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Short Communication

Follow-Up of Papanicolaou (Pap) in HIV-positive and HIV-negative Women

Shahana A. Choudhury[1]*, Vladimir Berthaud[2], Gwinnett Ladson[3], and Abosede Osijo[4]

[1]Department of Pediatrics, Meharry Medical College (MMC), USA

[2]Department of Internal Medicine, Meharry Medical College (MMC), USA

[3]Department of Obstetrics and Gynecology, Meharry Medical College (MMC), USA

[4]Department of Internal Medicine, Meharry Medical College (MMC), USA

***Corresponding author**

Shahana A. Choudhury, Department of Pediatrics, Meharry Medical College (MMC), 1005 D.B Todd Blvd, Nashville, TN 37208, Tel: 615-327- 6332; Fax: 615-327-5989; Email: schoudhury@mmc.edu

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Abstract

Introduction: Persistent high-risk HPV (hrHPV) is considered a risk for the progression from pre-cancer to invasive cervical cancer (ICC). According to viral profiles, persistence of hrHPV infection may present as a chronic persistent infection or reinfection. Limited data exists regarding persistence of hrHPV in HIV-infected and -uninfected individuals.

Methods: We tracked the Papanicolaou (Pap) results in forty-seven HIV-positive and 304 HIV-negative women five years after baseline testing.

Results: Follow-up Pap results were available in twenty-one of the forty-seven (45%) HIV-positive and thirty-seven of the 304 (12%) HIV-negative women. On follow-up, HIV-positive women were significantly (p=0.002) more likely to be at higher risk of persistent hrHPV infection and abnormal cytology (LGSIL/HGSIL) than their negative counterparts. In both the baseline and follow-up studies, hrHPV was significantly (p=0.000) associated with abnormal cytology in both HIV-positive and -negative women. HIV-positive women were significantly (p= 0.001) more likely than their negative counterparts to have missed an opportunity to reassess their hrHPV status with follow-up Pap testing.

Conclusion: HIV-positive women remain at significantly higher risk for a persistent hrHPV infection and abnormal cervical cytology than their HIV-negative counterparts. Both HIV-positive and -negative women have evidence of poor compliance with follow-up Pap testing. Among all ethnic groups enrolled in the baseline study, Hispanic women were most likely to have missed follow-up Pap testing. Whether persistence of abnormal Pap is due to chronic persistent infection or reinfection cannot be determined from this study. Further studies involving a larger sample size to demonstrate persistence patterns are recommended.

INTRODUCTION

Data regarding persistence and persistence patterns of high-risk (hr) HPV in both HIV-positive and HIV-negative women and adolescents in the US are sparse (1,2). The most typical course of an HPV infection is spontaneous clearance. When the virus does not clear, it can integrate into the host genome, causing precancerous transformation. The time required for clearance varies by HPV type (3-5). Risk factors for higher prevalence of abnormal cervical cytology due to hrHPV infection may include persistence, immunosuppression, older age, concurrent sexually transmitted infections, and race/ethnicity.

Oncoviruses are necessary but not sufficient for cancer development; host and environmental cofactors also contribute to pathogenicity (6,7). To establish long-term infection, oncoviruses rely on persistence to disseminate and then deploy powerful immune evasion programs. When these oncoviruses overcome the host's ability to maintain homeostasis, they trigger cellular changes that ultimately lead to cancer. The high-risk alpha HPVs that specifically infect mucosal epithelial cells are responsible for nearly all cases of cervical carcinoma. Studies have reported that HPVs retain differentiated epithelial cells in a DNA-synthesis competent state, a strategy required for triggering cancer development (8). It is well-documented that hrHPVs can establish a long-term, persistent infection in epithelial cells, avoiding immune destruction. HrHPV E6 and E7 genes encode potent oncoproteins, which hinder innate immunity by inhibiting interferon signaling (9).

The description of HPV persistence is unclear in the literature. Chronic persistence may be defined as being positive for the same type of HPV at two consecutive time points, and reinfection defined as recovery followed by infection with the same or a different genotype. A recent study determined that persistence of hrHPV is higher in African American women (OR 1.61) than in European women (10). A recent prospective study determined the effect of psychosocial stresses on the progression from squamous intraepithelial lesions (SIL) to progressive/persistent lesions in HIV-infected women (11).

