncervical cancers in the United States (US) from 1998-2003 in the "prevaccine era," with the goal of providing an important frame of reference for the

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TABLE 1
Summary of Molecular-Virologic Associations Between Alpha-Human Papillomaviruses and a Select Group of Human Epithelial Malignancies*

	High-Risk DNA Present	Tumor Specificity	E6/E7 Expression	Clonality-Copy No.	Clonality-Variant Analysis	Clonality Integration	Malignant Phenotype†
Cervix	++	++	++	++	++	++	++
Vulva	++	+	+	?	?	+	?
Vagina	++	+	?	?	?	+	?
Anus	++	++	+	?	?	+	?
Penis	++	+	+	+	+	+	?
Oropharynx	++	++	++	++	+	++	+
Oral cavity	+/−	?	+/−	?	?	?	?
Larynx	+/−	?	?	?	?	?	?
Conjunctiva	+/−	+	+	?	?	?	?
Esophagus	+/−	+/−	?	+	?	?	X
Colon	+/−	?	?	?	?	?	X
Retinoblastoma	−/−	?	?	?	?	?	X
Breast	+/−	?	?	?	?	?	X
Prostate	+/−	?	?	?	?	?	X
Lung	+/−	?	?	?	?	?	X
Bladder	?	?	?	?	?	?	X

*The summary presented here is based on the review of hundreds of relevant references by the commentary authors and on the authors' joint interpretation of the literature. Specific references are not provided due to space constraints. Please see references 8 and 9 for further information.

†Dependence of the malignant phenotype on viral oncogene expression (E6/E7) has been demonstrated by molecular methods.

++Demonstrated by multiple methods, multiple investigators, and on multiple samples.

+Demonstrated, but by few investigators in a small number of samples.

?No data in the literature.

−Negative studies performed, but by few investigators in a small number of samples.

−−Definitive negative studies performed.

X Not warranted based on available data.

"vaccine era," subsequent to Food and Drug Administration approval of a prophylactic HPV vaccine in 2006. Given 1) HPV16 or 18 infection is necessary for development of approximately 70% of cervical cancers,[1] and 2) the current generation prophylactic HPV vaccines have demonstrated an approximate 90% to 98% efficacy for prevention of cervical HPV16 or 18 infection and related dysplasias among fully vaccinated women naive for vaccine HPV types,[2,3] the decline in cervical cancer incidence that has occurred over time in the "Papanicolaou (Pap) smear era"[4] is anticipated to continue in the vaccine era.[5] In this commentary, we will focus on the potential impact of the HPV vaccine on noncervical cancers.

A classic paradigm for HPV-mediated carcinogenesis has evolved from studies of cervical cancer, where HPV infection is a necessary cause of virtually all cases.[6,7] However, the 1-to-1 relation between HPV and cervical cancer appears to be the exception rather than the rule for HPV-associated human cancers, as only a subset of each of the noncervical cancers is believed to be attributable to HPV infection.[8] A potential limitation of the estimates presented in this monograph is that they do not account for the etiologic heterogeneity among noncervical cancers by either establishing uniform criteria for a causal association or by estimating the proportion of cancers at each noncervical site that is attributable to HPV infection.

Clearly, an assessment of HPV-causality must precede an assessment of the proportion of cancers at an anatomic site that is attributable to HPV infection and the potential impact of an HPV vaccine on those cases. Viral-tumor associations (eg, presence and integration of high-risk HPV genome in tumors and expression of E6/E7 oncogenes) are critical for establishing a causal association between HPV and human cancers (Table 1). In addition, classic epidemiological associations (eg, strength and consistency of associations[9]) and distinctive characteristics of accepted HPV-associated cancers (eg, associations with sexual behavior and increased incidence in immunosuppressed populations,[8] Table 2 updated in the current monograph to reflect new data since 2003) are also critical in establishing an etiologic role for HPV. Although all of these criteria have been fulfilled for cervical cancer and have clearly established HPV as a human carcinogen, some of them have not yet been demonstrated for several noncervical cancers widely accepted as being etiologically related to HPV infection (Tables 1 and 2). Their acceptance arises because causal criteria are not

