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

Supplement to Cancer

Incidence of In Situ and Invasive Vulvar Cancer in the US, 1998–2003

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This supplement to Cancer was supported by Cooperative Agreement Number U50 DP424071-04 from the Centers for Disease Control and Prevention.

The findings and conclusions of this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Dr. Giuliano has acted as a member of the Speakers Bureau and Advisory Board for Merck and Company, and has received a research grant from the company.

Dr. Smith has received research grants, honoraria, and consulting fees from GlaxoSmithKline and Merck Corporation.

For more information on vulvar cancers, please visit www.cdc.gov/cancer/gynecologic

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BACKGROUND. The human papillomavirus (HPV) vaccine has been shown to prevent precancerous lesions of the vulva with the potential to prevent a percentage of vulvar cancers. To provide a baseline picture before HPV vaccine implementation, the authors described vulvar cancer epidemiology by age, race, ethnicity, and histology in the US.

METHODS. The authors examined incidence data from 39 population-based cancer registries that met high-quality data standards from 1998 to 2003, covering approximately 83% of the US population. They limited their analysis to in situ and invasive vulvar squamous cell carcinomas (SCCs). In situ vulvar cancers did not include vulvar intraepithelial neoplasia type 3 (VIN 3).

RESULTS. SCC accounted for 77% of in situ cases and 75% of invasive vulvar cancers, an annual burden of 1498 in situ and 2266 invasive SCC vulvar cancers. Greater than 75% of the in situ and invasive SCCs had no specific histology identified. White women had the highest rates of vulvar cancer; the incidence rates of invasive vulvar SCC among black women and Hispanic women were approximately one-third lower than for their counterparts (white women and non-Hispanic women, respectively). For women aged <50 years, the age-specific rates of invasive SCC were approximately the same among whites and blacks. Increases in rates after age 50 years, however, were noted to be more rapid among white than among black women.

CONCLUSIONS. Distinct age-specific incidence rate patterns of invasive vulvar SCC by race and ethnicity and the higher incidence rates observed among white women compared with women of other races and ethnicities were opposite to patterns noted for cervical cancer. Underestimations of the burden of in situ vulvar cancers were a result of the inability to examine VIN 3 in the authors’ data. Encouragement of cancer registries to report and submit VIN 3 data and more research on data quality will allow a thorough assessment of the impact of HPV vaccine by providing a basis for examining the true burden and quality of these precancerous vulvar tumors. Increased documentation of histologic subtypes in pathology reports and in cancer registry data can help differentiate the burden of HPV-associated types from non–HPV-associated types of vulvar cancers. Cancer 2008;113(10 suppl):2865–72. Published 2008 by the American Cancer Society.*

KEYWORDS: vulvar cancer, human papillomavirus, HPV vaccine, cancer registries.

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Vulvar cancer is a rare malignancy. Previous literature indicated that 40% of all vulvar cancers are attributed to human papillomavirus (HPV). Results from recently completed clinical trials demonstrate that a widely disseminated HPV vaccine has the potential to decrease the burden of HPV-associated precancers and cancers. In the US, vulvar cancer accounts for approximately 4% of cancers in the female reproductive organs and 0.6% of all cancers in women. Most vulvar neoplasms are squamous cell in origin. Squamous cell vulvar cancer is characterized by 3 patterns: warty, basaloid, or keratinizing. Warty and basaloid patterns are considered HPV-associated (nonkeratinizing). HPV-associated vulvar cancers are typically undifferentiated and multifocal, and they are found in women with a younger mean age at the time of diagnosis and with similar risk factors for cervical cancer. The precursor categories for the vulva similar to those of the cervix are known as vulvar intraepithelial neoplasia (VIN). However, the natural history of progression from precancer to invasive cancer of the vulva is less clear, and is not considered to be similar to the natural history of cervical cancer. In contrast, keratinizing vulvar tumors occur in older women and are more likely to be HPV-negative; they are preceded by vulvar precancers that are considered differentiated; and they appear with lichen sclerosis or epithelial hyperplasia. This type of invasive vulvar cancer is not considered to proceed through small transitional stages, as in intraepithelial neoplasia.

