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Using Population-based Cancer Registry Data to Assess the Burden of Human Papillomavirus-associated Cancers in the United States: Overview of Methods

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

Supplement to ***Cancer***

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Increased attention to human papillomavirus (HPV)-associated cancers in light of the recent release of an HPV vaccine, as well as increased availability of cancer registry data that now include reporting from a large proportion of the US population, prompted the current assessment of HPV-associated cancers. This article describes methods used to assess the burden of HPV-associated cervical, vulvar, vaginal, penile, anal, and oral cavity/oropharyngeal cancers in the United States during 1998 through 2003 using cancer registry data, and it provides a brief overview of the epidemiology of these cancers. ***Cancer* 2008;113(10 suppl):2841–54.** *Published 2008 by the American Cancer Society.**

KEYWORDS: methods, human papillomavirus, cancer, surveillance.

Persistent infection with the human papillomavirus (HPV) is considered to be a cause of nearly all cervical cancer.[1] It is believed that HPV also is associated with approximately 90% of anal cancers; 40% of penile, vaginal, and vulvar cancers; 25% of oral cavity cancers; and 35% of oropharyngeal cancers.[2,3] A quadrivalent HPV vaccine that protects against HPV type 6 (HPV-6), HPV-11, HPV-16, and HPV-18 has been approved for use in the United States for females ages 9 years to 26 years, and a bivalent vaccine that protects against HPV-16 and HPV-18 currently is under review by the US Food and Drug Administration. It has been demonstrated that the HPV vaccine reduces the incidence of cervical, vaginal, and vulvar precancers, offering hope for the reduction in incidence of these diseases and the corresponding invasive cancers among women.[4,5] Current studies are assessing the efficacy of the vaccine on HPV-associated disease in men.[6] Close surveillance of these cancers will be necessary to ensure that high-risk populations are being reached by vaccination programs.

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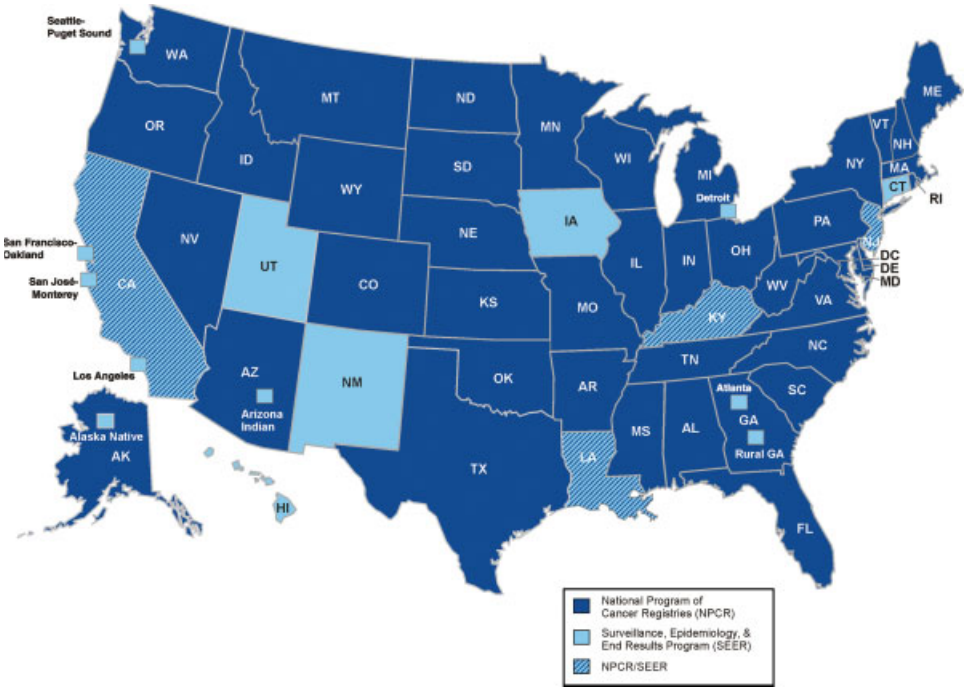

FIGURE 1. States and metropolitan areas supported by the National Program of Cancer Registries, which is administered through the Centers for Disease Control and Prevention, and the Surveillance, Epidemiology, and End Results Program, which is administered through the National Cancer Institute.

Increased attention to HPV-associated cancers in light of the recent release of the vaccine, as well as increased availability of cancer registry data, prompted the current *Supplement* of *Cancer* titled "Assessing the Burden of HPV-Associated Cancers in the United States" (ABHACUS). The major purposes of this *Supplement* are to assess the current burden of anogenital and oropharyngeal cancers associated with HPV within the United States and to provide a baseline for monitoring future trends in HPV-associated cancers. This article describes methods used to assess the burden of HPV-associated cancers in the United States—methods that are common to several articles in the *Supplement*. This article describes the data sources, case definitions, variables, and analytic methods of descriptive epidemiologic articles that are included in this *Supplement*, and it provides an overall picture of the burden of HPV-associated cancers.

Data Sources: Cancer Registry and Mortality Surveillance Systems

We used cancer incidence data from population-based cancer registries that participate in the Center for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results Program (SEER).[7-9] The SEER Program began in 1973 as a result of the National Cancer Act. SEER began collecting and publishing cancer incidence and survival data from 5 state cancer registries and from 4 metropolitan population-based cancer registries covering approximately 10% of the US population. Over time, the program has expanded its coverage of the population to include 9 states and 6 metropolitan areas, in total covering 26% of the population. Recognizing the need for more complete local, state, regional, and national cancer incidence data, Congress established the NPCR in 1992.[10] The NPCR now supports cancer registries in 45 states, the District of Columbia, and 3 US territories, and it covers 96% of the population (Fig. 1). NPCR and SEER provide dual support to 4 statewide cancer registries. These SEER metropolitan-area and special population cancer registries report their incidence data to both NCI and to the NPCR statewide cancer registries in their respective states. Together, NPCR and SEER now collect cancer incidence data for the entire US population. Both NPCR data and SEER data are collected and reported by use of standard data items and uniform codes and procedures, as documented by the North American Association of Central Cancer Registries (NAACCR).[11] Registries in each program also collect additional data items as required by their funding

