RESEARCH

Racial/ethnic disparities in HPV-associated anogenital cancers among males in the United States: a population-based retrospective cohort study

Seiichi Villalona[1], Simone Sukhdeo[1], Daisy Reinoso[1], Antoinette M. Stroup[2,3], Jeanne M. Ferrante[3,4*]

[1] Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA
[2] Department of Biostatistics & Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA
[3] Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA
[4] Department of Family Medicine and Community Health, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

*Corresponding author: Jeanne M. Ferrante, Email: jeanne.ferrante@rutgers.edu

ABSTRACT

Little is known regarding racial/ethnic differences in human papillomavirus (HPV)-associated anogenital cancer among males. This population-based retrospective cohort study included 39,601 males diagnosed with HPV-associated invasive penile and anorectal cancers between 2005-2016 from the North American Association of Central Cancer Registries. We evaluated the association of race/ethnicity with late-stage diagnosis, survival, and mortality of anogenital cancers among males in the United States using multivariable logistic regression and Cox proportional hazard models. Hispanic and Non-Hispanic (NH) Black males had highest age-adjusted incidence of penile and anorectal cancer, respectively. Higher odds of late-stage penile cancer were observed among NH Black (adjusted odds ratios [aOR] 1.22, 95% CI 1.07-1.39) and Hispanic males (aOR 1.17, 95% CI 1.04-1.31). Higher odds of late-stage anorectal cancer were observed among NH Black (aOR 1.25, 95% CI 1.14-1.36) and NH Other males (aOR 1.29, 95% CI 1.01-1.66). Compared to all other groups, NH Black males had the lowest cumulative and mean survival of both cancers and higher cancer-specific mortality (penile adjusted hazards ratios [aHR] 1.23, 95% CI 1.01-1.49; anorectal aHR 1.25, 95% CI 1.10-1.42). There are different racial/ethnic disparities in health outcomes among males depending on site of HPV-associated anogenital cancer. Interventions to increase HPV vaccination rates, early detection, and treatment of anogenital cancers in males are needed, particularly among men of color.

KEYWORDS: Human Papillomavirus (HPV), anorectal cancer, penile cancer, males, racial/ethnic disparities.

Citation: Villalona S et al (2022) Racial/ethnic disparities in HPV-associated anogenital cancers among males in the United States: a population-based retrospective cohort study. Cancer Health Disparities 6:e1-25. doi:10.9777/chd.2022.1006

INTRODUCTION

Human papillomavirus (HPV)-associated cancers have become an increasing healthcare burden, accounting for over 46,000 cancer cases per year in the United States (Centers for Disease Control and Prevention, 2021). HPV infection often precedes the development of anogenital (AG) cancers, with approximately 64% of penile cancers and 91% of anal cancers attributable to HPV, particularly from oncogenic strains 16 and 18 (Centers for Disease Control and Prevention, 2021). In 2022, there will be an estimated 2,070 and 3150 new cases of penile and anorectal cancers, respectively, among males in the U.S.(Siegel et al., 2022). While incidence of cervical cancer has been declining in females due to widespread use of Papanicolaou smears, there has been a steady increase in HPV-associated cancers among males over the last few decades (Liao et al., 2022), highlighting the importance of targeting male HPV-associated AG cancer in public health efforts.

Penile cancer comprises 0.2% of male-associated malignancies (Siegel et al., 2022), with higher incidences observed in Hispanic and NH Black males (Attalla et al., 2018; Sharma et al., 2016b). One potential risk factor for HPV-associated penile cancer is lack of circumcision. The Human Papillomavirus Infection in Men (HIM) study reported that circumcision was associated with reduced risk of HPV detection across all viral strains tested (Giuliano et al., 2010; Giuliano et al., 2009). Cultural differences in circumcision practice can create populations at greater risk for HPV infection and subsequent penile cancer. In the U.S., Hispanic males have lower rates of circumcision relative to other ethnic groups, which may shift the healthcare burden of penile cancer disproportionately on the male Hispanic population (Colón-López et al., 2010). Additional risk factors such as lack of insurance, lower education, and lower socioeconomic status (SES) may result in poorer prognosis and worse survival among Hispanic males (Attalla et al., 2018; Sharma et al., 2016a).

Anal cancer incidence is rising among men (annual increase of 1.2%) while declining among women (3.2% annual decrease) (Centers for Disease Control and Prevention, 2020). Notably, new cases are highest in NH Black males with an annual average percentage increase of 3.40% between 2001-2017, and studies have shown poorer survival outcomes in this population (Benard et al., 2008; Fields et al., 2019; Liao et al., 2022; Patel et al., 2020). It has been suggested that the rising incidence of anal cancer parallels a rising incidence of HIV infection in racial minority populations and men who have sex with men (MSM) due to HIV and HPV co-infection (Walsh et al., 2015; Ye et al., 2020). However, the trends in incidence of anal cancer and poorer survival in NH Black males most likely result from a combination of socioeconomic status, insurance, and treatment factors, in addition to sexual practices and HIV status (Bian et al., 2021; Fields et al., 2019; Gillis et al., 2020; Goksu et al., 2020).

Prior studies of HPV-associated cancers in men have focused on select subpopulations (e.g. HIV-positive men) or limited the inclusion of distinct minority groups. However, a more encompassing sample is necessary to explore the intersections of race/ethnicity, HPV-associated cancer incidence and outcomes, and social determinants of health (Baughman and Shah, 2016; Bojko et al., 2018; Goksu et al., 2020; Gupta et al., 2017; Ortiz et al., 2018; Walsh et al., 2015). In this present study, we compared differences in stage at diagnosis, survival, and mortality of AG cancers in males among different racial/ethnic groups, while controlling for age, area poverty level, area of residence, and insurance status, all factors previously suggested to impact survival in males with AG cancers (Attalla et al., 2018; Bojko et al., 2018). To our knowledge, this

is the largest population-based study to examine racial/ethnic disparities in incidence, late-stage diagnosis, survival and mortality of AG cancers among males across the U.S. Identifying populations at risk is important to understand which men to target preventive interventions.

MATERIALS AND METHODS

Data and Sample

This is a population-based retrospective cohort study of males in the U.S. diagnosed with invasive anogenital (AG) cancers between 2005-2016 within the North American Association of Central Cancer Registries (NAACCR) Cancer in North America (CiNA) Deluxe data file (North American Association of Central Cancer Registries, 2018). NAACCR CiNA is the most comprehensive cancer incidence database, covering 93% of the U.S. population, and it includes all 18 Surveillance, Epidemiology, and End Results (SEER) registries. The database contains de-identified demographic, cancer type, and treatment information from population-based cancer registries across the U.S. and Canada. For survival and mortality analyses, we used a subset of this data file, the CiNA Survival dataset, which includes cancer registries that meet the Surveillance, Epidemiology, and End Results (SEER) standards for follow-up or ascertainment of deaths. Data were accessed through the SEER*Stat software program and exported into the Statistical Package for the Social Sciences (SPSS) version 27 (IBM, Armonk, New York) for advanced analyses. This study was approved by the Institutional Review Boards at NAACCR and Rutgers, the State University of New Jersey.

We included males with tumors in the following anatomical sites under the International Classification of Diseases for Oncology (ICD-O)-3: rectum (C20.9); anus (C21.0); anal canal (C21.1); cloacogenic zone (C21.2); overlapping lesion of rectum, anus, and anal canal (C21.8); prepuce (C60.0); glans penis (C60.1); body of penis (C60.2); overlapping lesion of penis (C60.8); and penis (C60.9) for a total of 263,102 individual cases. We excluded persons <15 years of age (n=28); cases diagnosed at autopsy or by death certificate (n=1,538); and diagnosis in Puerto Rico (n=2,268). Because cancer registries do not collect HPV status of cancers, we used standard Centers for Disease Control and Prevention definitions of HPV-associated cancers, i.e., ICD-O-3 site codes (listed above) and histological codes (squamous cell carcinoma (SCC) 8050-8084; 8120-8131) to identify HPV-associated AG cancers (Centers for Disease Control and Prevention, 2020). HPV-associated AG cancers were restricted to microscopically confirmed cases.

Stage at Diagnosis

Stage at diagnosis was classified as local, regional, and distant based on the SEER Summary Stage 1977/2000/Derived variable. For the stage at diagnosis analyses, we excluded persons with unknown stage (n=21,212), resulting in a final analytic sample of 39,601 cases. We defined stage as "early" if the AG cancer was diagnosed with local stage disease, and "late" if the AG cancer was diagnosed with regional or distant stage disease (Yang et al., 2018).

Survival and Mortality

We excluded cases diagnosed after December 31, 2011 (n=67,720) for our survival and mortality analyses in order to have at least 5 years of follow-up. We also excluded cases where AG cancer was not the first primary malignancy (N=44,196), had unknown cause of death (N=9,165), or unknown survival time (N=18,149), resulting in a final analytic sample of 15,244 cases. Mean cancer-specific survival for each racial/ethnic group was generated within SEER*Stat using the actuarial method (Ohno-Machado, 2001), via the "SEER cause-specific death classification" variable from the NAACCR data file

(North American Association of Central Cancer Registries, 2018). This variable takes into account cause of death information (ICD-10 codes), site of original cancer diagnosis, tumor sequence, and diseases associated to the cancer of diagnosis, and it addresses known misclassifications in cause of death on death certificates for cancer (Howlader et al., 2010). Cases are categorized as: dead (attributable to this cancer diagnosis); alive or dead of other cause; and dead (missing/unknown cause of death) (Howlader et al., 2010). In cancer-specific mortality analyses, persons who died of causes other than AG cancer were censored.

