Disparity in the Persistence of High-Risk Human Papillomavirus Genotypes Between African American and European American Women of College Age

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Background. Cervical cancer incidence and mortality rates are higher in African Americans than in European Americans (white, non-Hispanic of European ancestry). The reasons for this disparity are not known.

Methods. We recruited a population-based longitudinal cohort of 326 European American and 113 African American female college freshmen in Columbia, South Carolina, to compare clearance of high-risk human papillomavirus (HR-HPV) infection between ethnicities. HPV testing and typing from samples obtained for Papanicolaou testing occurred every 6 months.

Results. African American participants had an increased risk of testing positive for HR-HPV, compared with European American participants, but the frequency of incident HPV infection was the same in African American and European American women. Thus, exposure to HPV could not explain the higher rate of HPV positivity among African American women. The time required for 50% of participants to clear HR-HPV infection was 601 days for African American women (n = 63) and 316 days for European American women (n = 178; odds ratio [OR], 1.61; 95% confidence interval [CI], 1.08–2.53). African American women were more likely than European American women to have an abnormal result of a Papanicolaou test (OR, 1.58; 95% CI, 1.05–2.39).

Conclusions. We propose that the longer time to clearance of HR-HPV among African American women leads to increased rates of abnormal results of Papanicolaou tests and contributes to the increased rates of cervical cancer observed in African American women.

Keywords. human papillomavirus; HPV; HPV persistence; health disparities; viral clearance.

Almost all cervical cancers (99.7%) have been associated with high-risk human papillomavirus genotypes (HR-HPV) [1]. Although most HR-HPV infections resolve within 12–24 months [2], persistence of HR-HPV infection increases the risk for development of precancerous cervical lesions and cervical carcinoma [3, 4]. Although the Papanicolaou (Pap) test has decreased the overall incidence and mortality of cervical cancer, this disease remains the eighth most common cancer among women in the United States [5].

In the United States, there is a disparity in cervical cancer incidence and mortality among different ethnic groups [6, 7]. The highest incidence of cervical cancer is observed in Hispanic women, while the highest mortality rate is observed in African American women [7]. Socioeconomic factors and access to healthcare have been postulated as possible explanations for the disparity in incidence and mortality rates of cervical cancer between different ethnic groups [8]. However, African
American women have a higher incidence of cervical cancer than white, non-Hispanic women, although both groups report similar rates of screening [9]. A comparison of treatment modalities found that African American women often receive less aggressive treatment for cervical cancer [6, 10]. In South Carolina, the incidence of cervical cancer is 37% higher and the mortality rate is 61% higher for African American women, compared with European American (white, non-Hispanic of European ancestry) women [11].

HPV infection rates are higher in adolescent and young adult women, likely because these women are being exposed to HPV for the first time [12]. The Carolina Women’s Care Study (CWCS) was established in 2004 to define determinants of and identify biomarkers associated with HR-HPV infection and persistence in European American and African American women of college age [13]. The CWCS allowed for longitudinal observation of female college students who were enrolled in the study as freshmen and received biannual visits throughout their college experience.

Our results demonstrate that HR-HPV infections persist longer in African American women, compared with European American women. Furthermore, African American women have an increased risk of having an abnormal result of a Pap test. We propose that this disparity in HPV persistence may contribute to the disparity in cervical cancer rates observed in African American women, compared with European American women.

PARTICIPANTS, MATERIALS, AND METHODS

Study Population
The CWCS was a prospective longitudinal study, with rolling enrollment commencing in November 2004 and follow-up continuing through April 2011, in the Women’s Care Clinic in the Thomson Student Health Center at the University of South Carolina. The study is described in detail elsewhere [13]. Approval for the study was obtained from the University of South Carolina Institutional Review Board.

Sample Acquisition
At each biannual visit, biometric measures were recorded. A pelvic examination included the collection of exfoliated cervical cells. As we described previously, a self-administered survey, completed at each visit, was designed to query lifestyle factors and underlying levels of stress, depression, or feelings of social discrimination [13].

Gynecologic Cytology
Pap tests were processed by LabCorp. Pap test samples were considered of adequate quality for interpretation upon the identification of endocervical cells. Abnormal Pap test classification includes diagnoses of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL).

