# Vulvar Cancer Incidence in the United States and its Relationship to Human Papillomavirus Vaccinations, 2001–2018

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## ABSTRACT

The human papillomavirus (HPV) vaccine was indicated for the prevention of vulvovaginal cancers in 2008, but its impact on the incidence of vulvar cancers within the US is unknown. To determine this, we conducted a secondary analysis of 88,942 vulvar cancer cases among women 20+ years old using the US Cancer Statistics 2001–2018 databases. Data were stratified by tumor behavior (*in situ* or invasive), age (20–44, 45–64, 65+ years old), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic), and US census region (Northeast, South, Midwest, West), and incidence rates and average annual percentage changes (AAPC) were calculated by group. Reversing previous trends, the incidence of vulvar carcinoma *in situ* significantly decreased between 2001 and 2018 among women from all age groups, races/ethnicities, and regions (combined AAPC, −4.3; 95% confidence interval (CI), −4.7 to −3.8). The incidence of invasive vulvar squamous cell carcinoma decreased significantly among 20- to 44-year-old women (AAPC, −0.8; 95% CI, −1.3 to −0.3), but significantly increased among those 45 to 64 (AAPC, 2.3; 95% CI, 1.8–2.8) and 65+ years old (AAPC, 1.2; 95% CI, 1.1–1.4). Regardless of tumor behavior, incidence was highest among non-Hispanic Whites and the Midwest region. Overall, the significant declines in vulvar carcinoma *in situ* among all ages, as well as invasive vulvar cancer among younger women, are encouraging and complement other recent data suggesting HPV vaccinations are already reducing anal and cervical cancer incidence. Over time, further declines in vulvar carcinoma incidence are likely as uptake and completion rates of the HPV vaccine increase in the US.

**Prevention Relevance:** We found evidence that HPV vaccinations likely contributed to a decrease in the incidences of vulvar carcinoma *in situ* and invasive vulvar carcinoma among 20- to 44-year-old women between 2001 and 2018. Our data add to the growing evidence that HPV vaccinations are reducing the incidence of HPV-related anogenital cancers.

## Introduction

Between 1999 and 2015, the incidence of invasive squamous cell carcinomas of the vulva (VSCC) within the US increased at a rate of 1.3% per year (1–3). VSCC is commonly associated with lichen sclerosis and typically diagnosed in older women (4, 5). Up to 40% of VSCC cases are associated with human papillomavirus (HPV) infection (6, 7). In contrast, carcinoma of the vulva *in situ* (VIS), which may include high grade vulvar intraepithelial neoplasia, (8) is primarily diagnosed in younger women (4, 5) and as many as 80% of cases are associated with HPV infection, predominately types 16 and 18 (6). VIS rates increased from 1973 to 2000, (9) but subsequent data on incidence rates (IR) have not been reported.

Both *in situ* and invasive vulvar cancers disproportionately affect non-Hispanic white women for reasons unknown (1, 2). Data from previous studies suggest that black women with certain vulvar cancer subtypes (i.e. basaloid and warty) linked to HPV infection are also at increased risk for VIS (10). However, the relationship between race, HPV infection, vulvar cancer subtype, and VIS incidence is currently not clear.

In 2006, the FDA approved a quadrivalent HPV vaccine for cervical cancer prevention in women 9 to 26 years old and subsequently, the Advisory Committee on Immunization Practices began recommending the routine delivery of the vaccine to 11- to 12-year-old females. The FDA later expanded their indication to include the prevention of vulvovaginal and oropharyngeal cancers in 2008 and 2020, respectively. HPV vaccine uptake among US adolescents has increased over time and up to date vaccine coverage typically increases with adolescent age (11). As of 2020, the CDC estimates that approximately 50% of adolescent males and 60% of adolescent

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Cancer Prev Res 2022;15:777–84

**doi:** 10.1158/1940-6207.CAPR-22-0086

females ages 13 to 17 are up to date on the HPV vaccine. To determine whether HPV vaccinations have had any impact on the incidence of VIS or invasive VSCC, recent data on the incidence trends of these cancers among US women are needed. We analyzed data from the US Cancer Statistics database, which covers 98% of the US population, to examine and compare VIS and invasive VSCC incidence trends between 2001 and 2018. We also conducted analyses to determine if there was a significant change in trends of average annual IRs during this interval. In addition, we examined rates by age group, race/ethnicity, and US region of residence to better understand the impact of the HPV vaccines on VIS and VSCC rates among women from diverse backgrounds.

