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Disparities in the Clinical Evolution of Anal Neoplasia in an HIV-infected Cohort

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Abstract

Background—A recent meta-analysis suggested that anal intraepithelial neoplasia and invasive anal cancer are more prevalent among Black men having sex with men (MSM).

Methods—Retrospective cohort of HIV-infected adult patients under care between 2001 and 2012. Disparities in clinical evolution of anal intraepithelial neoplasia to high-grade squamous intraepithelial lesion (HSIL) and invasive anal cancer were evaluated in a 3-state Markov model adjusted for cytology misclassification. We studied sociodemographic covariate effects for each state transition using multivariable models controlling for antiretroviral therapy and infrared coagulation treatment of HSIL.

Results—Among 2804 patients with a median age of 40 years, 78% were MSM and 38% non-white. There were no disparities in HSIL prevalence (14%) by age, sex, race, or risk group. After 4.0 years of follow-up, 23 patients developed IAC. Females and black patients had lower transition rates from <HSIL→HSIL (HR=0.35 & HR= 0.55, respectively); those with age>40 had lower rates of both <HSIL→HSIL progression (HR= 0.64) and HSIL→<HSIL regression (HR= 0.56); and MSM had higher rates of progression from <HSIL→HSIL (HR 3.30).. Controlling for antiretroviral therapy and infrared coagulation treatment IRC as time-updated covariates, the univariable effects of sex, black race, and HIV risk factor remained significant.

Conclusions—Black race was not associated with prevalent anal intraepithelial neoplasia nor with post-baseline progression of anal intraepithelial neoplasia.

Keywords

Anal intraepithelial neoplasia; Anal Cancer; Progression; Disparities; HIV; Race

Introduction

Chronic immunosuppression induced by human immune deficiency virus (HIV) facilitates the persistence of human papillomavirus (HPV) [1]. Analogous to cervical cancer, chronic HPV infection induces sequential changes in the anal canal mucosa called anal intraepithelial neoplasia (AIN) of which high-grade squamous intraepithelial lesion (HSIL)

is the immediate precursor of invasive anal cancer (IAC) [2]. In the United States, the incident rate is highest among black men who have sex with men (MSM) [3]. Black MSM have disproportionally have higher rates of lack of engagement in care, uncontrolled HIV infection and resulting immunosuppression [4]. A recent systematic review suggested that anal neoplasia outcomes including AIN and IAC may be more prevalent among black MSM than other groups [5].

We previously developed a multistate Markov model of AIN natural history. In this model, HSIL is assumed to be the immediate precursor lesion to invasive anal cancer, from which both progression to IAC and regression to less than HSIL (<HSIL) may occur. IAC is considered an absorbing state from which regression does not occur in the absence of definitive treatment. We demonstrated favorable effects for antiretroviral therapy use, higher CD4 cell counts, HIV viral load suppression, and infrared coagulation (IRC) ablation on selected AIN transition rates [6].

The aim of this study was to evaluate potential sociodemographic disparities in the baseline prevalence and clinical evolution of AIN in the University of California, San Diego Owen Clinic anal neoplasia cohort.

Methods

We assembled a clinical care cytology-based retrospective cohort including the anal cytology test results and invasive anal cancer (IAC) outcomes of all HIV-infected adults under care at the UCSD Owen Clinic between 2001 and 2012. Eligibility criteria, screening program characteristics, and study measure definitions were as previously reported [6]. In short, every adult HIV-infected patient attending care in our clinic underwent a baseline anal cytology test and digital rectal exam (DRE) at the time of clinic enrollment and yearly thereafter as part of their routine HIV care. Patients with any abnormal anal cytology results or anal symptoms were referred for a diagnostic high-resolution anoscopy (HRA) procedure. Preferential HRA referral was for patients with HSIL cytology results or abnormal DRE due to the limited number of providers trained in performing HRA. Entry was defined as the date of the first screening anal cytology obtained at clinic entry (for those who entered care after the inauguration of the screening program in 2001) or as the date of the first anal cytology (for those already under care when the screening program was started). A 3-state Markov model was estimated for all patients (inception cohort) according to cytology results: <HSIL↔HSIL→IAC. Cytology states were adjusted for misclassification using within-cohort estimates of sensitivity (0.66) and specificity (0.90), with concurrent HRA-directed biopsy as the reference standard [7]. State transition rates (per person-year) and prognostic covariate hazard ratios were estimated using the R package *msm* adjusted for antiretroviral therapy and time-updated IRC treatment [8]. The study was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the University of California, San Diego Human Research Protection Program (Project 071931).