Covariates

The main independent variable of interest, race/ethnicity, was based on self-report and categorized as NH White, NH Black, Hispanic, and NH Other (Asians/Pacific Islanders and American Indians/Alaskan Natives) as classified in the NAACCR Research File (North American Association of Central Cancer Registries, 2018). Other covariates considered in our analyses included: age at diagnosis, health insurance, county level attributes of residence (Metropolitan/Non-metropolitan, percent of persons below poverty), geographic region of the U.S., and treatment modality. The NAACCR CiNA Research file categorizes age at diagnosis in 5-year intervals (e.g. 35-39, 40-44). We grouped this into three categories: <54, 55-64, 65+ years. Health insurance categories included: private, Medicare, Medicaid, Other (Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified), and no insurance or self-pay. Metropolitan/Non-metropolitan county designations were broadly based on population size (metropolitan has 50,000 persons or more). Percent of persons below poverty was categorized as: <9.99%, 10-19.99%, and 20% or more below federal poverty levels. The four geographic regions of the U.S. were based on the U.S. Census Bureau: Northeast, South, Midwest, and West/Pacific (United States Census Bureau, 2018). Treatment modality included the first course of planned treatment and was categorized as: surgery only; radiation or chemotherapy only; surgery plus (radiation or chemotherapy); radiation and chemotherapy; all modalities; or no treatment.

Statistical Analysis

The number of new cases of HPV-associated AG cancer from 2005-2016 was extracted from SEER*Stat. Age-adjusted incidence rates, stratified by disease stage, anatomic site (penile or anorectal), and race/ethnicity were calculated directly from SEER*Stat. Bivariate relationship between demographic characteristics and late-stage diagnosis was evaluated using χ^2 tests and univariate logistic regression. Adjusted odds ratios (aOR) of late-stage diagnosis compared with early stage and corresponding 95% confidence intervals (CIs) were calculated for each category of race/ethnicity using multivariable logistic regression, adjusting for age at diagnosis, insurance, metropolitan/non-metropolitan residence, area poverty, and geographic region. Finally, interaction terms were included in our final model to examine how race/ethnicity modified the relationship between covariates and late-stage AG diagnosis.

We used Cox proportional hazards regression to generate adjusted cancer-specific survival curves for different racial/ethnic groups. We examined associations of race/ethnicity with mortality from AG cancers using Cox proportional regression models to estimate the hazards of death from AG cancer (with 95% CIs). We included the variables described above and stage at diagnosis as potential confounders in multivariable model 1. To determine the effect of treatment modality on the associations between race/ethnicity and AG cancer mortality, we

added treatment to multivariable model 2. Finally, to examine potential effect modification of race/ethnicity on the other variables, interaction terms were included in the final multivariable model 2.

We conducted initial sensitivity analyses including and excluding cases with unknown race/ethnicity and unknown covariates. We additionally conducted sensitivity analyses of AG cancers as an aggregate sample and then stratified by anatomic site (penile and anorectal). Results were similar with and without unknown race and other covariates, but different when stratified by anatomic site. Therefore, we present multivariable models excluding missing values and separately for penile and anorectal cancers.

RESULTS

Table 1 describes the characteristics of our study cohort stratified by race/ethnicity. Most of our study sample consisted of NH White males (75%), aged 65+ (43.1%), residing in large metropolitan areas (82.3%), covered by Medicare insurance (38.2%), living in counties with 10-19.99% poverty (69.2%), residing in the geographic South (38.6%), and with local disease stage at diagnosis (52.6%). A majority of the cases were anorectal cancers (63.1%). Compared to other racial/ethnic groups, a higher proportion of Hispanics (44.1%) and NH Black (52.2%) males were less than 54 years of age. Higher proportions of Hispanic (23.1%) and NH Black (22.6%) males had Medicaid or no health insurance. NH Black males represented the largest proportion of individuals living in counties with >20% of poverty (30.2%). Hispanic (56.2%) and NH Other (55.3%) males represented larger proportions of penile cancers, while NH Black males (70.7%) represented the highest proportion of anorectal cancers. All bivariate relationships were statistically significant using χ^2 tests (all *p*-values <0.01).

Table 1. Characteristics of HPV-associated anogenital cancers in males, United States, 2005-2016 (N = 39,601).

Characteristic*	Total N (%)	Hispanic N (%)	White NH N (%)	Black NH N (%)	Other, NH§ N (%)	Unknown N (%)
Overall	39,601 (100)	3,806 (9.6)	29,714 (75.0)	5,066 (12.8)	740 (1.9)	275 (0.7)
Age at diagnosis, years						
<54	12,436 (31.4)	1,679 (44.1)	7,772 (26.2)	2,643 (52.2)	224 (30.3)	118 (42.9)
55-64	10,089 (25.5)	883 (23.2)	7,761 (26.1)	1,182 (23.3)	195 (26.4)	68 (24.7)
65+	17,076 (43.1)	1,244 (32.7)	14,181 (47.7)	1,241 (24.5)	321 (43.4)	89 (32.4)
Residence						
Metropolitan	32,572 (82.3)	3,558 (93.5)	23,518 (79.1)	4,629 (91.4)	634 (85.7)	233 (84.7)
Non-metropolitan	6,419 (16.2)	232 (6.1)	5,633 (19.0)	425 (8.4)	96 (13.0)	33 (12.0)
Unknown	610 (1.5)	16 (0.4)	563 (1.9)	12 (0.2)	10 (1.4)	9 (3.3)
Insurance Status						
Private	8,748 (22.1)	829 (21.8)	6,818 (22.9)	895 (17.7)	168 (22.7)	38 (13.8)
Medicare	15,123 (38.2)	1,030 (27.1)	12,185 (41.0)	1,596 (31.5)	254 (34.3)	58 (21.1)

Medicaid	3,235 (8.2)	484 (12.7)	1,914 (6.4)	754 (14.9)	72 (9.7)	11 (4.0)
Other♦	3,530 (8.9)	280 (7.4)	2,719 (9.2)	434 (8.6)	67 (9.1)	30 (10.9)
No Insurance/Self-Pay	2,097 (5.3)	397 (10.4)	1,261 (4.2)	388 (7.7)	39 (5.3)	12 (4.4)
Unknown	6,868 (17.3)	786 (20.7)	4,817 (16.2)	999 (19.7)	140 (18.9)	126 (45.8)
% Persons Below Poverty at Residence						
< 9.9%	5,312 (13.4)	314 (8.3)	4,408 (14.8)	407 (8.0)	141 (19.1)	42 (15.3)
10-19.99%	27,396 (69.2)	2,738 (71.9)	20,873 (70.2)	3,115 (61.5)	481 (65.0)	189 (68.7)
≥ 20%	6,283 (15.9)	738 (19.4)	3,870 (13.0)	1,532 (30.2)	108 (14.6)	35 (12.7)
Unknown	610 (1.5)	16 (0.4)	563 (1.9)	12 (0.2)	10 (1.4)	9 (3.3)
Geographic Region						
Northeast	7,603 (19.2)	838 (22.0)	5,614 (18.9)	968 (19.1)	128 (17.3)	55 (20.0)
South	15,267 (38.6)	1,375 (36.1)	11,042 (37.2)	2,625 (51.8)	151 (20.4)	74 (26.9)
Midwest	8,172 (20.6)	247 (6.5)	6,815 (22.9)	975 (19.2)	88 (11.9)	47 (17.1)
West/Pacific	8,559 (21.6)	1,346 (35.4)	6,243 (21.0)	498 (9.8)	373 (50.4)	99 (36.0)
Stage at Diagnosis						
Local	20,814 (52.6)	1,970 (51.8)	15,921 (53.6)	2,408 (47.5)	374 (50.5)	141 (51.3)
Regional	12,574 (38.6)	1,255 (33.0)	9,207 (31.0)	1,811 (35.7)	247 (33.4)	54 (19.6)
Distant	3,025 (7.6)	266 (7.0)	2,241 (7.5)	443 (8.7)	64 (8.6)	11 (4.0)
Unknown	3,188 (8.1)	315 (8.3)	2,345 (7.9)	404 (8.0)	55 (7.4)	69 (25.1)
Anatomical Site						
Penile	14,612 (36.9)	2,140 (56.2)	10,477 (35.3)	1,482 (29.3)	409 (55.3)	104 (37.8)
Anorectal	24,989 (63.1)	1,666 (43.8)	19,237 (64.7)	3,584 (70.7)	331 (44.7)	171 (62.2)
Treatment						
Surgery Only	15,431 (39.0)	1,940 (51.0)	11,251 (37.9)	1,745 (34.4)	375 (50.7)	120 (43.6)
Radiation or Chemo	2,472 (6.2)	164 (4.3)	1,906 (6.4)	357 (7.0)	29 (3.9)	16 (5.8)
Surgery + (Radiation or Chemo)	3,834 (9.7)	411 (10.8)	2,801 (9.4)	532 (10.5)	73 (9.9)	17 (6.2)
Radiation + Chemo	9,556 (24.1)	604 (15.9)	7,533 (25.4)	1,245 (24.6)	132 (17.8)	42 (15.3)
All Modalities	4,740 (12.0)	347 (9.1)	3,620 (12.2)	701 (13.8)	63 (8.5)	9 (3.3)
No Treatment	3,553 (9.0)	338 (8.9)	2,590 (8.7)	486 (9.6)	68 (9.2)	71 (25.8)

NH, Non-Hispanic. Chemo, Chemotherapy.