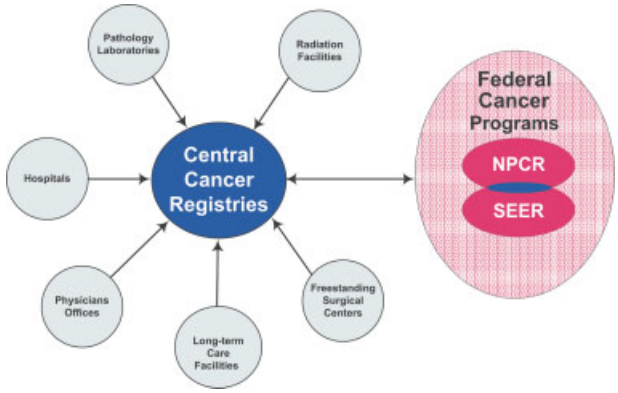

FIGURE 2. Collection and consolidation of data from patient facilities to federal cancer programs. The National Program of Cancer Registries (NPCR) is administered through the Centers for Disease Control and Prevention (available at: http://www.cdc.gov/cancer/npcr/ accessed on March 3, 2008). The Surveillance, Epidemiology, and End Results Program (SEER) is administered through the National Cancer Institute (available at: http://seer.cancer.gov/ accessed on March 3, 2008). Central cancer registries also submit data to the North American Association of Central Cancer Registries, which is an association of population-based cancer registries.

agencies. Reportable cancers include in situ or invasive primary cancers of all sites except in situ cancer of the cervix, for which collection stopped in 1996.[12] Basal and squamous cell carcinomas (SCCs) of the skin are also excluded, with the exception of those on the skin of the genital organs. Cancer cases were coded according to the version of the International Classification of Diseases for Oncology (ICD-O) that was in use at the time of diagnosis. The second edition of the ICD-O (ICD-O-2) was used during the diagnosis years from 1998 through 2000, and the third edition of the ICD-O (ICD-O-3) was used for the diagnosis years from 2001 through 2003; the data from 1998 through 2000 were converted to ICD-O-3 codes.[13-16]

Hospitals and other facilities that diagnose or treat cancer collect and report cancer incidence data to central cancer registries (Fig. 2). SEER registries also collect follow-up information for determination of cancer survival statistics. Medical and demographic information for cancer cases is obtained primarily from medical records. Although the majority of cancer cases still are reported by hospitals, data increasingly are obtained from nonhospital sources, such as pathology laboratories, radiation facilities, freestanding surgical centers, long-term care facilities, and physicians' offices. A small percentage ($\leq$5%) of medical and demographic information is obtained solely from death certificates. At the central cancer registries, staff consolidates the data received from hospitals and other facilities and use death certificate data to update the vital status of cases already in the registry.[17] These tasks are completed before the data are submitted to either or both federal agencies (Fig. 2). Central cancer registries submit deidentified data to these agencies to be used for publication in statistical and analytic summaries and for release in restricted datasets for research.

We used cancer mortality data obtained from death certificates that contained demographic information and cause of death throughout the United States and that were coded according to the version of the ICD-O that was in use at the time of death. These data are reported to state vital statistics offices and consolidated into a national database by the CDC through the National Vital Statistics System.[18] The underlying cause of cancer death is coded to the primary cancer site according to the version of the International Classification of Diseases (ICD) in use at the time of death and is grouped for maximum comparability among ICD versions.[13,14,19] The US Standard Certificate of Death, which is used as a model by the state, was revised in 2003.[20] This report includes data from 4 states (California, Idaho, Montana, and New York), which implemented the 2003 revision of the US Standard Certificate of Death in 2003. For the remaining 46 States and the District of Columbia that collected and reported death data in 2003, the data were based on the 1989 revision of the US Standard Certificate of Death. The 2003 revision of the US Standard Certificate of Death allows the reporting of more than 1 race (multiple races).[20]

Data Sources: Databases Used in This *Supplement*

Cancer incidence data were included in this *Supplement* if the cancer registry met the following publication criteria for the *United States Cancer Statistics* (USCS) report for all years from 1998 through 2003: Case ascertainment was at least 90% of expected cases (with the expected cases estimated by using methods developed by NAACCR), $\geq$97% of cases passed a standard set of computerized edits, $\leq$5% of cases were reported by death certificate only, $\leq$5% of cases were missing information on race, $\leq$3% of cases were missing information on sex, and $\leq$3% of cases were missing information on age.[7,21]

Although NPCR and SEER registries currently (since 1998) cover 100% of the US population, only registries that meet USCS publication criteria for all 6 years were included in this analysis to ensure that high-quality data were used. NPCR and SEER data from 39 registries met the data quality criteria for inclusion in this report. Figure 3 shows a map of the cancer registries that are included in our database.

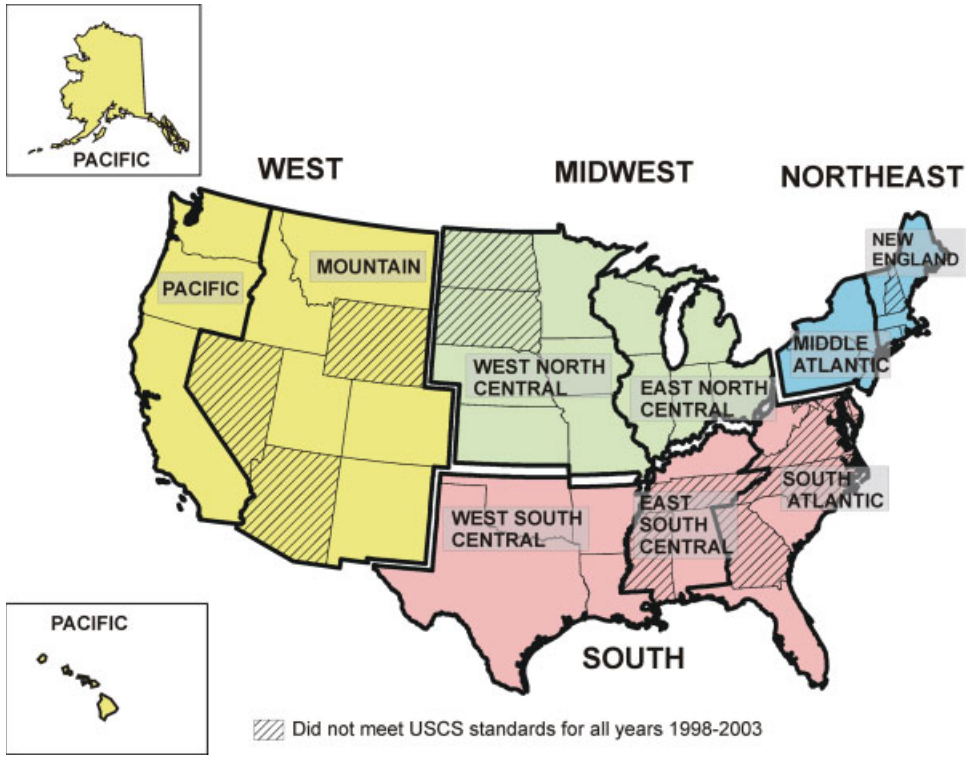

FIGURE 3. States by US Census region and division (total population coverage, 83%). Population coverage by region: Northeast, 98%; Midwest, 98%; South, 63%; West, 88%. States that did not meet the inclusion criteria were not included because they did not meet standards for high-quality data collection for all years from 1998 through 2003 (see Havener, 2004[21]). USCS indicates United States Cancer Statistics.

