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Sociodemographic Predictors of Anal Cancer Screening and Follow up in HIV Infected Individuals

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Abstract

Background—Anal cancer in the United States is generally rare; however, HIV infected individuals are 28 times more likely to be diagnosed with anal cancer than the general population.

Objective—to examine the rates and sociodemographic predictors of anal cancer screening and follow up anoscopy in a sample of HIV infected individuals.

Methods—Data for this study (n=200) were derived from a retrospective chart review of randomly selected HIV infected individuals. Data analyses included Pearson's correlation coefficient statistic to examine bivariate associations and logistic regression modeling for prediction of anal Pap test screening and follow up anoscopy.

Results—Screening rates and follow up after an abnormal anal Pap test were low. Females were less likely to be screened for anal cancer (OR=.244, p=.007). Men who have sex with men (MSM) were almost four times more likely to be screened for anal cancer (OR= 3.7, p=.02). MSMs were six times more likely to have follow up after an abnormal anal Pap test compared to heterosexual men or women of any sexual orientation (OR=6.88, p=.002).

Conclusions—High-risk groups for anal cancer should be targeted for preventative measures as part of a cancer prevention plan to decrease the personal and clinical burden associated with anal cancer.

Implications for Practice—Cancer prevention is a multistep process that requires screening and follow up efforts, where healthcare providers play a vital role in these efforts. Findings from this study can inform strategies to improve screening and follow up rates in HIV infected individuals.

INTRODUCTION

Human papillomavirus (HPV) is one of the most common sexually transmitted infections in the United States. HPV is transmitted through sexual contact, which is also the most common mode of transmission for HIV, where co-infection with HIV and HPV is common.^{1,2} HPV infection is also a significant cause of anal cancer and precancerous intraepithelial

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lesions and is associated with 80% of anal cancer cases in the United States.^{1,3,4} Due to immunosuppression, HPV-related anal cancer occurs in excess rates in persons with HIV/AIDS.^{5,6}

The global incidence of anal cancer for the general population ranges from 0.1 to 2.8 cases per 100,000 persons/years among men and 0.0 to 2.2 cases per 100,000 person/years among women.⁷ Anal cancer in the United States is also generally rare with an overall incidence of 0.9 cases per 100,000 person/years. However, individuals infected with HIV have the highest incidence for anal cancer and carry the greatest burden of anal cancer rates compared to the general HIV uninfected population.^{6,8} A meta-analysis found HIV infected men and women are 28 times more likely to be diagnosed with anal cancer than the general HIV uninfected population.⁹ Specifically, HIV infected men who have sex with men (MSMs) are at greatest risk for anal cancer (adjusted incidence rate of 80.3 per 100,000 person/years) and are more likely to have anal HPV infection than HIV uninfected men.^{1,10} A study with a sample of HIV infected MSMs found anal HPV infection to be as high as 93% compared with 60% of HIV uninfected MSM¹¹.

Anal cancer is also a significant cause of mortality in HIV infected individuals.⁶ The overall five year survival rate for the general population for localized disease is 78% compared to 18% for distant disease; where cancer specific mortality has not been found to differ by HIV status.^{12,13} Of concern is that since the introduction of highly active antiretroviral therapy (HAART), there has been no significant improvements in survival, tumor control, or better tolerability of chemoradiation therapy.¹⁴

The anal Papanicolaou (Pap) test is a recommended primary screening procedure used to detect pre-cancerous changes in the anal canal. Similar to the cervix, the anal canal has a transformation zone that is vulnerable to dysplasia from HPV infection.¹⁵ Suggested screening guidelines first released by the New York State Department of Health AIDS Institute recommend targeted annual anal cancer screening with anal Pap tests for MSMs, all HIV-infected patients with a history of anogenital warts, and HIV-infected women with a history of cervical or vulvar dysplasia.^{16,17} Any abnormal findings of any grade should be referred for high-resolution anoscopy along with anal biopsy.¹⁸

Sigel et al¹⁹ proposed a conceptual model for cancer screening in HIV-infected patients where the benefits and harms of screening are considered for individualized patient care (Figure 1). Specifically, three factors should be considered for a screening program in this group: 1) the patient's age-related life expectancy based on comorbid conditions; 2) the patient's individual cancer risk; 3) an estimate of the harms and benefits associated with the screening.¹⁹ A cancer screening test should provide increased life expectancy while decreasing morbidity risk.