Results

Table 1 presents the main sociodemographic, HIV and AIN-related characteristics of the overall inception cohort and stratified according to the race-ethnicity category. Overall, patients had a median age of 40 years-old and were followed for a median time of 4-years. Nine out of ten patients were male, 80% of them were MSM. According to race, 38% were non-White including 13% who were Black. Most patients (75%) were taking antiretroviral therapy, and 50% had controlled viremia (< 400 copies/ml). At baseline, there was no difference according to race in the prevalence of antiretroviral therapy use, the proportion of HIV patients with viral suppression or prevalence of HSIL anal cytology ($\sim 14\%$). There was a higher proportion of females (25%) among Black patients than in other groups. Hispanic patients were younger and presented with lower CD4 cell counts (< 350 cells/mm³) than other groups at study entry. The median follow-up time of Black, Whites and Hispanic patients was similar and ranged from 49–52 months but considerably higher than patients in the other/unknown racial category (35 months). During the follow-up period, Black patients had a lower median number of collected sequential anal cytology tests than other groups (3 vs. 4). White patients had a higher proportion of ever developing an HSIL cytology (41%) in comparison to Hispanics (38%) and Blacks (33%). There were no racial differences in the proportion of patients undergoing IRC ablation of HSIL lesions. A total of 23 patients developed IAC with similar distribution in the proportion of IAC cases among all race categories.

Table 2 shows covariate effects on different transition states of anal dysplasia according to Markov model estimates. In unadjusted analysis of progression to HSIL, female sex, age 40.5 years, and black race were associated with significantly lower transition rates (than their comparators) from $<$ HSIL to HSIL with hazard ratios (HR) of 0.35, 0.64 and 0.55, respectively. In contrast, MSM HIV transmission risk factor was associated with a substantially increased rate of transition from $<$ HSIL to HSIL (HR 3.30). With regard to regression of HSIL, those with age above 40.5 years had a lower rate of HSIL to $<$ HSIL regression (HR= 0.56) while MSM had a higher rate of HSIL regression (HR 1.90). After controlling for antiretroviral therapy use and timed-updated IRC treatment, all observed unadjusted effects remained significant with the exception of the effect of higher age on the transition from $<$ HSIL to HSIL.

Discussion

This study found no differences in the baseline prevalence of HSIL, the immediate precursor of IAC, nor in the proportion of observed IAC cases according to race category after a median of 4-years of follow-up. In addition, race was not associated with a more rapid progression rate between the AIN states in unadjusted and adjusted Markov models.

The presented results contrast with the findings of a recent meta-analysis, which observed that anal dysplasia was more frequent in Black MSM than in non-Black MSM (55 vs. 44%), although the reported difference was not statistically significant [5]. The meta-analysis also suggested that rates of anal cancer were higher in Blacks than in Whites, albeit, there were considerable referral bias and heterogeneity in outcomes of included studies that made

interpretation of the meta-analysis results difficult [5]. We previously showed that including patients with only higher severity of disease overestimates outcomes in anal neoplasia [9]. The present study uses an inception cohort, where a group of individuals was identified and assembled for subsequent study at an early and uniform point in the course of the specified health condition. The study population at the UCSD Owen Clinic mirrors the HIV epidemic distribution in San Diego County. Overall 5.6% of the population are Black, but HIV prevalence in the Black community is approximately 12% in San Diego County [10].

Social disparities do exist in HIV health care [11]. Lack of engagement in care is a prevalent problem among minorities such as the Black community. This results in a higher proportion of patients with uncontrolled HIV infections and transmission risk [11]. Noteworthy, we observed that in our cohort Black patients had a lower median number of serial anal cytology tests than other groups. We speculate that this is due to higher rates of missed appointments rather than differences in provider's treatments. This speculation is indirectly supported by the similar proportion of patients receiving antiretroviral therapy regardless of race group in our clinic. Similarly, there were no differences in the proportion of IRC treatments according to race groups, once patients were diagnosed with anal HSIL lesions. Nevertheless, despite the aforementioned difference, the relative homogenous follow-up time among Blacks, Hispanics and Whites (4-years) and sample size provided us robust estimates suggesting that AIN may progress to HSIL at a slower rate in black than in white patients. This observation should not deter ongoing efforts to improve access and engagement in care among minorities including Blacks. Even in the absence of a worsening effect of black race on the clinical evolution of AIN, lack of engagement in care could potentially influence delay in care, diagnosis and worst anal neoplasia outcomes.

