Behavioral Risk Factors for the Presence of Anal dysplasia in HIV+ Individuals

Dickerson, Taylor D. BS; Metzger Charlotte L. MPH; Hagensee Michael E. MD, PhD

Louisiana State University Health Sciences Center School of Medicine

tgrif3@lsuhsc.edu

Background

- Infection with Human Papillomavirus (HPV) is an accepted prerequisite for anogenital malignancies
  - Accounts for 91% of anal and cervical cancer[1].
  - Prevalence of anal cancer has doubled in the last 40 years with Caucasian women and African American men being affected most[1,6]
- Cervical cancer has declined over the past 40 years due to cervical Pap smear cytology, biopsy histology, and disease.
  - The correlation is weaker between screening with anal Pap smears and disease outcome.

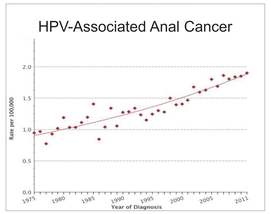

Figure 1: HPV-associated anal cancer rates in women from 1975 – 2011 (CDC website)

- The rate of anal cancer in MSM (men who have sex with men) is 35 per 100,000 which is similar to women with cervical cancer (45 per 100,000) prior to Pap smear screening[2].
  - Anal HPV can be detected in 76% of HIV+ women and 90% of HIV+ MSMs[2].
- Anal detection of Epstein Barr Virus (EBV) has been proposed by the Hagensee lab as a possible biomarker for anal dysplasia[7]

Hypothesis

Biomarkers for anal dysplasia can be connected with behavioral risk factors to allow for more precise prediction of current and future anal disease.

Demographics

	HOP	OMC	p-value
Gender			**<0.0001**
Male	26/44; 59.1%	32/32; 100%	
Female	18/44; 40.9%	0/32; 0%	
Race			**0.002**
African-American	28/44; 63.6%	8/30; 26.7%	
Caucasian	16/44; 36.4%	22/30; 73.3%	
Age			0.902
Mean	46.73	48.03	
Range	29-68	23-76	
≥ 50 years	20/44; 45.5%	15/32; 46.8%	
<50 years	24/44; 54.5%	17/32; 53.1%	
Health Insurance			**<0.0001**
Medicaid	19/30; 63.3%	1/32; 3.1%	
Non-medicaid	11/30; 36.7%	31/32; 96.9%	
CD4 Count			0.524
Range	23 - 1171	7 - 1509	
CD4 < 200	10/44; 22.7%	4/32; 12.5%	
200 < CD4 < 500	16/44; 36.4%	13/32; 40.6%	
CD4 > 500	18/44; 40.9%	15/32; 46.9%	
HIV Viral Load			**<0.0001**
Median	50	39.99	
Range	19 - 85,851	20 - 2,044,234	
VL < 40	23/44; 52.27%	29/32; 90.6%	
VL ≥ 40	21/44; 47.73%	21/44; 9.4%	
Pap Dysplasia			**0.002**
Normal + ASCUS	18/44; 40.9%	25/32; 78.1%	
LSIL + HSIL	24/44; 54.5%	6/32; 18.8%	
Missing	2/44; 4.5%	1/32; 3.1%	
EBV and/or HPV Viral Load			**0.003**
HR HPV Only	13/44; 29.5%	16/32; 50.0%	
EBV & HR HPV	27/44; 61.4%	6/32; 18.8%	

Table 1: LSU HSC HIV Outpatient Program (HOP) is largely African-American (80%) individuals of low socioeconomic status with about 50% having health care insurance. Conversely, the Ochsner Medical Center (OMC) HIV clinic consists of 60% Caucasian individuals, most of which have health care insurance[7]. There were statistically significant differences between both sites that if ignored could hide behavioral risk factors associated with anal dysplasia.

Results

OMC		p-value
Smoking Status		0.457
Smokers	1/6; 16.7%	
Non-Smokers	5/6; 83.3%	
Health Insurance		0.618
Medicaid	0/6; 0%	
Non-Medicaid	6/6; 100%	
Total Lifetime Male Sexual Partners		0.489
Mean	50.28	
Median	35	
0-4	1/6; 16.7%	
5-9	2/6; 33.3%	
10-20	0/6; 6.3%	
>20	1/6; 16.6%	
Lifetime Female Sexual Partners		0.184
Yes	1/3; 33.3%	
No	3/3; 67.7	
Anal Sex in Last 3 Months		1.0
Yes	2/5; 40%	
No	3/5; 60%	
Vaginal Sex in Last 3 Months		0.660
Yes	0/6; 0%	
No	6/6; 100%	
Oral Sex		0.576
Yes	3/3; 50%	
No	3/3; 50%	
Lifetime Abnormal Pap Smear		0.545
Yes	1/6; 40%	
No	5/6; 60%	