Currently no randomized control trials have been conducted to test the reliability and validity of a screening program for anal cancer. Albeit unproven, screening procedures for anal dysplasia may have the same success of decreasing mortality and morbidity that has been seen with cervical cancer.²⁰ Despite the lack of conclusive evidence and formal screening guidelines, some clinics have implemented screening programs for anal cancer in

an effort to alter the increasing clinical burden of anal cancer in HIV infected individuals.^{16,20}

Screening for anal cancer may be beneficial in cancer prevention but requires multiple visits that include the Pap screening test, referral to follow up anoscopy after an abnormal Pap test, and the possible treatment of pre-cancerous lesions. Adequate screening and follow up of anal dysplasia in HIV infected individuals are needed for a successful cancer prevention plan. However, the factors associated with anoscopy screening and follow up for anal cancer has been virtually unstudied in the HIV infected population, a population who bears the greatest risk for HPV related cancers. Previous studies found high risk groups such as HIV infected men who have sex with men (MSM), women with history of cervical dysplasia, individuals with low CD4 counts, >45 years of age, current smoker, and individuals who engage in anoreceptive intercourse are at considerable risk for anal cancer and may benefit from screening.^{21–23} Our study sought to examine if these factors were predictors of anal cancer screening and follow up. Therefore, the purpose of this study is to first describe anal cancer screening and follow up rates after an abnormal anal Pap test and secondly, examine the sociodemographic predictors of anal cancer screening and follow up in a sample of HIV infected individuals.

METHODS

Study Design and Sample Size

This study was a retrospective chart review of electronic medical records of HIV infected individuals enrolled at a large comprehensive metropolitan HIV care Infectious Disease Program (IDP) between January 2010 and December 2013. The sample size for the chart review was determined by using the recommendations set by Gearing, Mian, et al.²⁴ The authors propose the expected proportion within the population that will have the measure of interest is >50% and to sample 10% of this proportion, as a good rule of thumb, to obtain a sample size for chart audits. A total of 3,134 patients were seen at the clinic during the study's sampling time frame thus it is estimated that 1,500 of these patients were to have a history of anal dysplasia, therefore the original target sample size for this review was 150 medical charts. For this study, the sample size was increased to 200 medical charts to better capture screening and follow up rates in this population.

Study Setting and Sample

The target sample population were patients managed at a large metropolitan HIV clinic located in the Southeast region of the United States. This clinic offers its patients on-site subspecialty care including anal Pap tests and follow up with high resolution anoscopy. Using a random number generator, electronic medical records were randomly selected from a generated patient list of male and female patients seen at the clinic within the study's time period. The timeframe for this study was selected to correspond with the approximate time HPV testing was commonly made available in the clinical setting. The inclusion criteria for the medical record to be reviewed were: 1) managed and enrolled in the IDP between January 2010 to December 2013; 2) received ongoing primary care at the clinic within the

study's time period; 3) 18 years or older. Medical records that did not have at least two documented clinic visits within the study time period were excluded.

A preliminary analysis found an underrepresentation of women in the chart review. To capture more women and with permission from the study's principal investigator, we used a random selection of participants from a list of unlinked medical record numbers from the closed KHARMA study.²⁵ The KHARMA (Keeping Healthy and Active with Risk reduction and Medication Adherence) study was a randomized controlled behavioral clinical trial that enrolled 207 HIV infected women managed at the IDP. Using the clinic's generated patient list and de-identified and unlinked medical record numbers from the KHARMA study, medical records were randomly selected and reviewed until a sample of 200 was reached (Figure 2).