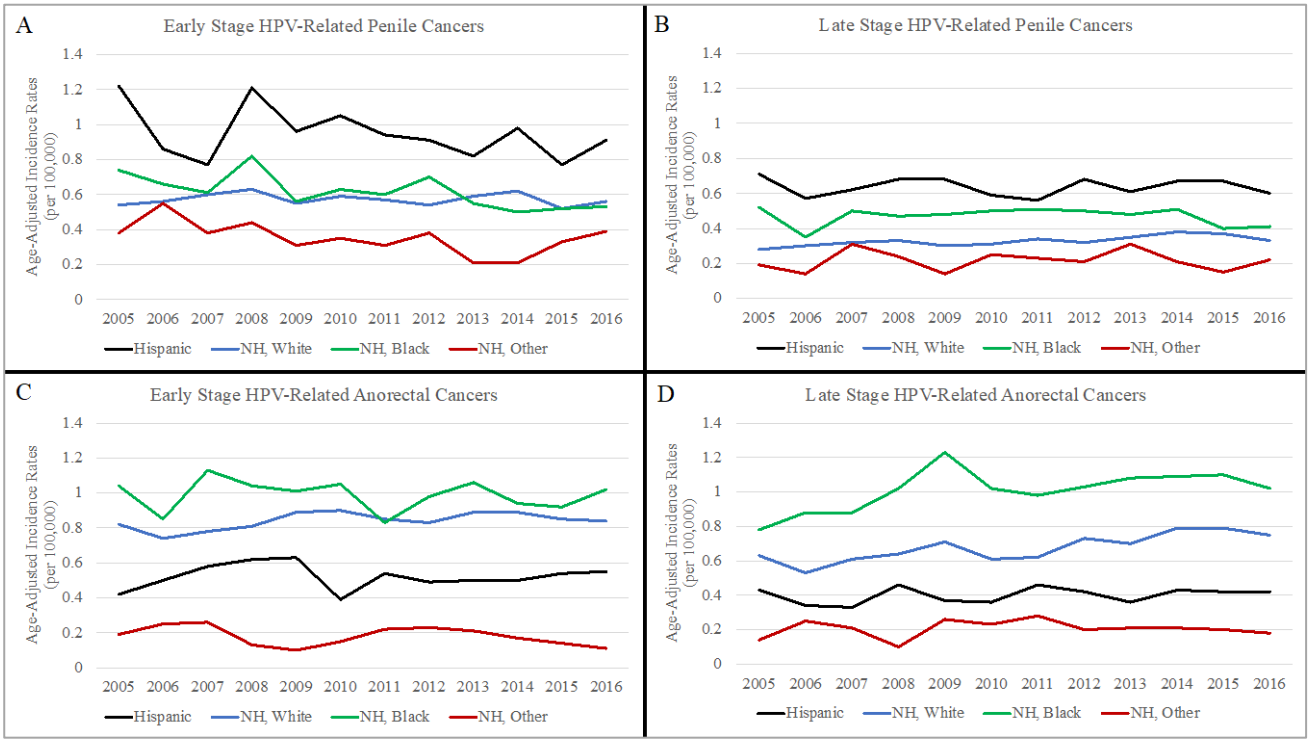
* All variables were statistically significant at $p < 0.01$ in bivariate analyses using χ^2 tests.

§ Includes Asian, American Indian, Alaska Native, and Pacific Islander

♦Other insurance includes Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified.

Figure 1 describes the age-adjusted incidence rates of HPV-associated AG cases from 2005-2016 by race/ethnicity and stage, stratified by anatomic site. The incidence rate of penile cancer remained relatively stable for all groups, while there were slight increases in late stage anorectal cancers among NH Black and NH White males. Relative to the other groups, Hispanics had the highest incidence rate of penile cancers irrespective of disease stage (1A, 1B), while NH Black males had the highest incidence rate of anorectal cancers (1C, 1D).

Figure 1: Incidence of HPV-Associated Anogenital Cancers by Stage among Males, 2005-2016 (N= 36,413)[†]



[†]Cases with unknown tumor stage were excluded.

Stage at Anogenital Cancer Diagnosis

Males with anorectal cancers had higher odds of late-stage diagnosis (aOR 1.32, 95% CI 1.26-1.39) relative to penile cancers (data not shown). Table 2 describes factors associated with late stage diagnosis of penile and anorectal cancers. Compared to NH White males, higher odds of late-stage penile cancers were observed in NH Black (aOR 1.22, 95% CI 1.07-1.39) and Hispanic males (aOR 1.17, 95% CI 1.04-1.31). Other independent factors associated with late-stage diagnosis of penile cancer included having Medicaid (aOR 1.50, 95% CI 1.28-1.76) or no insurance (aOR 1.54, 95% CI 1.30-1.82).

Among anorectal cancers, NH Other (aOR 1.29, 95% CI 1.01-1.66) and NH Black males (aOR 1.25, 95% CI 1.14-1.36) had higher odds of late-stage diagnosis relative to NH White males. Additionally, males older than 55 years (55-64: aOR 1.17, 95% CI 1.08-1.25; 65+: aOR 1.10, 95% CI 1.01-1.19), as well as those with Medicaid (aOR 1.62, 95% CI 1.46-1.79), other (aOR 1.12, 95% CI 1.02-1.24), or no

insurance/self pay (aOR 1.76, 95% CI 1.55-2.00) had higher odds of late-stage anorectal cancer diagnosis. Residential characteristics (metropolitan/non-metropolitan, area poverty, and geographic region) were not associated with late stage diagnosis of penile or anorectal cancers.

Table 2. Predictors of Late Stage HPV-Associated Anogenital Cancers among Males in the United States, 2005-2016 (N= 30,319)†

Characteristic	Penile Cancers (n=11,533)	Anorectal Cancers (n=18,786)
Race/Ethnicity	**aOR# (95% CI)**	**aOR# (95% CI)**
NH, White	1.00	1.00
Hispanic/Latino	1.17 (1.04, 1.31)*	0.94 (0.83, 1.06)
NH, Black	1.22 (1.07, 1.39)*	1.25 (1.14, 1.36)*
NH, Other§	1.11 (0.88, 1.40)	1.29 (1.01, 1.66)*
Age at diagnosis (years)		
< 54	1.00	1.00
55-64	1.11 (0.99, 1.26)	1.17 (1.08, 1.25)*
65 +	0.91 (0.80, 1.04)	1.10 (1.01, 1.19)*
Insurance Type		
Private	1.00	1.00
Medicare	1.12 (0.99, 1.26)	1.01 (0.93, 1.09)
Medicaid	1.50 (1.28, 1.76)*	1.62 (1.46, 1.79)*
Other♦	0.98 (0.84, 1.14)	1.12 (1.02, 1.24)*
No Insurance/Self Pay	1.54 (1.30, 1.82)*	1.76 (1.55, 2.00)*
Residence		
Large Metropolitan	1.00	1.00
Non-Metropolitan	0.97 (0.87, 1.06)	1.01 (0.93, 1.10)
% Persons below Poverty at Residence		
< 9.9%	1.00	1.00
10-19.99%	0.98 (0.88, 1.10)	1.01 (0.92, 1.10)
≥ 20%	0.92 (0.80, 1.07)	1.00 (0.89, 1.12)
Geographic Region		
Northeast	1.00	1.00
South	0.96 (0.85, 1.08)	1.03 (0.93, 1.13)
Midwest	1.01 (0.88, 1.15)	0.97 (0.88, 1.08)
West/Pacific	1.04 (0.91, 1.18)	1.07 (0.96, 1.18)

HPV, human papillomavirus; NH, Non-Hispanic; aOR, adjusted odds ratio; CI, confidence interval

† Cases with unknown stage and unknown covariates were excluded.

[#] Adjusted for all other variables in table

[*] p ≤0.01

[§] Includes Asian, American Indian, Alaska Native, and Pacific Islander

♦Other insurance includes Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified.

In interaction analyses for penile cancers, race/ethnicity modified the relationship between late-stage diagnosis and other factors (Supplemental Table 1). Compared with their NH White counterparts of the same age group, Hispanic males under the age of 55 (aOR 1.51, 95% CI 1.26-1.80) and NH Black males aged 65 and older (aOR 1.77, 95% CI 1.20-2.61) had higher odds of late-stage diagnosis. NH Black males with private insurance, living in large metropolitan or low poverty (<10% of population below poverty) areas, or who lived in the South or Western/Pacific regions were also found to have higher odds of late-stage diagnosis compared to NH White males. Additionally, Hispanic males were found to have higher odds of late-stage diagnosis when living in large metropolitan or low poverty areas and in the Western/Pacific region. Interestingly, NH Black males living in high poverty areas (≥20% of population below poverty) had significantly lower odds of late-stage penile cancer compared to NH White males (aOR 0.55, 95% CI 0.32-0.95). For anorectal cancer, the only significant finding was that NH Other males aged 65 years and older were observed to have over 3 times higher odds of late-stage diagnosis (aOR 3.01, 95% CI 1.50-6.02) relative to NH White males in the same age group (results not shown).