The International Agency for Research on Cancer (IARC) recently published a monograph synthesizing data from case series and case-control studies from 1994 through 2004. The IARC researchers concluded that HPV DNA prevalence among keratinizing vulvar cancers was <10%, compared with a 55% HPV DNA prevalence in basaloid and warty vulvar cancers. Furthermore, HPV type 16 (HPV–16) was the predominant HPV type in high-grade vulvar precancer and vulvar cancer, particularly basaloid and warty cancer. Among vulvar cancers, HPV–18, HPV–31, HPV–33, and HPV–45 were identified to play a smaller role than in cervical cancer. A systematic literature review of HPV type-specific distribution in vulvar cancers summarized data from 2168 vulvar cases (1226 invasive and 942 precancerous vulvar lesions). HPV DNA prevalence in invasive vulvar cancer (36%) was notably lower than that found in precancerous lesions (76%). In a case series from Germany, Hampl et al recently reported that 92% of vulvar cancer precursor lesions were associated with HPV, whereas only 60% of vulvar cancer had HPV DNA detected. HPV–16 or HPV–18 was detected in 76% of high-grade vulvar precancers, compared with 42% of the vulvar cancers.

Since the 1970s, the rate of vulvar carcinoma in situ (VIS) reported to cancer registries within the US has increased, whereas the rate of invasive cancer has remained relatively stable. Because of the rarity of this cancer, there are few descriptive and analytic epidemiologic studies of vulvar cancer in the literature. By using what to our knowledge is the largest available collection of aggregated data from population-based cancer registries in the US, we believe the current study will contribute to our knowledge and may provide some clues for enhanced surveillance of VIS and invasive vulvar cancer as a means of monitoring the impact of the HPV vaccine.

MATERIALS AND METHODS
We analyzed data for 1998 through 2003 from 39 population-based cancer registries that participate in the Centers for Disease Control and Prevention (CDC)’s National Program of Cancer Registries (NPCR) and/or the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program, covering 83% of the US population. These registries have met the criteria for inclusion in the United States Cancer Statistics series for all years we examined, and they have consented to have their data used for this study. We adhered to the criteria set by the overall methods of this supplement. Because the SEER program is the only US source for population-based survival data, we completed our survival analysis by using the 1996 to 2003 data from 17 SEER registries covering 26% of the US population. For mortality statistics, we used data from CDC’s national vital statistics system, described in more detail elsewhere in the supplement.

This study includes incident cases of primary VIS and invasive vulvar cancer coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography (site) codes C51.0–C51.9. Although ICD-O-3 topographic codes for specific anatomic locations within the vulva are available, most of the cases were coded as vulvar none otherwise specified. Therefore, we could not examine vulvar cancer incidence by anatomic subsite. Although the natural history of vulvar cancer is not the same as cervical cancer, the terminology of precancerous lesions is similar. Vulvar intraepithelial lesions types 1, 2, and 3 (VIN 1, 2, and 3) and VIS are considered the separate stages leading to invasive vulvar cancer. VIN 3 is often considered synonymous with VIS. HPV-associated VIN 2, VIN 3, and VIS have
been identified as precursor lesions in the development of HPV-associated vulvar cancer, whereas VIN 1 is not considered a precancerous lesion. In the cancer registry, VISs were all cancers with a behavior code of 2. VIN 3 (codes as ICD code of 8077 with a behavior code of 2) cases were not included because they were not available in the analytic data file for most cancer registries. We grouped vulvar cancers into major histologic groups as determined by pathologists from the steering committee and as referenced elsewhere in the supplement: squamous cell carcinomas (SCCs), adenocarcinomas (ACs), other carcinomas (specified and nonspecified), and noncarcinomas. To assess the HPV-associated burden, we limited our analysis to SCCs. We also examined specific squamous cell histologies, such as not otherwise specified (ICD O-3 code 8070), keratinizing (8071), nonkeratinizing (8072), basaloid (8083), and warty/verrucous (8051). Cancers were staged according to SEER summary stage.