These registries cover approximately 83% of the US population: 84% of whites, 74% of blacks, 90% of Asian/Pacific Islanders (APIs), and 91% of Hispanics. Regionally, 98% of the population in the Northeast and Midwest are covered, 63% of the South is covered, and 88% of the West is covered. Because SEER has been in existence since 1973, analyses of treatment, trends and survival, which require data over a longer period of time, were limited to SEER data only.

NPCR data for this *Supplement* were reported to the CDC as of January 31, 2006. SEER data were reported to the NCI as of November 2005 and were made available through the SEER Program limited-use data file that was released in April 2006.[22] Data from states that are supported by both NPCR and SEER are presented as reported to the CDC as of January 2006 unless stated otherwise.[7]

Variation by race (white, black, and API) and Hispanic ethnicity were examined extensively for this *Supplement*. NPCR and SEER obtain information on race and Hispanic ethnicity from medical records. Identification of Hispanic ethnicity for cancer cases was augmented by a hierarchical algorithm that used race, birthplace, sex, maiden name, and surname.[23] The CDC and other national partners have established a strategy to improve identification of American Indian/Alaska Native (AI/AN) cases; however, data on AI/ANs are not presented as a separate category in this *Supplement*, because such an identification strategy was not complete for all years in our dataset.[24]

Cancer death data for the years 1998 through 2003 are based on records of deaths that occurred from 1998 through 2003 for which the records were received as of February 28, 2005. Cancer deaths that were diagnosed before 1999 were recoded to ICD-O-3 categories. Because the 2003 revision of the US Standard Certificate of Death allows for the selection of multiple races, multiracial decedents were recoded to a single race (either white, black, AI/AN, or API) according to their combination of races, Hispanic origin, sex, and age indicated on the death certificate.[25]

The population denominator data for calculating cancer incidence and mortality rates were obtained from the 2000 US Census and modified by SEER for the purpose of improving the accuracy of rates for the population of Hawaii.[26]

TABLE 1
Estimated Percentage Attributable to Human Papillomavirus*

Cancer Site	% Attributable to HPV	Reference	Among HPV-positive, % Attributable to HPV-16 and HPV-18	Reference(s)
Cervix	100	Parkin & Bray 2006[2]	70	Munoz 2004[49]
Vagina	40	Parkin & Bray 2006[2]	80	Daling 2002[50]
Vulva	40	Parkin & Bray 2006[2]	80	Trimble 1996[51]; Iwasawa 1997[52]
Penis	40	Parkin & Bray 2006[2]	63	Rubin 2001[53]
Anus	90	Parkin & Bray 2006[2]	92	Daling 2004[54]; Frisch 1999[55]
Oral cavity	25	Kreimer 2005[3]	95	Kreimer 2005[3]
Oropharynx	35	Kreimer 2005[3]	89	Kreimer 2005[3]

HPV indicates human papillomavirus.
*This table was adapted from Parkin & Bray 2006[2] with updates based on Kreimer 2005.[3] See text for further discussion of HPV-attributable fractions.

Case Definition and Explanation of Potential Association With HPV

This *Supplement* highlights the 6 cancer sites (cervical, vulvar, vaginal, anal, penile, and oral cavity/oropharynx) that are considered to have sufficient evidence for HPV as a carcinogen (Table 1).[27] According to Parkin and Bray, the strict definition of population attributable fraction needs to be modified when noncervical HPV-associated cancers are considered, because the prevalence of HPV infection among individuals in the control group (cancer-free) at the particular anatomic site currently is unknown.[2,28] The prevalence of HPV DNA detection varies considerably by type of assay and detection method. For the noncervical HPV-associated cancers, the percentage attributable fraction refers to the general percent of those cancers in which HPV DNA can be demonstrated in tumor cells, or HPV prevalence. For this *Supplement*, attributable fractions were based on the work by Parkin with an update on oral cavity and oropharyngeal cancers based on a systematic review by Kreimer (Table 1).[2,3] The attributable fractions may be considered by some to be a conservative estimate of attributable fraction (or HPV DNA prevalence) for many of the sites. Taking into account a lack of systematic reviews of HPV DNA prevalence in most of the noncervical cancers, the different methodologies for determining HPV DNA prevalence and the geographic variability in the HPV-type distribution of the cancers, we believed that using this conservative estimate was most appropriate. We realize that the attributable fraction may change with additional research on HPV detection methods and systematic reviews. Thus, when we describe the burden, we are not taking into account the attributable fraction for each site. Instead, we are reporting the burden of potentially HPV-associated cancers, which were defined by focusing on specific sites and specific histologies, and we refer to these as 'HPV-associated.' This article and others that describe the burden of HPV-associated cancers in this *Supplement* do not attempt to provide actual estimates of the attributable fraction of HPV in these cancers but provide basic information about cancers in sites that are believed to be primarily HPV-associated. The information about burden provided in this *Supplement* can be compared over time by using the standardized criteria provided—independent of any variation that may occur over time in the estimated attributable fraction.

We identified 5 HPV-associated sites for females (cervix, vulva, vagina, anus, and oral cavity/oropharynx) and 3 sites for males (penis, anus, and oral cavity/oropharynx). Cases were grouped according to the ICD-O-3 site categories listed in Table 2. Specific HPV-associated subsites were identified for cancers of the oral cavity and oropharynx.[29] To further identify those cancers most likely to be HPV-associated, we also limited analyses by ICD-O-3 histology code (Table 3). Cervical cancer was limited to carcinomas (ICD-O-3 histology codes 8010-8671 and 8940-8941).[1,30] In all other sites, SCCs are most likely to be associated with HPV; thus, HPV-associated cancers of the vulva, vagina, penis, anus, and oral cavity/oropharynx were defined as SCCs (ICD-O-3 histology codes 8050-8084 and 8120-8131).[2] Analyses that were limited by histology (or that described the distribution of histology) were confined to tumors with microscopically confirmed histology (Fig. 4).