Supplemental Table 1: Interactions of Race/Ethnicity with Covariates, Late-Stage Diagnosis from HPV-Associated Penile Cancers among Males in the United States, 2005-2016 (N=11,533) [†]

Characteristic	aOR (95% CI)	p-value
Age at diagnosis (years)		0.01
< 54		
NH, White	1.00	
Hispanic/Latino	1.51 (1.26, 1.80)	<0.01
NH, Black	1.08 (0.85, 1.36)	0.53
NH, Other[§]	1.41 (0.90, 2.21)	0.13
55-64		
NH, White	1.00	
Hispanic/Latino	1.05 (0.77, 1.44)	0.74
NH, Black	1.21 (0.84, 1.74)	0.30
NH, Other	0.75 (0.36, 1.56)	0.45
65 +		
NH, White	1.00	
Hispanic/Latino	0.73 (0.52, 1.02)	0.06
NH, Black	1.77 (1.20, 2.62)	<0.01
NH, Other	0.80 (0.38, 1.69)	0.56

Insurance Type		0.67
Private		
NH, White	1.00	
Hispanic/Latino	1.14 (0.91, 1.41)	0.25
NH, Black	1.37 (1.02, 1.83)	0.03
NH, Other	1.08 (0.70, 1.67)	0.71
Medicare		
NH, White	1.00	
Hispanic/Latino	1.16 (0.82, 1.63)	0.40
NH, Black	0.70 (0.47, 1.04)	0.08
NH, Other	1.21 (0.59, 2.51)	0.60
Medicaid		
NH, White	1.00	
Hispanic/Latino	1.12 (0.76, 1.66)	0.57
NH, Black	0.88 (0.54, 1.43)	0.60
NH, Other	0.74 (0.32, 1.69)	0.48
Other♦		
NH, White	1.00	
Hispanic/Latino	1.20 (0.78, 1.84)	0.41
NH, Black	0.87 (0.53, 1.44)	0.59
NH, Other	1.67 (0.65, 4.34)	0.29
No Insurance/Self Pay		
NH, White	1.00	
Hispanic/Latino	1.28 (0.86, 1.90)	0.23
NH, Black	0.73 (0.43, 1.22)	0.23
NH, Other	1.10 (0.39, 3.12)	0.86
Residence		0.27
Large Metropolitan		
NH, White	1.00	
Hispanic/Latino	1.31 (1.19, 1.46)	<0.01
NH, Black	1.25 (1.11, 1.42)	<0.01
NH, Other	1.20 (0.95, 1.50)	0.12
Non-Metropolitan		
NH, White	1.00	
Hispanic/Latino	1.10 (0.74, 1.65)	0.64
NH, Black	1.40 (0.96, 2.06)	0.08

NH, Other	0.73 (0.34, 1.57)	0.42
% Persons below Poverty at Residence		0.14
< 9.9%		
NH, White	1.00	
Hispanic/Latino	1.51 (1.11, 2.07)	0.01
NH, Black	1.68 (1.13, 2.50)	0.01
NH, Other	1.31 (0.80, 2.14)	0.29
10-19.99%		
NH, White	1.00	
Hispanic/Latino	0.87 (0.59, 1.28)	0.48
NH, Black	0.62 (0.38, 1.00)	0.05
NH, Other	0.96 (0.50, 1.84)	0.91
≥ 20%		
NH, White	1.00	
Hispanic/Latino	0.77 (0.48, 1.22)	0.27
NH, Black	0.55 (0.32, 0.95)	0.03
NH, Other	1.29 (0.52, 3.23)	0.58
Geographic Region		0.02
Northeast		
NH, White	1.00	
Hispanic/Latino	1.12 (0.89, 1.39)	0.33
NH, Black	1.07 (0.80, 1.42)	0.64
NH, Other	1.34 (0.85, 2.10)	0.21
South		
NH, White	1.00	
Hispanic/Latino	1.01 (0.55, 1.88)	0.97
NH, Black	1.78 (1.10, 2.89)	0.02
NH, Other	1.65 (0.96, 2.82)	0.07
Midwest		
NH, White	1.00	
Hispanic/Latino	0.83 (0.40, 1.73)	0.62
NH, Black	0.49 (0.20, 1.22)	0.12
NH, Other	1.29 (0.49, 3.40)	0.60
West/Pacific		
NH, White	1.00	
Hispanic/Latino	1.53 (1.05, 2.24)	0.03

NH, Black	1.46 (1.00, 2.13)	0.05
NH, Other	1.40 (0.85, 2.31)	0.18

OR, odds ratio; aOR, adjusted odds ratio; NH, Non-Hispanic

† Cases with unknown stage and unknown covariates were excluded.

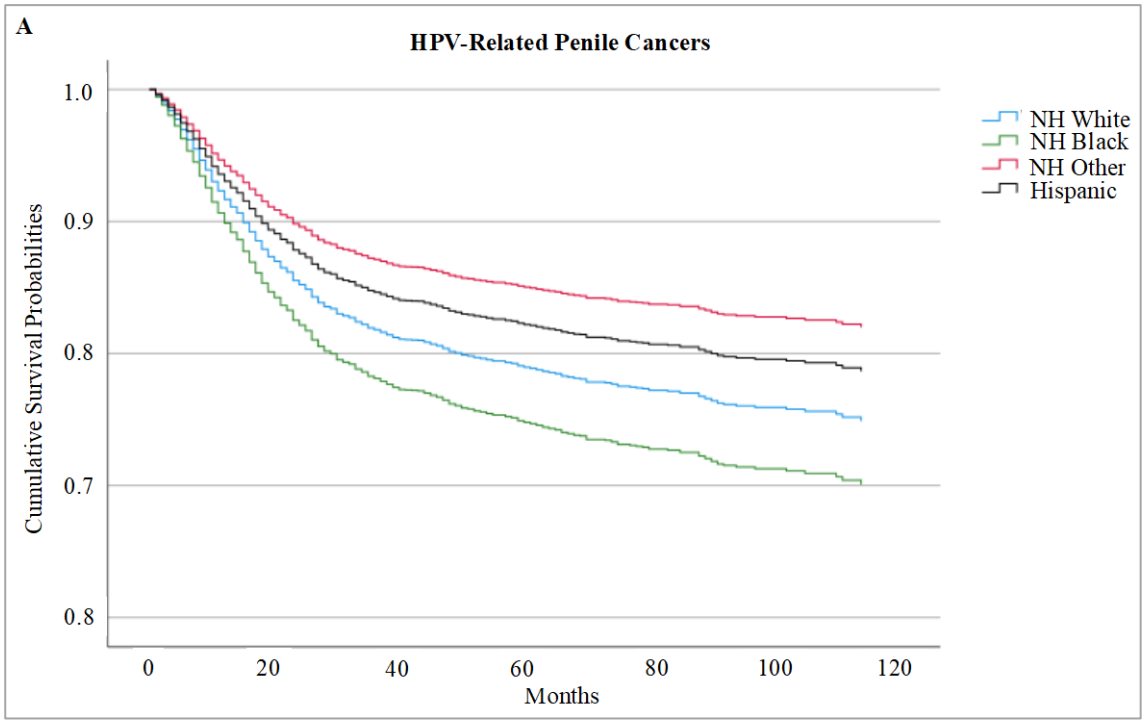
§ Includes Asian, American Indian, Alaska Native, and Pacific Islander

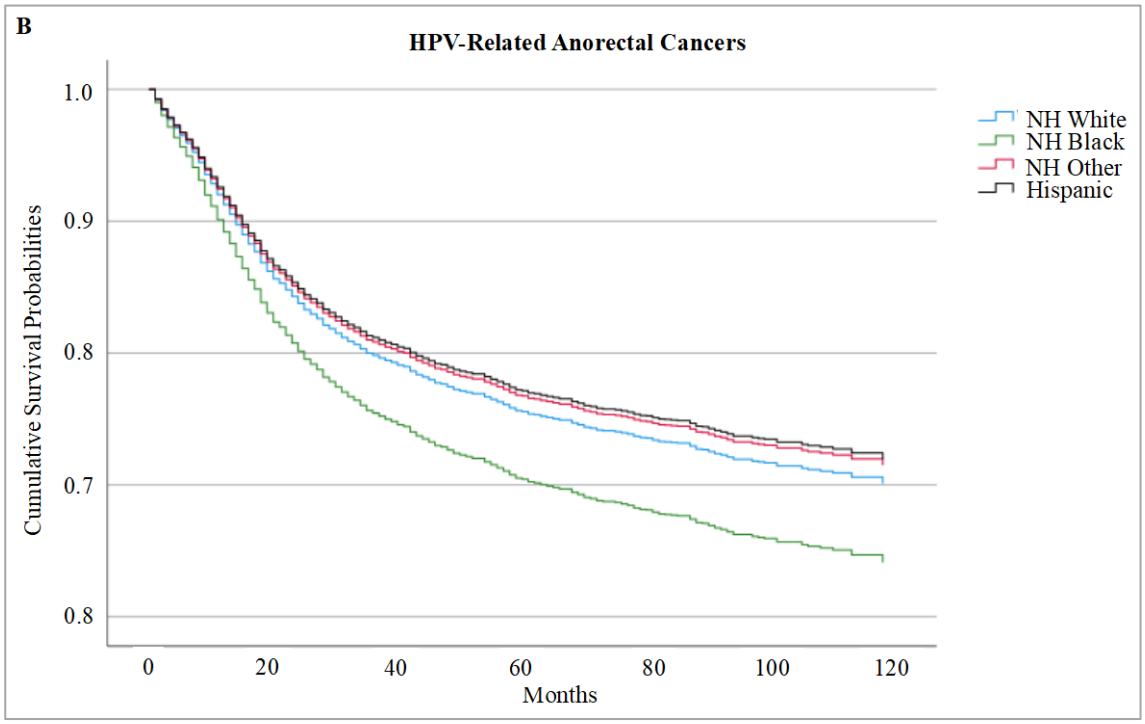
♦Other insurance includes Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified.

Anogenital Cancer Survival and Mortality

Figure 2 represents the adjusted cumulative survival of HPV-associated AG cancers. NH Black males had lower cumulative (Fig. 2) and mean survival times (Table 3) relative to the other racial/ethnic groups for both penile and anorectal cancers. Conversely, NH Other males had higher cumulative (Fig. 2) and mean survival (Table 3) of penile cancers relative to the other racial/ethnic groups.