Data Collection

After approval from the university's Institutional Review Board and from the hospital's Research Oversight Committee, data collection was conducted using a standardized data abstraction instrument created by the investigator. Electronic medical records were reviewed for demographic information including age, race/ethnicity, gender, and insurance status. Medical notes were reviewed for information on date of HIV diagnosis, marital or partner status, smoking status, and sexual orientation. Laboratory results were reviewed for the patient's most recent CD4+ cell counts. Laboratory and biopsy results were reviewed for history of anal Pap testing and follow up with high resolution anoscopy within the three year time frame of the study. Medical notes were also reviewed for documented anal Pap testing and/or referral for follow up anoscopy. An anal Pap test or follow up anoscopy was recorded as absent if it was not documented as performed, either by a clinic provider or an outside clinic provider. Data was abstracted by four reviewers under the supervision of the investigator. For quality control, approximately 10% of the medical records were audited by the investigator to assure agreement of coding and all data were double-entered.

Data Analysis

Statistical analyses were conducted using IBM SPSS Statistics 20.²⁶ Demographic information was examined using descriptive analyses such as means, frequencies, and standard deviations. Pearson's *r* was used to examine bivariate associations between sociodemographic factors and anal cancer screening and follow up anoscopy. Variables that showed association with the event in bivariate analysis with $p < .20$ were included in the logistic regression model. Multiple logistic regressions were used to model receipt of anal Pap tests and follow up with anoscopy. Two predictive models were built: the dependent variable in the first model was whether an individual received an anal Pap test within the study time period (yes/no); the second model was whether an individual received a follow up anoscopy after an abnormal anal Pap test (yes/no). Variables that were significant at $p < .05$ were kept in the final model.

RESULTS

A total of 342 medical records were randomly selected and reviewed using the inclusion criteria; 142 medical records did not meet the inclusion criteria and were excluded. Of the 200 medical records, 99 were female and 101 were male. A majority of the sample were documented as Black (74%), non-smokers (47.5%), single/not married (66%), and reported Medicare as the primary source of health insurance (38.5%). The mean reported age was 49.7 years (age range 25–76 years; Table 1).

Only 29% (n=58) of the sample had a documented anal Pap test during the study time period. Of the individuals with a documented anal Pap test, 70% (n = 40) had an abnormal anal Pap and 93% (n=37) were recommended for follow up with an anoscopy. Sixty-five percent (n=24) of the men and women recommended for anoscopy did not have a documented follow-up anoscopy (Figure 3).

Gender ($r=-.41$, $p=.00$), men who have sex with men (MSM) ($r=.43$, $p=.00$), CD4+ cell count ($r=-.10$, $p=.14$), and age ($r=-.26$, $p=.00$) met the bivariate criteria and were entered into the model using backwards stepwise approach to predict occurrence of anal Pap test screening. For model 2, gender ($r=-.14$, $p=.06$), health insurance ($r=-.12$, $p=.13$), MSM ($r=.30$, $p=.00$), CD4+ cell count ($r=-.10$, $p=.20$), and age ($r=-.15$, $p=.05$) were selected and entered into the logistic regression model using backwards stepwise approach to predict anoscopy follow up (Table 1). It is important to note, gender and MSM were highly correlated in this analysis ($r=-.55$, $p=.00$).

The final regression model indicated gender and MSM significantly predicted receipt of an anal Pap test. Females were less likely to be screened for anal cancer (OR=.24, $p=.00$). Whereas, MSM are almost four times more likely to be screened for anal cancer (OR= 3.7, $p=.02$). Men who have sex with men was included in the final model as an independent predictor of follow-up anoscopy after an abnormal anal Pap test where MSMs were six times more likely to have an anoscopy after an abnormal anal Pap test compared to heterosexual men or women of any sexual orientation (OR=6.88, $p=.00$; see Table 2).

