





Incidence Trends and Burden of Human Papillomavirus-Associated Cancers Among Women in the United States, 2001-2017

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Abstract

Human papillomavirus (HPV)-associated anal and oropharyngeal cancer incidence has increased in recent years among US women. However, trends in incidence and burden (annual number of cases) of noncervical HPV-associated cancers relative to cervical cancer remain unclear. Using the 2001-2017 US cancer statistics dataset, we evaluated contemporary incidence trends and burden (annual number of cases) of HPV-associated cancers among women by anatomic site, race or ethnicity, and age. Overall, cervical cancer incidence plateaued among White women but continued to decline among Black and Hispanic women. Anal cancer incidence surpassed cervical cancer incidence among White women aged 65-74 years of age (8.6 and 8.2 per 100 000 in 2015) and 75 years or older (6.2 and 6.0 per 100 000 in 2014). The noncervical cancer burden ($n = 11\,871$) surpassed the cervical cancer burden ($n = 11\,527$) in 2013. Development of efficacious screening strategies for noncervical cancers and continued improvement in cervical cancer prevention are needed to combat HPV-associated cancers among women.

Human papillomavirus (HPV) primarily causes 5 (cervical, anal, oropharyngeal, vaginal, and vulvar) squamous epithelial cancers among women. While widely implemented screening programs have led to a decline in cervical cancer incidence (1), a marked increase in anal and oropharyngeal cancer incidence occurred in the last 2 decades in the United States, particularly among White women and those aged 50 years and older (2,3). As a result, the incidence and the number of new cancers (ie, burden) of these noncervical cancers may have surpassed cervical cancer in certain age and race or ethnic groups; however, such evidence is currently lacking.

We analyzed the 2001-2017 US Cancer Statistics dataset (4). HPV-associated cancers were identified based on International Classification of Diseases for Oncology-3 site and histology codes

(5,6). SEER*Stat version 8.3.5 was used to calculate incidence rates. JoinPoint software version 4.7.0 was used to estimate piecewise-log-linear trends and derive annual and average annual percentage changes (APCs and AAPCs) (7). P values were estimated using the permutation distribution of the test statistic (statistical significance at $P < .05$, 2-sided). Cancer burden (ie, incident cases) was a function of population size and composition. Detailed methods are available in the [Supplementary Methods](#) (available online).

During 2001-2017, 378 629 HPV-associated cancer cases were diagnosed among women nationally. Case distribution and incidence rates by age, race or ethnicity, and year of diagnosis are presented in [Supplementary Table 1](#) (available online).

Overall, during 2001-2012, cervical cancer incidence declined (APC = -1.5% , 95% confidence interval [CI] = -1.9% to -1.1%)