Figure 2: Cumulative Survival of HPV-Associated Anogenital Cancers among Males, 2005-2011 (N= 11,432)*





*Mantel-Cox log rank tests for cumulative survival were statistically significant at p<0.01.

Table 3. Mean Survival of Males with HPV-Associated Anogenital Cancers by Race/Ethnicity, United States, 2005-2011 (N=11,258)*

	Overall Mean months (95% CI)	Hispanic Mean months (95% CI)	NH White Mean months (95% CI)	NH Black Mean months (95% CI)	NH Other§ Mean months (95% CI)
Penile	102.94 (101.60-104.27)	105.62 (102.42-108.82)	102.91 (101.31-104.50)	95.68 (91.11-100.26)	112.05 (105.60-118.50)
Anorectal	98.10 (97.03-99.17)	100.81 (96.69-104.92)	99.28 (98.08-100.47)	90.64 (87.65-93.63)	95.53 (86.25-104.81)

HPV, human papillomavirus; NH, Non-Hispanic

*Unadjusted; All log rank Mantel-Cox tests were statistically significant at p<0.01

§ Includes Asian, American Indian, Alaska Native, and Pacific Islander

Table 4 describes the predictors of AG cancer-specific mortality stratified by anatomic site. In multivariable analyses adjusting for all covariates except treatment (Model 1), independent predictors of higher penile cancer-specific mortality included: NH Black race, Medicaid or Medicare, regional or distant stage diagnosis, and residence in high poverty (20%) areas. Penile cancer-specific mortality was significantly lower in males living in the geographic South and Midwest compared to the Northeast. After adjusting for treatment, there was an attenuation of mortality for stage at diagnosis (Model 2). Higher mortality was observed for all treatment groups compared to surgery alone, with individuals receiving no treatment experiencing more than 3.5 times higher cancer-specific mortality (aHR 3.54, 95% CI 2.61-4.80).

Among males with anorectal cancers, after adjusting for all covariates except treatment (Model 3), independent predictors of higher cancer-specific mortality included: NH Black race; all insurances compared to private; regional or distant stage at diagnosis; and residence in moderate to high poverty areas. Similar relationships were found after adjustment for treatment (Model 4) with a few notable exceptions. We found that residence in the Western/Pacific region became significantly higher than the Northeast and a sizable attenuation of hazards for regional and distant stage. Men who received no treatment experienced more than 4.5 times higher cancer-specific mortality (aHR 4.53, 95% CI 3.57,-5.74).

Table 4. Predictors of Cause-Specific Mortality from HPV-Associated Anogenital Cancers among Males in the United States, 2005-2011 (N=11,432)[†]

	Penile Cancers (n=4,383)		Anorectal Cancers (n=7,049)	
	Multivariable Model 1	Multivariable Model 2	Multivariable Model 3	Multivariable Model 4
Characteristic	aHR[#] (95% CI)	aHR[##] (95% CI)	aHR[#] (95% CI)	aHR[##] (95% CI)
Race/Ethnicity				
NH, White	1.00	1.00	1.00	1.00
Hispanic/Latino	0.84 (0.70, 1.02)	0.83 (0.69, 1.00)	0.95 (0.78, 1.15)	0.93 (0.76, 1.13)
NH, Black	1.25 (1.03, 1.51)*	1.23 (1.01, 1.49)*	1.29 (1.14, 1.46)*	1.25 (1.10, 1.42)*
NH, Other[§]	0.72 (0.48, 1.09)	0.69 (0.45, 1.05)	0.97 (0.67, 1.40)	0.94 (0.65, 1.38)
Age at diagnosis (years)				
< 54	1.00	1.00	1.00	1.00
55-64	1.19 (0.99, 1.44)	1.21 (1.01, 1.46)*	1.04 (0.94, 1.17)	1.00 (0.90, 1.12)
65 +	1.17 (0.95, 1.44)	1.23 (0.99, 1.53)	1.09 (0.96, 1.24)	1.00 (0.88, 1.13)
Insurance Type				
Private	1.00	1.00	1.00	1.00
Medicare	1.27 (1.04, 1.54)*	1.28 (1.05, 1.56)*	1.72 (1.51, 1.95)*	1.72 (1.50, 1.96)*
Medicaid	1.34 (1.05, 1.71)*	1.28 (1.00, 1.64)*	1.67 (1.44, 1.93)*	1.67 (1.44, 1.94)*
Other[♦]	0.94 (0.74, 1.18)	0.91 (0.72, 1.15)	1.34 (1.16, 1.56)*	1.32 (1.14, 1.54)*
No Insurance/Self Pay	1.04 (0.80, 1.35)	1.06 (0.81, 1.38)	1.27 (1.07, 1.51)*	1.21 (1.01, 1.44)*
Stage at Diagnosis				
Local	1.00	1.00	1.00	1.00
Regional	3.45 (3.02, 3.94)*	3.02 (2.63, 3.48)*	2.30 (2.08, 2.54)*	2.18 (1.96, 2.43)*
Distant	18.14 (14.65, 22.46)*	11.52 (9.08, 14.61)*	7.40 (6.58, 8.33)*	6.14 (5.41, 6.96)*
Residence				
Large Metropolitan	1.00	1.00	1.00	1.00
Non-Metropolitan	1.02 (0.88, 1.19)	1.03 (0.88, 1.20)	0.93 (0.82, 1.05)	0.91 (0.80, 1.04)
% Persons below Poverty at Residence				

< 9.9%	1.00	1.00	1.00	1.00
10-19.99%	1.10 (0.89, 1.35)	1.11 (0.90, 1.37)	1.26 (1.08, 1.46)*	1.24 (1.06, 1.45)*
≥ 20%	1.33 (1.04, 1.70)*	1.33 (1.04, 1.71)*	1.42 (1.18, 1.70)*	1.38 (1.14, 1.67)*
Geographic Region				
Northeast	1.00	1.00	1.00	1.00
South	0.79 (0.65, 0.97)*	0.77 (0.63, 0.95)*	1.13 (0.97, 1.32)	1.16 (0.99, 1.35)
Midwest	0.74 (0.59, 0.93)*	0.73 (0.58, 0.93)*	1.05 (0.88, 1.26)	1.12 (0.94, 1.35)
West/Pacific	0.86 (0.69, 1.08)	0.84 (0.67, 1.05)	1.14 (0.97, 1.35)	1.21 (1.02, 1.44)*
Treatment Modality				
Surgery Only		1.00		1.00
Radiation or Chemotherapy Only		2.40 (1.72, 3.35)*		2.45 (1.99, 3.01)*
Surgery + Radiation or Chemotherapy		2.15 (1.80, 2.55)*		1.27 (0.97, 1.66)
Radiation + Chemotherapy		1.86 (1.16, 2.96)*		1.50 (1.26, 1.79)*
All Modalities		2.06 (1.57, 2.71)*		1.23 (1.02, 1.49)*
No Treatment		3.54 (2.61, 4.80)*		4.53 (3.57, 5.74)*

HPV, human papillomavirus; NH, Non-Hispanic; HR, hazards ratio; aHR, adjusted hazards ratio

† Cases with unknown stage and unknown covariates were excluded.

Adjusted for all other variables excluding treatment modality

##Adjusted for all other variables including treatment modality

* p ≤0.01

§ Includes Asian, American Indian, Alaska Native, and Pacific Islander

♦Other insurance includes Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified.

In interaction analyses (Supplemental Table 2), race/ethnicity modified the relationship of penile cancer mortality and age, stage, residence in a metropolitan area, and geographic region. Compared with NH white males of the same age group, NH Black males less than age 55 years had higher hazards of death (aHR 1.53, 95% CI 1.09-2.14). Relative to NH White males diagnosed at the same stage, lower cancer-specific mortality was observed in NH Other (aHR 0.35, 95% CI 0.14-0.84) and Hispanic males (aHR 0.45, 95% CI 0.21-0.97) with local and distant stage penile cancers, respectively. Lower cancer-specific mortality was also observed in NH Black males living in the Midwest (aOR 0.36, 95% CI 0.14-0.90) and Hispanic males living in the Northeast (aOR 0.37, 95% CI 0.20-0.67) compared to NH White males living in those regions. For anorectal cancer mortality, there were no significant interactions between race/ethnicity and other variables.