TABLE 2
Summary of Epidemiological Associations Between Alpha-Papillomaviruses and a Select Group of Human Epithelial Malignancies*

	Natural History Studies		Case-Control Studies of HPV Exposure					Populations at Risk		
	Prevention Trials	Observational Cohorts	L1 Serology-Temporal	L1 Serology-Cross-Sectional	HPV DNA Detection	E6/E7 Serology	Sexual Behavior	Immunosuppressed-HIV	Immunosuppressed-Transplant	Prior HPV-associated Cancer
Cervix	++	++	++	++	++	++	++	++	++	++
Vulva	+	+	+	++	XX	XX	++	+	+	+
Vagina	+	+	+	++	XX	XX	++	+	+	+
Anus	?*	++	+	++	++	+	++	++	+	+
Penis	?*	?*	+	++	?	+	+	+	+	+
Oropharynx	?	?*	+	++	+	++	++	+	+	+
Oral cavity	X	X	+	+	−	+	−	+/−	+	?
Larynx	X	X	−	+/−	?	?	?	+/−	−	?
Conjunctiva	?	?	?	?	?	?	?	+	+	?
Esophagus	X	?	+/−	+/−	?	?	?	−	+	?
Colon	X	X	?	?	?	?	?	−	+	−
Retinoblastoma	X	X	X	X	X	X	X	?	?	?
Breast	X	X	?	−	?	?	−	−	−	−
Prostate	X	X	+/−	+/−	−	?	++	−	−	?
Lung	X	X	?	−	?	?	?	+	+	?
Bladder	X	X	?	−	?	?	?	−	+	?

*The summary presented here is based on the review of hundreds of relevant references by the commentary authors and on the authors' joint interpretation of the literature. Specific references are not provided due to space constraints. Please see references 8 and 9 for further information.

++Repeatedly demonstrated by multiple methods, multiple investigators, and on multiple samples.

+Demonstrated, but by few investigators in a small number of samples.

?No data in the literature.

−Negative studies performed, but by few investigators in a small number of samples.

−−Definitive negative studies performed.

?*Studies ongoing.

X Not warranted based on available data.

XX Data no longer necessary because of prevention trial data.

equally weighted. For example, evidence from natural history studies, as with HPV and anal cancer,[10] and intervention trials, as with vulvar and vaginal dysplasia,[11] render other types of evidence less critical.

In contrast to the widely accepted HPV-associated cancers, many of the other cancers hypothesized to possibly be HPV-associated (eg, prostate, breast, colon, lung) lack both molecular and epidemiological evidence in support of a causal role for HPV (Tables 1 and 2) and, therefore, have not been included in the current monograph. By itself, HPV DNA detection, frequently performed by qualitative polymerase chain reaction (PCR) alone, should not be considered as sufficient evidence for a causal association; it may be particularly problematic for anatomic sites, such as the genital tract, with a high prevalence of HPV infection.[12,13] Instead, the detection of viral sequences should provide the rationale for examining their etiological significance by other laboratory analyses and epidemiological assessments. Laboratory-based assays should include demonstration of the specificity of the viral DNA in tumor cell nuclei, detection of viral oncogene expression, demonstration of a clonal association between virus and tumor (eg, integration, viral load, variant analysis), and dependence of the malignant phenotype upon viral gene expression (Table 2). There is little evidence to date that a hit-and-run mechanism (wherein the virus plays a role in initiation and/or promotion of cancer but is not necessary for maintenance of the malignant phenotype) accounts for a substantial proportion of tumors actually caused by HPV, and it is best, therefore, not to include such considerations at this time in estimates of causality or attributable fraction. From an epidemiological perspective, associations with sexual behavior and increased risk in immunosuppressed populations appear particularly important distinctions for cancers caused by HPV, in addition to the classic Hill criteria for causal inference (plausibility, strength of association, consistency, specificity, temporality, biological

TABLE 3
Characteristics of HPV-Positive and HPV-Negative Vulvar and Head and Neck Squamous Cell Carcinomas

