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Racial Differences in HPV Types Amongst US Women with HIV and Cervical Precancer

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Abstract

Objective: Recent studies reported lower human papillomavirus 16 (HPV16) prevalence in cervical precancer among African American than Caucasian women in the general population. We assessed this relationship in women with HIV.

Design: Women living with or at risk for HIV in the Women's Interagency HIV Study were followed semi-annually with Pap tests, colposcopy/histology (if indicated), and collection of cervicovaginal lavage samples for HPV testing by PCR. Racial and ethnic groups were defined using genomic Ancestry Informative Markers (AIMs).

Results: Among 175 cases of cervical intraepithelial neoplasia 3 or worse (CIN-3+), 154 were diagnosed in women with HIV. African American (27%) and Hispanic (37%) cases were significantly less likely than Caucasian (62%) women to test positive for HPV16 (p=0.01). In multivariate logistic regression models, these associations remained significant for African

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Author Contributions

MJK and HDS conceived of and designed the study. LSM, IE, NAH, KA, HM, GD, CC collected and/or managed the data. JMP and RDB performed HPV testing. XX, XX, LLR, MK and BA analyzed the data with input from MJK and HDS. MJK and HDS drafted the manuscript. All authors revised the manuscript and gave final approval.

Americans (odds ratio=0.13; 95% confidence interval 0.04–0.44; p=0.001) but not Hispanics, after controlling for HIV status, CD4 count, history of AIDS, age, smoking, and sexual behavior. Limiting the analysis to women with HIV did not change the findings.

Conclusion: HPV16 prevalence is lower in African American compared to Caucasian women with HIV and cervical precancer, independent of immune status. Future studies to determine why these racial differences exist are warranted, and whether there are similar associations between race and invasive cervical cancer in women with HIV. Further, HPV types not covered by quadrivalent and bivalent vaccines may play an especially important role in cervical precancer among HIV-positive African American women, a possible advantage to using nonavalent HPV vaccine in this population.

Keywords

human papillomavirus; HIV; race; ethnicity; cervical precancer

Introduction

Women with human immunodeficiency virus (HIV) infection have several-fold greater risk of invasive cervical cancer [1–3] and precancer (i.e., cervical intraepithelial neoplasia 3 or more severe lesions [CIN-3+]) [4], as well as infection with oncogenic human papillomaviruses (oncHPV) [5, 6], the major risk factor for cervical cancer and precancer. While HPV16 accounts for approximately half of invasive cervical cancers in the general population [7], HPV16 has the weakest association with changes in host immune status of any oncogenic HPV type, as measured by HIV status and CD4+ T-cell count [8, 9]. Consistent with this, the prevalence of HPV16 found in women with CIN3+ was significantly lower among women with HIV (29%) than in women without HIV (62%) in the Women's Interagency HIV Study (WIHS) [10] and other studies [11, 12].

Interestingly, two recent reports in the general United States (US) population indicated that the distribution of oncHPV types in cervical precancer varied by self-reported racial group. Specifically, the proportion of CIN3+ cases positive for either HPV16 or 18 was significantly lower in African American (41%) compared with Hispanic (46%) and non-Hispanic Caucasian women (60%) [13]. In a second study, African American and Hispanic women had a lower prevalence of HPV16 or 18 in CIN2+ lesions compared with Caucasian women [14]. Additional recent studies (but not all) found low HPV16 and sometimes also HPV18 among African Americans in the general population, even in the absence of cervical precancer [15–20]. One prior study in women with HIV by Whittemore et al. (2016) did not find similar racial differences, but studied young individuals, 13–26 years of age, without cervical precancer. Therefore, the objective of the current study was to assess for differences in HPV16 prevalence in women with HIV and CIN-3+ across racial and ethnic groups, and for the first time to use genomic Ancestry Informative Markers (AIMs) as an adjunct to self-report to optimally characterize these racial and ethnic groups.

Methods

The WIHS is an ongoing prospective cohort study of health outcomes among 2791 women with HIV and 975 women at risk for HIV, enrolled from six clinical sites across the US, during 1994–1995 and again during 2001–2002. As previously described [21, 22], semi-annual visits include a gynecologic examination with specimen collection, including a Pap test and cervicovaginal lavage for HPV testing, using a well-established polymerase chain reaction (PCR) assay [5, 23]. All cervical cytology was centrally interpreted using the 1991 or 2001 Bethesda System criteria for cytologic diagnosis [24, 25]. Colposcopy was required for any epithelial cytologic abnormality, including borderline lesions (ASC-US). HPV DNA PCR detection methods in the WIHS have been described previously [5, 23, 26]. In brief, HPV DNA was detected using a well-established degenerate primer MY09/MY11/HMBO1 PCR assay. Primer set PC04/GH20, which amplifies a cellular β-globin DNA fragment, was used as an internal control to assess the adequacy of amplification. The amplification products were then probed for the presence of "any HPV" DNA with a generic probe mixture, and probed for individual HPV types using filters hybridized with type-specific biotinylated oligonucleotides for >40 individual HPV DNA types. β-globin negative specimens were excluded. Written informed consent was obtained from all participants, and the study was approved by each local institutional review board. The analysis included all women in the WIHS who were diagnosed with CIN3+ through visit 35 (up to 17 years of follow-up).