Supplemental Table 2: Interactions of Race/Ethnicity with Covariates, Cancer-Specific Mortality from HPV-Associated Penile Cancers among Males in the United States, 2005-2011 (N=4,383)[†]		
	Penile Cancer-Specific Mortality	
Characteristic	aHR (95% CI)	p-value
Age at diagnosis (years)		0.44
< 54		
NH, White	1.00	
Hispanic/Latino	1.06 (0.79, 1.43)	0.70
NH, Black	1.53 (1.09, 2.14)	0.01
NH, Other[§]	0.75 (0.33, 1.69)	0.48
55-64		
NH, White	1.00	
Hispanic/Latino	0.87 (0.53, 1.43)	0.58
NH, Black	0.67 (0.39, 1.14)	0.14
NH, Other	0.50 (0.09, 2.77)	0.43
65 +		
NH, White	1.00	
Hispanic/Latino	1.01 (0.56, 1.78)	0.99
NH, Black	1.25 (0.69, 2.25)	0.46
NH, Other	1.44 (0.17, 12.00)	0.73
Insurance Type		0.31
Private		
NH, White	1.00	
Hispanic/Latino	0.79 (0.54, 1.16)	0.23
NH, Black	1.16 (0.74, 1.81)	0.52
NH, Other	0.70 (0.31, 1.59)	0.40
Medicare		
NH, White	1.00	
Hispanic/Latino	1.11 (0.61, 2.04)	0.73
NH, Black	0.76 (0.39, 1.47)	0.42
NH, Other	0.53 (0.06, 5.08)	0.58
Medicaid		
NH, White	1.00	
Hispanic/Latino	1.04 (0.55, 1.96)	0.91
NH, Black	0.94 (0.45, 1.95)	0.87

NH, Other	0.24 (0.04, 1.39)	0.11
Other[¶]		
NH, White	1.00	
Hispanic/Latino	1.98 (0.98, 3.98)	0.06
NH, Black	1.78 (0.88, 3.60)	0.11
NH, Other	0.37 (0.02, 5.75)	0.48
No Insurance/Self Pay		
NH, White	1.00	
Hispanic/Latino	1.48 (0.75, 2.91)	0.26
NH, Black	1.51 (0.71, 3.20)	0.28
NH, Other	-----	-----
Stage at Diagnosis		0.01
Local		
NH, White	1.00	
Hispanic/Latino	0.81 (0.60, 1.07)	0.14
NH, Black	1.20 (0.88, 1.62)	0.24
NH, Other	0.35 (0.14, 0.84)	0.02
Regional		
NH, White	1.00	
Hispanic/Latino	0.79 (0.52, 1.19)	0.26
NH, Black	1.06 (0.68, 1.65)	0.79
NH, Other	2.21 (0.58, 8.41)	0.24
Distant		
NH, White	1.00	
Hispanic/Latino	0.45 (0.21, 0.97)	0.04
NH, Black	0.80 (0.37, 1.70)	0.56
NH, Other	-----	-----
Residence		0.41
Large Metropolitan		
NH, White	1.00	
Hispanic/Latino	0.86 (0.73, 1.02)	0.09
NH, Black	1.31 (1.09, 1.57)	0.01
NH, Other	0.63 (0.42, 0.96)	0.03
Non-Metropolitan		
NH, White	1.00	
Hispanic/Latino	1.56 (0.87, 2.80)	0.14

NH, Black	1.27 (0.75, 2.14)	0.38
NH, Other	0.85 (0.22, 3.32)	0.82
% Persons below Poverty at Residence		0.14
< 9.9%		
NH, White	1.00	
Hispanic/Latino	0.24 (0.09, 0.64)	0.01
NH, Black	1.01 (0.53, 1.93)	0.97
NH, Other	0.35 (0.09, 1.40)	0.14
10-19.99%		
NH, White	1.00	
Hispanic/Latino	3.50 (1.06, 11.62)	0.04
NH, Black	1.72 (0.74, 4.01)	0.21
NH, Other	0.63 (0.11, 3.60)	0.60
≥ 20%		
NH, White	1.00	
Hispanic/Latino	3.71 (1.06, 13.03)	0.04
NH, Black	1.45 (0.58, 3.61)	0.42
NH, Other	2.43 (0.40, 14.92)	0.34
Geographic Region		0.01
Northeast		
NH, White	1.00	
Hispanic/Latino	0.37 (0.20, 0.67)	0.01
NH, Black	0.91 (0.49, 1.69)	0.76
NH, Other	0.45 (0.14, 1.43)	0.18
South		
NH, White	1.00	
Hispanic/Latino	0.70 (0.33, 1.45)	0.34
NH, Black	0.49 (0.23, 1.04)	0.06
NH, Other	0.59 (0.07, 5.10)	0.63
Midwest		
NH, White	1.00	
Hispanic/Latino	0.44 (0.13, 1.47)	0.18
NH, Black	0.36 (0.14, 0.90)	0.03
NH, Other	3.27 (0.36, 30.07)	0.29
West/Pacific		
NH, White	1.00	

Hispanic/Latino	1.26 (0.61, 2.59)	0.53
NH, Black	0.46 (0.17, 1.22)	0.12
NH, Other	0.55 (0.09, 3.54)	0.53
Treatment Modality		0.54
Surgery Only		
NH, White	1.00	
Hispanic/Latino	0.82 (0.67, 1.00)	0.05
NH, Black	1.22 (0.98, 1.51)	0.07
NH, Other	0.58 (0.35, 0.97)	0.04
Radiation or Chemotherapy Only		
NH, White	1.00	
Hispanic/Latino	1.74 (0.61, 4.91)	0.30
NH, Black	2.21 (0.93, 5.23)	0.07
NH, Other	-----	-----
Surgery + (Radiation or Chemotherapy)		
NH, White	1.00	
Hispanic/Latino	1.47 (0.91, 2.34)	0.11
NH, Black	0.76 (0.44, 1.30)	0.32
NH, Other	0.51 (0.12, 2.26)	0.38
Radiation + Chemotherapy		
NH, White	1.00	
Hispanic/Latino	-----	-----
NH, Black	-----	-----
NH, Other	-----	-----
All Modalities		
NH, White	1.00	
Hispanic/Latino	1.18 (0.56, 2.49)	0.65
NH, Black	1.17 (0.46, 3.00)	0.74
NH, Other	-----	-----
No Treatment		
NH, White	1.00	
Hispanic/Latino	0.82 (0.67, 1.00)	0.05
NH, Black	1.04 (0.47, 2.30)	0.92
NH, Other	-----	-----

HR, hazards ratio; aHR, adjusted hazards ratio; NH, Non-Hispanic

† Cases with unknown stage and unknown covariates were excluded.

§ Includes Asian, American Indian, Alaska Native, and Pacific Islander.

♦Other insurance includes Indian/Public Health Service, Military, TRICARE, Veterans Affairs, and insurance not otherwise specified.

---- suppressed for unreliable estimates due to case counts below 6.

DISCUSSION

To our best knowledge, the present study is the most comprehensive examination of HPV-associated AG cancer health outcomes among males living across the United States. Prior studies have focused on one particular outcome or did not include covariates such as insurance status or geographic region in their analyses (Huang et al., 2020; Osazuwa-Peters et al., 2021; Slopnick et al., 2016). This study contributes to the literature of HPV-associated AG cancers in specifically analyzing the disparities in incidence, late-stage, survival, and mortality among males of multiple racial/ethnic groups.

Previous incidence estimates of HPV-associated AG cancers in the United States have been based on study populations consisting primarily of NH White and NH Black men due to sample size considerations and the relative rarity of penile and anal cancer compared to other cancer types (Arora et al., 2017; Baughman and Shah, 2016; Bian et al., 2021; Centers for Disease Control and Prevention, 2020). Similar to other studies, NH White males represented the largest proportion of our study sample, regardless of anatomic site or stage (Huang et al., 2020; Osazuwa-Peters et al., 2021), while NH Black males had the highest incidence and mortality of anorectal cancers (Arora et al., 2017; Deshmukh et al., 2020; Goksu et al., 2020). Additionally, we found Hispanic males had the highest age-adjusted incidence rate of penile cancers regardless of disease stage, and NH Black males had later stage at diagnosis, lower survival, and higher mortality for both penile and anorectal cancers. Furthermore, certain subgroups of Hispanic and NH Other males were found to have higher late stage diagnosis of penile (Hispanics living in South and West/Pacific) and anorectal cancer (NH Other males 65 years and older). Inclusion of Hispanic and NH Other males (Asian, Pacific Islander, Native American, Alaskan Native) and controlling for potential confounders contribute uniquely to the literature about male HPV-associated AG cancers, which can lead to more targeted interventions to reduce the incidence, later stage at diagnosis, and mortality in men of color.

The lower survival and higher mortality rates among NH Black males for both penile and anorectal cancers may be associated with delayed treatment initiation, later stage at diagnosis, lower rates of radiation therapy, and SES disparities (Ahmad et al., 2019; Attalla et al., 2018; Baughman and Shah, 2016; Fields et al., 2019; Goksu et al., 2020; Gupta et al., 2017). However, our observed disparity in mortality persisted after controlling for stage, treatment, and markers of SES. A potential contributing factor may be HIV co-infection with HPV. Studies have noted disporportionately higher rates of contracting HIV among NH Black men, especially men who have sex with men (MSM) relative to white men, and there has been a rise in the HIV-infection of NH Black males over the last three decades (Heckman et al., 1999; Leeds and Fang, 2016; Millett et al., 2007). HIV is a known risk factor for anal cancer, and the co-infection of HIV and HPV represents a significant challenge to a progressively diminished immune system (Burd, 2003). Additional clinician-related challenges include a lack of formal recommendations for use of anal Pap tests, relative infrequency of anal cancer cases, and lack of familiarity with the procedure and purpose of anal Pap testing (Liszewski et al., 2014). Studies examining the potential cost-effectiveness of anal

cytology screening have found that screening MSM every 2–3 years would be cost-effective and have life-expectancy benefits, and that screening could be easily incorporated into a primary care practice (Goldie et al., 2000; Siddharthan et al., 2019). NH Black MSM are 80% less likely to report anal cancer screening relative to their NH White counterparts, and thus, less likely to benefit from early detection of anal cancer (Hicks et al., 2019), potentially leading to later stage at diagnosis and higher mortality.

Though penile cancer incidence is rare, it can cause significant psychological distress, especially related to a man's self-esteem and sexual function (Harju et al., 2021). Our study findings showing Hispanic males having the highest age-adjusted incidence rates of penile cancer is consistent with previous studies (Huang et al., 2020; Ortiz et al., 2018). We also found Hispanic males to be diagnosed at later stages compared with NH White males, particularly among Hispanic males living in the South and West/Pacific regions of the U.S. Researchers partially attribute this to the lower rates of circumcision among Hispanic males (Colón-López et al., 2010), and lack of circumcision may be more prevalent among recent Hispanic immigrants who predominantly reside in the South and Western U.S. (Passel et al., 2022). Circumcision potentially has a protective mechanism by decreasing the likelihood of phimosis and by removing the foreskin as a site susceptible to the development of penile cancer (Larke et al., 2011). This may be why Hispanic males with HIV have higher penile cancer rates but lower anal cancer rates compared with NH White and Black males with HIV (Cruz et al., 2019; Ortiz et al., 2018).

