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Higher Prevalence of Human Papillomavirus-Related Cervical Precancerous Abnormalities in HIV-Infected Compared to HIV-Uninfected Women

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Abstract

Introduction: Persistent high risk human papillomavirus (hrHPV) has been associated with cervical abnormalities and cancer. There are few studies comparing HIV-infected with uninfected African American women from the Southern U.S. We evaluated medical records of a women's cohort in an urban clinic in Tennessee to assess the prevalence of hrHPV and cytology correlates, as well as HPV vaccination rates.

Methods: We reviewed medical records of 50 HIV infected and 304 HIV uninfected women, including Pap smears and hrHPV.

Results: HIV-infected women were older than HIV-uninfected women (p<0.0001) and were more likely to have hrHPV (p=<0.0001) and LGSIL/HGSIL (p=0.006). Within the HIV uninfected group, Hispanic women were younger than non-Hispanic African American women (p=0.04) and non-Hispanic white women (p=0.0002). Non-Hispanic African-American women were younger (p=0.004) than non-Hispanic white women. Both HIV-uninfected and HIV-infected women had an 11-fold and 5-fold odds, respectively, of having precancerous lesions when harboring hrHPV, compared to hrHPV-uninfected women. Of the 125 HIV-uninfected women, only 17% had

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received at least one dose of the HPV vaccine. None of the 21 vaccine recipients had evidence of SILs compared to 9% of vaccine non-recipients (p=0.35, Fisher's exact test).

Conclusion: HIV-infected women remained at significantly higher risk for developing cervical precancerous lesions when exposed to hrHPV than their uninfected counterparts. Hispanic women were least likely to have been vaccinated. Missed HPV vaccination trended towards being associated with a higher odds of precancerous lesions. Routine HPV vaccination should be reinforced for adolescents and young women using public hospital facilities of all races and ethnic backgrounds.

Keywords

HPV; HIV; cervix; screening; southern US; health disparities; HPV vaccine; Race/ethnicity

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide.[1–3] Human papillomavirus (HPV) accounts for the vast preponderance of invasive cervical cancers (ICC).[4] Of >140 HPV types identified,[5] about 30–40 are anogenital types,[5,6] while 15–20 are oncogenic.[16,18,31,33,35,39,45,51,52,56,58,59,68] A majority of ICC worldwide are caused by HPV 16 (54%) and HPV 18 (13%), though data from low and middle income countries are scarce when compared to high income nations.[7] Precancerous lesions such as, cervical intraepithelial neoplasia (CIN) grade 2 and 3 lesions and adenocarcinoma in situ are markers of those women at highest risk for the development of ICC.

In the United States, conspicuous health disparities exist in the prevalence of ICC among racial/ethnic groups.[8] The reported incidence rates are significantly higher in African American (odds ratio [OR] 1.34) and Hispanic (OR 1.55) women compared to white women.[9] ICC incidence among HIV-infected females in the US is over three times higher among HIV-infected compared to uninfected women (16 vs. 5 per 100,000 person-years).[10]

Studies have described HPV prevalence and types in HIV-infected women,[11] and have compared these parameters to HIV-uninfected U.S. women.[12–17]

While race/ethnicity and immunodeficiency may affect rates of HPV infection, persistent high risk HPV (hrHPV) has been consistently and strongly associated with cervical intraepithelial neoplasia (CIN).[18,19] Given a dearth of such data from the American South, we evaluated the association of HPV infection on cervical abnormalities in African-American and women of other ethnic/racial backgrounds in public sector urban clinics in Nashville, Tennessee.

METHODS

We reviewed electronic medical records in a cohort of 50 HIV-infected and 304 HIV-uninfected women after obtaining approval from Institutional Review Board of Meharry Medical College. All women had attended Meharry's Community Wellness and Obstetrics/Gynecology out-patient clinics. Data included patient demographics (age, race/ethnicity), HIV status, HPV vaccination status, Pap test results, and colposcopy results. From records

of HIV-infected women, we abstracted their CD4+ cell count and viral load data. Using cervical cytology (Papanicolaou [Pap] test), we used the 2001 Bethesda classification: atypical squamous cell of undetermined significance (ASCUS), low and high grade squamous intraepithelial lesions (LGSIL/HGSIL), and atypical glandular cells. We defined "abnormal cytology" in women only when they had either LGSIL or HGSIL. The screening Pap test used was a liquid based SurePath™ test (an image guided system) performed at Lab Corp (Birmingham, AL).