Racial and ethnic groups were based on genomic ancestry informative markers (AIMs), as previously reported [27, 28], and secondarily by self-report. Briefly, a genome-wide association study (GWAS) was conducted amongst WIHS women who provided informed consent for genetic testing (n=3353). Race/ethnicity was assessed using principal components analysis of 185 independent AIMs single nucleotide polymorphisms (SNPs) from across the human genome known to differ in allele frequency between the major racial/ethnic groups common in the WIHS.

Descriptive statistics were used to examine differences in characteristics between women with HIV to those without HIV at the time of histologic diagnosis of CIN3+, using the t-test (to assess means), Wilcoxon test (for medians), or Pearson χ^2 test (for proportions). Fisher's exact test was used to compare differences in type-specific HPV by race and ethnicity. Multivariate logistic regression was used to explore the association of race/ethnicity with HPV16 infection, after adjusting for race and other established cervical risk factors.

Results

Overall, 2791 women with HIV and 975 women at risk for HIV were enrolled in WIHS. CIN3+ was found in 154 (5.5%) women with HIV and 21 (2.2%) women without HIV across all 35 visits analyzed; i.e., a total of 62,178 person-visits (a median of 18 person-visits). Two HIV-infected women had invasive cancer. Table 1 shows selected demographic and clinical characteristics at the time of diagnosis of CIN3+. Women without HIV were on average younger and more likely than women with HIV to be less than 30 years of age.

Of the 175 women diagnosed with CIN3+, AIMs data were available in 168 (96%). The HPV type-specific distribution by race among all CIN3+ cases is shown in Table 2. A total of 54 (31%) cases of CIN3+ were associated with HPV16 infection and 17 (10%) were associated with HPV18. However, African American (27%) and Hispanic (37%) women were significantly less likely than Caucasian (62%) women to have HPV16-associated CIN3+ (p=0.01). The prevalence of HPV18 did not differ by racial or ethnic group.

In multivariate logistic regression analysis among all women with CIN3+ (Supplemental Table 1), those with HIV were significantly less likely than women without HIV to test positive for HPV16, after adjustment for multiple relevant covariates, including age, race/ethnicity based on AIMs data, WIHS enrollment period, smoking, lifetime number of sexual partners, number of sexual partners in the 6 months before CIN3+ diagnosis, current CD4 count, and history of AIDS (consistent with our prior report) [10]. A very high life-time (but not recent) number of sex partners was also associated with HPV16-positive CIN-3+. Moreover, in these same models, African American women with CIN3+ were approximately 85% less likely to have HPV16 detected compared with Caucasian women (Odds Ratio [OR] 0.13, 95% Confidence Interval [CI] 0.04–0.44, p=0.001) (Supplemental Table 1). Hispanic ethnicity however was not significantly associated with HPV16 detection in multivariate analysis (p=0.81), and the prevalence of no other oncHPV type differed significantly by race/ethnicity in multivariate models that excluded the category “Other”. Similar associations were observed for women who self-reported their race as African American (OR 0.07, 95% CI 0.02–0.27, p<0.0001). There was high concordance for race using AIMs data versus self-report among women with CIN3+ (kappa=0.63, 95% CI 0.53–0.72) and for all WIHS patients with available HPV data (kappa=0.72, 95% CI 0.70–0.74).

There were no racial differences in HPV16 prevalence among all WIHS women (including all women with and without cervical disease). That is, lower HPV16 prevalence among African American women with HIV was only observed in the setting of cervical disease. Importantly, the findings did not change when the definition of precancer was expanded to include not only WIHS women with CIN3+, but also the subset of CIN2 confirmed by concomitant high-grade squamous intraepithelial lesion (HSIL) of the severe subtype – a total of N=250 women (Supplemental Table 2).

