Demographic disparities of penile cancer in Appalachian Kentucky

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Introduction: *Appalachian Kentucky is a region characterized by poor healthcare literacy and access. We investigate the disparities in demographic distribution and outcomes of penile squamous cell carcinoma (pSCC) in rural Kentucky.*

Materials and methods: *Data were retrieved for patients with pSCC from 1995-2015 from the Kentucky Cancer Registry and the Surveillance, Epidemiology and End Results Program (SEER) and were used to investigate differences between Appalachian Kentucky and the remainder of the state and country.*

Results: *The incidence of pSCC from 1995-2015 in Appalachian Kentucky was over 60% higher than non-Appalachian regions (2.6 vs. 1.6 cases/100,000 people). Nearly 40% were from Appalachian counties. They presented with similar grade and pT stage at diagnosis but were more likely to have pN+ disease ($p < 0.001$). Rates of cancer-specific mortality (CSM) were similar between the two regions, but patients with CSM exhibited shorter survival interval from diagnosis in Appalachia (median 20 vs. 26 months, $p = 0.016$). Compared to national SEER data, patients from Appalachian Kentucky presented with similar grade and stage but exhibited higher rates of CSM (24.0% vs. 20.1%, $p = 0.029$). African Americans (AA) comprised only 5% of patients but exhibited high pathologic stage at presentation ($p = 0.041$) and shorter survival intervals (median 12 vs. 23 months, $p = 0.023$) compared to Caucasians.*

Conclusions: *There is a disproportionately high rate of pSCC in Appalachian Kentucky. Both Appalachian and AA men exhibited more advanced disease at presentation and shorter survival, identifying socioeconomic and racial disparities which can be targeted to improve outcomes in high risk individuals.*

Key Words: penile cancer, Appalachia, health disparities

Introduction

Squamous cell carcinoma of the penis (pSCC) is a relatively uncommon disease in industrialized countries and accounts for 0.2% of male malignancies annually in the United States.[1] The incidence is highest in developing countries, with human papillomavirus (HPV) being a well-characterized risk factor, implicated in half the cases of pSCC. Other risk factors include phimosis, lack of circumcision, poor hygiene, and tobacco use.[2] The diagnosis of pSCC is associated with significant stage-dependent mortality and treatment-related morbidity. Previous studies have identified several socioeconomic risk factors for advanced stage and poor clinical outcomes. Large, population-based studies have implicated disparities in insurance status, level of education, income, ethnicity/race, and marital status with oncologic outcomes.[1,3-5] In a National Cancer Center Database (NCDB) study, non-metropolitan patients more commonly exhibited node-positive disease and worse overall survival (OS) compared to urban and rural populations.[1]

The Appalachian region is a defined geographically-based region spanning 13 states in Eastern and Southeastern United States which encompasses an estimated 25 million Americans. This area has long been recognized as one of the most socially and economically disadvantaged areas of the United States.

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Previous studies have noted disparities in healthcare in this area as compared to non-Appalachian regions, including outcomes in all-cause mortality, cancer mortality, cardiovascular mortality, lung disease, and diabetes.[6-7]

While previous studies have demonstrated inferior outcomes in the Appalachian population, there is little data regarding genitourinary malignancy outcomes in these patients. In this study, we investigate clinicopathologic and socioeconomic characteristics as well as cancer-specific outcomes in patients diagnosed with pSCC in Appalachian Kentucky and compare these to a national cohort to further characterize risk factors for advanced disease, treatment disparities, and outcomes in this underserved region. We hypothesize that patients within the Appalachian region of Kentucky exhibit higher incidence of pSCC, have more advanced disease at the time of diagnosis, and have worse clinical outcomes relative to non-Appalachian Kentuckians and the comparative national cohort. By recognizing these disparities in the diagnosis and outcome of pSCC we hope to identify barriers to healthcare access that may be improved to reduce morbidity in this vulnerable population.

Materials and methods

A retrospective review of all patients diagnosed with invasive pSCC indexed in the Kentucky Cancer Registry (KCR) from 1995-2015 was performed. The KCR is a population-based central cancer registry for the state of Kentucky and was one of the initial expansion statewide registries to be incorporated into the Surveillance Epidemiology and End Results (SEER) program. Data abstracted included age at diagnosis, TNM staging, histologic grade, treatment modality, demographic characteristics and cancer-specific mortality.