HPV DNA Testing and Typing
DNA was extracted from exfoliated cervical cells as previously described [13]. The presence of HPV was determined by real-time polymerase chain reaction (PCR), using PGMY09/11 primers as described in detail elsewhere [13]. We used the INNO-LiPA HPV AMP Kit and the INNO-LiPA Genotyping Extra Kit (Fujirebio Europe) to determine the type(s) of HPV present in the real-time PCR–positive samples. INNO-LiPA identifies 7 low-risk HPV types (LR-HPV; types 6, 11, 40, 43, 44, 54, and 70) and 15 HR-HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82). The kit also detects 5 HPV types of probable HR (types 26, 53, 66, 69, and 74). In addition to the type-specific probes, the linear array contains 2 generic HPV probe mixtures that hybridize with virtually any HPV–derived amplification product. Samples that tested positive for one or both of the generic HPV bands but negative for the type-specific bands were considered HPV positive and were included in the analysis for total HPV infections. However, these samples were excluded from analysis of type-specific LR-HPV and HR-HPV infections. Furthermore, to eliminate false-positive results, we included in the analysis for type-specific HPV infections only positively identified HPV types and not those classified as possible HPV types by the INNO-LiPA HPV typing method.

Statistical Analysis
Student t tests and χ^2 tests were used to evaluate differences of continuous and categorical variables, respectively, between African American and European American participants. Vaccine uptake was indicated with documentation of at least 1 dose of the quadrivalent HPV vaccine (Gardasil). Tobacco use is defined as consumption of ≥25 cigarettes per month.

Generalized linear mixed effects regression models with a logit link were used to evaluate the associations of ethnicity with HPV positivity and abnormal results of Pap tests. The probability of abnormal Pap test results for African American and European American females was calculated from the generalized linear mixed effects model of abnormal Pap test results, by ethnicity.

To analyze the clearance of HPV infection, the semiparametric maximum likelihood–based proportional hazards model for the interval-censored data was used because, in practice, the clearance of HPV infection cannot be exactly observed. Instead, only the times of the last positive test result and the first negative test result for infection can be observed (ie, only the interval for clearance can be observed). In the survival analysis, we adopted the method developed by Pan [14]. The proportional hazards model is fit to interval-censored data by means of the iterative convex minorant algorithm. This model allows for inference of
relative hazards from interval-censored event data. In the analysis, the model was used to estimate the infection clearance probabilities and to compare the ethnicity effects. Besides the estimate of the ethnicity effect, the bootstrap method was used to calculate the standard error of the effect estimate based on 500 bootstrapping samples. From this, the odds ratio (OR) and its 95% confidence interval (CI) can be computed. intcox [15], an R package, was used to implement the analysis. Inclusion criteria for survival analysis were as follows: participants age 18–25 years at enrollment, >2 study visits, and detection of HR-HPV during at least 1 visit. Tests for detection of 15 HR-HPV were performed, and each type was evaluated separately to determine the longest type-specific infection period per participant. Type-specific infections selected for analysis required an HR-HPV–negative test result at enrollment, unless the individual tested positive for the same HR-HPV type on ≥3 consecutive visits. The longest infection period was determined by calculating the number of days between the first and last consecutive visits during which the same HR-HPV type was detected. Only the HR-HPV infection with the longest duration, limited to 1 such infection per person, was used in the survival analysis. All statistical analyses were conducted using R, version 2.15.0 [16].

RESULTS

Population Characteristics

Our study included 113 African American and 326 European American women (Table 1). The 2 groups were similar in age at enrollment and completed on average the same number of study visits per person (mean, 4.8 visits). Their age of sexual debut was similar (African American women, 16.3 years; European American women, 16.6 years). Both groups had equivalent lifetime numbers of sex partners at enrollment (mean, 3.8 partners) and acquired new sex partners at the same rate (African American women, 1.3 partners/year; European American women, 1.4 partners/year). There were no significant differences between the 2 groups with respect to their psychological measures of stress (Center for Epidemiologic Studies Depression scale), depression (Everyday Depression scale), or feelings of discrimination (Table 1). African American women were significantly less likely than European American women to be vaccinated against HPV during the study (Table 1). There was a significant difference in tobacco use, with African American women being significantly less likely to smoke (Table 1).