HOP		p-value
Lifetime Male Partners		
Males		0.805
Mean	18.7	
Median	9	
0-4	6/18; 33.3%	
5-9	2/18; 11.1%	
10-20	5/18; 27.8%	
>20	5/18; 27.8%	
Females		0.418
Mean	5	
Median	1	
0-4	4/6; 66.7%	
5-9	1/6; 16.7%	
10-20	1/6; 16.7%	
>20	0/6; 0%	
Lifetime Female Partners		
Males		0.395
Mean	4.85	
Median	1	
Yes	9/18; 50%	
No	9/18; 50%	
Females		0.923
Mean	8.6	
Median	0	
Yes	3/5; 60%	
No	2/5; 40%	
Smoking Status		0.276
Smokers	16/24; 66.7%	
Non-smokers	8/24; 33.3%	
Health Insurance		0.823
Medicaid	10/16; 62.5%	
Non-Medicaid	6/16; 37.5%	
Lifetime Abnormal Pap Smear		1.0
Yes	23/24; 95.8%	
No	1/24; 4.2%	
Anal Sex in Last 3 Months		
Males		1.0
Yes	5/11; 45.5%	
No	6/11; 55.5%	
Females		0.333
Yes	1/3; 33.3%	
No	2/3; 66.7%	
Vaginal Sex in Last 3 Months		
Males		
Yes	N/A	
No	N/A	
Females		1.0
Yes	3/3; 100%	
No	0/3; 0%	
Oral Sex in Last 3 Months		
Males		0.559
Yes	6/10; 60%	
No	4/10; 40%	
Females		1.0
Yes	2/3; 66.7%	
No	1/3; 33.3%	

Table 2: **No trend or significance was found** with the above behavioral risk factors as predictors of low-grade and high-grade intraepithelial anal lesions.

Significant findings within MSM cohort		HOP	OMC	p-value
Viral Presence	EBV + HR HPV	18	3	
	HR HPV Only	9	6	
				0.122
Dysplasia Presence	LSIL + HSIL	19	4	
	Normal + ASCUS	8	11	
				0.01
Abnormal Anal Pap Smear in Lifetime	Yes	27	1	
	No	0	13	
				< 0.0001
Health Insurance	Medicaid	7	0	
	Non-Medicaid	10	15	
				0.008

Table 3: When comparing high-risk MSM population at both sites, the above variables were significant predictors of anal dysplasia. When controlling for age and race, being MSM (a male who had a male partner in his lifetime) was found to be marginally significant (p-value = 0.0607).

Discussions

- Demographics of the two sites vary significantly (Table 3), but treatment is identical.
  - A decade ago, both sites used anal Pap smears as a screening tool for anal dysplasia
- Statistically significant differences found between the two sites may be due to differences in the overall health of the subjects, thus a more extensive study and questionnaire is required to look into this further.
- **Limitations**:
  - Our method involved asking subjects about specifics of their sexual history thus they may not have provided full disclosure.
  - Another difficulty was that only subjects with a partner within three months of the interview had a thorough sexual history obtained. Even then, very little is obtained about the sexual history of the partners. This significantly reduced our subject population.
  - A final limitation, is that most subjects enrolled at OMC are HIV primary care patients coming in for a routine checkup, whereas subjects at the HOP are referred to the study because of previous history of an abnormal Pap smear.
- Overall, increasing the population may reveal more trends. One solution is to extend the thorough sexual history portion of the questionnaire to subjects with a partner within a year of the interview as well as to include information about past partners sexual history.

Conclusions

Behavioral risk factors were not found to predict anal dysplasia. When controlling for age and race, having male partners was found to be a marginally significant predictor (p-value = 0.0607). OMC and HOP have significantly different cohorts.

More participants may reveal behavioral trends, but currently socioeconomic status and other factors that distinguish OMC and HOP from one another predict anal dysplasia. Future studies could obtain an extensive sexual history that includes information about the subject's anal sex practices and their past partner's sexual history.

Methods

- Participants undergo the informed consent process then demographic, clinical, and questionnaire information is obtained.
- Anal Pap smears for the clinic and the lab are collected.
  - Pap smear are read according to the Bethesda 2001[14]
  - A medical record review is done and the HIV viral load and CD4 cell count within three months is recorded
  - HPV genotype (Roche linear array), EBV viral load (PCR), protein concentration ELISA kits are run in lab.
- Statistical analysis was done using SPSS comparing the biomarker EBV and high-risk HPV, which is defined by HR - IARC8, and the presence of anal dysplasia.
  - Normal cytology is defined as both normal Pap smear or those with atypical squamous cell of unknown significance (ASCUS)
  - An abnormal Pap smear is defined as either low or high grade squamous intraepithelial lesion.
  - Behavioral risk factors were analyzed as predictors of anal dysplasia at the same time point with focus on prediction model of low or high grade anal dysplasia. These relationships were tested using Fisher exact test the population as a whole, the clinic site, participant's gender, and participant's sexual preferences were variables used to divide the population into subgroups.

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