SEER*stat software (National Cancer Institute, Bethesda, Md) was used to generate frequency and age-adjusted (using the US 2000 population standard) incidence rates, confidence intervals, and rate ratios by race/ethnicity. We also calculated age-specific incidence rates by race/ethnicity. All rates are expressed per 100,000 female population. Counts and rates based on fewer than 6 cases were not included.

RESULTS
During the years 1998 through 2003, 12,554 VISs and 18,066 invasive vulvar cancers were diagnosed in the 39 registries. SCCs represented approximately 77% of all VISs and 75% of all invasive vulvar cancers. The majority of SCCs were reported as not otherwise specified (85% for VIS cases and 73% for invasive cases). Approximately 20% of invasive SCCs (19%) were keratinizing. Bowen disease (ICD O-3 8081 with behavior code 2) accounted for 13% of in situ vulvar SCCs (Table 1). Bowen disease is a historical term used to define preinvasive vulvar lesions. Greater than 60% of invasive cancers were reported as moderately or well differentiated. The remaining cancers were identified as poorly differentiated or unknown. Greater than 92% of in situ cancers were identified as of unknown differentiation.

**Incidence of Vulvar SCC by Race, Ethnicity, and Geographic Regions**
White women had the highest incidence of vulvar cancer. Incidence rates among black women were 28% lower than for white women (\(P < .05\)) for VIS (0.9 per 100,000 vs 1.3) and 28% lower (1.3 vs 1.8) (\(P < .05\)) for invasive vulvar SCC (Table 1). Asian/Pacific Islander (API) women had the lowest rates of VIS and invasive vulvar SCC among all race groups. The rates of SCC were lower among Hispanic women than among non-Hispanic women for both VIS (0.6 vs 1.3, or 54% lower) and invasive (1.3 vs 1.8, or 28% lower) vulvar SCC. The incidence rate in the Northeast region was significantly lower (\(P < .05\)) than in the other 3 regions of the US for in situ vulvar SCC. For invasive vulvar SCC, incidence rates were similar in the Northeast and Midwest regions, while the rates in the South and West regions were significantly lower (\(P < .05\)) than in the other 2 regions.

**Age-specific Incidence and Mortality Rates of Vulvar SCC**
Incidence rates of in situ vulvar SCC increased with age until ages 40 to 49 years and then declined gradually, whereas the rates of invasive vulvar SCC gradually increased until ages 60 to 69 years, followed by a sharp increase with advancing age (Fig. 1). For VIS cancers, a similar pattern with age was observed among white and black women, with a peak incidence among women in the group ages 40 to 49 years, followed by a plateau and then a decline. Among Hispanic women, the rate of VIS cancers increased with age, peaked at age 70 to 79 years with no early age plateau, and then declined in the older age groups. Among API women, the increase in the incidence of VIS cancers was more gradual than for other racial ethnic groups (Fig. 2a).

For invasive vulvar SCC, the age-specific incidence rates were similar for white and black women aged <50 years. After age 50 years, rates increased with advancing age and more rapidly increased among white women than among black women. Similarly, rates were lower among white and black women aged <60 years. Among women aged \(\geq 70\) years, incidence rates were much higher for white and Hispanic women than for black women. Among those aged \(\geq 80\) years, the rates were similar for white women and Hispanic women. Vulvar cancer incidence among API women remains significantly lower than among other racial and ethnic groups throughout the lifespan (Fig. 2b).

Vulvar cancer mortality rates increased with age, particularly after the age range of 70 to 79 years among white women. Mortality rates for white and Hispanic women continued to rise sharply with age (Fig. 2c).
Approximately 62% of vulvar SCCs were in the form of localized disease at diagnosis, 28% were regional, 3.4% were distant, and 5.9% were unstaged. Black and API women were significantly less likely than white women to be diagnosed with localized disease ($P < .05$) (Table 2). API women had the lowest percentage of localized disease among all races examined (51% vs 58% for black women and 63% for white women). Although Hispanic women were less likely than non-Hispanic women to be diagnosed with localized disease, the difference did not reach statistical significance.