To detect hrHPV, we used Hybrid Capture® 2 High-Risk HPV DNA Test™ (Digene Corporation, Gaithersburg, MD, USA) technology that detects 13 high-risk HPV types using full genome probes. Any identified oncogenic serotype was considered hrHPV.[16,18,31,33,35,39,45,51,52,56,58,59,68]

RESULTS

HIV-infected women: Forty-six women were non-Hispanic African American, four were non-Hispanic white, and none was Hispanic. HIV-infected women (mean age 47 years) were older than HIV-uninfected women (mean age 32 years, p<0.0001). HIV-infected women were more likely to have hrHPV (p=<0.0001) and abnormal cytology (LGSIL/HGSIL) (p=0.006) than HIV-uninfected women (see Table 1). All eight HIV-infected women with LGSIL/HGSIL (100%) had hrHPV, while 11 of 42 HIV-infected women without LGSIL/HGSIL (26%) were hrHPV positive (p=<0.0001, 2-tailed Fisher's exact test). CD4+ cell counts were lower in women with abnormal cytology and hrHPV than those without one or both of these parameters, but this was not statistically significant with our sample sizes (see Table 2). All women were receiving combination antiretroviral therapy (ART), but we did not have data as to their adherence.

HIV-uninfected women: Hispanic women (n=27) were younger (mean age 28 years) than the non-Hispanic African Americans (n=200; mean age 32 years; p=0.04) and non-Hispanic whites (n=45; mean age 37 years; p=0.0002). Non-Hispanic African American women were also younger than non-Hispanic white women (p=0.004) (see Table 3). (Race/ethnicity was either "other" or was unknown in 32 women.) Among these HIV-uninfected women, 8 of 39 (21%) women with hrHPV had abnormal cytology (LGSIL/HGSIL) compared with 6 of 265 (2.3%) women who were hrHPV negative (p=<0.0001) (see Table 4).

Only 125 women were considered likely to have been offered routine HPV vaccination during their adolescence, based on their being ages ≤29 years at the time of data collection, i.e., they had to be ≤18 years of age since year 2002 when HPV vaccination was recommended for routine use in the US. We termed these women "vaccine-eligible." Among these vaccine-eligible young women, only one of 16 (6%) Hispanic women had received at least one dose of HPV vaccine compared to 17 of 86 (20%) of non-Hispanic African American and 2 of 12 (17%) non-Hispanic white women; the other 11 vaccine-eligible women belonged to the "other" or "unknown" group, of whom only 1 of 11 (9%) had received the vaccine (see Table 3).

None of the 21 vaccine recipients had evidence of an abnormal cytology (LGSIL/HGSIL) compared to 9% (9/104) of vaccine non-recipients in the same age group (p=0.4, Fisher's exact test). When adding ASCUS to SIL, none of the vaccine recipients (0 of 21) had any cytological abnormalities (LGSIL, HGSIL, or ASCUS) compared to 17% (18 of 104) of those not vaccinated (p=0.04). Risk for having developed precancerous lesions when hrHPV infected, in our study was found to be higher (11-fold) in HIV-uninfected women compared to HIV infected women (5-fold) (see Table 4).

DISCUSSION

We found that both HIV-infected and uninfected women in a public hospital in Nashville, TN had high prevalence of hrHPV associated precancerous cervical lesions. HPV is one of the best recognized oncogenic viruses. It has been suggested by Mesri et al[20] that oncoviruses are necessary but not sufficient to cause cancer development; host and environmental cofactors also contribute to the pathogenesis of the disease. Oncoviruses have been suggested to rely on persistence to disseminate and then deploy powerful immune evasion programs to establish long-term infection. Some viruses have evolved anti-apoptotic and proliferative genetic features that can induce cancer hall-marks in the infected cell.[21] The authors have further postulated that when these oncoviruses overcome the ability of the host to maintain homeostasis, they trigger cellular changes ultimately leading to cancer. The "high-risk" alpha HPVs that specifically infect mucosal epithelial cells are responsible for nearly all cases of cervical carcinoma. HPVs have been reported to retain differentiated epithelial cells into a DNA-synthesis competent state, a strategy required to trigger cancer development.[22]

HIV-infected women have impaired cell mediated immunity. Therefore, it is not surprising that HIV-infected women in our study, as in many others dating back to the 1980s, had a higher prevalence of hrHPV infection.[15–17] It is well documented that hrHPVs can establish long-term persistent infection of epithelial cells, avoiding immune destruction. HrHPV E6 and E7 genes encode potent oncoproteins which hinder innate immunity by inhibiting interferon signaling.[23] Although, HIV-infected women in our study, who developed abnormal cervical cytology (LGSIL or HGSIL) associated with hrHPV did not show significantly lower CD4+ cell counts than those with normal cytology, a larger sample size may show such a difference. Nevertheless, it is important to maintain integrity of the immune system in HIV-infected women through ART-mediated immune reconstitution.[24,25] In addition, HPV vaccination may be considered for all HIV-infected women, regardless of their age.

HPV vaccine rates were low. No HIV-uninfected women who had received at least a single dose of the HPV vaccine had any precancerous lesions. Although with our small sample size, this marked difference was not statistically significant, it would have been significant if the proportions had remained the same but the sample size were doubled. Of course, we already know that HPV vaccine indeed prevents the development of precancerous cervical lesions. Among the unvaccinated women, Hispanics were least likely to have been vaccinated. Therefore, routine HPV vaccination should be reinforced in minority and public sector clinic populations, especially in Hispanic adolescents.