Some articles in this *Supplement* examine the burden of in situ cancer (behavior code of 2 in the NPCR and SEER databases). Vulvar, vaginal, and anal intraepithelial neoplasia lesions (specifically, vulvar intraepithelial neoplasia 3, vaginal intraepithelial neoplasia 3, and anal intraepithelial neoplasia 3) with an ICD-O-3 histology code of 8077 and behavior code of 2 are required to be reported by NPCR and

TABLE 2
Definitions for Site Recode and Histology Codes

Site	ICD-O-3 Site Code	ICD-O-3 Histology Code*
Cervix uteri	C53	All carcinomas (squamous cell, adenocarcinoma, adenosquamous/glassy cell, small cell neuroendocrine, other and unspecified)
Endocervix	C53.0	
Exocervix	C53.1	
Overlapping lesion of cervix uteri	C53.8	
Cervix uteri	C53.9	
Vagina	C52	Squamous cell carcinomas†
Vagina, NOS	C52.9	
Vulva	C51	Squamous cell carcinomas†
Labium majus	C51.0	
Labium minus	C51.1	
Clitoris	C51.2	
Overlapping lesion of vulva	C51.8	
Vulva, NOS	C51.9	
Anus, anal canal, and anorectum	C21	Squamous cell carcinomas†
Anus, NOS	C21.0	
Anal canal	C21.1	
Cloacogenic zone	C21.2	
Overlapping lesion of rectum, anus and anal canal	C21.8	
Rectum‡	C20.9	
Penis	C60	Squamous cell carcinomas
Prepuce (foreskin)	C60.0	
Glans penis	C60.1	
Body of penis	C60.2	
Overlapping lesion of penis	C60.8	
Penis, NOS	C60.9	
Base of tongue and lingual tonsil		Squamous cell carcinomas
Base of tongue, NOS	C01.9	
Lingual tonsil	C02.4	
Tonsil (including Waldeyer ring)		Squamous cell carcinomas
Tonsillar fossa	C09.0	
Tonsillar pillar	C09.1	
Overlapping lesion of tonsil	C09.8	
Tonsil, NOS	C09.9	
Waldeyer ring	C14.2	
Other oropharynx, potentially HPV-associated		Squamous cell carcinomas
Overlapping lesion of tongue	C02.8	
Lateral wall of oropharynx	C10.2	
Overlapping lesion of oropharynx	C10.8	
Oropharynx, NOS	C10.9	
Pharynx, NOS	C14.0	
Overlapping lesion of lip, oral cavity, and pharynx	C14.8	

ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition; NOS, not otherwise specified; HPV, human papillomavirus.

*All carcinomas defined as ICD-O-3 histology codes 8010-8671, 8940-8941. Squamous cell carcinomas (SCCs) defined as ICD-O-3 histology codes 8050-8084, 8120-8131.

†This article and others in the current supplement that examined National Program of Cancer Registries/Surveillance, Epidemiology, and End Results excluded code 8077/2 (intraepithelial neoplasia 3) for vaginal, vulvar, and anal cancers.

‡SCCs of the rectum are included. Because the rectum is made up of glandular cells and not squamous cells, we assumed that microscopically confirmed rectal SCCs were miscoded to the rectum or were overlapping anal lesions and treated these cancers like anal cancers (see Joseph 2007[36]).

SEER registries but are not collected uniformly; thus, they were excluded from all analyses.[31] It is believed generally that these lesions are associated with HPV.[32] We have chosen to refer to these lesions by using Arabic numerals in accordance with World Health Organization terminology (eg, cervical intraepithelial neoplasia is referred to as CIN-3 rather than CIN-III). The collection of penile intraepithelial neoplasia (PIN-3) has not been required by NPCR and SEER since 2000.[31]

Anal and rectal SCCs were considered to be HPV-associated cancers for the purpose of our analyses. Anal SCCs are associated strongly with HPV.[33-36] The majority of rectal cancers are adenocarcinomas, which are not considered HPV-associated. True rectal SCCs are rare, but they generally may be HPV-associated; overlapping SCCs of the anus also may be misclassified as rectal SCCs.[36,37] These cancers were included in our analyses of HPV-associated anal cancers (Table 2).[34,38] After we limited the analyses to microscopically confirmed SCCs, only 1.9% of invasive rectal cancers and 2.9% of all in situ rectal cancers were considered HPV-associated, whereas 77.9% of invasive anal cancers and 65.5% of in situ anal cancers were considered HPV-associated.

Oral cavity and oropharyngeal sites that are considered HPV-associated were grouped into 3 major anatomic subsites: the tonsil, including the Waldeyer ring; the base of tongue and lingual tonsil; and other HPV-associated sites within the oropharynx (Table 2). These sites were identified as having the strongest correlation with HPV by the scientific writing group on oral cavity and oropharyngeal cancers on the basis of existing literature and expert advice.[29]

TABLE 3
General Histologic Classification of Invasive and In Situ Cancers Examined in the Current Supplement "Assessing the Burden of HPV-Associated Cancers in the United States"*

Histology	ICD-O-3 Codes
Carcinomas	8010-8671, 8940-8941
Squamous cell and transitional cell	8050-8084, 8120-8131
Basaloid and cloacogenic	8123, 8124
Keratinizing	8071
Nonkeratinizing	8072, 8073
Verrucous	8051
Adenocarcinomas	8140-8149, 8160-8162, 8190-8221,8260-8337, 8350-8551, 8570-8576, 8940-8941
Adenosquamous and glassy cell	8560, 8015
Small cell/neuroendocrine	8013, 8041-8045, 8240-8246
Other specified carcinomas	8014, 8030-8040, 8046, 8090-8110, 8150-8157, 8170-8180, 8230-8239, 8247-8255, 8340-8347, 8561-8562, 8580-8671
Unspecified carcinomas	8010-8012, 8020-8022
Noncarcinomas	All remaining values

ICD-O-3 indicates International Classification of Diseases for Oncology, 3rd Edition.
*This article and others in the current supplement that examined National Program of Cancer Registries/ Surveillance, Epidemiology, and End Results excluded code 8077/2 (intraepithelial neoplasia 3) for vaginal, vulvar, and anal cancers.

Statistical Analysis

Age-adjusted incidence and death rates were calculated per 100,000 persons unless specified otherwise. Rates were age-adjusted to the 2000 US standard population by the direct method using 19 age groups (ages <1 year, 1-4 years, 5-9 years, 10-14 years, 15-19 years, ... ≥85 years).[39] Cancer cases with unknown sex or age were excluded from all analyses.