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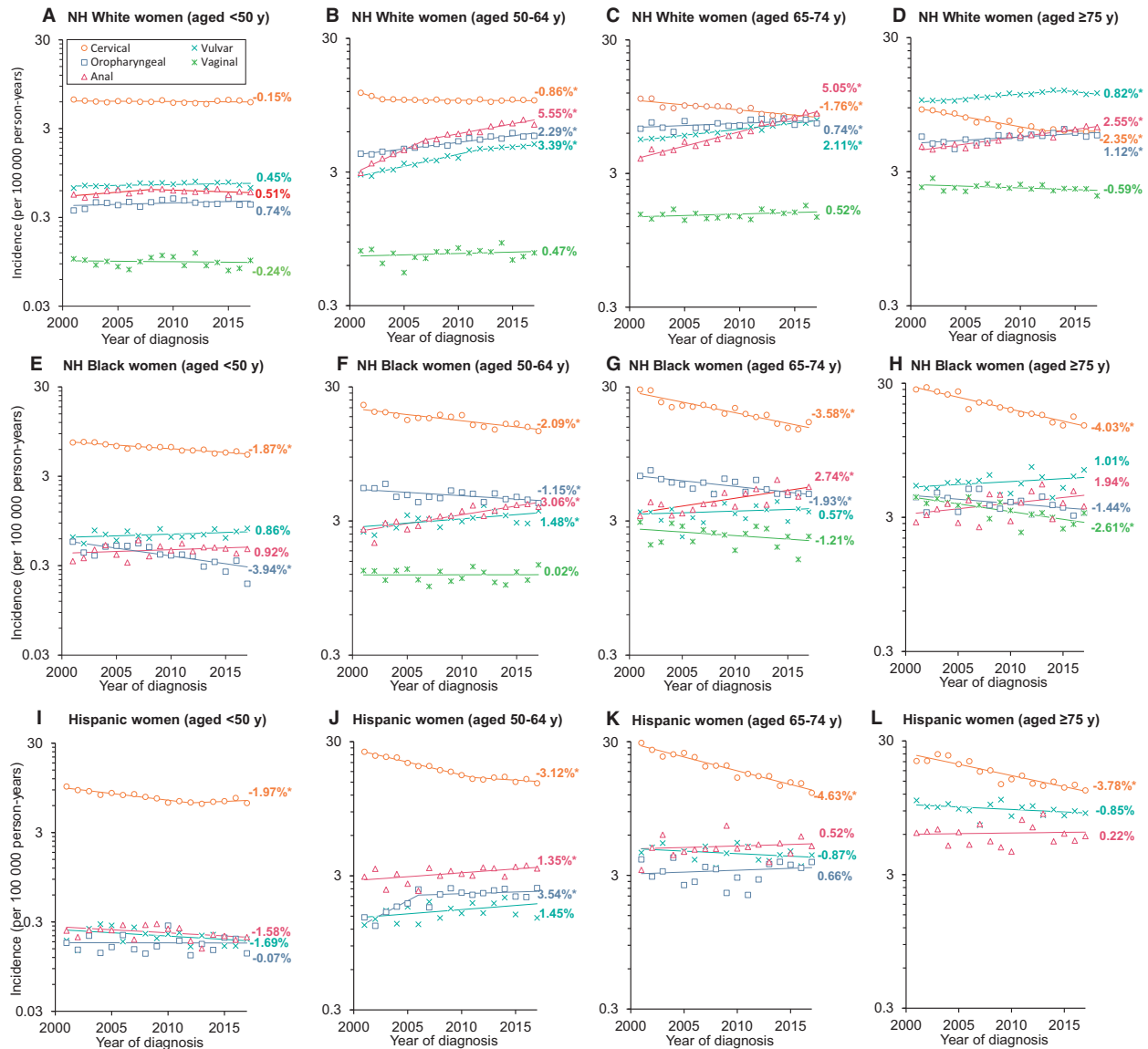


Figure 1. Trends in the annual incidence rates of cervical, anal, vulvar, vaginal, and oropharyngeal cancers among women according to age at diagnosis and race/ethnicity: National Program of Cancer Registries and Surveillance Epidemiology, and End Results program (2001-2017). Data markers represent the observed incidence rates (cases per 100000 person-years). Panels A, B, C, and D show cervical, anal, vulvar, vaginal, and oropharyngeal cancer incidence trends among White women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. Panels E, F, G, and H show cervical, anal, vulvar, vaginal, and oropharyngeal cancer incidence trends among Black women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. Panels I, J, K, and L show cervical, anal, vulvar, vaginal, and oropharyngeal cancer incidence trends among Hispanic women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. Rates are age-adjusted to the 2000 US standard population. NH = non-Hispanic. * $P < .05$.

and then plateaued during 2012-2017 (APC = 0.4%, 95% CI = -1.0% to 1.8%). In contrast, anal cancer incidence continued to rise (APC₂₀₀₁₋₂₀₀₉ = 4.1%, 95% CI = 3.2% to 5.0%; APC₂₀₀₉₋₂₀₁₇ = 2.0%, 95% CI = 1.3% to 2.7%), whereas vulvar cancer incidence stabilized after an initial increase (APC₂₀₀₁₋₂₀₁₂ = 1.7%, 95% CI = 1.4% to 2.0%; APC₂₀₁₂₋₂₀₁₇ = 0%, 95% CI = -0.9% to 0.9%) (Supplementary Figure 1, A; Supplementary Table 2, available online). After an initial increase in oropharyngeal cancer, incidence declined albeit the change was not statistically significant (APC₂₀₀₁₋₂₀₁₅ = 1.0%, 95% CI = 0.7% to 1.3%; APC₂₀₁₅₋₂₀₁₇ = -3.3%, 95% CI = -9.2% to 2.9%); no statistically significant change occurred in vaginal cancer incidence over time. The noncervical HPV-associated cancer burden ($n=11871$) surpassed the cervical cancer burden ($n=11527$) in 2013

(Supplementary Table 1; Supplementary Figure 2, B available online).