Although Hispanic and African American women had a higher prevalence of abnormal cytology or hrHPV than did white women, the former had received a Pap test at a significantly younger age than the white women. We do not know whether this suggests poor follow up care in the minority women or whether white women using this public hospital are simply not getting tested at rates comparable to white women in higher income venues.

One of the limitations of our study is that a cross-sectional clinical survey cannot determine if the higher prevalence of abnormal cytology in the HIV-infected group is due to persistence of hrHPV, recurrence, or new infection. Indeed, our study has demonstrated that the risk of harboring hrHPV in HIV-infected or uninfected women is associated with significantly higher risk for developing precancerous lesions (LGSIL or HGSIL), 11-fold higher in HIV-uninfected women and five-fold higher in HIV-infected women (see Table 4). Our sample sizes are too small to make definitive statements about CD4+ cells and risk, or the impact of HPV vaccine, though our trends are what might be expected.

Data regarding impact of persistence of serotype specific hrHPV infection on subsequent development of precancerous lesions in HIV-infected or uninfected women stratified by race and ethnicity in the U.S. are scarce. Hence, prospective studies could assess the real-world impact of serotype-specific HPV persistence and HPV vaccine benefits in disease progression and cervical neoplasia development in minority women in the South.

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Table 1.

High-risk human papillomavirus (hr-HPV) infection in HIV-infected and HIV-uninfected women in a public hospital in Nashville, Tennessee, 2012–2015

	HIV Infected (n = 50)	HIV Uninfected (n = 304)	P
Age in years, Mean (± SD)	47 (± 11)	32 (± 11)	<0.0001 *
Proportion with hr-HPV (%)	19/50 (38)	39/304 (13)	<0.0001 #
Proportion with LGSIL/HGSIL (%)	8/50 (16)	14/304 (5)	0.006 #
Proportion with LGSIL/HGSIL/ASCUS/Dysplasia (%)	15/50 (30)	37/304 (12)	0.003 #

* Two-tailed t-test

Two-tailed Fisher's Exact test

Table 2.

Immunologic, virologic and cytologic parameters by hrHPV Status in 50 HIV-infected Women

	hrHPV (n = 19)	No hrHPV (n = 31)	P
CD4+ cells/μL Mean (± SD)	519 (± 330)	632 (± 304)	0.22 *
Viral load copies/mL Mean (± SD)	1099.79 (± 4706.22)	5570.58 (± 16837.58)	0.26 *
Proportion LGSIL/HGSIL (%)	8/19 (16)	0/31 (0)	<0.0001 #

*Two-tailed t-test

#Two-tailed Fisher's Exact test

Table 3.

Cervical and HPV data by race and ethnicity of the 304 HIV-uninfected women in the study

All HIV-uninfected women (n = 304)	**Hispanic (n = 27)**	**Black (n = 200)**	**White (n = 45)**	***Other (n = 12)**	**Unknown (n = 20)**
Age in years Mean (± SD)	28 (± 8.3)	32 (± 10.8)	37 (+10.6)	37 (± 14)	32 (± 13)
Proportion LGSIL or HGSIL (%)	1/27 (3.7)	11/200 (5.5)	1/45 (2.2)	0/12 (0)	1/20 (5.0)
Proportion infected with hr-HPV (%)	3/27 (11)	24/200 (12)	3/45 (07)	2/12 (17)	5/20 (25)
Among women eligible for HPV vaccine (n=125), the proportion not receiving the vaccine (%)	15/16 (94)	69/86 (80)	10/12 (83)	3/3 (100)	7/8 (88)
Women eligible for receipt of HPV vaccine (n = 125)#					
LGSIL/HGSIL among Vaccine Non-Recipients (%)	1/15 (7%)	6/69 (9%)	1/10 (10%)	0/3 (0%)	1/7 (14%)
LGSIL/HGSIL among Vaccine Recipients (%)	0/1	0/17	0/2	0/0	0/1

*includes Asian, Middle-Eastern, and American Indian

#p=0.35 by two-tailed Fisher's Exact test, comparing proportion of SIL in vaccine-recipients of all races/ethnic groups combined (0/21) with SIL in all vaccine non-recipients (9/104).

Table 4.

Risk of abnormal cytology comparing 50 HIV-infected and 304 HIV-uninfected women with and without high-risk human papillomavirus infection (hr-HPV)

	HIV Infected (n = 50)		HIV Uninfected (n = 304)	
	hrHPV	**No hrHPV**	**hrHPV**	**No hrHPV**
Cases with LGSIL/HGSIL	8	0	8	6
Control with Normal Cytology	11	31	31	259
Total	19	31	39	265
Odds Ratio	5.29 *		11.14	
(95% CI)	*		(3.11–41.11)	
P value	0.0001 #		<0.0001 #	

*Exact confidence levels not possible with zero count cells for HIV-infected group

#Chi square test