Our study has important limitations. 1) There is possible residual state misclassification after correcting for the fallibility of cytology using HRA-directed biopsy as reference standard HRA-directed biopsy. However, an HRA-directed biopsy is itself a fallible reference standard. 2) The <HSIL state is a heterogeneous state including some HPV-uninfected patients. Nonetheless, similar HIV-infected cohorts have demonstrated high incidence and persistence of oncogenic HPV2. 3) Model inferences are most robust for HIV-infected MSM. 4) The slightly lower number of anal cytology examinations among black patients may have introduced some degree of ascertainment bias in estimation of AIN transition rates. Gruger et al. have demonstrated in a simulation study that when the interval between successive tests is chosen on the basis of the current observation (as would be the case in severity-based examination schedules), little bias is anticipated. However, if the examination interval is determined by patient self-selection, considerable bias is likely [12]. 4) The observed associations for sex, age, MSM, and race on selected AIN state transitions may reflect underlying biological differences, but may also be attributable to non-biological factors or to unmeasured confounding. Replicate analysis in other cohorts is needed.

In conclusion, unlike previous reports, black race was not associated with either prevalent AIN nor with worsening post-baseline transition of AIN states.

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Bibliography

1. Cachay ER, Mathews WC. Human papillomavirus, anal cancer, and screening considerations among HIV-infected individuals. *AIDS Rev*. 2013; 15:122–133. [PubMed: 23681437]
2. Berry JM, Jay N, Cranston RD, Darragh TM, Holly EA, Welton ML, Palefsky JM. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. *Int J Cancer*. 2014; 134:1147–55. [PubMed: 23934991]
3. CDC. HIV surveillance report (2014). Atlanta, GA: US Department of Health and Human Services, CDC; 2015. <http://www.cdc.gov/hiv/library/reports/surveillance/> [Accessed 17 November 2016]
4. Cohen SM, Hu X, Sweeney P, Johnson AS, Hall HI. HIV viral suppression among persons with varying levels of engagement in HIV medical care, 19 US jurisdictions. *J Acquir Immune Defic Syndr*. 2014; 67:519–27. [PubMed: 25230292]
5. Walsh T, Bertozzi-Villa C, Schneider JA. Systematic review of racial disparities in human papillomavirus-associated anal dysplasia and anal cancer among men who have sex with men. *Am J Public Health*. 2015; 105:e34–45. [PubMed: 25713941]
6. Mathews WC, Agmas W, Cachay ER, Cosman BC, Jackson C. Natural history of anal dysplasia in an HIV-infected clinical care cohort: estimates using multi-state Markov modeling. *PLoS One*. 2014; 9:e104116. [PubMed: 25101757]
7. Mathews WC, Cachay ER, Caperna J, Sitapati A, Cosman B, et al. Estimating the accuracy of anal cytology in the presence of an imperfect reference standard. *PLoS One*. 2010; 5:e12284.
8. Jackson CH. Multi-State Models for Panel Data: The msm Package for R. *Journal of Statistical Software*. 2011; 38:1–29.
9. Mathews WC, Cachay ER, Agmas W, Jackson C. Effects of Referral Bias on Estimates of Anal Intraepithelial Neoplasia Progression and Regression Rates in a 3-State Markov Model. *Medicine (Baltimore)*. 2015; 94:e1476. [PubMed: 26334910]
10. Health and human services agency, county of San Diego. [Accessed 25 October 2016] http://www.sandiegocounty.gov/hhsa/programs/phs/documents/HAEU_BiAnnual_Report_2012_final.pdf
11. Lewis CF, Rivera AV, Crawford ND, Gordon K, White K, et al. Individual and Neighborhood Characteristics Associated with HIV Among Black and Latino Adults Who Use Drugs and Unaware of Their HIV-Positive Status, New York City, 2000–2004. *J Racial Ethnic Health Disparities*. 2016; 3:573–581.
12. Grüger J, Kay R, Schumacher M. The validity of inferences based on incomplete observations in disease state models. *Biometrics*. 1991; 47:595–605. [PubMed: 1912263]