Among White women younger than 50 years, no statistically significant change in cervical cancer incidence occurred from 2001 to 2017 (AAPC = -0.2%, 95% CI = -0.5% to 0.2%). Among those aged 50-64 years, after an initial decline (APC₂₀₀₁₋₂₀₀₃ = -6.0%, 95% CI = -10.3% to -1.5%), cervical cancer incidence stabilized in recent years (APC₂₀₀₃₋₂₀₁₇ = -0.1%, 95% CI = -0.3% to 0.1%) (Figure 1, A). Among age groups 50-64 years, 65-74 years, and 75 years and older, a statistically significant increase in anal, oropharyngeal, and vulvar cancer incidence occurred (Figure 1, B-D). Notably, with an annual increase of 5.1% (95% CI = 4.6% to 5.5%) in those aged 65-74 years and 2.6% (95% CI = 2.1% to 3.0%) among those aged 75 years and older, anal cancer

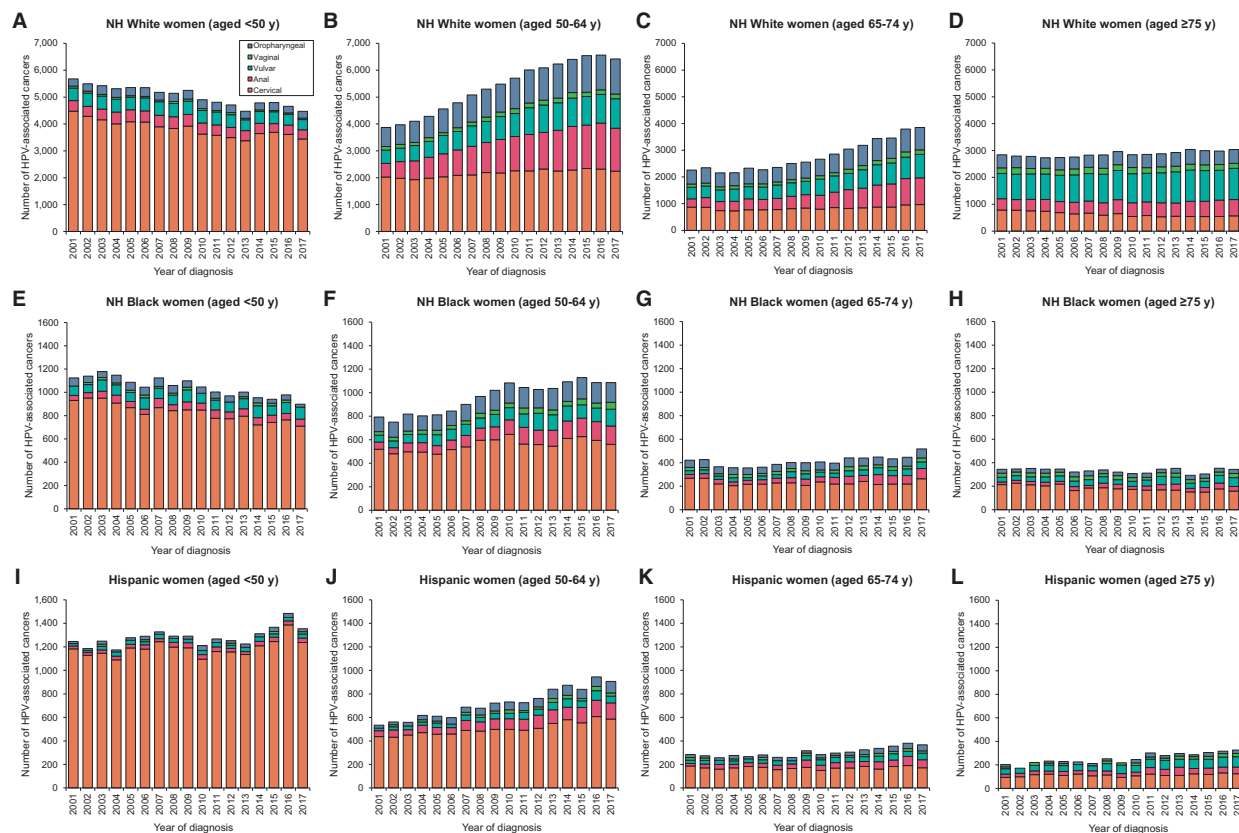


Figure 2. Burden (annual number of cases) of cervical, anal, vulvar, vaginal, and oropharyngeal cancers among women according to age at diagnosis at race or ethnicity: National Program of Cancer Registries and Surveillance Epidemiology, and End Results program (2001-2017). Vertical bars represent the burden (annual number of cases). Panels A, B, C, and D show cervical, anal, vulvar, vaginal, and oropharyngeal cancer burden among White women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. Panels E, F, G, and H show cervical, anal, vulvar, vaginal, and oropharyngeal cancer burden among Black women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. Panels I, J, K, and L show cervical, anal, vulvar, vaginal, and oropharyngeal cancer incidence burden among Hispanic women younger than 50 years, aged 50-64 years, 65-74 years, and 75 years and older, respectively. HPV = human papillomavirus; NH = non-Hispanic.