	Vulvar Cancer		Head and Neck Squamous Cell Carcinoma	
Characteristic	**HPV-Positive**	**HPV-Negative**	**HPV-Positive**	**HPV-Negative**
Median age	Younger	Older	Younger	Older
Sexual behavior	Associated	Not associated	Associated	Not associated
Pathology	Warty or basaloid	Keratinizing	Poorly differentiated or basaloid	Keratinizing
Precursor lesion	Vulvar intraepithelial neoplasia	Lichen Sclerosis, epithelial hyperplasia	Undefined	Mild, moderate, severe dysplasia
p53 mutations	Infrequent	Common	Infrequent	Common
p16 expression	High	Low	High	Low
Anatomic site	No distinction	No distinction	Oropharynx	All sites including oropharynx
Anatomic subsite	No distinction	No distinction	Palatine and lingual tonsil	All sites including tonsil
Other risk factors	Tobacco use	Tobacco use	Marijuana, immunosuppressives	Tobacco and alcohol use
Proportion of total	~28-50%	~50-72%	~22-26%	~74-78%
Proportion of HPV-positive attributable to HPV16/18	~86%	NA	~90-95%	NA
Prognosis	Inconsistently improved	Inconsistently worse	Consistently improved	Consistently worse

gradient, coherence, experimental evidence, and analogy).[14]

Currently, a proportion of vulvar, vaginal, anal, and oropharyngeal cancers among women, and a proportion of penile, anal, and oropharyngeal cancers among men are widely accepted as linked to HPV infection. We have, therefore, focused on these cancers. The etiologic heterogeneity observed for noncervical cancers that have a proportion associated with HPV infection is exemplified by vulvar and head and neck squamous cell carcinomas, with the HPV-associated cancers behaving as distinct clinicopathological entities (Table 3). For vulvar cancers, high-risk HPVs are associated with tumors of basaloid or warty histopathology that occur in younger women and have risk factor profiles related to sexual behavior.[15-20] Analogous to the histopathological progression for cervical cancer, HPV-associated vulvar carcinoma is preceded by vulvar intraepithelial neoplasia. By contrast, HPV-negative vulvar cancers have keratinizing histopathology, occur in older women, are unrelated to sexual behavior, and may be preceded by lichen sclerosis et atrophicus or epithelial hyperplasia. As with HPV-positive vulvar cancers, HPV-positive head and neck cancers are associated with poorly differentiated or basaloid histopathology, occur in younger men and women, and have risk factors related to sexual behavior.[21,22] HPV-positive head and neck cancers also arise predominantly from the lingual and palatine tonsils within the oropharynx (thus accounting for the use of anatomic site as a surrogate for the HPV-associated subset of head and neck cancers). Importantly, a common feature of HPV-associated noncervical cancers is that, regardless of anatomic site, the overwhelming majority (~86% to 95%) are associated with HPV types 16 and 18. Molecular alterations indicative of the function of high-risk HPV oncoproteins, E6 and E7, are found in HPV-positive vulvar and head and neck cancers; p53 mutations are less frequent,[22,23] and diffuse nuclear and cytoplasmic p16 expression is more frequent than in HPV-negative tumors.[24-27] HPV-positive head and neck cancers appear to have an improved prognosis when compared with HPV-negative head and neck cancers,[28] but this biological behavior has been inconsistently observed for its vulvar counterpart.[16,29-31]

Analogous differences among age at onset, histopathology, sexual behavioral associations, and biological behavior are emerging for HPV-positive and -negative penile,[32-42] anal,[43-45] and vaginal squamous cell carcinomas.[46,47] It is important to note, however, that the clinicopathological patterns observed for HPV-associated and unassociated cancers noted above are not absolute; 2 etiologically distinct cancers may, nevertheless, present as phenotypically identical tumors. How is the attributable fraction for HPV at an anatomic site best determined, given that 2 etiologically distinct cancers may have an identical clinical presentation? Detection of HPV DNA currently provides the best estimate of the etiologic fraction. Such estimates may come from case series, literature surveys, meta-analysis or multisite, international surveys, and are frequently based upon HPV genomic DNA detected by PCR alone. These data are acceptable, given other evidence in Tables 1 and 2 that support a causal role for HPV in these tumors. However, it should be recognized that such data

likely provide an upper bound for the true etiologic fraction, given the potential for false-positive results when compared with more comprehensive analyses. For example, HPV DNA detection in head and neck cancers by PCR alone appears to overestimate the etiologic fraction when compared with more detailed analysis.[48]