HPV Prevalence and Incidence

Within our cohort of 439 African American and European American participants and 2121 clinic visits, 42.7% of visits (906) yielded an HPV-positive test result (Table 2). There was a significant difference between African American and European American women in the percentage of visits during which HPV was detected (Table 2). European American women were HPV positive on 40.0% of the visits, whereas African American women were HPV positive on 51.0% of the visits (P < .0001, by χ² analysis). This difference was observed for both HR-HPV types (European American women, 37.1%; African American women, 47.4%) and LR-HPV types (European American women, 8.7%; African American women, 14.4%). African American and European American participants had very similar frequencies of concurrent infections by multiple HPV types, with an average of 2.3 HR-HPV types detected per visit

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Carolina Women’s Care Study Participants, Overall and by Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Participants</td>
</tr>
<tr>
<td>Study visits, no.</td>
</tr>
<tr>
<td>Days between study visits, no.</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
</tr>
<tr>
<td>Age at first sexual activity, y</td>
</tr>
<tr>
<td>Lifetime history of vaginal sex partners at enrollment, no.</td>
</tr>
<tr>
<td>New sex partners, no./y</td>
</tr>
<tr>
<td>CESD</td>
</tr>
<tr>
<td>Everyday Depression scale</td>
</tr>
<tr>
<td>Discrimination scale</td>
</tr>
<tr>
<td>HPV vaccine receiptᵇ</td>
</tr>
<tr>
<td>Tobacco use</td>
</tr>
</tbody>
</table>

Data are no. (%) of women or mean value ± SD.
Abbreviations: CESD, Center for Epidemiologic Studies Depression scale; HPV, human papillomavirus.
ᵃ Values reflect the significance of differences between African American and European American participants. The Student t test was used, unless otherwise indicated.
ᵇ At least 1 dose of the quadrivalent HPV vaccine (Gardasil).
ᶜ By the Fisher exact test.

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in which any HPV type was detected (Table 2). We also determined the number of visits at which new HR-HPV infections could be detected; there was no difference between African American and European American women in the frequency of study visits with a new HR-HPV type detected, with about 1 new HR-HPV type detected every 3 visits (Table 2).

Factors Associated With HR-HPV Infection
We next explored risk factors associated with HR-HPV infection. A logistic mixed-effects regression model with a random intercept, taking into account differences in the numbers of visits per person and repeated visits, determined that African American ethnicity and lifetime number of sex partners were significantly associated with being positive for HR-HPV (Table 3). The similar incidence rates of HR-HPV infection between European American and African American women indicated similar levels of exposure to HPV between the 2 groups, yet African American women tested positive for HR-HPV more often than European American women (OR, 1.62; Table 3). This finding suggested that clearance of HR-HPV may be different between African American and European American women.

Clearance of HPV Infection in European American and African American Women
To compare clearance of HR-HPV between African American and European American women, we performed a survival analysis that used the longest HR-HPV infections in participants ages 18–25 years at enrollment. HR-HPV infections selected for analysis required negative HR-HPV test results at enrollment, unless ≥3 consecutive visits yielded positive test results for the same HR-HPV type. The longest HR-HPV infection duration per individual was calculated as the number of days between the first and last consecutive visits during which tests were positive for the same HR-HPV type. Of the 326 European American participants, 1 was >25 years of age, 63 had a single study visit, 70 did not have HPV detected during the study, and 14 had HR-HPV detected at enrollment that cleared after 1 or 2 visits, leaving 178 individuals with 702 HR-HPV infections and a mean number (±SD) of 3.9 ± 2.2 HR-HPV types detected per person. Of the 113 African American participants, 39 did not have HPV detected during the study, 5 had only 1