DISCUSSION

The goal of anal cancer screening is to capture and treat anal intraepithelial neoplasia (AIN) II and III before progression to carcinoma.²⁷ Our exploratory study found anal cancer screening is performed at low rates; and in addition, revealed a considerable break down in follow up care after an abnormal anal Pap test. A previous study examined agreement between anal Pap cytology and histopathology and found that 40% (n=642) of a 1732 HIV infected cohort received repeat Pap testing within three years of the anal Pap smear.²⁸ Our study found only 29% of the sample had a history of an anal Pap test and only 46% of those who were recommended for follow up actually received follow up anoscopy. The reasons for low follow up rates warrant further examination in future studies. Although no formal guidelines for anal cancer screening are established, increased efforts are needed to ensure patients *who are screened* receive the necessary follow up and treatment as part of a cancer prevention plan. One observational study found the median time from progression of high

grade AIN to cancer was 8.6 months for participants who did not receive the necessary follow up anoscopy.²⁹

Men who have sex with men and gender were significant predictors of anal cancer screening. Despite overall low screening rates in this study, we found the high-risk group, MSMs, are nearly four times more likely to be screened for anal cancer. Anal cancer screening may be highly beneficial in this group where a study with a sample of MSM found anal HPV infection to be as high 93% among HIV infected men compared with 60% among HIV uninfected men.²⁸ Our findings reveal that this high-risk group is being captured for anal cancer screening at the IDP.

Similar to MSM, HIV infected women with a history of cervical dysplasia are considered a high-risk group due to an increased risk for anal intraepithelial neoplasia and are recommended to be screened for anal cancer.²³ Despite the fact that 65% of the women in this study had a documented history of an abnormal cervical Pap test, they were less likely to be screened for anal cancer. HIV infected women in this study are a high-risk group for anal cancer, yet are not being captured for anal cancer screening. In fact, Koijic et al found anal HPV infection to be more common than cervical HPV in both HIV infected and HIV uninfected women.³⁰ This finding suggests the need for increased anal cancer screening efforts in HIV infected women where there is a high incidence of abnormal cervical Pap smears. HIV infected women may benefit from a targeted anal cancer screening program similar to that for HIV infected MSM. It is essential to provide the necessary resources and cancer prevention strategies to help decrease the personal costs and burden from anal cancer in HIV infected women.

Similarly to many cancers, the risk for anal cancer increases with age and the median age for anal cancer is above 50 years. Due to the effects of HIV treatment, HIV infected persons are living longer and experiencing more comorbidities associated with aging. Although age did not enter our model as a predictor for anal cancer screening or follow up, there was a significant relationship between age and screening. Those who received an anal Pap test, had a younger mean age (45.88 years) than those who did not have a documented anal Pap test (51.55 years; $t= 3.749$, $p=.00$.) Therefore, important screening in an aging HIV infected population may be omitted and more research to examine reasons for this is warranted.

Men who have sex with men was the only significant predictor in the final model for receiving a follow up anoscopy. MSMs were six times more likely to receive follow up care after an abnormal anal cancer Pap test. Given that HIV-infected MSM carry the greatest burden for anal cancer incidence, it is very likely this group is often managed and followed more closely to monitor for AIDS-related disease.

Cost effectiveness of anal cancer screening

To date, there is no randomized clinical trial to support the rationale for an anal cancer screening program. The benefits of screening for anal cancer are inferred from the success of the national cervical cancer screening program. Goldie et al evaluated the cost effectiveness of screening HIV infected MSMs for anal dysplasia using a transition Markov model.³¹ The authors found performing annual anal Pap testing was the most cost-effective screening

method and provided almost a three month gain in quality adjusted life expectancy (QALY), compared to no screening, with a cost-effectiveness ratio of \$13,000 per quality-adjusted life year saved. Similarly, Ong et al evaluated the cost effectiveness of screening for anal cancer using digital rectal exams in HIV infected MSMs.³² The average lifetime cost of screening and managing anal cancer ranged from \$373 for no screening to \$4,468 for annual screening of men over the age of 50. QALYs gained for no screening was 35.11 versus 35.24 for annual screening of men 50. QALY was also calculated and compared among no screening and several screening strategies and found that all screening strategies for anal cancer increased the number of gained QALYs. The authors concluded regular anal screening for HIV-infected MSMs aged 50 may be cost effective and should be implemented. Another study found anal cancer screening to be cost effective when compared to no screening, for high risk HIV infected women.³³