An additional complicating factor, imparted by the etiologic heterogeneity among HPV-associated noncervical cancers, for estimating the potential impact of the HPV vaccine on cancer incidence is that the proportion of cases attributable to a given etiology, such as HPV, may vary over time. Such variation is particularly relevant for these cancers, as the relative incidence of HPV-positive and HPV-negative cases may be influenced by the distribution of demographic (eg, age, sex, race, ethnicity) and risk factors (eg, sexual behavior, smoking) for both entities within populations. As documented in this monograph, age, sex, race, and ethnicity can strongly influence the incidence patterns for all HPV-associated noncervical cancers, but these incidence patterns may differ significantly across cancer sites. In addition, oral cancers (comprised of constituent sites within the oral cavity and oropharynx) exemplify a situation where the proportion of HPV-associated cancers has not been static, resulting from both an increase in the number of HPV-associated cancers and a decrease in cases not associated with HPV.[49] For oral cancers, it is possible to use anatomic site (eg, tonsil and base of tongue tumors) as a surrogate for HPV-associated tumors. According to Surveillance, Epidemiology, and End Results (SEER) data for covering 9% of the US population, overall oral cancer incidence rates steadily declined from 1973 to 2004. However, recent data indicate that incidence rates for tonsil and base of tongue cancers increased significantly in the US from 1973 to 2004, in contrast to declines in incidence observed for the majority of oral cavity tumors.[49] Similarly, as reported in previous studies and as shown in Figure 1, the long-term incidence of anal and vulvar cancers in the US is also currently increasing,[50,51] whereas incidence for cancers of the cervix, penis, and vagina appears to be decreasing.[4,52]

Although it may be possible on a case-by-case level to determine a given cancer as being HPV-associated or unassociated, how is this determined and tracked over time at a population level, and how can we assess the potential future impact of the HPV vaccine at the population level? Given that virtually all cervical cancers and the vast majority of anal cancers are caused by HPV, predominantly HPV16 and 18, the potential impact of the vaccine on these cancers can be assessed by tracking their incidence over time. However, additional data will be necessary for other HPV-associated noncervical cancers. Epidemiological surrogates for HPV-associated cancers, such as anatomic site (for oropharyngeal cancers), age (for vulvar and oropharyngeal cancers), and histology (eg, basaloid vs keratinized, for all), may be used to track changes over time. This presupposes that the accepted criteria for histological subtypes are uniformly applied for classification and reporting. Unfortunately, it is probable that currently observed age associations might have arisen from birth cohort effects, which, therefore, may dissipate over time. In addition, surrogate markers, such as age and histology, may also substantially misclassify HPV-associated and unassociated cancers, perhaps biasing estimates of vaccine effectiveness toward the null. Given drawbacks of these indirect approaches, a direct approach would be to compare the HPV-etiologic fraction at the population level between the prevaccine era and the vaccine era. Such efforts, which would entail representative sampling and categorization of tumor HPV status, are currently underway for the prevaccine era. In addition, as birth cohorts from 1980 and later receive the vaccine, the long-term impact could manifest as a strong birth cohort effect, if a substantial percentage of these cohorts are vaccinated.

Several additional factors may influence the efficacy of the HPV vaccine for noncervical cancers. Although it is encouraging that the current HPV vaccines appear equally immunogenic in boys and girls,[53] and studies are currently underway, there are as yet no data demonstrating that the vaccines are effective, for either sex, against cancers that occur in both men and women (anal and oropharyngeal cancers). Although the vaccines have been shown to be effective in women against lesions at genital mucosal and cutaneous sites,[11] and the systemic humoral immune response appears important for protection,[54] it remains possible that vaccine efficacy may be somewhat dependent upon the anatomic site of infection. Conversely, as HPV16 and 18, the 2 high-risk HPV types currently covered by the vaccine, are found in an even higher percentage of the noncervical HPV-positive cancers than in cervical cancers, the current vaccines, therefore, could theoretically prevent a higher proportion of, for example, HPV-positive oropharyngeal cancers (90 % to 95%)[55,56] than cervical cancers (~70% to 76%).[1] The vaccine may also be expected to prevent a higher proportion of anal and cervical cancers than penile and vulvar cancers, because the etiologic fraction appears higher for the former cancers. Vaccine effectiveness may