Incidence and death rates and 95% confidence intervals were calculated in SEER*Stat (version 6.2.4), a statistical software package that was developed by

	All histologies			Microscopically confirmed		Limited by histology and microscopic confirmation		
	N	Rate		Percent		N	Rate	Percent of all
Cervix	67,838	9.2		97.5%		65,074	8.9	95.9%
Vagina	5,626	0.7		96.5%		3,604	0.5	64.1%
Vulva	18,411	2.3		98.1%		13,597	1.7	73.9%
Penis	5,398	0.9		97.9%		4,967	0.8	92.0%
Anus	19,611	1.4	Limited by microscopic confirmation	99.0%	Limited by ABHACUS histology	15,279	1.1	77.9%
Male	7,683	1.2		99.0%		5,530	0.8	72.0%
Female	11,928	1.5		99.0%		9,749	1.3	81.7%
Rectum	146,392	10.4		97.9%		2,826	0.2	1.9%
Male	83,449	13.5		98.2%		967	0.2	1.2%
Female	62,943	7.9		97.4%		1,859	0.2	3.0%
Oral Cavity and Oropharynx	47,925	3.4		96.9%		44,160	3.1	92.1%
Male	36,515	5.6		97.0%		33,946	5.2	93.0%
Female	11,410	1.5		96.4%		10,214	1.3	89.5%
ALL	**311,201**	**22.0**		**97.7%**		**149,507**	**10.6**	**48.0%**

FIGURE 4. Invasive cancers that were examined in the *Assessing the Burden of HPV-Associated Cancers in the United States* (ABHACUS) supplement: United States, 1998 through 2003. Data are from 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. These registries cover approximately 83% of the US population. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population. 'All histologies' excludes International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes 9050 (mesothelioma), 9140 (Kaposi sarcoma), and 9590-9989 (lymphomas and leukemias). Cervical cancers were limited to carcinomas only (ICD-O-3 histology codes 8010-8671 and 8940-8941). All other sites were limited to squamous cell carcinomas only (ICD-O-3 histology codes 8050-8084 and 8120-8131). Oral cavity and oropharyngeal cancers were limited to the subsites specified in Table 2.

the NCI.[40] Confidence intervals were based on the Gamma method and used the modification detailed by Tiwari et al.[41] Rates were calculated by age, race (white, black, and API), ethnicity (Hispanic or non-Hispanic), stage, and US Census region (Northeast, South, East or West) (Fig. 3). The race category labeled as 'all races combined' and the overall cancer rates include individuals of all races: white, black, AI/AN, API, other, and unknown. Other and unknown categories were not reported on separately, because denominator information was not available for these groups; thus, the sum of the individual race categories (white, black, and API) will not equal the 'all races combined' category. Hispanic ethnicity included individuals from all race categories.

Cancers were staged according to SEER Summary Stage 1977 (for cases diagnosed before 2001) and SEER Summary Stage 2000 (for cases diagnosed in 2001 or later). For some cancer sites, differences between the 2 staging schemes can result in inconsistent staging.[42,43] Coding for regional and distant stages of cancers of the vagina and some oral cavity and oropharyngeal subsites was not consistent between the 2 schemes; thus, we reported only early or late stage for vaginal and oral cavity/oropharyngeal cancers. Where early or late stage is reported, early stage includes localized stage, and late stage includes regional and distant stages. Certain articles in this *Supplement* also examine tumor grade, with cancer cells classified by the degree of microscopic abnormality and the likelihood of growth and metastasis.[30]

RESULTS

This section is intended to provide a general overview of the distribution of these cancers in the context of all HPV-associated cancers. Comprehensive descriptions of each cancer can be found in individual articles in this *Supplement*.[29,36,44-47]

Table 4 displays age-adjusted cancer incidence rates for the invasive cancers included in this article by registry. In total, there were 149,507 cases of invasive HPV-associated cancer from 1998 through 2003. Cervical carcinomas, as expected, were the most frequent cancers examined in our study, with an average of 10,846 cases per year, followed by oral cavity and oropharyngeal SCCs, with an average of 7360 cases per year. The averages were 3018 cases of anal and rectal SCCs per year and 2266 vulvar SCCs per year. Penile and vaginal cancers were rare, with average annual counts of 828 and 601 per year, respectively. The South Atlantic division had the highest rates of cervical, anal, and oral cavity/oropharyngeal cancers, whereas the West South Central division had the highest rates of vaginal and penile cancers. The East South Central division had the highest rate of vulvar cancer. Figure 5 displays age-adjusted cancer incidence rates for invasive cancers by Census division.

Rate and percentage distributions of invasive cancers associated with HPV by sex, cancer site, age, race, ethnicity, disease stage, and region are shown in Table 5. There were 104,097 cases of HPV-associated cancers among women during 1998 through 2003. The median age at diagnosis for cervical carcinoma was 47 years. Other invasive HPV-associated cancers tended to be diagnosed later, with a median age >60 years at diagnosis. Approximately 50% of vaginal and vulvar SCCs were diagnosed among women aged ≥ 70 years. Black women had higher rates of invasive cervical carcinoma, and vaginal SCCs, and oral cavity/oropharyngeal SCCs, whereas white women had higher rates of vulvar and anal SCCs. Hispanic women had higher rates of cervical cancer than non-Hispanic women, whereas non-Hispanic women had higher rates of oral cavity and oropharyngeal cancers. All HPV-associated cancers among women were diagnosed most often at the localized stage, with the exception of oral cavity and oropharyngeal SCCs, which were diagnosed more frequently at the regional stage. The South had the highest rates of cervical, vaginal, anal, and oral cavity/oropharyngeal cancers, whereas the Midwest had the highest rate of vulvar cancer.

There were 45,410 cases of HPV-associated cancers among men from 1998 through 2003. Among men, those with invasive anal and oral cavity/oropharyngeal SCCs were younger at diagnosis (median ages, 57 years and 58 years, respectively) than men with invasive penile SCCs (median age at diagnosis, 68 years). API men had lower rates of all invasive HPV-associated cancers, whereas black men had higher rates of invasive anal and oral cavity/oropharyngeal SCCs. Hispanic men had higher rates of invasive penile SCC, and non-Hispanic men had higher rates of invasive anal and oral cavity/oropharyngeal SCCs. Invasive penile and anal SCCs in men were diagnosed most often at the localized stage. Invasive oral cavity and oropharyngeal cancers were most likely to be diagnosed at the regional stage. The rate of invasive penile SCC was lowest for men in the West, whereas the rate of invasive anal SCC was lowest in the Midwest. The rates of invasive oral cavity and oropharyngeal SCCs among men were highest in the South.