No differences in mortality were observed between Hispanic and NH White males for either AG cancer. However, interaction analyses revealed lower cancer-specific mortality in Hispanic males with distant disease and those living in the Northeasten region of the country relative to NH White males of the same disease stage and region, respectively. This trend recurs throughout cancer research and other disease studies and has led to the emergence of a "Hispanic Paradox" or "Healthy Migrant Effect," which suggest that migration demands exerted a selective effect that leads to better health and mortality outcomes compared to NH White and NH Black males in similarly disadvantaged conditions (Thomson et al., 2013). However, extreme caution should be used when considering this hypothesis during health intervention planning because of the serious impact on health policy and likelihood of negatively impacting healthcare delivery to Hispanic populations that may still be at risk, including MSM and HIV-positive Hispanic males.

NH Other males were observed to have the lowest age-adjusted incidence of penile and anorectal cancer among all groups. The population that compose NH Other are under-studied, therefore, it is unclear why they have lower incidence of HPV-associated cancers and improved prognosis relative to other racial/ethnic groups. Among men, Asians and Pacific Islanders have the lowest incidence of HPV infection and lower probability of acquiring new HPV infections relative to other ethnic groups (Schabath et al., 2013). Additionally, Asians have been found to have lower cancer-specific mortality of any cancer compared to NH White males in all insurance status categories (Benard et al., 2008; Pan et al., 2017). Our study reveals additional health outcomes among NH Other males with HPV-associated AG cancers, particularly in certain subgroups. For example, NH Other males were found to have similar odds of late-stage diagnosis and risks of mortality from penile cancers relative to NH White males. However, those diagnosed at local stage had 0.35 times lower hazards of death compared to NH White males diagnosed at local stage. Conversely, NH Other males with anorectal cancer had 29% higher odds of late-stage diagnosis

relative to NH White males; specifically, those older than 65 years of age had three times higher odds of late-stage diagnosis relative to NH White males of the same age group. Future studies are necessary in understanding why certain subgroups of NH Other males experience better outcomes in penile cancer, while other subgroups have worse outcomes for anorectal cancer.

Limitations

Though our study included several established variables contributing to stage at diagnosis and overall survival in male AG cancers across racial/ethnic groups, the NAACCR database does not contain other information, such as sociocultural and behavioral factors as well as comorbidities that may impact our results. Known risk factors for anal and penile cancer include anal intercourse, lack of circumcision, immunosuppression, HIV-infection, and solid-organ transplantation (Amirian et al., 2013; Clifford et al., 2020; van der Zee et al., 2013). These factors may be differentially distributed across racial/ethnic groups and within subgroups of MSM and those engaging in higher-risk sexual behaviors (Amirian et al., 2013). Additionally, HPV status was not molecularly determined but based on supposition that cancers at particular sites and histologies are associated with HPV (Centers for Disease Control and Prevention, 2020), which may have led to misclassification of cases and an overestimate of the number of AG squamous cell carcinomas in our cohort. Furthermore, a limitation of the NAACCR database is a lack of information on the immigration status or birthplace of individuals identified as Hispanic or Asian. Since intragroup variability may be substantial among Hispanics (Martinez Tyson et al., 2018) and Asians (Thompson et al., 2016), future studies are needed to disentangle and understand AG outcomes among different Hispanic ethnicities and Asian subgroups.

CONCLUSION

This study highlights different racial/ethnic disparities in health outcomes among males depending on site of HPV-associated AG cancer. When considering the strong association between HPV and anal (>90%) and penile cancer (64%), as well as the potential reduction of cancer risk with HPV vaccination (Stier et al., 2016), our findings call for increasing HPV immunizations among all males. Additionally, increasing awareness of symptoms and signs of penile and anal cancer, as well as the utility of anal pap smears in high-risk populations may help to improve early detection, particularly in men of color. Finally, improving access to treatment is paramount for decreasing mortality in males with HPV-associated AG cancers, especially for Black men.

Author Contributions

SV, AMS, and JMF designed the research study. SV, AMS, JMF acquired and analyzed the data. All authors interpreted the data. SV, SS, DR drafted the manuscript. AMS and JMF revised the manuscript critically for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval

This study was approved by the Institutional Review Boards at the North American Association of Central Cancer Registries (NAACCR) and Rutgers, the State University of New Jersey (Pro2019001220).

Funding

No funding was received for this research.

Conflict of Interest

AMS received travel expenses while serving as President and Representative-at-Large of the Board of Directors for the North American Association of Central Cancer Registries (NAACCR) and the

NAACCR Communications Steering Committee. The other authors have no conflicts of interests to declare.

Acknowledgement

The data underlying this article were provided by The North American Association of Central Cancer Registries, which granted access to the Cancer in North America Deluxe file.

We thank Anna Petrova, MD, PhD, MPH and Ambarina Faiz, MD, PhD for their feedback on the analysis as part of Seiichi Villalona's Distinction in Research Program at Rutgers Robert Wood Johnson Medical School.

REFERENCES

Ahmad, T.R., Susko, M., Lindquist, K., and Anwar, M. (2019). Socioeconomic disparities in timeliness of care and outcomes for anal cancer patients. Cancer Med *8*, 7186-7196.

Amirian, E.S., Fickey Jr, P.A., Scheurer, M.E., and Chiao, E.Y. (2013). Anal cancer incidence and survival: comparing the greater San-Francisco bay area to other SEER cancer registries. PLoS One *8*, e58919.

Arora, N., Gupta, A., Zhu, H., Christie, A., Meyer, J.J., Khan, S.A., and Beg, M.S. (2017). Race-and sex-based disparities in the therapy and outcomes of squamous cell carcinoma of the anus. J Natl Compr Canc Netw *15*, 998-1004.

Attalla, K., Paulucci, D.J., Blum, K., Anastos, H., Moses, K.A., Badani, K.K., Spiess, P.E., and Sfakianos, J.P. (2018). Demographic and socioeconomic predictors of treatment delays, pathologic stage, and survival among patients with penile cancer: a report from the National Cancer Database. Urol Oncol *36*, 14.e17-14.e24.

Baughman, D.M., and Shah, B.K. (2016). Disparities in receipt of radiotherapy and survival by age, sex, and race among patients with non-metastatic squamous cell carcinoma of the anus. J Gastointest Oncol *7*, 968-973.

Benard, V.B., Johnson, C.J., Thompson, T.D., Roland, K.B., Lai, S.M., Cokkinides, V., Tangka, F., Hawkins, N.A., Lawson, H., and Weir, H.K. (2008). Examining the association between socioeconomic status and potential human papillomavirus-associated cancers. Cancer *113*, 2910-2918.

Bian, S.X., Chen, D.H., and Lin, E. (2021). Racial disparities in receipt of standard chemoradiation in anal squamous cell carcinoma, an analysis of the National Cancer Database. Cancer Med *10*, 575-585.

Bojko, M.M., Kucejko, R.J., and Poggio, J.L. (2018). Racial disparities and the effect of county level income on the incidence and survival of young men with anal cancer. Health equity *2*, 193-198.

Burd, E.M. (2003). Human papillomavirus and cervical cancer. Clin Microbiol Rev *16*, 1-17.

Centers for Disease Control and Prevention (2020). Definitions of Risk Factor-Associated Cancers. Available at: https://www.cdc.gov/cancer/uscs/public-use/predefined-seer-stat-variables.htm. Accessed March 1, 2020.

Centers for Disease Control and Prevention (2021). Cancers Associated with Human Papillomavirus, United States—2014–2018. USCS Data Brief, no. 26. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. Available at: https://www.cdc.gov/cancer/uscs/about/data-briefs/no26-hpv-assoc-cancers-UnitedStates-2014-2018.htm. Accessed April 6, 2022.

Clifford, G.M., Georges, D., Shiels, M.S., Engels, E.A., Albuquerque, A., Poynten, I.M., de Pokomandy, A., Easson, A.M., and Stier, E.A. (2020). A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. Int J Cancer Res *148*, 38-47.

Colón-López, V., Ortiz, A.P., and Palefsky, J. (2010). Burden of human papillomavirus infection and related comorbidities in men: implications for research, disease prevention and health promotion among Hispanic men. P R Health Sci J *29*, 232-240.

Cruz, A., Chen, D., Hsu, P., Pandit, V., Omesiete, P., Vij, P., and Nfonsam, V. (2019). Racial and gender disparities in the incidence of anal cancer: analysis of the Nationwide Inpatient Sample (NIS). J Gastointest Oncol *10*, 37-41.

Deshmukh, A.A., Suk, R., Shiels, M.S., Sonawane, K., Nyitray, A.G., Liu, Y., Gaisa, M.M., Palefsky, J.M., and Sigel, K. (2020). Recent trends in squamous cell carcinoma of the anus incidence and mortality in the United States, 2001–2015. J Natl Cancer Inst *112*, 829-838.

Fields, A.C., Welten, V.M., Lu, P., Goldberg, J.E., Irani, J., Bleday, R., and Melnitchouk, N. (2019). Does race impact survival for patients with anal squamous cell carcinoma? J Surg Oncol *120*, 1201-1207.

Gillis, J.L., Grennan, T., Grewal, R., Ogilvie, G., Gaspar, M., Grace, D., Lofters, A., Raboud, J.M., Saarela, O., and MacPherson, P. (2020). Low human papillomavirus (HPV) knowledge related to low risk perception among men living with HIV: Implications for HPV-associated disease prevention. Prev Med *141*, 106274.