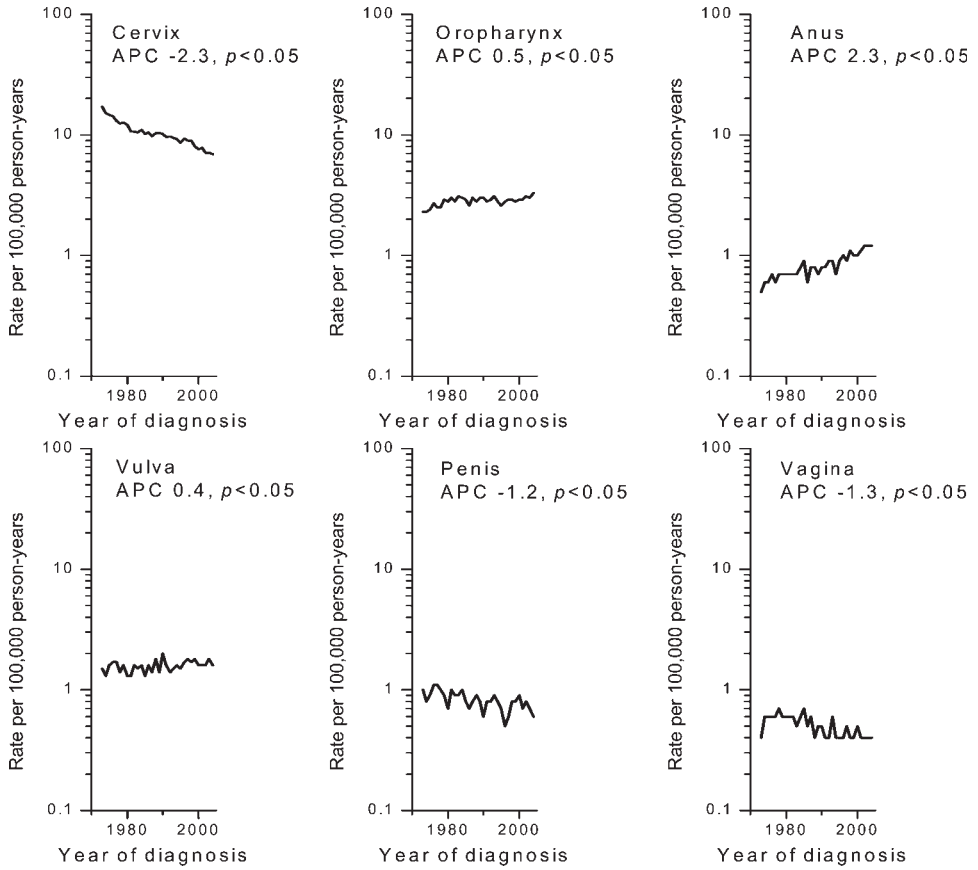

FIGURE 1. Incidence trends for HPV-associated cancers in the US, 1973-2004 are depicted. Incidence rates for HPV-associated cancers in the US were derived from 9 population-based cancer registries covered by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER 9) program during 1973-2004.[65] These registries cover approximately 9% of the US population. Anatomic site classifications are identical to those used in the ABHACUS monograph as described in Watson et al. Table 2,[58] with the exception of rectal cancers, which were not included in this analysis. Incidence rates are shown for cancers of the cervix (ICD-O-3 topography codes: C530-539; all histologies), anus (ICD-O-3 topography codes: C210-218; restricted to squamous cell histologies: ICD-O-3 codes: 8050-8084 and 8120-8131), oropharynx (restricted to sites believed to be HPV-associated with ICD-O-3 codes: C019, C024, C028, C090-099, C102, C108, C109, C140, C142, and C148; restricted to squamous cell histologies: ICD-O-3 codes: 8050-8084 and 8120-8131), penis (ICD-O-3 topography codes: C600-609; restricted to squamous cell histologies: ICD-O-3 codes: 8050-8084 and 8120-8131), vagina (ICD-O-3 codes: C529; restricted to squamous cell histologies: ICD-O-3 codes: 8050-8084 and 8120-8131), and vulva (ICD-O-3 codes: C510-519; restricted to squamous cell histologies: ICD-O-3 codes: 8050-8084 and 8120-8131). Rates are age-adjusted to the US 2000 population. APC denotes the annual percentage change in incidence; APC was calculated in log-linear models by regressing the calendar year of diagnosis on the log of the age-adjusted rate by using SEER*Stat.[65] The *P*-value for the annual percentage change in incidence rates during 1973 to 2004 is also shown in each panel.