## Materials and Methods

### Data sources

We used 2001–2018 population-level data from the National Program of Cancer Registries (NPCR) data set and the NCI's Surveillance, Epidemiology, and End Results (SEER) Program public data sets (12). These data sets include cancer incidence data from central cancer registries reported to NPCR in 46 states, the District of Columbia, and Puerto Rico (13) and to SEER in 4 states. The 2001–2018 registry data that met the US Cancer Statistics publication criteria covered 98% of the United States population. The Institutional Review Board at The University of Texas Medical Branch, Galveston, TX determined that our data analyses were not considered human subject research.

### Case definitions

Vulvar carcinomas were identified using site codes C51.0–51.9 as per the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Data were filtered for squamous cell carcinomas only using histology codes 8050–8076, 8083–8084, and 8123–8124, then separated into vulvar carcinoma *in situ* (behavior code = 2) and invasive (behavior code = 3) VSCC cases. Histology code 8077, "squamous intraepithelial neoplasia, high-grade", was additionally included among VIS cases as per ICD-0-3 recommendations (14).

### Demographic characteristics

Our analyses included a total of 88,942 women ≥20 years old and diagnosed with VIS/VSCC from 2001 to 2018. Patient age was categorized as 20–44, 45–64, or 65+ years old. Racial/Ethnic groupings were Non-Hispanic White, Non-Hispanic Black, and Hispanic as identified via the North American Association of Central Cancer Registries Hispanic/Latino Identification Algorithm (NHIA; ref. 15). Other races/ethnicities were excluded due to insufficient cases. We used the four US census regions (Northeast, Midwest, South, and West) to classify region of residence.

### Statistical analyses

Average annual rates per 100,000 population were age-adjusted (using 19 age groups) by the direct method to the 2000 US standard population (16). Corresponding 95% confidence intervals (CI) were calculated as modified gamma intervals (17). Annual percentage changes (APC) for each subgroup were calculated using the weighted least squares method. Population estimates for rate denominators were a modification of annual county population estimates by age, sex, bridged race, and ethnicity produced by the US Census Bureau in collaboration with CDC and with support from NCI (18). Changes in 2001–2018 IRs were calculated using joinpoint regression (19), with up to 3 joinpoints being allowed. The trend of the line segment was used to quantify the APC. The average annual percentage change (AAPC) for 2001–2018 was calculated using a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the length of each segment over the interval (20). All statistical analyses were performed using SEER*Stat v8.3.9 (21). A two-tailed $t$ test was used to determine if any calculated AAPC was significantly different from 0 using a $P$ value cutoff of $< 0.05$.

### Data availability

The data analyzed in this study were obtained from the publicly available US Cancer Statistics 2001–2018 database www.cdc.gov/cancer/uscs/public-use.

## Results

Overall, VIS incidence significantly decreased (AAPC, −4.3; 95% CI, −4.7 to −3.8) and overall invasive VSCC incidence significantly increased (AAPC, 1.3; 95% CI, 1.1–1.6) among US women from 2001 to 2018 (**Table 1**). VIS incidence was lowest among vaccine-eligible women between 20 and 44 years of age (IR, 0.8; 95% CI, 0.8–0.9) during the 2001–2018 period, and higher among women 45 to 64 years old (IR, 1.9; 95% CI, 1.9–2.0) than among women 65 years old or more (IR, 1.5; 95% CI, 1.5–1.5). Overall, the average annual VIS IRs significantly decreased over time for all three age groups: (20–44 AAPC, −6.5; 95% CI, −7.0 to −5.9; 45–64 years old AAPC, −3.6; 95% CI, −4.2 to −3.1; 65+ AAPC, −2.2; 95% CI, −2.9 to −1.5) from 2001 to 2018 (**Fig. 1**). Invasive VSCC incidence was highest among women 65 years or older from 2001 to 2018 (IR, 8.2; 95% CI, 8.1–8.3), followed by women 45 to 64 years old (IR, 3.3; 95% CI, 3.3–3.3) and women 20 to 44 years old (AAPC, 0.7; 95% CI, 0.7–0.7; **Table 1**). During the 2001–2018 period, invasive VSCC incidence significantly decreased among 20- to 44-year-old women (AAPC, −0.8; 95% CI, −1.3 to −0.3) but increased significantly among women 45 to 64 years old (AAPC, 2.3; 95% CI, 1.8–2.8) and 65 years old or more (AAPC, 1.2; 95% CI, 1.1–1.4; **Fig. 1**). To determine if the HPV vaccines might have impacted VIS or invasive VSCC incidence among vaccine-eligible women (20–44 years old) from 2001 to 2018, we used joinpoint regression modeling to detect any potential years marking a significant change in trends of average annual IRs. However, we did not detect any significant joinpoint between 2001 and 2018 in any age group for either *in situ* or invasive cases.