Giuliano, A.R., Anic, G., and Nyitray, A.G. (2010). Epidemiology and pathology of HPV disease in males. Gynecol Oncol *117*, S15-S19.

Giuliano, A.R., Lazcano, E., Villa, L.L., Flores, R., Salmeron, J., Lee, J.H., Papenfuss, M., Abrahamsen, M., Baggio, M.L., and Silva, R. (2009). Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int J Cancer *124*, 1251-1257.

Goksu, S.Y., Ozer, M., Kazmi, S., Aguilera, T.A., Ahn, C., Hsiehchen, D., Sanjeevaiah, A., Maxwell, M.C., Beg, M.S., and Sanford, N.N. (2020). Racial Disparities in Time to Treatment Initiation and Outcomes for Early Stage Anal Squamous Cell Carcinoma. Am J Clin Oncol *43*, 762-769.

Goldie, S.J., Kuntz, K.M., Weinstein, M.C., Freedberg, K.A., and Palefsky, J.M. (2000). Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus–negative homosexual and bisexual men. Am J Med *108*, 634-641.

Gupta, A., Arora, N., Zhu, H., Christie, A., Meyer, J.J., Khan, S.A., and Beg, M.S. (2017). Racial and gender disparities in therapy and outcomes of squamous cell cancer of the anus. J Clin Oncol *35, no.4_suppl (February 01, 2017)*, 691.

Harju, E., Pakarainen, T., Vasarainen, H., Tornava, M., Helminen, M., Perttila, I., and Kaipia, A. (2021). Health-related quality of life, self-esteem and sexual functioning among patients operated for penile cancer - A cross-sectional study. J Sex Med *18*, 1524-1531.

Heckman, T.G., Kelly, J.A., Bogart, L.M., Kalichman, S.C., and Rompa, D.J. (1999). HIV risk differences between African-American and white men who have sex with men. J Natl Med *91*, 92-100.

Hicks, J.T., Hwang, L.Y., Baraniuk, S., White, M., Chiao, E.Y., Onwuka, N., Ross, M.W., and Nyitray, A.G. (2019). Factors associated with self-reported anal cancer screening history in men who have sex with men. Sex Health *16*, 96-98.

Howlader, N., Ries, L.A., Mariotto, A.B., Reichman, M.E., Ruhl, J., and Cronin, K.A. (2010). Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst *102*, 1584-1598.

Huang, T., Xu, Y., Hu, G., Zhu, D., Xiao, S., and He, R. (2020). Racial/ethnic disparities in penile squamous cell carcinoma incidences, clinical characteristics, and outcomes: A population-based study, 2004–2016. Urol Oncol *38*, 688 e611-688 e619.

Larke, N.L., Thomas, S.L., dos Santos Silva, I., and Weiss, H.A. (2011). Male circumcision and penile cancer: a systematic review and meta-analysis. Cancer Causes Control *22*, 1097-1110.

Leeds, I.L., and Fang, S.H. (2016). Anal cancer and intraepithelial neoplasia screening: a review. World J Gastrol Surg *8*, 41-51.

Liao, C.I., Francoeur, A.A., Kapp, D.S., Caesar, M.A.P., Huh, W.K., and Chan, J.K. (2022). Trends in human papillomavirus-associated cancers, demographic characteristics, and vaccinations in the US, 2001-2017. JAMA Netw Open *5*, e222530.

Liszewski, W., Ananth, A.T., Ploch, L.E., and Rogers, N.E. (2014). Anal Pap smears and anal cancer: what dermatologists should know. J Am Acad Dermatol *71*, 985-992.

Martinez Tyson, D., Medina-Ramirez, P., Flores, A.M., Siegel, R., and Aguado Loi, C. (2018). Unpacking Hispanic ethnicity-cancer mortality differentials among Hispanic subgroups in the United States, 2004-2014. Front Public Health *6*, 219.

Millett, G.A., Flores, S.A., Peterson, J.L., and Bakeman, R. (2007). Explaining disparities in HIV infection among black and white men who have sex with men: a meta-analysis of HIV risk behaviors. AIDS *21*, 2083-2091.

North American Association of Central Cancer Registries (2018). Cancer in North America (CiNA) Data Products. Available at: https://www.naaccr.org/cina-research/. Accessed March 1, 2020.

Ohno-Machado, L. (2001). Modeling medical prognosis: survival analysis techniques. J Biomed Inform *34*, 428-439.

Ortiz, A.P., Engels, E.A., Nogueras-González, G.M., Colón-López, V., Soto-Salgado, M., Vargas, A., Machin, M., and Shiels, M.S. (2018). Disparities in human papillomavirus-related cancer incidence and survival among human immunodeficiency virus-infected Hispanics living in the United States. Cancer *124*, 4520-4528.

Osazuwa-Peters, N., Simpson, M.C., Rohde, R.L., Challapalli, S.D., Massa, S.T., and Adjei Boakye, E. (2021). Differences in sociodemographic correlates of human papillomavirus-associated cancer survival in the United States. Cancer Control *28*, 1-12.

Pan, H.Y., Walker, G.V., Grant, S.R., Allen, P.K., Jiang, J., Guadagnolo, B.A., Smith, B.D., Koshy, M., Rusthoven, C.G., and Mahmood, U. (2017). Insurance status and racial disparities in cancer-specific mortality in the United States: a population-based analysis. Cancer Epidemiol Biomark Prev *26*, 869-875.

Passel, J.S., Lopez, M.H., and Cohn, D.V. (2022). U.S. Hispanic population continued its geographic spread in the 2010s. Available at: https://www.pewresearch.org/fact-tank/2022/02/03/u-s-hispanic-population-continued-its-geographic-spread-in-the-2010s/. Accessed March 22, 2022.

Patel, K.S., Alhatem, A., Gadde, U., Ahlawat, S., Lambert, C., Schwartz, R.A., and Dalla Piazza, M. (2020). Insurance status and level of education predict disparities in receipt of treatment and survival for anal squamous cell carcinoma. Cancer Epidemiol *67*, 101723.

Schabath, M.B., Villa, L.L., Lin, H.-Y., Fulp, W.J., Akogbe, G.O., Abrahamsen, M.E., Papenfuss, M.R., Lazcano-Ponce, E., Salmerón, J., and Quiterio, M. (2013). Racial differences in

the incidence and clearance of human papilloma virus (HPV): the HPV in men (HIM) study. Cancer Epidemiol Biomark Prev *22*, 1762-1770.

Sharma, P., Ashouri, K., Zargar-Shoshtari, K., Luchey, A.M., and Spiess, P.E. (2016a). Racial and economic disparities in the treatment of penile squamous cell carcinoma: results from the National Cancer Database. Urol Oncol *34*, 122. e129-115.

Sharma, P., Zargar-Shoshtari, K., Pettaway, C.A., Schabath, M.B., Giuliano, A.R., and Spiess, P.E. (2016b). Disparities in penile cancer. Cancer Control *23*, 409-414.

Siddharthan, R.V., Lanciault, C., and Tsikitis, V.L. (2019). Anal intraepithelial neoplasia: diagnosis, screening, and treatment. Ann Gastroenterol *32*, 257-263.

Siegel, R.L., Miller, K.D., Fuchs, H.E., and Jemal, A. (2022). Cancer statistics, 2022. CA Cancer J Clin *72*, 7-33.

Slopnick, E.A., Kim, S.P., Kiechle, J.E., Gonzalez, C.M., Zhu, H., and Abouassaly, R. (2016). Racial disparities differ for African Americans and hispanics in the diagnosis and treatment of penile cancer. Urology *96*, 22-28.

Stier, E.A., Chigurupati, N.L., and Fung, L. (2016). Prophylactic HPV vaccination and anal cancer. Hum Vaccin Immunother *12*, 1348-1351.

Thompson, C.A., Gomez, S.L., Hastings, K.G., Kapphahn, K., Yu, P., Shariff-Marco, S., Bhatt, A.S., Wakelee, H.A., Patel, M.I., Cullen, M.R., *et al.* (2016). The burden of cancer in Asian Americans: A report of national mortality trends by Asian ethnicity. Cancer Epidemiol Biomarkers Prev *25*, 1371-1382.

Thomson, E.F., Nuru-Jeter, A., Richardson, D., Raza, F., and Minkler, M. (2013). The Hispanic Paradox and older adults' disabilities: is there a healthy migrant effect? Int J Environ Res Public Health *10*, 1786-1814.

United States Census Bureau (2018). 2010 Census regions and divisions of the United States. Available at: https://www.census.gov/geographies/reference-maps/2010/geo/2010-census-regions-and-divisions-of-the-united-states.html. Accessed December 20, 2020.

van der Zee, R.P., Richel, O., De Vries, H., and Prins, J.M. (2013). The increasing incidence of anal cancer: can it be explained by trends in risk groups. Neth J Med *71*, 401-411.

Walsh, T., Bertozzi-Villa, C., and Schneider, J.A. (2015). 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 *105*, e34-e45.

Yang, D.X., Soulos, P.R., Davis, B., Gross, C.P., and Yu, J.B. (2018). Impact of widespread cervical cancer screening: number of cancers prevented and changes in race-specific incidence. Am J Clin Oncol *41*, 289-294.

Ye, Y., Burkholder, G.A., Wiener, H.W., Griffin, R., Aslibekyan, S., Fry, K., Khan, A., and Shrestha, S. (2020). Comorbidities associated with HPV infection among people living with HIV-1 in the southeastern US: a retrospective clinical cohort study. BMC Infect Dis *20*, 1-9.