| Rate (95% CI) | Rate Ratio | Average Annual Incidence Count % | Rate (95% CI) | Rate Ratio | Average Annual Incidence Count % |
|--------------|------------|----------------------------------|--------------|------------|----------------------------------|
| Invasive ($n=13,597$; Median Age, 69 y) | In Situ ($n=8986$; Median Age, 49 y) |
| **Race** | | | **Race** | | |
| White | 1.8 (1.7-1.8) | 2056 | 90.7 | 1.3 (1.2-1.3) | 1297 | 86.6 |
| Black | 1.3 (1.2-1.4) | 0.7 | 157 | 0.9 (0.9-1.0) | 0.7 | 119 | 7.9 |
| API | 0.4 (0.3-0.5) | 0.2 | 16 | 0.1 (0.1-0.2) | 0.1 | 7 | 0.5 |
| **Ethnicity** | | | **Ethnicity** | | |
| Non-Hispanic | 1.8 (1.7-1.8) | 2153 | 95.0 | 1.3 (1.3-1.3) | 1427 | 95.3 |
| Hispanic | 1.3 (1.2-1.4) | 0.7 | 114 | 0.6 (0.6-0.7) | 0.5 | 70 | 4.7 |
| **Region** | | | **Region** | | |
| Northeast | 1.8 (1.8-1.9) | 594 | 26.2 | 0.9 (0.9-0.9) | 256 | 17.1 |
| Midwest | 1.9 (1.8-1.9) | 1.0 | 672 | 29.6 | 1.4 (1.3-1.4) | 1.5 | 143 | 30.2 |
| South | 1.7 (1.7-1.8) | 0.9 | 604 | 26.6 | 1.5 (1.5-1.6) | 1.7 | 501 | 33.5 |
| West | 1.4 (1.4-1.5) | 0.8 | 398 | 17.5 | 1.0 (1.0-1.1) | 1.2 | 287 | 19.2 |
| **Histology for SCC** | | | **Histology for SCC** | | |
| Verrucous papilloma (8051) | 0.04 (0.04-0.05) | NA | 56 | 2.5 | $\$ | NA | $\$ | 0.2 |
| NOS (8070) | 1.3 (1.2-1.3) | 1693 | 73.2 | 1.1 (1.0-1.1) | NA | 1285 | 85.8 |
| Keratinizing (8071) | 0.3 (0.3-0.3) | NA | 432 | 19.0 | 0.0 (0.0-0.0) | NA | 6 | 0.4 |
| Non Keratinizing (8072) | 0.02 (0.02-0.03) | NA | 29 | 1.3 | $\$ | NA | $\$ | 0.1 |
| Bowen disease (8081) | $\$ | $\$ | NA | $\$ | 0.1 | (0.2-0.2) | NA | 195 | 13.0 |
| Basoloid (8083) | 0.01 | $\$ | NA | 15 | 0.7 | $\$ | NA | $\$ | 0.1 |
| All other | 0.06 (0.1-0.1) | NA | 74 | 3.3 | $\$ | NA | $\$ | 0.3 |
| **Grade** | | | **Grade** | | |
| Well differentiated | 0.4 (0.4-0.4) | NA | 576 | 25.4 | 0.0 (0.0-0.0) | NA | 38 | 2.5 |
| Moderately differentiated | 0.6 (0.6-0.6) | NA | 819 | 36.1 | 0.0 (0.0-0.0) | NA | 18 | 1.2 |
| Poorly differentiated | 0.2 (0.2-0.3) | NA | 324 | 14.3 | 0.0 (0.0-0.0) | NA | 44 | 2.9 |
| Undifferentiated | 0.0 (0.0-0.0) | NA | 11 | 0.5 | 0.0 (0.0-0.0) | NA | 9 | 0.6 |
| Unknown | 0.4 (0.4-0.4) | NA | 537 | 23.7 | 1.1 (1.1-1.2) | NA | 1389 | 92.7 |
| **Stage** | | | **Stage** | | |
| Localized | 1.1 (1.1-1.1) | | 1,415 | 62.4 | NA |
| Regional | 0.5 (0.5-0.5) | 0.4 | 640 | 28.2 | |
| Distant | 0.1 (0.1-0.1) | 0.1 | 77 | 3.4 | |
| Unstaged | 0.1 (0.1-0.1) | 0.1 | 134 | 5.3 | |

Stage of Vulvar SCC by Race and Ethnicity

Approximately 62% of vulvar SCCs were in the form of localized disease at diagnosis, 28% were regional, 3.4% were distant, and 5.9% were unstaged. Black and API women were significantly less likely than white women to be diagnosed with localized disease ($P < .05$) (Table 2). API women had the lowest percentage of localized disease among all races examined (51% vs 58% for black women and 63% for white women). Although Hispanic women were less likely than non-Hispanic women to be diagnosed with localized disease, the difference did not reach statistical significance.