**Table 1.** Age-adjusted IR of *in situ* (VIS) and invasive vulvar carcinomas (VSCC) from 2001 to 2018, stratified by age group, race/ethnicity, or U.S. census region.

| Characteristics | *In situ* (VIS) | | Invasive (VSCC) | |
|---|---|---|---|---|
| | Cases no. (%) | IR (95% CI) | Cases no. (%) | IR (95% CI) |
| Overall IR[a] | 26,071 (29.3 %) | 1.3 (1.3–1.3) | 62,871 (70.7 %) | 2.9 (2.8–2.9) |
| Age (y) | | | | |
| 20–44 | 6,976 (26.8) | 0.8 (0.8–0.9) | 5,836 (9.3) | 0.7 (0.7–0.7) |
| 45–64 | 13,115 (50.3) | 1.9 (1.9–2.0) | 22,937 (36.5) | 3.3 (3.3–3.3) |
| 65+ | 5,980 (22.9) | 1.5 (1.5–1.5) | 34,098 (54.2) | 8.2 (8.1–8.3) |
| Race/ethnicity | | | | |
| Hispanic | 1,318 (5.1) | 0.5 (0.5–0.6) | 3,308 (5.3) | 1.7 (1.7–1.8) |
| NH White | 22,235 (85.3) | 1.5 (1.5–1.5) | 54,260 (86.3) | 3.1 (3.1–3.1) |
| NH Black | 2,518 (9.7) | 1.0 (1.0–1.0) | 5,303 (8.4) | 2.1 (2.1–2.2) |
| Region | | | | |
| Northeast | 4,661 (17.9) | 1.2 (1.2–1.3) | 13,408 (21.3) | 3.0 (3.0–3.1) |
| Midwest | 6,705 (25.7) | 1.5 (1.5–1.5) | 16,123 (25.6) | 3.2 (3.1–3.2) |
| South | 10,680 (41.0) | 1.4 (1.4–1.4) | 23,182 (36.9) | 2.8 (2.8–2.9) |
| West | 4,025 (15.4) | 1.0 (0.9–1.0) | 10,158 (16.2) | 2.3 (2.3–2.3) |
| Overall AAPC[b] | **−4.3 (−4.7 to −3.8)[b]** | | **1.3 (1.1–1.6)[b]** | |

Abbreviation: NH, non-Hispanic.
[a]IRs were calculated as cases per 100,000 person-years and age-adjusted to the 2000 U.S. standard population.
[b]Bolded values are statistically significant ($P < 0.05$).

When data are stratified by race/ethnicity, VIS incidence was highest among non-Hispanic Whites (IR, 1.5; 95% CI, 1.5–1.5) and lowest among Hispanics (IR, 0.5; 95% CI, 0.5–0.6) from 2001 to 2018 (**Table 1**). Average annual VIS IRs significantly decreased over time for all groups analyzed (Hispanic AAPC, −4.7; 95% CI, −5.8 to −3.7; non-Hispanic White AAPC, −4.2; 95% CI, −4.6 to −3.7; non-Hispanic Black AAPC, −2.6; 95% CI, −3.7 to −1.6; **Fig. 2**). Invasive VSCC incidence was also