Table 2. Prevalence and Incidence of Human Papillomavirus (HPV) Infection

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>European American</th>
<th>African American</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study visits</td>
<td>2121 (100.0)</td>
<td>1594 (75.1)</td>
<td>527 (24.8)</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Study visits with a new HR-HPV type detected, no.</td>
<td>0.29 ± 0.30</td>
<td>0.29 ± 0.29</td>
<td>0.31 ± 0.31</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>HPV type detected, by cancer risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>906 (42.7)</td>
<td>637 (40.0)</td>
<td>269 (51.0)</td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>High risk</td>
<td>842 (39.7)</td>
<td>592 (37.1)</td>
<td>250 (47.4)</td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low risk</td>
<td>214 (10.1)</td>
<td>139 (8.7)</td>
<td>76 (14.4)</td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>High-risk HPV types detected per visit, no.</td>
<td>2.30 ± 1.47</td>
<td>2.30 ± 1.47</td>
<td>2.31 ± 1.48</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Cervical cytology result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within normal limits</td>
<td>1805 (85.1)</td>
<td>1386 (87.0)</td>
<td>419 (79.5)</td>
<td></td>
</tr>
<tr>
<td>ASCUS</td>
<td>151 (7.1)</td>
<td>102 (6.4)</td>
<td>49 (9.3)</td>
<td></td>
</tr>
<tr>
<td>LSIL</td>
<td>141 (6.7)</td>
<td>93 (5.8)</td>
<td>48 (9.1)</td>
<td></td>
</tr>
<tr>
<td>HSIL</td>
<td>24 (1.1)</td>
<td>13 (0.8)</td>
<td>11 (2.1)</td>
<td></td>
</tr>
</tbody>
</table>

Data are no. (%) of study visits or mean value ± SD.
Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
<sup>a</sup> By the Student t test, unless otherwise indicated.
<sup>b</sup> By the χ<sup>2</sup> test.
<sup>c</sup> Data are no. of high-risk HPV types detected per visit during which any HPV type was detected.

Table 3. Multivariable Analysis of the Association Between Ethnicity and High-Risk Human Papillomavirus (HPV) Infection

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European American</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.62 (1.01–2.58)</td>
<td>.0434</td>
</tr>
<tr>
<td><strong>HPV vaccine receipt</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>At least 1 dose</td>
<td>1.18 (0.76–1.85)</td>
<td>.4606</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.20 (0.67–2.16)</td>
<td>.5424</td>
</tr>
<tr>
<td><strong>Sex partners, lifetime no.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>At least 1</td>
<td>1.03 (1.02–1.05)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Analysis controlled for HPV vaccine uptake, smoking status, and lifetime number of sex partners.
Abbreviation: CI, confidence interval.
study visit, and 6 had HR-HPV detected at enrollment that cleared during the study, leaving 63 individuals with a total of 270 infections and a mean number (±SD) of 4.3 ± 2.5 HR-HPV types detected per person. There was no statistically significant difference in the number of HPV types per person detected between African American and European American participants included in the survival analysis (P = .31, by the Student t test).

A semiparametric maximum likelihood–based proportional hazards model for interval-censored data was used to compare the duration of HR-HPV infections between African American and European American participants (Figure 1). The time required for 50% of these infections to clear was nearly double for African American women (601 days), compared with European American women (316 days; Figure 1). The odds of an African American woman not clearing an HR-HPV infection were 1.61 times the odds for a European American woman (95% CI, 1.08–2.53; Figure 1). Neither the number of study visits (5.9) nor the interval between study visits were statistically different between the European American and African American participants included in the survival analysis (Figure 1).

Abnormal Cervical Cytology Findings for European American and African American Women
Since African American women clear HR-HPV infections more slowly than European American women, we explored whether abnormal results of Pap test were more frequent among African American women. We obtained 2121 Pap test results over the course of the study. The distribution of Pap test results across African American and European American participants is shown in Table 2. Abnormal Pap test results (ASCUS, LSIL, and HSIL) were significantly more frequent for African American women (20.5%) than for European American women (13.0%; P = .0002; Table 2). A logistic mixed-effects regression model with a random intercept was used to investigate the association of ethnicity, lifetime number of sex partners, HPV vaccination, and smoking with an abnormal Pap test result. African American ethnicity was significantly associated with having an abnormal Pap test result (OR, 1.58; 95% CI, 1.05–2.39), even when controlling for lifetime number of sex partners, HPV vaccine receipt, and smoking (Table 4). A significant positive correlation between abnormal Pap test results and lifetime number of sex partners was found. Receipt of at least 1 dose