Discussion

Recent studies, including population-based investigations, have reported lower prevalence of HPV16, and sometimes HPV18, in African American women with and without cervical precancer [13, 14, 16–18]. This could potentially lead to increased precancer risk in African Americans immunized with quadrivalent or bivalent HPV vaccines targeting HPV16/18 but not other oncHPV types, relative to HPV vaccine immunized Caucasian women. The current study however was the first, to our knowledge, to study these relationships in women living with HIV, a population at high risk for cervical precancer and cancer compared to women without HIV. The results showed markedly lower odds of HPV16-positive precancer amongst African American than Caucasian women even after accounting for HIV status and CD4 count. Some studies in the general population also found reduced HPV16 prevalence in Hispanics [13, 14, 29]. While our data in Hispanic versus Caucasian women living with HIV

were suggestive of such an association it did not reach significance in this analysis, after adjusting for covariates.

These results are particularly noteworthy as recent meta-analysis showed that HPV16 was less prevalent among HIV-positive than HIV-negative cervical cancer (in Africans) and precancer patients (worldwide) [11, 12]. The current data additionally show that even among HIV-positive women with cervical precancer, those of African descent are more likely to test positive for HPV types other than HPV16, than Caucasian women. Future US studies in a larger multi-racial HIV-positive population, involving laser capture microdissection, would be useful in confirming these findings. Possible reasons for low HPV16 prevalence in African Americans with HIV and precancer include racial differences in distribution and prevalence of HPV infection within sexual networks, host susceptibility, and differential ability to clear HPV infection [15, 19].

Overall, if the single most important factor determining HPV vaccine effectiveness is the HPV types targeted then these data suggest that use of the nonavalent is preferable to either the quadrivalent or bivalent vaccine. On the other hand, immunogenicity has been shown to be greater with the bivalent vaccine [30, 31], which may be important in immunosuppressed populations. Recent data also show that even if precancer in HIV-positive women involves a greater diversity of HPV types compared with the general population [10, 11], the proportion of HPV16 infection that progresses to cervical precancer (and possibly cancer) is far higher than other oncHPV types [23]. The optimal approach for HPV vaccination and for primary HPV screening (in which an HPV assay and not cytology is the initial test) has not been fully determined in HIV-positive women, and cannot be adequately extrapolated from studies in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic and clinical characteristics at diagnosis of women with cervical intraepithelial neoplasia 3 or more severe lesions (CIN-3+) by HIV status and CD4 Count

	HIV- (N = 21)	HIV+				P-value 1*	P-value 2†
		Total (N = 154)	CD4>500 (N = 25)	CD4:200–500 (N = 65)	CD4<200 (N = 62)		
Age, yrs							
Mean (SD)	32.7 (8.2)	39.6 (8.1)	37.0 (8.5)	39.5 (8.2)	40.6 (7.8)	**0.0003**	**0.001**
Age, N (%)						**0.004**	**0.02**
<30	10 (48)	19 (12)	8 (32)	6 (9)	5 (8)		
30–34	4 (19)	29 (19)	4 (16)	15 (23)	10 (16)		
35–39	3 (14)	37 (24)	5 (20)	16 (25)	15 (24)		
40–44	1 (5)	30 (19)	4 (16)	13 (20)	13 (21)		
>=45	3 (14)	39 (25)	4 (16)	15 (23)	19 (31)		
AIMs Race, N (%)						0.21	0.11
White	4 (19)	17 (12)	4 (17)	9 (14)	4 (7)		
Hispanic	0 (0)	19 (13)	4 (17)	10 (16)	5 (8)		
Black	16 (76)	96 (65)	13 (57)	41 (65)	41 (68)		
Others	1 (5)	15 (10)	2 (9)	3 (5)	10 (17)		
Enrollment period, N (%)						0.07	0.11
1994–95	12 (57)	117 (76)	16 (64)	50 (77)	50 (81)		
2001–02	9 (43)	37 (24)	9 (36)	15 (23)	12 (19)		
Smoking, N (%)						0.09	0.16
Never smoked	4 (19)	30 (20)	4 (16)	12 (19)	14 (23)		
Former smoker	7 (33)	21 (14)	3 (12)	13 (21)	5 (8)		
Current smoker	10 (48)	101 (66)	18 (72)	38 (60)	43 (69)		
Lifetime # of male sexual partner, N (%)						0.36	0.88
<5	1 (5)	28 (18)	4 (16)	11 (17)	12 (20)		
5–9	7 (33)	36 (24)	7 (28)	16 (25)	13 (21)		
10–49	8 (38)	46 (30)	8 (32)	21 (33)	17 (28)		
>=50	5 (24)	42 (28)	6 (24)	16 (25)	19 (31)		
# of male sexual partner past 6 months, N (%)						0.10	**0.02**
0	5 (24)	52 (34)	12 (50)	17 (27)	23 (37)		
1	12 (57)	85 (56)	12 (50)	36 (57)	35 (56)		
2	0 (0)	7 (5)	0 (0)	3 (5)	4 (6)		
>=3	4 (19)	7 (5)	0 (0)	7 (11)	0 (0)		
CD4+ count, N (%)							
>500		25 (16)					
200–500		65 (43)					