Table 1

Patient characteristics in the entire cohort and according to race and ethnicity

Factor	All (n = 2804)	White (n = 1730)	Hispanic (n = 490)	Black (n = 357)	Other/unknown (n=227)	p
Follow-up in months, median (IQR)	48.5 (24.2–86.0)	49.4 (24.1–88.1)	52.9 (27.8–89.8)	48.5 (25.1–84.9)	35.7 (20.1–61.9)	< 0.001
Age at 1st cytology, median (IQR)	40.2 (34.1–46.4)	41.1 (35–47.1)	37.8 (32.5–44.9)	40.5 (34.4–46.4)	37.9 (32.1–44.4)	< 0.001
Sex (%)						
Male	2494 (88.9)	1610 (93.1)	423 (86.3)	266 (74.5)	195 (85.9)	< 0.001
Female	(11.1)	120 (6.9)	67 (13.7)	91 (25.5)	32 (14.1)	
HIV risk factor (%)						
MSM	2180 (77.7)	1450 (83.8)	359 (73.3)	212 (59.4)	159 (70.0)	
IDU (not MSM)	133 (4.7)	82 (4.7)	13 (2.7)	28 (7.8)	10 (4.4)	< 0.001
Heterosexual (not IDU)	367 (13.1)	139 (8.0)	92 (18.8)	102 (28.6)	34 (15.0)	
Other/unknown	124 (4.4)	59 (3.4)	26 (5.3)	15 (4.2)	24 (10.6)	
Ongoing Smoking	837 (29.9)	588 (34.0)	82 (16.7)	135 (37.8)	32 (14.1)	< 0.001
Taking antiretroviral therapy (%)	2097 (74.8)	1300 (75.1)	365 (74.5)	267 (74.8)	165 (72.7)	0.88
1st CD4+ category (<350/mm³)	1230 (44.2)	722 (41.9)	260 (53.6)	149 (41.7)	99 (46.3)	< 0.001
Plasma viral load						
>400	1439 (51.8)	887 (51.5)	235 (48.5)	178 (49.9)	112 (52.8)	0.60
400	1365 (49.2)	836 (48.5)	250 (51.5)	179 (50.1)	100 (47.2)	
Year of 1st cytology, median (IQR)	2004 (2002–2007)	2004 (2001–2007)	2005 (2003–2008)	2004 (2002–008)	2003 (2002–2006)	< 0.001
1st cytology period (%)						
2001–2006	2018 (72.0)	1286 (74.3)	311 (63.5)	240 (67.2)	181 (79.7)	< 0.001
2007–2012	786 (28.0)	444 (25.7)	179 (36.5)	117 (32.8)	46 (20.3)	
HSIL- 1st cytology (%)	393 (14.0)	250 (14.5)	62 (12.7)	47 (13.2)	34 (15)	0.70
Worst cytology group: HSIL (%)	1113 (39.7)	721 (41.7)	186 (38.0)	119 (33.3)	87 (38.3)	0.022

Factor	All (n = 2804)	White (n = 1730)	Hispanic (n = 490)	Black (n = 357)	Other/unknown (n=227)	p
Median N@ of anal cytologies (IQR)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (3.0–6.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	< 0.001
1 IRC treatment (%)	218 (7.8)	137 (7.9)	41 (8.4)	18 (5)	22 (9.7)	0.16
Invasive anal cancer cases (%)	23 (0.8)	15 (0.9)	5 (1.0)	3 (0.8)	0 (0)	0.54

IQR = interquartile range; MSM = men who have sex with men; IDU = intravenous drug use; HSIL = high-grade squamous intraepithelial lesion; IRC = infrared coagulation

Unadjusted and adjusted hazard ratios for sociodemographic effects on anal intraepithelial transition rates

Table 2

Factor	<HSIL → HSIL		HSIL → <HSIL		HSIL → IAC	
	Unadjusted	Adjusted HR (95% C.I.)	Unadjusted	Adjusted HR (95% C.I.)	Unadjusted	Adjusted HR (95% C.I.)
Sex (Male [ref])						
Female	0.35 * (0.16 – 0.72)	0.38 * (0.18 – 0.78)	0.50 (0.24 – 1.00)	0.54 (0.26 – 1.10)	0.0006 (6.1x10 ⁻²⁸ – 5.8x10 ²⁰)	0.00003 (2.1x10 ⁻¹²³ – 3.2x10 ¹¹³)
Age (< 40.5 [ref])						
40.5	0.64 * (0.46 – 0.90)	0.74 (0.52 – 1.03)	0.56 * (0.40 – 0.79)	0.58 * (0.41 – 0.82)	1.90 (0.80 – 4.50)	1.75 (0.73 – 4.20)
HIV Risk (Not MSM [ref])						
MSM	3.30 * (1.87 – 5.70)	3.10 * (1.78 – 5.30)	1.90 * (1.12 – 3.10)	1.80 * (1.07 – 2.90)	1.10 (0.33 – 3.80)	1.10 (0.33 – 3.80)
Race/ethnicity (white [ref])						
Hispanic	0.80 (0.50 – 1.30)	0.75 (0.47 – 1.20)	1.20 (0.75 – 1.90)	1.06 (0.67 – 1.70)	1.70 (0.59 – 4.60)	1.63 (0.59 – 4.50)
Black	0.55 * (0.32 – 0.93)	0.51 * (0.30 – 0.88)	0.57 (0.30 – 1.11)	0.50 (0.24 – 1.02)	1.37 (0.39 – 4.80)	1.40 (0.40 – 4.92)

Adjusted for antiretroviral therapy and time-updated infrared coagulation therapy

HSIL= high-grade squamous intraepithelial lesion; HR = hazard ratio; C.I. = confidence interval; MSM = men who have sex with men; IDU = intravenous drug use

* Indicates P value < 0.05