Among cancers for which both women and men were at risk, anal cancers were more common among

TABLE 4
Average Annual Incidence Counts and Rates of Invasive Cancers Associated With Human Papillomavirus by Registry: United States, 1998-2003*,†

	Cervix		Vagina		Vulva		Anus‡		Penis		Oral Cavity and Oropharynx‡		Average Annual Total
Registry	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
Alaska	22	7.8	—§	—§	5	2.0	8	1.7	—§	—§	18	3.8	55
Alabama	217	9.1	14	0.5	50	2.0	51	1.1	14	0.7	151	3.3	496
Arkansas	145	10.3	9	0.6	24	1.6	39	1.4	15	1.2	99	3.5	331
California	1552	9.2	72	0.4	232	1.4	439	1.4	90	0.7	919	3.0	3304
Colorado	154	7.0	7	0.3	27	1.3	48	1.2	11	0.7	103	2.6	349
Connecticut	134	7.0	9	0.4	44	2.0	39	1.1	16	1.0	112	3.1	354
District of Columbia	37	11.8	3	1.0	5	1.6	13	2.4	—§	—§	29	5.1	—§
Delaware	38	8.9	3	0.6	9	2.0	8	1.0	—§	—§	28	3.4	—§
Florida	907	10.3	43	0.4	171	1.6	323	1.7	69	0.8	799	4.3	2311
Hawaii	59	9.2	—§	—§	6	0.9	9	0.7	—§	—§	31	2.4	108
Idaho	41	6.6	3	0.4	8	1.3	14	1.1	4	0.8	33	2.7	103
Illinois	640	10.0	30	0.4	121	1.8	146	1.2	41	0.8	389	3.2	1366
Indiana	269	8.6	17	0.5	63	1.9	76	1.3	22	0.8	193	3.2	640
Iowa	123	8.2	9	0.4	41	2.3	32	1.0	13	0.9	78	2.5	295
Kansas	112	8.2	5	0.3	24	1.5	33	1.2	7	0.6	71	2.7	251
Kentucky	230	10.7	12	0.5	47	2.1	55	1.3	24	1.3	138	3.3	506
Louisiana	236	10.4	15	0.6	53	2.3	59	1.4	17	1.0	152	3.5	533
Massachusetts	225	6.4	17	0.4	71	1.8	77	1.2	26	0.9	209	3.2	624
Maine	54	7.5	5	0.6	19	2.4	22	1.5	7	1.1	55	3.8	161
Michigan	420	8.1	30	0.5	110	2.0	111	1.1	35	0.8	317	3.2	1022
Minnesota	167	6.6	12	0.5	52	1.9	44	0.9	21	1.0	126	2.6	421
Missouri	266	9.0	13	0.4	62	1.9	72	1.3	21	0.9	194	3.3	628
Montana	37	7.9	—§	—§	7	1.3	11	1.1	5	1.1	30	3.1	—§
Nebraska	69	8.1	3	0.3	17	1.6	20	1.1	8	1.1	42	2.4	159
New Jersey	443	9.6	19	0.4	89	1.8	101	1.1	32	0.9	260	3.0	945
New Mexico	73	7.9	5	0.5	13	1.4	22	1.2	5	0.7	36	2.0	154
New York	925	8.9	49	0.4	190	1.7	265	1.4	67	0.8	535	2.8	2031
Ohio	493	8.2	30	0.5	130	1.9	138	1.2	34	0.7	343	2.9	1168
Oklahoma	170	9.7	10	0.5	36	1.9	50	1.4	14	0.9	111	3.2	390
Oregon	137	7.7	9	0.4	36	1.8	56	1.6	10	0.6	118	3.3	366
Pennsylvania	568	8.5	39	0.5	157	1.9	158	1.2	45	0.8	430	3.2	1396
Rhode Island	42	7.3	3	0.4	16	2.4	16	1.4	5	0.9	31	2.8	111
South Carolina	209	9.8	12	0.5	44	2.0	47	1.2	15	0.9	156	3.8	482
Texas	1018	10.0	55	0.6	144	1.5	240	1.3	78	1.0	551	3.0	2086
Utah	59	6.2	3	0.3	12	1.4	18	1.1	4	0.5	32	1.9	128
Vermont	28	8.4	3	0.7	7	2.0	5	0.8	3	1.0	18	2.7	64
Washington	213	7.0	12	0.4	53	1.7	76	1.3	16	0.6	184	3.2	552
Wisconsin	211	7.7	13	0.4	53	1.7	50	0.9	17	0.7	170	3.1	513
West Virginia	110	10.9	8	0.6	22	1.9	31	1.5	11	1.1	69	3.3	250
Average annual total	10,846	8.9	601	0.5	2266	1.7	3018	1.3	828	0.8	7360	3.1	24,918
No. for 1998-2003	65,074		3604		13,597		18,105		4967		44,160		149,507

*Only carcinomas are included for cervical cancers. Only squamous cell carcinomas (SCCs) are included for vulvar, vaginal, penile, anal and oral cavity/oropharyngeal cancers. All histologies were microscopically confirmed.

†Data are from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program and meet high-quality data criteria. These registries cover approximately 83% of the US population. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population.

‡Anal cancers include SCCs coded to the rectum. Oral cavity and oropharyngeal cancers are limited to the subsites specified in Table 2.

§Indicates that the cell was suppressed because the average annual count was <3 during the 6-year period.

women, whereas men had higher rates of oral and oropharyngeal cancers. Men tended to be diagnosed with invasive anal and oral cavity/oropharyngeal SCCs at younger ages than women. White women had the highest rate of invasive anal SCC, whereas blacks had the highest rate among men.

Table 6 examines in situ vulvar, vaginal, penile, anal, and oral cavity/oropharyngeal SCCs by age,