HPV Vaccination

HPV vaccination may be another effective strategy for cancer prevention in this population. The quadrivalent HPV vaccine has been shown to be efficacious against anal HPV infections, including in high-risk groups such as MSMs and HIV infected men and women.^{34–37} Specifically, a sub-study of a larger double-blind randomized trial of MSMs (aged 16 to 26 years of age) found the quadrivalent HPV vaccine to be efficacious in reducing the incidence of persistent anal infection associated with HPV- 6, 11, 16, and 18.³⁶ The efficacy against HPV -6, 11, 16, and 18 was 50.3% and the rate of infection from the four types was reduced by 48.5%. Additionally, a significant reduction in persistent anal HPV caused by the four types was reduced by 59.4% in this sample. The safety profile is favorable where no vaccine related adverse events were reported. The authors concluded the quadrivalent vaccine can be a useful tool to prevent HPV related disease, and potentially even cancer in the high risk MSM population.

Currently the Advisory Committee on Immunization Practices (ACIP) recommends routine two dose HPV vaccination to start at 11 or 12 years of age. Females should be vaccinated through age 26 and up to age 21 for males who were not previously vaccinated. However, vaccination with three doses is recommended up to age 26 for HIV infected individuals and MSMs.

Implications for Practice

Despite the lack of formal guidelines to support anal cancer screening, there is compelling evidence that screening with anal Pap testing may be beneficial in high-risk groups. It is imperative for advanced practice nurses, nurses, and other members of the healthcare team to identify high-risk groups that may benefit from anal cancer screening (i.e. HIV infected men and women, MSMs, and women with a history of high grade cervical dysplasia). Diligent follow-up of those who screen abnormal is also important and patients should be connected to cancer preventative resources for screening and any necessary follow up care. Evidence based patient education should be included in the care and management of HIV infected individuals and include information regarding anal cancer risk, HPV, and HPV vaccination. Lastly, there is a need for more evidence based educational programs to improve understanding of anal cancer risk and to improve screening.

Limitations—The main limitation of this study is that data pertaining to other determinates of anal cancer screening and follow up such as social support, HIV-related stigma, health beliefs, knowledge, or provider-related factors were unable to be captured in the medical record review. Additionally, data was not available for every variable in every medical record, which presents a missing data bias. It is important to note that sexual orientation was only documented if the patient was a MSM. Sexual practices for women were not documented in the medical records. Thus, gender and MSM were highly correlated and may jointly predict anal cancer screening and follow up. More data is required to tease apart the effect of each variable. Lastly, the sample population was enrolled at a comprehensive IDP in a high-resource setting with trained clinicians, cytology, anoscopy, biopsy, and necessary treatment available for its patients. This setting and its sample may not be a representative sample of the general HIV infected population. However, this bias would suggest the possibility of even lower rates of anal cancer screening and follow up in less resource intense settings. Despite these limitations, this study provided new findings of the sociodemographic risk factors for anal cancer screening and anoscopy follow up.