also be influenced by the timing of infection relative to that of vaccination. Current data link acquisition of oral HPV infection largely to sexual behavior.[57] However, it remains possible that oral infections ultimately leading to cancer may, in some unusual instances, be acquired peripartum and via nonsexual, oral to oral transmission and, therefore, could precede vaccination.

Despite the above-noted considerations, it is nevertheless possible and informative to estimate the number of cancers in the US that are potentially attributable to HPV infection (and to HPV types 16 and 18) and theoretically preventable via HPV vaccination. This monograph has used results from Parkin and Bray[58] and Kreimer et al[56] to estimate the number of cancers potentially attributable to HPV infection in the US.[59] In both articles,[56,58] data were generated largely from studies conducted in populations outside of the US. However, there may be considerable variation between these estimates (referred to subsequently as "worldwide") and US-specific estimates for the proportion of cancers that are attributable to HPV infection (Table 4 and Figs. 2 and 3). For example, for oropharyngeal cancers, in con-

TABLE 4
Estimated Annual Number of Cases for HPV-associated and HPV16/18-associated Invasive Cancers in the US, 1998-2003

	Proportion of All Cancers That Is HPV-Associated, %, (95% CI)[a]	Proportion of All Cancers That Is HPV16/18-Associated, %, (95% CI)[a]	Proportion of HPV-Associated Cancers That Is Attributable To HPV16/18 (95% CI)[a]	Annual No. of Cases, 1998-2003[b]	Annual No. of HPV-Associated Cases, 1998-2003 (95% CI)[a]	Annual No. of Cases, HPV16/18-Associated, 1998-2003 (95% CI)
US-specific Estimates						
Cervix[c]	96[d] (95-97)	76 (NA)[e]	76 (NA)	10,846	10,412 (NA)	8243 (NA)
Oropharynx[f]	63 (50-75)	60 (47-72)	95 (82-99)	7360	4637 (3673-5549)	4416 (3433-5329)
Anus[g]	93 (86-97)	87 (82-91)	93 (89-96)	2547	2371 (2180-2481)	2211 (2078-2318)
Vulva[h]	51 (37-65)	44 (30-58)	86 (76-96)	2266	1153 (841-1464)	988 (687-1307)
Vagina[i]	64 (43-82)	56 (35-76)	88 (62-98)	601	385 (255-493)	347 (121-263)
Penis[j]	36 (26-47)	31 (22-42)	87 (69-96)	828	298 (215-389)	257 (182-348)
Total				24,448	19,256[k]	16,462[l]
Worldwide Estimates[m]						
Cervix	100	70	70	10,846	10846	7592
Oropharynx	35	31	89	7360	2576	2293
Anus	90	83	92	2547	2292	2109
Vulva	40	32	80	2266	906	725
Vagina	40	32	80	601	240	192
Penis	40	25	63	828	331	209
Total				24,448	17,191	13,120

[a] Exact 95% binomial confidence interval calculated from data in reference manuscript by use of STATA version 8.0. The upper and lower bound for the 95% CI on the proportion were used to calculate the upper and lower bounds for annual number estimates.

[b] Derived from data presented in Watson M et al, Table 4.[58] Limited to microscopically confirmed cases. Includes all histologies for cervical cancer. Limited to squamous cell carcinomas for all other cancers.

[c] Calculated from data presented in Clifford G et al.[61]

[d] Although 99.7% of cervical cancers are considered HPV-associated based on data from Walboomers et al,[7] data have been calculated according to data presented in the reference.

[e] Not available. Data could not be generated from reference manuscript.