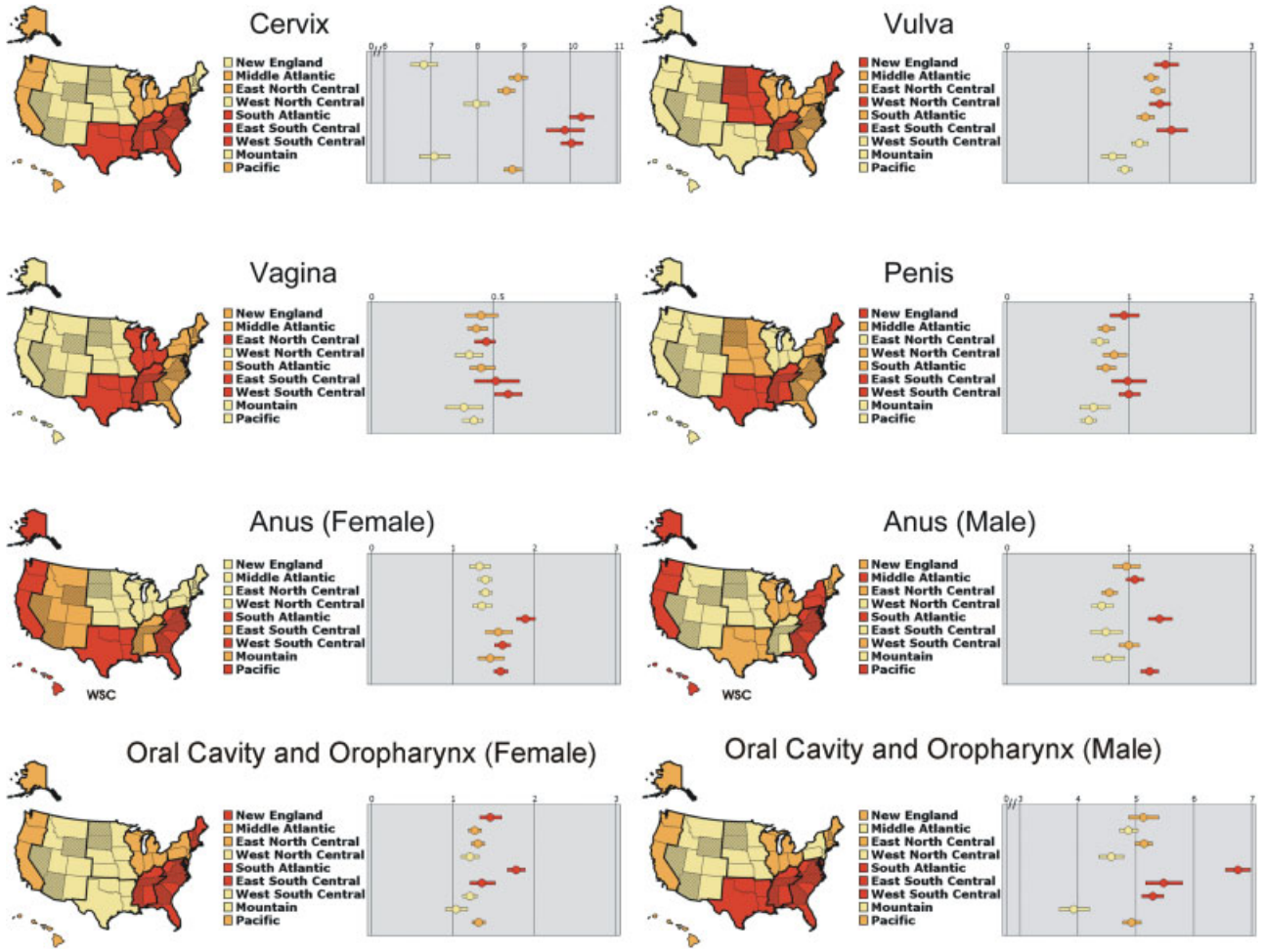

FIGURE 5. Rates of invasive human papillomavirus-associated cancers by US Census Division. Only carcinomas are included for cervical cancers. Only squamous cell carcinomas (SCCs) are included for vulvar, vaginal, penile, anal and oral cavity/oropharyngeal cancers. All histologies were confirmed microscopically. Data are from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program and meet high-quality data criteria. These registries cover approximately 83% of the US population. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population. Note that the rate scale varies by cancer site. These maps were developed by James Cucinelli (IMS, Inc.) and Dave Stinchcomb (National Cancer Institute) based on the micromaps design.

race, ethnicity, and region. There were 15,593 noncervical in situ cancers that were considered to be HPV-associated from 1998 through 2003; 11,379 of those cancers were diagnosed in women, and 4214 were diagnosed in men. Generally, the patterns were similar to those observed for invasive disease.

Data Limitations

Cancer registry data do not contain information on the presence of HPV in tumor tissue. To minimize this limitation, we chose sites with an established HPV association and limited our analyses by histology and microscopic confirmation. Case-level data on other risk factors for these cancers, such as smoking and high parity, also are not available from cancer registries. We excluded registries that did not meet USCS standards for data quality and timeliness for any year during 1998 through 2003; thus, these data do not cover the entire population of the United States. A lower proportion of the population was included from the South (63%) than from any other US Census region because of the exclusion of more registries from this region. However, an analysis of cervical cancer that included more states from the South but was limited to more recent years revealed that the rates in this region remained significantly increased compared with other regions.[45] Thus, we believe that differences between the South and other

TABLE 5
Invasive Cancers Associated With Human Papillomavirus by Selected Characteristics: United States, 1998-2003*,†

	Female										Male					
	Cervix		Vulva		Vagina		Anus		Oral Cavity and Oropharynx		Penis		Anus		Oral Cavity and Oropharynx	
Feature	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%
Overall	8.9	100	1.7	100	0.5	100	1.5	100	1.3	100	0.8	100	1.0	100	5.2	100
Median age, y	47		69		70		62		64		68		57		58	
Age, y																
<30	1.4	6.3	<0.1	0.7	<0.1	0.5	<0.1	0.3	<0.1	0.5	<0.1	0.4	<0.1	0.6	<0.1	0.2
30-39	13.5	22.1	0.7	5.5	0.1	3.4	0.4	3.7	0.3	2.7	0.2	3.7	0.6	9.7	0.7	2.0
40-49	15.8	26.3	1.8	14.2	0.4	10.5	1.9	17.8	1.2	12.4	0.5	9.6	1.4	23.3	5.8	18.3
50-59	14.5	18.0	2.5	14.6	0.7	15.6	3.3	22.8	2.9	23.3	1.1	16.9	1.9	22.6	14.8	33.6
60-69	14.8	12.5	3.7	15.1	1.3	19.3	4.3	20.1	4.8	26.0	2.5	24.4	2.6	19.6	18.0	25.6
≥70	12.3	14.8	8.4	49.9	2.3	50.7	5.2	35.3	4.7	35.3	4.5	44.9	3.1	24.2	13.1	20.3
Race																
White	8.4	79.1	1.8	90.7	0.4	82.2	1.6	89.9	1.3	87.1	0.8	88.3	1.0	85.6	5.1	86.5
Black	12.6	14.5	1.3	6.9	0.7	14.0	1.3	7.8	1.5	10.5	0.8	7.8	1.2	11.4	6.8	11.1
API	8.3	3.9	0.4	0.7	0.3	2.0	0.4	1.0	0.5	1.3	0.4	1.4	0.2	0.7	1.7	1.1
Ethnicity																
Non-Hispanic	8.4	84.2	1.8	95.0	0.4	90.9	1.5	92.8	1.4	96.0	0.8	87.3	1.0	93.4	5.3	94.8
Hispanic	14.2	15.8	1.3	5.0	0.6	9.1	1.5	7.2	0.7	4.0	1.3	12.7	0.8	6.6	3.6	5.2
Stage‡																
Localized	4.7	52.3	1.1	62.4	0.2	44.4	0.8	51.2	0.3	22.4	0.5	62.4	0.5	53.7	0.8	15.3
Regional§	2.8	31.5	0.5	28.2	0.2	42.0	0.4	25.6	0.9	70.2	0.2	27.7	0.3	25.1	4.0	77.9
Distant	0.8	9.1	0.1	3.4			0.1	8.2			0.0	3.2	0.1	6.5		
Unstaged	0.6	7.1	0.1	5.9	0.1	13.6	0.2	15.0	0.1	7.4	0.1	6.7	0.2	14.7	0.4	6.8
Region																15.3
Northeast	8.4	22.3	1.8	26.2	0.4	23.7	1.4	21.9	1.3	23.6	0.9	24.2	1.0	23.8	4.9	22.0
Midwest	8.5	25.5	1.9	29.6	0.4	26.9	1.4	24.9	1.3	26.0	0.8	26.5	0.8	22.1	5.0	26.1
South	10.1	30.6	1.7	26.6	0.5	30.4	1.7	30.9	1.5	30.0	0.9	31.4	1.1	29.4	5.9	31.3
West	8.5	21.6	1.4	17.5	0.4	19.0	1.6	22.3	1.3	20.3	0.7	18.0	1.1	24.7	4.7	20.5

API indicates Asian/Pacific Islander.