CONCLUSION

Currently, no previous studies were found that examined the sociodemographic predictors of anal cancer screening and follow up after an abnormal anal Pap among HIV infected individuals. Our study addressed this gap and found sexual orientation and gender were independent predictors of anal cancer screening and follow up anoscopy. Findings from this study can inform strategies to improve screening rates, especially for HIV infected women, in efforts to decrease anal cancer morbidity and mortality. Cancer prevention is a multistep process that requires both screening and follow up efforts, and health care providers play a vital role in these efforts. The health care team is responsible for coordinating and providing care for HIV infected patients and is at the forefront of facilitating adherence to screening and follow up care. Future research should be directed at examining the multi-factorial predictors of anal cancer screening and follow up anoscopy in efforts to increase screening in individuals infected with HIV. All high-risk groups for anal cancer should be targeted for preventative measures as part of a cancer prevention plan to decrease the personal and clinical burden associated with anal cancer.

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Figure 1. Conceptual model for consideration of cancer screening in asymptomatic HIV-infected patients.¹⁹

Figure 2.
Electronic Medical Records Selection and Exclusion.

Figure 3.
Anal cancer screening and follow up patterns in men and women with HIV (N=200)

Table 1

Sociodemographic Characteristics and Bivariate Associations to Anal Pap Screening and Follow Up Anoscopy (N=200)

Variable	n (%)	Correlation to receiving Anal Pap test (<i>p</i> -value) ^a	Correlation to receiving anoscopy(<i>p</i> -value) ^a
Gender^b		<i>r</i> = -.412 (<i>p</i> =.000)	<i>r</i> = -.144 (<i>p</i> =.061)
Male	101 (51%)		
Female	99 (49%)		
Race		<i>r</i> =.040 (<i>p</i> =.612)	<i>r</i> =-.078 (<i>p</i> =.353)
White	10 (5%)		
Black	148 (74%)		
Hispanic	9 (4.5%)		
Other	33 (16.5%)		
Smoking status		<i>r</i> = .073 (<i>p</i> =.317)	<i>r</i> =.066 (<i>p</i> =.400)
No	95 (47.5%)		
Yes	92 (46%)		
Not documented	13 (6.5%)		
Health Insurance		<i>r</i> = -.042 (<i>p</i> =.559)	<i>r</i> =-.117 (<i>p</i> =.128)
None	42 (21%)		
Medicaid	63 (31.5%)		
Medicare	77 (38.5%)		
Private	10 (5%)		
Other	8 (4%)		
Marital/partner status		<i>r</i> = .019 (<i>p</i> =.814)	<i>r</i> = -.003 (<i>p</i> =.972)
Single/divorced/widowed	132 (66%)		
Married/live in partner	16 (8%)		
Not documented	52 (26%)		
MSM	41 (20.5%)	<i>r</i> = .434 (<i>p</i> =.000)	<i>r</i> = .300 (<i>p</i> =.000)
Non-MSM	189 (79.5%)		
CD4+ cell count	Mean= 459.8 (SD=346.7)	<i>r</i> = -.107 (<i>p</i> =.137)	<i>r</i> = -.100 (<i>p</i> =.197)
Age	Mean= 49.7 (SD= 9.8)	<i>r</i> = -.262 (<i>p</i> =.000)	<i>r</i> = -.149 (<i>p</i> =.055)

Abbreviations: MSM, men who have sex with men.

^a Pearson's *r* correlation.

^b Chart documented biological sex.

Table 2

Logistic Regression Models of Predictors to Anal Pap Test Screening and Follow Up Anoscopy in HIV infected Individuals

Variable	OR	95% CI	p-value
<i>Model 1: Anal Pap Screening^a</i>			
Constant	3.54		
Sex			
Male	Reference	(.09, .68)	.007
Female	.244		
Age	.959	(.92, 1.00)	.068
MSM	3.70	(1.24, 10.97)	.019
Non-MSM	Reference		
<i>Model 2: Follow up Anoscopy^b</i>			
Constant	.042		
Non-MSM	Reference		
MSM	6.88	(2.02, 23.52)	.002

^aR²= .24 (Cox & Snell), .35 (Nagelkerke); final model χ^2 (3)= 42.95, p= .000

^bR²= .06 (Cox & Snell), .14 (Nagelkerke); final model χ^2 (1)= 9.35, p= .002.