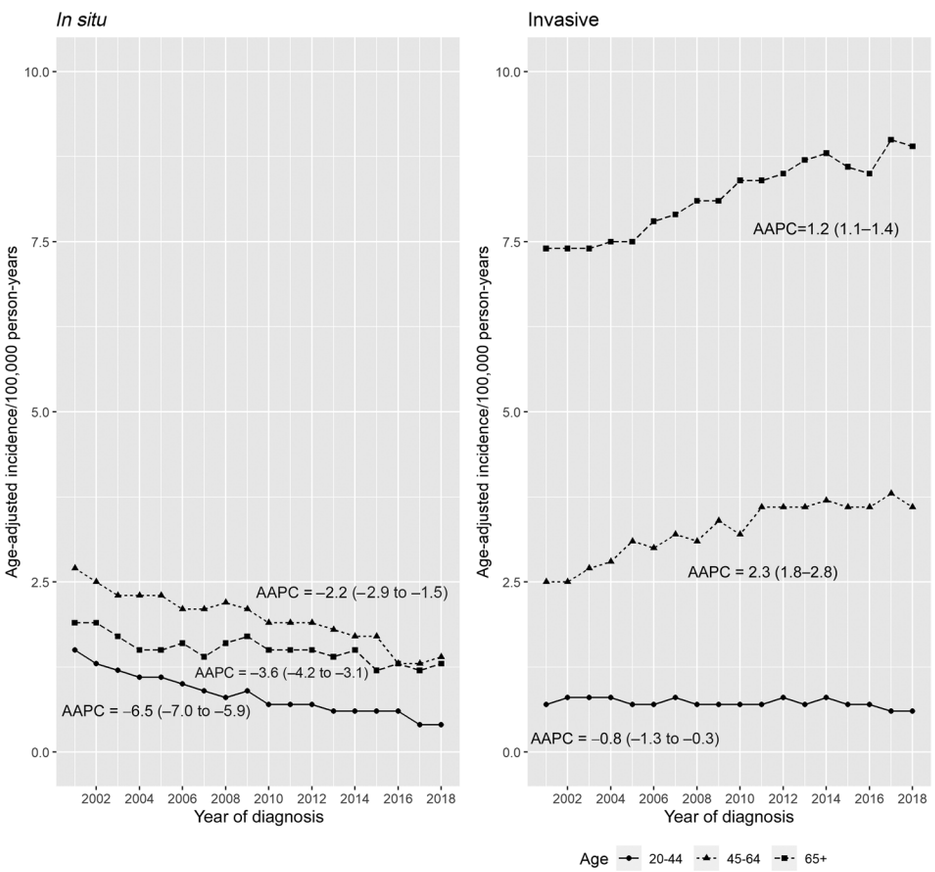


**Figure 1.**
Age-adjusted incidence of vulvar carcinomas from 2001 to 2018, stratified by tumor behavior and age group. Line graphs showing average age-adjusted annual IRs for vulva *in situ* (left) and invasive VSCC (right) in the United States from 2001 and 2018 for 20–44 (circle), 45–64 (triangle) and 65+-year-old (square) women. AAPC with 95% CIs is indicated for each group.