**Figure 1.** Survival analysis of the longest detected high-risk human papillomavirus (HR-HPV) type per study participant. A Cox proportional hazards model incorporating interval-censored data was used to calculate the clearance of HR-HPV infections in African American and European American participants. The longest HR-HPV infection per participant was used in the analysis. Abbreviation: CI, confidence interval.
The observed differences in abnormal Pap test results between Pap test result, indicating that HR-HPV status is responsible for HR-HPV 11.86 (8.20 – 17.15) when we included ethnicity, HPV vaccine receipt, smoking, and lifetime number of sex partners as covariates (Table 5). As expected, when HR-HPV was included in the model, ethnicity was not found to be a significant risk factor for an abnormal Pap test result, indicating that HR-HPV status is responsible for the observed differences in abnormal Pap test results between African American and European American women. Overall, our results strongly suggest that the increased risk of an abnormal Pap test result observed among African American women and the increased likelihood of being HR-HPV positive at any one visit is not due to differences in exposure to HPV; rather, it is due to an increased duration of HR-HPV infections.

**DISCUSSION**

The CWCS compared the natural history of HPV infections in African American and European American women of college age. Our ultimate goal is to discover the biological factors that contribute to HPV persistence in an attempt to understand the cervical cancer disparities that exist between African American and European American women. Over the past 35 years, the overall incidence of invasive cervical cancer has decreased by 54% in the United States, with a greater decline in incidence observed among African American women, compared with European American women [17]. However, the absolute incidence of invasive cervical cancer still remains higher for black women than white women [17], especially in women aged >50 years [18, 19], although the prevalence of Pap test screening for African American and European American women is similar [9]. In South Carolina, the age-adjusted incidence of cervical cancer is about 50% higher in African American women than European American women [11]. Although the disparity in cervical cancer incidence and mortality is most often attributed to sociodemographic and healthcare factors, biologic and genetic factors should not be overlooked.

HPV infection is common, with an overall prevalence of 26.8% among US females aged 14–59 years [12]. While several previous studies explored the natural history of HPV infection in women of college age [2, 20–22], this is the first study designed specifically to compare HPV incidence, prevalence, and persistence between African American and European American women. In our initial article describing the CWCS, we reported that 28.5% of the study participants tested positive for HR-HPV at enrollment and that the prevalence of HR-HPV infection was slightly greater in African American women (34.5%), compared with European American women (27.6%), although this difference was not statistically significant [13]. Here, we demonstrate that CWCS participants tested positive for HR-HPV at 39.7% of the 2121 study visits, which is consistent with the HR-HPV prevalence reported by others for women of college age [2, 21, 22]. Importantly, African American participants had a significantly greater percentage of study visits in which they tested positive for HR-HPV types (47.4%), compared with European American participants (37.1%), a difference that could not be explained by known risk factors, such as lifetime number of sex partners or smoking, nor by increased numbers of incident HPV infections among African American participants during the study. Psychological stress can lead to...
relative immune suppression. However, we did not detect a difference in stress, depression, or feelings of discrimination between African American and European American women.

Overall, our results are consistent with other reports of HPV prevalence in African American women. A higher age-adjusted prevalence of HR-HPV in African American women (49.7%), compared with European American women (20.2%), has previously been described, although the study size was small (82 women from Pittsburg, with a mean age of 53 years) [23]. Similarly, in a large population study of HPV prevalence in the United States that used urine specimens collected from women aged 18–25 years, African American women had a weighted HPV prevalence of 35.0%, compared with 25.3% among European American participants [24]. The overall prevalence of HR-HPV among African American women (age range, 18–24 years) from Atlanta, Georgia, was reported to be 42.4% [25]. Two recent studies reported that African American women were less likely than European American to have HPV types 16/18 detected [26, 27].