	HIV- (N = 21)	HIV+				P-value 1*	P-value 2†
		Total (N = 154)	CD4>500 (N = 25)	CD4:200–500 (N = 65)	CD4<200 (N = 62)		
<200		62 (41)					
HIV viral load, N (%)							**0.002**
<=4000		73 (48)	17 (68)	34 (53)	21 (34)		
4001–20,000		23 (15)	5 (20)	11 (17)	6 (10)		
20,001–100,000		32 (21)	3 (12)	12 (19)	17 (27)		
>100,000		25 (16)	0 (0)	7 (11)	18 (29)		
AIDS history, N (%)							**0.01**
No		87 (56)	17 (68)	43 (66)	25 (40)		
Yes		67 (44)	8 (32)	22 (34)	37 (60)		

*Comparing HIV+ with HIV- women.

†Comparing HIV+/CD4>500, CD4:200–500, CD4<200 with HIV- women.

Table 2.

Type-specific human papillomavirus prevalence in women with cervical intraepithelial neoplasia 3 or more severe lesions (CIN-3+) using genomic ancestry informative markers (AIMs) to characterize racial and ethnic groups, N (%)

HPV Type	White (N = 21)	Hispanic (N = 19)	Black (N = 112)	Others (N = 16)	P-value*	P-value†
16	13 (61.9)	7 (36.8)	30 (26.8)	4 (25.0)	**0.02**	**0.01**
18	1 (4.8)	4 (21.1)	10 (8.9)	2 (12.5)	0.33	0.22
31	3 (14.3)	5 (26.3)	10 (8.9)	2 (12.5)	0.15	0.06
33	0 (0.0)	3 (15.8)	11 (9.8)	5 (31.3)	**0.02**	0.19
35	1 (4.8)	3 (15.8)	17 (15.2)	3 (18.8)	0.57	0.47
39	1 (4.8)	1 (5.3)	8 (7.1)	2 (12.5)	0.87	1.00
45	2 (9.5)	0 (0.0)	4 (3.6)	1 (6.3)	0.32	0.34
51	1 (4.8)	2 (10.5)	8 (7.1)	1 (6.3)	0.91	0.77
52	1 (4.8)	1 (5.3)	16 (14.3)	2 (12.5)	0.60	0.42
56	1 (4.8)	1 (5.3)	14 (12.5)	2 (12.5)	0.73	0.56
58	2 (9.5)	0 (0.0)	16 (14.3)	2 (12.5)	0.38	0.24
59	0 (0.0)	1 (5.3)	1 (0.9)	2 (12.5)	**0.03**	0.25
68	1 (4.8)	1 (5.3)	10 (8.9)	0 (0.0)	0.84	1.00
73	1 (4.8)	0 (0.0)	8 (7.1)	1 (6.3)	0.89	0.84
30	1 (4.8)	1 (5.3)	14 (12.5)	4 (25.0)	0.26	0.56
53	2 (9.5)	1 (5.3)	23 (20.5)	2 (12.5)	0.34	0.20
54	2 (9.5)	1 (5.3)	17 (15.2)	1 (6.3)	0.67	0.63
61	1 (4.8)	0 (0.0)	18 (16.1)	2 (12.5)	0.17	0.09
62	2 (9.5)	0 (0.0)	15 (13.4)	3 (18.8)	0.28	0.30
66	1 (4.8)	1 (5.3)	7 (6.3)	0 (0.0)	0.94	1.00
70	1 (4.8)	1 (5.3)	17 (15.2)	1 (6.3)	0.48	0.33
71	1 (4.8)	3 (15.8)	16 (14.3)	1 (6.3)	0.60	0.51
72	3 (14.3)	0 (0.0)	5 (4.5)	3 (18.8)	**0.04**	0.14
81	3 (14.3)	3 (15.8)	11 (9.8)	3 (18.8)	0.53	0.52
83	1 (4.8)	0 (0.0)	19 (17.0)	3 (18.8)	0.09	0.06
84	1 (4.8)	1 (5.3)	13 (11.6)	4 (25.0)	0.27	0.74
Other	8 (38.1)	4 (21.1)	57 (50.9)	8 (50.0)	0.10	**0.04**

*Fisher's exact test p-values.

†P-values excluding the race = Others category.