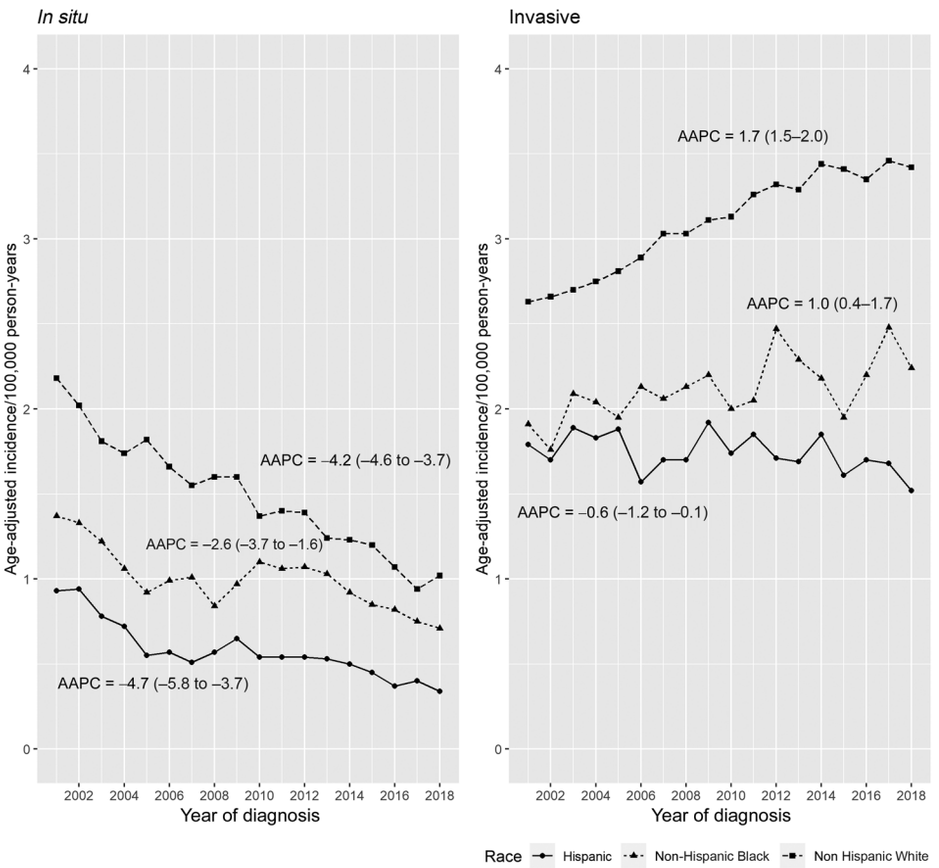


**Figure 2.**
Age-adjusted incidence of vulvar carcinomas from 2001 to 2018, stratified by tumor behavior and race/ethnicity. Line graphs showing average age-adjusted annual IRs for vulva *in situ* (left) and invasive VSCC (right) in the United States from 2001 and 2018 for Hispanic (circle), non-Hispanic Black (triangle), and non-Hispanic White (square) women. AAPC with 95% CIs is indicated for each group.

greatest among non-Hispanic Whites (IR, 3.1; 95% CI, 3.1–31) and lowest among Hispanics (IR, 1.7; 95% CI, 1.7–1.8) from 2001 to 2018 (**Table 1**). Whereas average annual VSCC incidence significantly decreased among Hispanics during this period (AAPC, −0.6; 95% CI, −1.2 to −0.1), trends of VSCC incidence significantly increased among non-Hispanic Whites (AAPC, 1.7; 95% CI, 1.5–2.0) and non-Hispanic Blacks (AAPC, 1.0; 95% CI, 0.4–1.7; **Fig. 2**).

Among the 4 US census regions, VIS incidence between 2001 and 2018 was greatest within the Midwest region (IR, 1.5; 95% CI, 1.5–1.5) and lowest within the West region (IR, 1.0; 95% CI, 0.9–1.0; **Table 1**). During the 2001–2018 period, average annual IRs of VIS significantly decreased in all 4 US census regions (Northeast AAPC, −2.0; 95% CI, −2.7 to −1.2; Midwest AAPC, −3.6; 95% CI, −4.3 to −2.9; South AAPC, −4.8; 95% CI, −5.3 to −4.2; West AAPC, −6.7; 95% CI, −7.3 to −6.0; **Fig. 3**). Invasive VSCC incidence was likewise greatest within the Midwest region (IR, 3.2; 95% CI, 3.1–3.2) and lowest within the West region (IR, 2.3; 95% CI, 2.3–2.3; **Table 1**). In contrast to VIS incidence however, average annual invasive VSCC incidence significantly increased within all 4 US census regions (Northeast AAPC, 1.5; 95% CI, 1.0–1.9; Midwest AAPC, 2.0; 95% CI, 1.7–2.4; South AAPC, 1.3; 95% CI, 1.0–1.6; West AAPC, 0.6; 95% CI, 0.0–1.1; **Fig. 3**).