incidence (8.6 and 6.2 per 100 000) surpassed cervical cancer incidence (8.2 and 6.0 per 100 000) in 2016 and 2014, respectively. Across 2001-2017, vulvar cancer incidence was higher than other HPV-associated cancers in White women aged 75 years and older. Although a statistically significant decline in cervical cancer incidence across all age groups (<50 years, 50-64 years, 65-74 years, ≥75 years) occurred in Black (AAPCs = -1.9%, -2.1%, -3.6%, and -4.0%, respectively) and Hispanic (AAPCs = -2.0%, -3.1%, -4.6%, and -3.8%, respectively) women, cervical cancer incidence continued to remain higher than other HPV-associated cancers (Figure 1, E-L). Detailed findings, including APCs and AAPCs, are shown in Supplementary Table 2 (available online).

Cervical cancer burden increased in White women aged 50-74 years, Black women aged 50-64 years, and across all ages among Hispanic women (Figure 2). The annual number of anal, oropharyngeal, vaginal, and vulvar cancer cases increased in all age and racial or ethnic groups. Notably, anal cancer burden surpassed cervical cancer burden in White women aged 65-74 years and 75 years and older. Vulvar cancer continued to remain the most common HPV-associated cancer among White women aged 75 years and older. Among other race or ethnic groups, cervical cancer continues to remain the leading HPV-associated cancer.

The collective burden of HPV-associated cancers has increased among US women. This finding reflects recent

stabilization in cervical cancer and concurrent increases in oropharyngeal, anal, and vulvar cancer incidence, particularly among non-Hispanic White women.

Plateauing of cervical cancer incidence may have resulted from the recent decline in cervical cancer screening rates (8-10). The rise in anal and oropharyngeal cancers is possibly due to the increased acquisition of HPV infection attributable to changes in sexual behaviors (2,11,12). However, the role of HPV infection may be limited in the rising rates of vulvar cancer given the low observed prevalence of HPV DNA in vulvar cancer tissues among elderly women (13). Although these factors explain the changes in incidence, the increasing burden may be attributable to the population growth of women aged 50 years and older (14).

No evidence-based screening recommendations exist for non-cervical HPV-associated cancers. Because of the current inability to detect HPV-induced precancers and insufficient diagnostic technology to detect early cancers, oropharyngeal cancer screening is not possible (15). Similar to cervical cancer, anal and vulvar cancers have precancerous lesions that are amenable to screening using cytology or HPV testing, and diagnostic biopsies can also be obtained while performing high-resolution anoscopy or pelvic examination. Age is considered an important factor for defining cancer-screening thresholds for screening initiation and termination. Comparable anal and vulvar cancer

incidence with cervical cancer incidence among certain groups, and, as recently described by Tota et al. (16), the satisfaction of all criteria set forth by the World Health Organization (Wilson and Jungner's criteria) (17) for the implementation of cancer screening make these diseases suitable targets for age-based screening evaluation. However, given that population-wide screening may still not be cost-effective, further research is needed to identify groups at elevated risk for these cancers (18–24).

The HPV vaccine may reverse the rising HPV-associated cancer burden in the future (25,26). However, the lack of improvement in HPV vaccination coverage in recent years (27,28), the growing sentiment of HPV vaccine hesitancy and ignorance (29–31), and the anticipated population growth of women aged 65 years and older (14) imply that HPV-associated cancer burden will continue to increase for several decades. Under such circumstances, the implementation of effective screening algorithms for birth cohorts who may not benefit from HPV vaccination becomes increasingly crucial.

The strength of this study is the use of nationwide, high-quality data. A limitation is that cancers were classified based on histologic criteria and not the actual assessment of individual tumors for the presence of HPV DNA. Therefore, a large fraction of cancer cases with tumor sites with a low-HPV DNA detection rate (eg, vulva) may not be HPV associated.

Our findings highlight the need to evaluate optimal age-based screening algorithms for noncervical HPV-associated cancers. Continued improvement in cervical cancer prevention is also crucial.

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Data Availability

The US Cancer Statistics Databases (National Program of Cancer Registries and Surveillance Epidemiology and End Results) are publicly available at <https://www.cdc.gov/cancer/uscs/public-use/about.htm>. Documentation for data use is also available at <https://www.cdc.gov/cancer/uscs/public-use/us/index.htm>.

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