Although most HR-HPV infections are transient, persistent HR-HPV infection is a strong predictor of cervical intraepithelial neoplasia (CIN) and ultimately cervical cancer, especially in women with persistent HPV types 16/18 [4, 28, 29]. Thus, HPV persistence is a pivotal event in the pathway leading to cervical cancer. To our knowledge, comparisons of HR-HPV clearance times between African American and European American women have not been previously reported. We found that the time required to clear 50% of HR-HPV infections in African American participants was much longer (601 days) than that for European American participants (316 days) and that the odds of an African American woman not clearing HR-HPV are 1.61 times those for a European American woman. Our reported clearance times for HR-HPV among European American are in line with those previously reported. For example, studies in a predominately white, non-Hispanic cohort aged 18–35 years in Arizona reported that the median clearance time for HR-HPV was 298 days [30], while a study of female university students in Montreal revealed a mean duration of incident HR-HPV infection of about 495 days [20]. The median time to clearance of HR-HPV among women from Oahu, Hawaii, was 224 days [31], and the median duration of new HPV infections in a college-aged cohort in New Jersey was 243 days [2].

As would be expected, we found that infection with HR-HPV was strongly associated with an abnormal Pap test result. Despite the intrinsic limitations of the Pap test (it is suitable for screening, not diagnosis), African American participants were 1.6 times as likely as European American participants to have an abnormal Pap test result. On the basis of a logistic model, we estimate that 32% of African American women but only 19% of European American women aged 18–25 years will develop abnormal cervical cytology findings. We believe that the greater risk of an abnormal Pap test result among African American women is a direct consequence of the increased prevalence and persistence of HR-HPV in African American versus European American participants. Multiple HR-HPV infections are common [32], but we found no difference between European American and African American participants in the mean number of HR-HPV types detected per visit in which any HPV type was detected. Additionally, there is some controversy over the effect of multiple HPV types on abnormal cytology findings, with some, but not all [32], studies reporting associations between multiple types and abnormal cytology findings [33–35]. We found no association between infection with multiple HR-HPV types and the presence of cervical abnormalities at baseline [13].

An important question raised by these studies is why HR-HPV infections persist longer in African American women. HR-HPV variants may influence clearance by the host and the development of disease [36]. Host factors may also favor HPV persistence. Genetic susceptibility to HPV infection, persistence, and progression has been a topic of considerable study [37]. Studies using the Swedish national registries support a hereditary component to cervical cancer [38], but the causative loci remain elusive. The immune system is an important determinant in the pathogenesis of HPV-mediated disease [39], raising the possibility that alterations in genes modulating the immune system play a role in the differences in HPV clearance between African American and European American women. Several studies exploring an interaction between polymorphisms of the HLA complex and HPV acquisition, HPV persistence, and invasive cervical cancer suggest that HLA polymorphisms may play a role in the susceptibility to HPV persistence and HPV-induced lesions [40, 41]. Two polymorphisms in the TAP1 gene have been associated with high-grade CIN [42], and polymorphisms in the promoter of the gene encoding Toll-like receptor 9 have been associated with cervical cancer susceptibility [43]. Variations in the production of cytokines and chemokines could also play important roles in HPV persistence and ultimately cervical cancer. Polymorphisms of cytokine genes could alter both cytokine production and function. A study in a cohort of Mexican women found that a single-nucleotide polymorphism in the promoter of the gene encoding human interleukin 10 is associated with an increased risk of HPV-induced cervical lesions [44]. Low blood levels of interleukin 6 but not interleukin 10 in a cohort of Brazilian women were associated with HPV persistence [45]. Genetic polymorphisms of cancer-susceptibility genes, including p53 and MDM2, the FAS gene promoter, and GST, have also been linked to HPV infection and progression [46]. Single-nucleotide polymorphisms in the PRDX3 and RPS19 genes were associated with HPV persistence and cervical cancer [47]. The methylation state of host genes [48] or HPV DNA [49] may also contribute to HPV persistence and CIN, suggesting that host differences in
enzymes responsible for methylation could also affect HPV clearance. Future studies using high-throughput genomic approaches will seek to identify the molecular determinants leading to increased HPV persistence in African American women. Once the gene(s) responsible for HPV persistence have been identified, it may be possible to develop molecular screening tests to identify women most likely to be susceptible to persistent HR-HPV infections and to concentrate future cervical cancer screening programs on those women.

Notes

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