## Discussion

This study is the first to provide a comprehensive analysis of both VIS and VSCC incidence within the US since the approval of the HPV vaccines in 2006. We found that VIS incidence is falling among US women regardless of age, race/ethnicity, or region of residence, reversing previous trends (9). Although VIS incidence dramatically fell from 2001 to 2018, the negative trend in IR was continuous across 2001–2018 without any significant change in slope. This suggests that while HPV vaccination probably had a positive impact after its introduction in 2006, other factors which caused the rates to decline before 2006 may have also contributed to declining VIS rates between 2006 and 2018. One possible contributor is decreasing cigarette usage within the US, (22) a significant risk factor for VIS (23, 24) that may not be related to invasive VSCC risk (25). Declining rates of high-grade cervical intraepithelial neoplasia (CIN) over time, due in part to HPV vaccination, (26) may have also impacted VIS incidence given that a previous diagnosis with CIN is a significant risk factor for VIS (27).

Consistent with previous analyses, we found that non-Hispanic white women demonstrated the highest IRs of VIS and VSCC (1, 2, 28, 29). In addition, the incidence of both VIS and VSCC were greatest within the Midwest region of the US, likely reflecting the higher proportion of non-Hispanic white

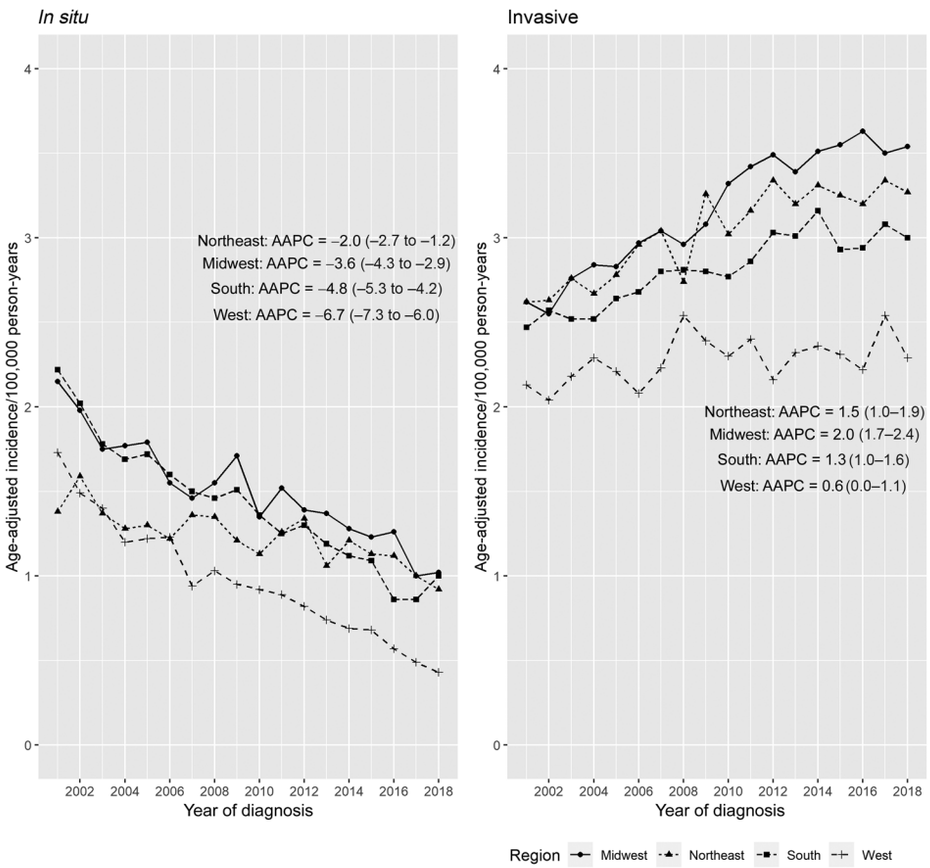


**Figure 3.**

Age-adjusted incidence of vulvar carcinomas from 2001 to 2018, stratified by tumor behavior and U.S. census region. Line graphs showing average age-adjusted annual IRs for vulva *in situ* (left) and invasive VSCC (right panel) in the United States from 2001 and 2018 in U.S. census regions, Northeast (triangle), Midwest (circle), South (square), and West (cross). AAPC with 95% CIs is indicated for each group.

women living in this region compared with others (30). One potential explanatory factor for higher rates among non-Hispanic Whites is the increased frequency of pubic hair removal among this population relative to other races/ethnicities as one study found that shaving the genital area was associated with VSCC (31–33). Another possible factor could be the greater prevalence of smoking among non-Hispanic Whites (22, 34).