[f] Calculated from data presented in Fakhry C et al.[60]

[g] Calculated from data presented in Daling JR et al.[62]

[h] Calculated from data presented in Madeleine MM et al.[63]

[i] Calculated from data presented in Daling JR et al.[64]

[j] Calculated from data presented in Heiderman DA et al.[35] Restricted to high-risk alpha-papillomaviruses.

[k] 95% Confidence Interval = 17,576-20,788, assuming fixed number of 10,412 cervical cancer cases.

[l] 95% Confidence Interval = 14,744-17,808, assuming fixed number of 8243 cervical cancer cases.

[m] Numbers calculated from proportions presented in Table 1 of Watson et al.[58]

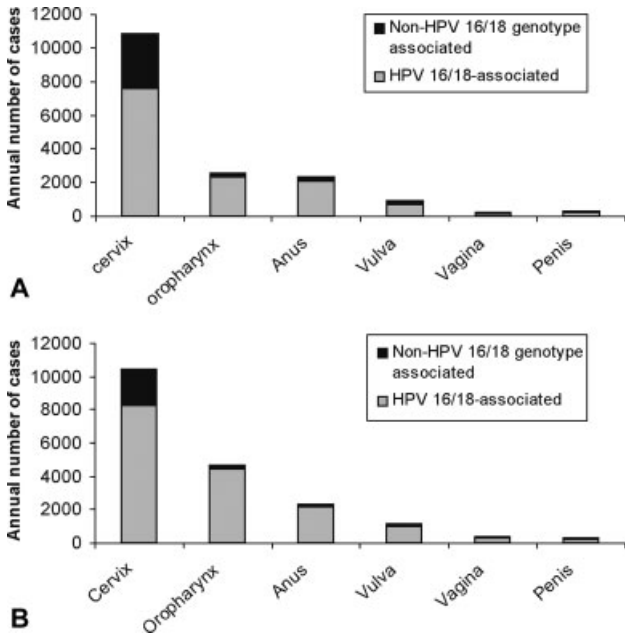

FIGURE 2. (**A**) Estimated annual number of HPV-associated cancers in the US, 1998-2003, are shown in this panel. Numbers are based on worldwide estimates of the proportion of HPV-associated cancers. (**B**) Estimated annual number of HPV-associated cancers in the US, 1998-2003, are shown. Numbers are based on US-specific estimates of the proportion of HPV-associated cancers. The estimated annual number of HPV-associated cancers in the US during 1998-2003 are based on data presented in Watson et al.[58] The Watson data are from 39 population-based cancer registries that participate in the National Program of Cancer Registries (NPCR) and/or the Surveillance, Epidemiology, and End Results (SEER) Program and meet high-quality data criteria.[58] These registries cover approximately 83% of the US population. The values from which Figure 2 is derived are shown in Table 4. The total number of cases for each cancer is partitioned into the number of cases caused by HPV genotypes 16 and 18 (in grey), which are, therefore, potentially preventable by the currently available HPV vaccine, and the number of cases caused by other HPV genotypes are shown in black.