*Data are from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results (SEER) Program and meet high-quality data criteria (see Table 4 for a list of registries). These registries cover approximately 83% of the population for the period studied.

†The data represent incidence rates and % distribution of cases unless otherwise specified. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population. Hispanic origin is not mutually exclusive from race categories (white, black, API). Rates could not be calculated for individuals of other or unknown race/ethnicity; thus, percentage distributions for race categories do not total 100%. Only microscopically confirmed cervical carcinomas and squamous cell carcinomas (SCCs) for other sites were examined.

‡SEER Summary Stage 1977 was used for cancers diagnosed from 1998 through 2000, and SEER Summary Stage 2000 was used for cancers diagnosed from 2001 through 2003. Stage for vagina and some oral cavity and oropharyngeal subsites are not considered comparable between these staging schemes, so regional and distant stage were combined to make the 2 schemes comparable.

§Regional and distant stage have been combined for cancers of the vagina and oral cavity/oropharynx.

regions are representative and are not an artifact of lower population coverage in the South. There are several limitations concerning the collection of in situ tumors that may have influenced our analyses. Although NPCR and SEER require reporting of in situ tumors, the quality of the data is not as consistent as the quality of the data for invasive cancers.[31]

In summary, this *Supplement* represents our first attempt to assess the overall burden of HPV-associated cancers in the United States. The available data cover the majority of the US population. This comprehensive analysis sets the stage for monitoring the impact of the HPV vaccine and potential temporal and geographic changes in HPV-associated disease burden. By using population-based cancer registries, the ABHACUS *Supplement* has achieved its main purposes: assessing the current (prevaccine) burden of HPV-associated cancers and providing a baseline for monitoring future trends in these cancers. Histology categories are described comprehensively and are based on current knowledge. In addition, the focus on histologic-specific analyses and rare cancer sites should benefit planning for future etiological and clinical studies, as well as vac-

TABLE 6
In Situ Cancers Associated With Human Papillomavirus by Selected Characteristics: United States, 1998-2003*,†

	Female								Male					
	Vulva		Vagina		Anus		Oral Cavity and Oropharynx		Penis		Anus		Oral Cavity and Oropharynx	
Feature	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%
Overall	1.2	100	0.1	100	0.2	100	<0.1	100	0.4	100	0.2	100	0.1	100
Median age, y	49		59		53		65		63		45		60	
Age, y														
<30	0.2	5.6	<0.1	4.0	—§	—§	—§	0.7	<0.1	3.4	0.0	3.9	—§	0.3
30-39	1.4	17.0	0.1	8.7	0.1	12.0	—§	4.3	0.2	7.8	0.4	29.7	—§	1.4
40-49	2.4	28.4	0.2	19.8	0.3	27.4	<0.1	11.4	0.4	14.4	0.4	32.5	0.1	14.9
50-59	2.4	22.1	0.2	19.3	0.4	22.5	<0.1	16.4	0.6	17.6	0.3	17.6	0.1	30.6
60-69	2.1	12.7	0.3	18.6	0.4	15.8	0.1	32.1	1.2	22.1	0.2	8.8	0.2	29.5
≥70	1.7	14.1	0.4	29.6	0.3	21.1	0.1	35.0	1.7	34.6	0.2	7.6	0.2	23.4
Race														
White	1.3	86.6	0.1	83.2	0.2	87.0	<0.1	83.6	0.4	86.9	0.2	81.0	0.1	86.2
Black	0.9	7.9	0.1	9.0	0.1	8.5	<0.1	12.9	0.3	5.8	0.3	13.8	0.1	10.7
API	0.1	0.5	—§	1.3	—§	—§	—§	2.1	0.1	1.2	—§	—§	—§	1.4
Ethnicity														
Non-Hispanic	1.31	95.3	0.1	92.9	0.2	94.7	<0.1	97.9	0.4	93.5	0.2	90.0	0.1	96.7
Hispanic	0.61	4.7	0.1	7.1	0.1	5.3	—§	2.1	0.3	6.5	0.2	10.0	—§	3.3
Region														
Northeast	0.9	17.1	0.1	19.2	0.2	23.4	<0.1	21.4	0.3	18.7	0.2	21.3	0.1	21.5
Midwest	1.4	30.2	0.1	30.5	0.2	24.7	<0.1	23.6	0.4	27.6	0.1	18.3	0.1	28.4
South	1.5	33.5	0.2	33.0	0.2	27.3	<0.1	31.4	0.4	24.9	0.2	29.9	0.1	28.9
West	1.0	19.2	0.1	17.4	0.2	24.6	<0.1	23.6	0.5	28.8	0.2	30.4	0.1	21.2

API indicates Asian/Pacific Islander.

*Data are from 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 (see Table 4 for a list of registries). These registries cover approximately 83% of the population for the period studied.

†The data represent incidence rates and % distribution of cases unless otherwise specified. Rates are per 100,000 persons and are age-adjusted to the 2000 US standard population. Hispanic origin is not mutually exclusive from race categories (white, black, API). Rates could not be calculated for individuals of other or unknown race/ethnicity; thus, the percentage distribution for race categories does not total 100%. In situ cervical cancer is no longer reportable and, thus, was not included. Only microscopically confirmed squamous cell carcinomas (SCCs) were examined.

‡This article and others in the current supplement that examined National Program of Cancer Registries/Surveillance, Epidemiology, and End Results excluded code 8077/2 (intraepithelial neoplasia 3) for in situ vaginal, vulvar, and anal cancers.

§Indicates that the cell was suppressed because of a count <16 during the 6-year period.

cine interventions, by providing a critical baseline assessment of the population burden of HPV-associated malignancy. It is our hope that, with current population-based cancer registries covering 100% of the US population since 1998, we will be in a position to monitor changes in the burden of in situ and invasive HPV-associated cancers with more accuracy and precision.[21,48]

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