Immunosuppression

The immune response (IR) to HPV follows Th1 pathway. Subsequent to natural infection, the IR does not usually protect against future infections. In general, the normal host mounts an

effective cell-mediated immunity (CMI) following an infection (12), leading to the regression of lesions. However, impaired CMI will result in persistent infection and, in the case of oncogenic HPVs; there is an increased probability of progression to cervical intraepithelial neoplasia category 3 and invasive carcinoma. The reactivation of latent HPV infection at older age is another example of relative immunosuppression leading to cancerous lesions (13). Thus, HIV infectionassociated-immunosuppression promotes the persistence of HPV infection (14,15) which directly enhances HPV-associated oncogenesis at the molecular level. It is claimed that a protective IR to the virus is expressed as a serum neutralizing antibody to the major capsid protein L1, which develops after the induction of successful CMI (16,17). HIV-positive women do not mount an effective IR due to their impaired CMI. Thus, it is not surprising that many researchers had discovered a higher prevalence of hrHPV in HIV-positive women since the 1980s (18-20). Research suggests that CD8 cells and immune suppressive regulatory T (Tregs) cells infiltrate persistent HPV infection sites and exert a reduction of toll-like receptors (21). Studies have also suggested that persistent hrHPV infections in HIV-positive individuals are linked with aforementioned immunologic characteristics (22,23). Moreover, the incidence of invasive cervical cancer (ICC) among HIV-positive women in the US is over three times higher than among HIV-negative women (16 vs. 5 per 100,000 person-years) (24-27).

Age

As hrHPV prevalence declines with increasing age, it presents two peaks: a higher one at age (14 - 19 years old) and a lower one at age (30 - 34 years old) (28,29).

Concurrent Sexually Transmitted Infections

A higher prevalence and rapid progression of hrHPV infection can be promoted by concurrent sexually transmitted infections whose incidence is highest in women with HIV (common risk factors) and among African American women (higher rates in their partners) (30,31).

Race/Ethnicity

In the US, conspicuous health disparities exist in the prevalence of ICC among racial/ethnic groups (32). The reported incidence rates are significantly higher in African American (odds ratio [OR] 1.34) and Hispanic (OR 1.55) women than Caucasian women (33,34).

MATERIAL AND METHODS

Using electronic medical records, we followed up Pap smear results of a cohort of forty-seven HIV-positive and 304 HIV-negative (control) women (34) after a mean of five years (range, 3 - 8) to assess the state of cytology. HIV-positive women attended Meharry Community Wellness Center (MCWC), a state-designated AIDS Center of Excellence clinic, while HIV-negative women attended the Meharry Obstetrics/Gynecology (OBGYN) outpatient clinic. Data extracted for patients' health records included age, race/ethnicity, and HIV status, Pap test and colposcopy results. From the records of the HIV-positive women, we abstracted their current CD4+ cell count and viral load data. To determine the 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 (AGC). We defined "abnormal cytology" in women only when they had ASCUS, 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) a technology that detects thirteen high-risk HPV types using full genome probes. We considered the identified oncogenic genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68) as hrHPV.

RESULTS

Follow-up Pap test results were available for only twenty-one of the forty-seven (45%) HIV-positive women and thirty-seven of the 304 (12%) HIV-negative (control) women. Per Table 1, HIV-positive women were significantly older than their counterparts in both the initial or baseline and follow-up studies (involving all subjects). Overall, Hispanic women had a much lower rate of follow-up Pap smear (only one of the twenty-seven, or 4%), as opposed to non-Hispanic women (53 out of 327, or16%); (p=0.09). Among HIV-negative women, 1/27 Hispanics (04%) and 36/277 (13%) non-Hispanics had their follow-up Pap smear. HIV-positive women were significantly more likely than their negative counterparts to have hrHPV in both the initial and follow-up studies (Table 1). HIV-positive women were also considerably more likely to have abnormal cytology than their counterparts were.

Cohort patients who had a follow-up Pap: All HIV-positive women were non-Hispanic black. Of the thirty-seven HIV-negative women, only one was Hispanic and one was non-Hispanic white; the remainder of the thirty-five women were non-Hispanic black (Table 1). Of the forty-seven HIV-positive women from the initial study, eight (17%) women had been deceased. Of the remaining thirty-nine surviving women, six (15%) had relocated to another state; two (5%) had been transferred to another clinic and twenty-one (54%) had at least one follow-up Pap. Within the HIV-positive group, the mean (range) CD4 count and viral load at follow-up was 786/mm3 (218-1813) and 169 (<20-2,420) copies/ml respectively compared to the initial or baseline CD4 count and viral load of 572 (15-1228)/mm3 and 2,716 (75-66,341) copies/ml respectively. Within all groups, abnormal cytology was significantly (p=0.000) more likely to be associated with hrHPV (Table 2,3). In the follow-up study, evidence of persistent hrHPV associated with hrHPV at baseline was found to have significant (p=0.002) association in HIV-positive women only (Table 4).