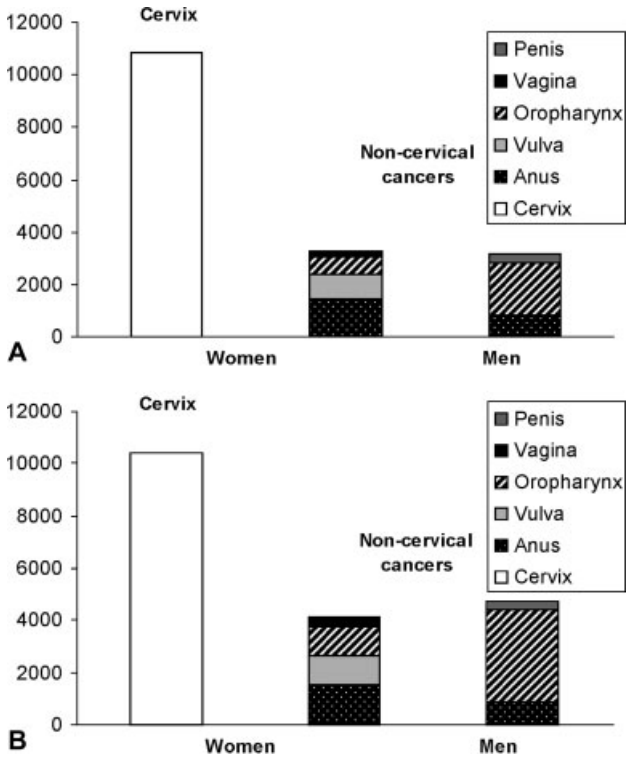

FIGURE 3. (**A**) Estimated annual number of HPV-associated cancers in the US by gender, 1998-2003, is depicted. Numbers are based on worldwide estimates of the proportion of HPV-associated cancers. (**B**) Estimated annual number of HPV-associated cancers in the US by gender, 1998-2003, is depicted. Numbers are based on US-specific estimates of the proportion of each cancer that is attributable to HPV infection.These numbers are based on data presented in Watson et al.[58] The Watson data are from 39 population-based cancer registries that participate in the National Program of Cancer Registries (NPCR) and/or the Surveillance, Epidemiology, and End Results (SEER) Program and meet high-quality data criteria.[58] These registries cover approximately 83% of the US population. The values from which Figure 3 is derived are shown in Table 4. Results are shown for cervical cancer, other HPV-associated cancers among women, and HPV-associated cancers among men. The annual number of each component cancer is also shown for noncervical HPV-associated cancers among women and for HPV-associated cancers among men.

trast to the worldwide estimates of 12% to 35%,[56,59] recent studies in the US indicate that a much higher proportion (~63%) of oropharyngeal cancers is attributable to HPV infection, which increases the number of HPV-associated cases of this cancer by more than 2 thousand (Table 4).[21,60] Therefore, with the exception of penile cancer (for which US-specific data are unavailable), we have applied estimates from population-based studies conducted in the US[35,60-64] to approximate the average annual number of cancers caused by HPV in the US during the period from 1998 to 2003 (Table 4). These differences in HPV-attributable proportions notwithstanding, the following general observations can be made from Figures 2 and 3 and Table 4. 1) The number of noncervical cancers caused by HPV in the US each year roughly approximates the number of cervical cancers. 2) The number of noncervical cancers that occur in men in the US each year roughly approximates noncervical cancers for women. 3) Cancers of the oropharynx, which occur largely among men, but also among women, account for a substantial proportion of HPV-associated cancers in the US, second only to cervical cancers. 4) The majority of HPV-associated cancers that occur in the US are attributable to HPV16 and 18 infections.

On the basis of these observations, we draw the following conclusions. 1) In countries with effective cervical cancer screening programs, HPV-associated noncervical cancers may represent a relatively high proportion of the total number of HPV-positive cancers. Given that there are no effective and widely applied screening programs for HPV-associated noncervical cancers and that the incidence for several of these cancers is currently increasing in the US, the HPV vaccines intended primarily for prevention of cervical cancers may possess great potential to affect the US public health by preventing noncervical cancers. This implication is, of course, dependent on the efficacy of the HPV vaccines against anal and oropharyngeal infections being similar to their efficacy against cervical, vaginal, and vulvar infections. 2) Vaccination strategies to reduce the incidence of cancer attributable to HPV infection in the US should probably take into account that a substantial proportion (about 25%) of cancers caused by HPV infection arise in men. As nonmandatory vaccination of adolescents in the US has traditionally led to vaccination of a minority of eligible individuals, it is unlikely that nonmandatory vaccination would lead to a significant degree of herd immunity. Under these circumstances, vaccination of boys and girls would theoretically provide the greatest impact of the HPV vaccines on cancer incidence in the US, although cost effectiveness would need to be considered. 3) The burden of HPV-associated oropharyngeal cancers is second only to cervical cancers in the US, and, therefore, the efficacy of the HPV vaccines in preventing oral infection by HPV16 and 18 warrants evaluation. 4) Future generation vaccines that include high-risk types other than HPV16 and 18 may provide limited additional benefit in the US against the widely recognized HPV-associated noncervical cancers, although new generation vaccines could protect against a higher proportion of cervical cancers and may affect cervical cancer screening algorithms.

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