Five-year Relative Survival Rates by Race, Ethnicity, and Age

The overall 5-year relative survival rate for vulvar SCC was 86% (Table 3). However, 5-year relative survival rates varied strikingly by race and age. API women had the lowest 5-year relative survival rate among all racial groups (73% vs 86% for white women and 85% for black women). Five-year relative survival rates decreased with advancing age. Among women aged ≤40 years, the 5-year relative survival rate was 96%, whereas among women aged ≥65 years, the survival rate was 72%. There were no significant differences in 5-year relative survival rates...
between Hispanic and non-Hispanic women for all stages combined and for individual specific stages.

**DISCUSSION**

To our knowledge, the current study is the first to provide a comprehensive summary of the burden of VISs and invasive vulvar cancers in the US for such a large proportion of the US population. By using data from 39 population-based cancer registries in the US, we were able to present cancer incidence by race and ethnicity as well as by geographic region. We found that the majority of vulvar cancers were SCCs in all racial and ethnic populations examined. The incidence of VISs and invasive SCCs varied significantly by race and ethnicity, with the highest rates observed among white women.

Historically, vulvar and vaginal cancers have been categorized together as 2 of the rarest female genital cancers. However, recent data indicate differences in these cancers with respect to HPV prevalence (higher in vaginal cancers), types of epithelium (vulvar cancers being stratified cornified squamous epithelium and vaginal cancers being similar to mucosa), and epidemiologic patterns.

In contrast to many other cancers, vulvar cancer appears to illustrate a reversal in the disparity gap (ie, for vulvar cancer, rates are higher in whites than in blacks, whereas for many other cancers, rates for blacks are higher than for whites). We observed significantly lower incidence rates among black, Hispanic, and API women than for white or non-Hispanic women for both VISs and invasive vulvar cancers. Kurman et al have suggested that the frequency of histologic subtypes may differ by race. They found more frequent HPV-associated vulvar cancers (basaloid/warty) among black women, and higher keratinizing and nonkeratinizing squamous cell cancers among white women. Given that: 1) an overwhelming majority of the cases did not have specified subtypes, 2) only <3% of vulvar cancers in the current study were identified as warty, 3) <1% of the invasive cancers were coded as basaloid, and 4) we had very limited numbers of cancers among non-
whites, we did not have sufficient sample size to examine differences in these histologic types, let alone by race and ethnicity. Because to our knowledge only a few studies have examined differences in vulvar cancer incidence by race, it remains unknown why the rate of this HPV-associated cancer is highest among white women. Possible factors that may contribute to the reporting of high rates may be increased or enhanced inspection during the screening and management of cervical disease, increased detection because of better visualization, and possibly different etiologies.

Similar to the rate of most cancers, but unlike that of cervical cancer, the rate of invasive vulvar cancer increases with age for all racial/ethnic groups examined, with a rapid rise in incidence observed in patients in their mid-60s. For VIS cancers, incidence rates peaked among women in their mid-40s, nearly 20 years earlier than for invasive vulvar cancers. Unfortunately, the histology for most vulvar cancers,