The overall incidence of invasive VSCC continued to climb within the US, likely because this disease primarily affects older women, takes many years to evolve, and is typically not HPV-related. Accordingly, HPV vaccinations might not impact invasive VSCC IRs in the short term and any future effects are less likely to be as pronounced as those observed with cervical cancer (6, 35). The continued increase of invasive VSCC incidence we observed among older women could be related to changes in the recommended frequency of Pap smears. In 2003, the US Preventive Services Task Force lowered the recommended frequency of Pap smears for women 30 years and younger from annually to once every 2 years, and in 2012, further reduced the frequency to once every 3 years. In addition, the screening interval for women 30 to 65 years old increased from 3 to 5 years (with the addition of an HPV test) and testing was no longer recommended for women 21 years old or younger in the 2012 update. Routine Pap smears were not recommended for women 65 years or older throughout the 2001–2018 period (36). Although annual pelvic exams were still recommended by the American College of Obstetricians and Gynecologists during that period, the reduced recommended frequency of Pap smears might have led many women to see their providers less, potentially resulting in missed opportunities for early VIS/VSCC intervention (37). Another potential contributing factor for increasing invasive VSCC incidence among older women may be the increasing population of immunocompromised women (3, 38) and degree of immunosuppressive drug use within the US, (39) as immunocompromised individuals are more susceptible to vulvar cancers (40, 41).

This study's main strength is the utilization of high-quality, population-level data from 2001 to 2018 that represent 98% of the US population. As vulvar cancers are relatively rare, the longer time frame used for analysis afforded enough data to achieve statistical conclusions. By separately analyzing *in situ* and invasive cases of VSCC, we were able to better assess the impact of the HPV vaccines. However, HPV vaccination status is not reported in the US Cancer Statistics databases. We were therefore unable to examine the direct relationship of HPV vaccinations to vulvar cancer incidence and were limited to using age as the primary determinant of vaccine eligibility during the study period. HPV/HIV infection status and cancer

screening prevalence are not reported in these databases either, so we were also unable to determine whether these factors had any impact on IRs.

In summary, we observed that the incidence of VIS is falling among all US women regardless of age, race/ethnicity, or region of residence, reversing previous trends. Although additional time may be necessary to determine the overall impact of the HPV vaccines on vulvar cancer, these vaccines are indicated for the prevention of all HPV-related anogenital and oropharyngeal cancers and recent data have already linked HPV vaccinations to reductions in cervical (42–44) and anal cancers (45, 46). Data from the New Mexico PAP Registry (47) and HPV-IMPACT study (48) provide even further evidence that the vaccines may already be reducing the incidence of HPV-related cancers. However, vaccine uptake among the eligible US population has remained less than ideal, particularly within the Southern and Midwestern parts of the US where HPV up-to-date vaccinations rates have struggled to reach even 50% (49). Continued physician encouragement of HPV vaccinations is therefore critical to further reduce the incidence of all HPV-related cancers.

## Authors' Disclosures

E.T. Hawk reports grants from NCI; other support from Boone Pickens Distinguished Chair for Early Prevention of Cancer; and grants from Cancer Prevention & Research Institute of Texas during the conduct of the study. T. Hoang reports grants from Cancer Prevention and Research Institute of Texas during the conduct of the study. No disclosures were reported by the other authors.

## Authors' Contributions

**A.B. Berenson:** Conceptualization, resources, supervision, funding acquisition, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **M. Chang:** Conceptualization, resources, data curation, software, formal analysis, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **E.T. Hawk:** Writing–original draft, writing–review and editing. **L.M. Ramondetta:** Writing–original draft, writing–review and editing. **T. Hoang:** Formal analysis, writing–review and editing.

## Acknowledgements

A.B. Berenson presented this study at the American College of Obstetricians and Gynecologists annual meeting held in San Diego in May 2022. This work was supported by the Cancer Prevention and Research Institute of Texas (CPRIT, grants #PP190004, #PP200048, #PP200005, and #PP210020 to A.B. Berenson).

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Received February 21, 2022; revised April 13, 2022; accepted August 1, 2022; published first October 10, 2022.

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