DISCUSSION

Our study has demonstrated poorer compliance with follow-up Pap testing in HIV-negative versus HIV- positive women (12% vs 54%), which could be explained by increased awareness among HIV-positive women and better access to comprehensive services. The lower adherence with follow-up Pap testing in

Table 1: Baseline and Follow-Up Study: HIV-Positive and Negative.

	Baseline			Follow-Up		
	HIV	Control	p	HIV	Control	p
Number All subjects	47	304		21	37	
Age years Mean (± SD)	47 (10.74)	32 (11.09)	*0.000	49 (10.88)	38 (10.99)	*0.006
Ethnicity n (%)	^Hisp= 0 ^^NHisp= 47 (100)	^Hisp=27 (09) ^^NHisp= 277 (91)		^Hisp=0 ^^NHisp=21 (100)	^Hisp=1 (03) ^^NHisp=36 (97)	
Race n (%)	Black=44 (94) White=3 (06)	Black=200 (66) White=45 (15) Unknown=59 (19)		Black=21 (100) White=0	Black= 35 (94) White=1 (03) Unknown=1 (03)	
HrHPV n (%)	18/47 (38)	40/304 (13)	#0.000	9/21 (43)	5/37 (13)	#0.02
Abnormal cytology n (%)	14/47 (30)	33/304 (11)	#0.002	7/21 (33)	5/37 (13)	#0.09

*Two tailed t test # Two-tailed Fisher's Exact test ^Hisp= Hispanic; ^^NHisp= Non-Hispanic

Table 2: Differentiation of Abnormal Cytology: Baseline and Follow-Up Study: HIV-Positive and Negative.

	Baseline (All subjects)			Follow-up		
	HIV	Control	*p	HIV	Control	*p
Negative n (%)	33/47 (70)	271/304 (89)	0.003	14/21 (67)	32/37 (86)	0.1
ASC-US n (%)	7/47 (15)	21/304 (07)	ns	4/21 (19)	2/37 (05)	ns
LGSIL n (%)	6/47 (13)	9/304 (03)	ns	3/21 (14)	2/37 (05)	ns
HGSIL n (%)	1/47 (02)	3/304 (01)	ns	0/21 (0)	1/37 (03)	ns

*p= Two-tailed Fisher's Exact Test

Table 3: Cohort Baseline and Follow-Up Study: HV-Positive and Negative: Abnormal Cytology Related To hrHPV.

	Baseline study			Follow-Up study		
Groups	^Abn Cyto with hrHPV n (%)	^Abn Cyto without hrHPV n (%)	*p	^Abn Cyto with hrHPV n (%)	^Abn Cyto without hrHPV n (%)	*p
HIV	9/10 (90)	1/10 (10)	0.000	7/7 (100)	0/7 (0)	0.000
Control	6/6 (100)	0/6 (0)	0.000	4/5 (80)	1/5 (20)	0.000

*Two-tailed Fisher's Exact Test ^Abn Cyto=Abnormal Cytology

Table 4: Cohort Baseline and Follow-Up Study: HIV-Positive and Negative: Persistence of hrHPV.

	hrHPV at Follow-Up Study n (%)		
Groups	hrHPV at Baseline	Without hrHPV at Baseline	*p
HIV	8/9 (89)	1/9 (11)	0.002
Control	3/5 (60)	2/5 (40)	ns

*Two-tailed Fisher's Exact Test

Hispanic women can be explained by lack of health insurance coverage or inadequate cultural competence of medical providers including linguistically inappropriate communication. Per tables, one and two, HIV-positive women were significantly older than their counterparts in the initial and follow-up studies. The relatively older age of the HIV- positive women may be related to heightened awareness, higher rates of abnormalities, and specific guidelines requirements.

Our study demonstrated increased rates of hrHPV associated abnormal cytology in both HIV-positive and negative women,

corroborating that hrHPV are a strong predictor for abnormal cytology/precancerous lesions in HIV-positive and HIV-negative women. Nonetheless, evidence of persistent hrHPV at follow-up was significantly associated with hrHPV at baseline. This finding suggests that HIV-positive women remain at a higher risk for persistent hrHPV infection when compared with HIV-negative women. Therefore, preventing HPV infection should be the mainstay of treatment through timely HPV vaccination during adolescence and young adulthood in all women, particularly those living with HIV. Maintaining the integrity of the immune system through highly active antiretroviral therapy is the secondary mainstay for preventing HPV-related disease progression in HIV-infected women. The higher mean CD4 cell count and lower mean viremia observed at follow-up supports this statement. This may further explain why there is relative lack of disease progression (HGSIL) despite persistence of hrHPV among this cohort of HIV-positive women (Table 2).

However, our study does not show whether persistence of hrHPV is due to truly chronic infection or reinfection. We need to pursue larger prospective studies to differentiate between these two states.

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