### Table 2

|                      | Localized | Regional | Distant | Unstaged | Total |
|----------------------|-----------|----------|---------|----------|-------|
|                      | Count     | Rate     | %       | Count     | Rate  | %       | Count     | Rate  | %       | Count     | Rate  | %       |
| Race                 |           |          |         |           |       |         |           |       |         |           |       |         |
| White                | 7745      | 1.13     | 62.8    | 3479      | 0.49  | 28.2    | 423       | 0.06  | 3.4     | 687       | 0.09  | 5.6     | 12,334    |
| Black                | 544       | 0.74     | 57.8    | 293       | 0.41  | 31.1    | 32        | 0.05  | 3.4     | 72        | 0.1   | 7.7     | 941       |
| Asian/Pacific Islander | 48       | 0.18     | 51.1    | 36        | 0.14  | 36.3    | $         | $     | $       | 53        | 1.1   | 7.8     | 941       |
| Ethnicity            |           |          |         |           |       |         |           |       |         |           |       |         |
| Non-Hispanic         | 8101      | 1.12     | 62.7    | 3648      | 0.49  | 28.2    | 416       | 0.06  | 3.2     | 751       | 0.10  | 5.8     | 12,916    |
| Hispanic             | 390       | 0.72     | 57.3    | 190       | 0.38  | 27.9    | 47        | 0.09  | 6.9     | 54        | 0.11  | 7.9     | 681       |
| All races/ethnicities| 8491      | 1.08     | 100     | 3838      | 0.48  | 100     | 463       | 0.06  | 100     | 885       | 0.1   | 100     | 13,597    |

*Incidence data are from 39 population-based cancer registries that participate in the National Program of Cancer Registries and the National Cancer Institute’s 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 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130); (Tiwari mod) are 95% for rates and ratios.

‡Indicates that the rate is significantly different from the rate for the reference group (white for race; non-Hispanic for ethnicity) ($P < .05$).

§Rates and number suppressed as <6 per cell.

### Table 3

|                      | In Situ | Localized | Regional | Distant | Unstaged | All Stage |
|----------------------|---------|-----------|----------|---------|----------|-----------|
| Total Count          | 4862    | 98.8      | 91.10    | 52.3    | 29.5     | 41.9      | 85.7      |
| Race                 |         |           |          |         |          |           |           |
| White                | 4309    | 98.8      | 91.10    | 51.2    | 26.6     | 42.8      | 85.7      |
| Black                | 451     | 98.3      | 89.3     | 58.5    | 47.9     | $         | $         | 85.2      |
| Asian/Pacific Islander | 74    | 83.6      | 82.3     | 54.2    | $        | $         | 72.9      |
| Ethnicity            |         |           |          |         |          |           |           |
| Non-Hispanic         | 4522    | 98.9      | 91.40    | 52.5    | 27.6     | 44.3      | 86.1      |
| Hispanic             | 340     | 96.9      | 83.7     | 48.7    | 38.1     | $         | 79.3      |
| Age, y               |         |           |          |         |          |           |           |
| <40                  | 643     | 98.2      | 96.3     | 71.2    | 76.3     | 66.8      | 96.0      |
| 40-49                | 1003    | 98.2      | 96.7     | 82.6    | 33.9     | 68.2      | 95.5      |
| 50-64                | 1182    | 98.9      | 94.5     | 66.6    | 38.6     | 52.8      | 90.3      |
| ≥65                  | 2034    | 98.2      | 85.90    | 38.3    | 17.0     | 31.6      | 71.6      |

*Excluding the second and later primary tumors of vulvar cancer and death certificate and autopsy-only cases.

†Using the National Cancer Institute’s Surveillance, Epidemiology, and End Results program, 17 areas covering approximately 26% of the US population.

‡Vulvar intraepithelial neoplasia type 3 cases were not included.

§Suppressed due to <6 cases.
whether in situ or invasive, was not recorded with more specific subtypes, hence the code of “not otherwise specified.” By using the limited data available, we observed a higher percentage of keratinizing (non-HPV associated) vulvar cancers in older than in younger women (11% of all cases for women aged <50 years of age vs 17% of all cases of women aged 70–79 years). Relying on histologic distribution change from pathology reports to assess the impact of HPV vaccination may be difficult, given the relatively low numbers of cancers coded as basaloid or warty type. At this time, it is difficult to determine whether this is an issue in the practice of diagnoses or reporting. Increasing the documentation on histologic subtypes in pathology reports and in cancer registry data can help differentiate the burden of HPV-associated types from non–HPV-associated types of vulvar cancers. Relying on the grade of invasive vulvar cancers to determine vulvar cancers that are more or less likely to be HPV-associated may hold some promise. Approximately 60% of invasive vulvar cancers were identified as moderately or well differentiated (non–HPV-associated), coinciding well with the 60% of vulvar cancers considered to be non–HPV-associated. Unfortunately, grading did not extend to VIIs because the majority of those were not characterized by grade.

Although white women have higher rates of vulvar cancer than other racial/ethnic groups, black and API women were found to have higher percentages of advanced stages than white women, and API women had poorer survival rates. As advances in both prevention and treatment continue, monitoring further racial disparities will be paramount.

Common risk factors for vulvar cancers have included current cigarette smoking, decreased immunity, and prior cancer history. Current cigarette smoking has been associated with both VIIs and invasive vulvar cancers, with a general trend demonstrating a stronger association with VIS cancers.12-14 Similar to observations from other HPV-associated cancers, the relative risk of vulvar and vaginal in situ cancers is significantly elevated among women infected with the human immunodeficiency virus (HIV).15 Recent studies indicate that women with a history of cervical cancer and/or vaginal cancer have a higher risk of developing invasive vulvar cancer,16-18 and women diagnosed with vulvar cancer have a higher risk of developing anal and vaginal cancers as well as buccal cavity and pharyngeal cancers, suggesting a shared etiology of HPV in some cases.19 More research is needed for the development of a fuller understanding of the factors associated with HPV-associated and non–HPV-associated vulvar cancers.

The major limitation of the current study was the inability to examine VIN 3 from all cancer registries. The data for VIN 3 were not available in the majority of registries in the study data file. Data concerning VIN 3 are required by the SEER and the NPCR registries, but were not submitted at the national NPCR registry level in the most recent data submissions because of the following concerns. Similar to data on other counterparts (anal intraepithelial neoplasia or AIN 3, vaginal intraepithelial neoplasia or VaIN 3), data regarding VIN 3 are not required to be collected by the Commission on Cancer (CoC)-approved hospitals. Thus, there are ascertainment biases across different registries. Although not required by the CoC, states that emphasize the VIN 3 requirement will have more complete ascertainment from hospitals than states that do not. These 2 reasons can account for significant underestimation of the VIN 3/VIS lesions, because many pathologists consider these precancerous lesions (VIN 2 of 3/VIS) to be similar. From the years 1998 through 2003, among the SEER registries that continue to require the collection of these data, this code of VIN 3 accounted 63% of in situ vulvar cancers (data not shown), suggesting that the magnitude of the underestimation maybe large. In 2004, the International Society for the Study of Vulvovaginal Disease adopted a different classification system for VIN. This system classifies VIN into 2 major types: a usual type (HPV-associated) and a differentiated type (non–HPV-associated).19 This system basically eliminates VIN 1 as a category, and it combines VIN 2 and 3 on the grounds that VIN 1 has not been shown to be a reproducible diagnosis and VIN 2/VIN 3 are not reliably separated.20 To our knowledge, currently this international classification system has not permeated US pathology practices. How this classification system may impact cancer registries in the US will require further study. Encouraging cancer registries to report and submit VIN 3 data and more research on data quality will allow a thorough assessment of the impact of the HPV vaccine by providing a basis for examining the true burden and quality of these precancerous vulvar cancers.

In addition to the prevention of precancerous cervical cancer (cervical intraepithelial neoplasia type 2 of 3), the quadrivalent HPV vaccine has been approved and recommended for the prevention of precancerous vulvar (VIN 2 of 3) lesions.21 Among women initially naive to HPV–16 or HPV–18 who received all 3 doses, the vaccine was 100% effective (95% confidence interval [95% CI], 42%–100%) against VIN 2 of 3 associated with HPV–16 or HPV–18 among women. Among the intention-to-treat
portion of vulvar cancers. etiology and possible prevention of the remaining US. Further research needs to be done regarding the invasive vulvar carcinoma reported per year in the US. Vaccine has the potential to reduce by 40% the 3800 cases of HPV-associated squamous cell in situ and vaccine has the potential to reduce by 40% the 3800 cases of HPV-associated squamous cell in situ and invasive vulvar carcinoma reported per year in the US. Further research needs to be done regarding the etiology and possible prevention of the remaining portion of vulvar cancers.

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