Nationwide epidemiological datapoints identical to those obtained from the KCR were also obtained from SEER for comparative analysis from 1995-2015. SEER is a national cancer surveillance program which collects and publishes data on cancer incidence and survival from 19 different cancer registries around the nation (https://seer.cancer.gov/).

Patients diagnosed with invasive penile cancer in the state of Kentucky were divided into Appalachian vs. Non-Appalachian as designated in the KCR database. To contextualize the incidence of pSCC, the incidence of the most common other genitourinary malignancies in Appalachian and non-Appalachian Kentucky counties were also investigated. These patients are identified by their county of residence as stipulated by the Appalachian Regional Commission. Comparative analysis was performed using the Chi-square test for proportions and Mann-Whitney U tests for nonparametric, continuous data. The Kruskal-Wallis test was utilized for comparison of medians. From the SEER registry, only the state of Georgia contains Appalachian counties, which limited statistical analysis of Appalachian disparities nationally. Complete data was available for all patients in the KCR database. Patients with unknown datapoints in the SEER database were excluded from that respective analysis.

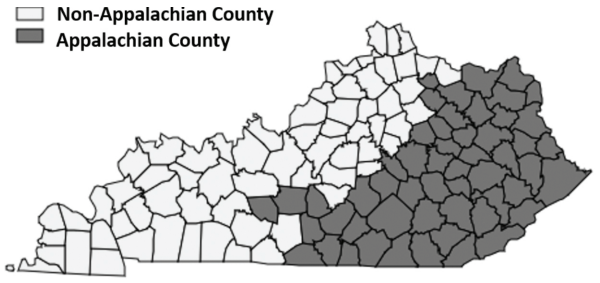
Results

In 2015, the most recent year with full data reported from the Kentucky Cancer Registry, residents in the state of Kentucky comprised just 1.3% of the total US population (https://data.census.gov). However, new diagnoses of pSCC in Kentucky comprised 3.1% of all new cases in the US, Table 1. Of the genitourinary malignancies studied, including prostate, bladder urothelial, renal cell and testis cancers, pSCC was most

TABLE 1. **Number of GU malignancies diagnosed in 2015. Kentucky data obtained from the Kentucky Cancer Registry. United States cancer data obtained from the American Cancer Society.[11] Total US population at risk obtained from https://data.census.gov**

	Kentucky	United States	KY proportion
Population at risk; total (male)	4,425,092 (2,174,892)	321,418,821 (158,167,834)	1.3% (1.4%)
Penile squamous cell carcinoma	56	1,820	3.1%
Prostate cancer	2,641	220,800	1.2%
Urothelial carcinoma of bladder	1,171	74,000	1.6%
Renal cell carcinoma	1,125	61,560	1.8%
Testis cancer	115	8,430	1.4%

TABLE 2. **Incidence of GU malignancy (per 100,000 people) between Appalachian and non-Appalachian counties in KY between 1995-2015. The Appalachian population at risk during this time included 12.1 million men. Map adapted from the Kentucky Cancer Registry**



	Kentucky Appalachian	
	Yes	No
Penile squamous cell carcinoma	2.6	1.6
Prostate cancer	122.1	140.8
Urothelial carcinoma of bladder	22.1	22.2
Renal cell carcinoma	16.8	17.7
Testis cancer	4.7	5.2

notably overrepresented in Kentuckians relative to the United States population. We further investigated the differences in clinicopathologic characteristics of these patients in Kentucky.

The incidence of prostate, bladder urothelial, renal cell, and testis cancers were higher in non-Appalachian regions, while the incidence of pSCC was 38% higher in Appalachian counties, Table 2. From 1995-2015, 700 patients were diagnosed with pSCC in Kentucky. Table 3 compares clinicopathologic factors in patients with pSCC with respect to Appalachian county residence in the state of Kentucky. Forty percent of Kentucky residents lived in Appalachian counties and greater than 99% of these patient were Caucasian. While Appalachian patients presented at a younger age (mean 62 vs. 65 years, $p = 0.005$), there was no difference with regard to grade or T stage at presentation. Notably, Appalachian patients presented more commonly with pathologic nodal positive disease (8.8% vs. 2.7%, $p < 0.001$). While cancer-specific mortality (CSM) was similar between the two regions, patients in Appalachia with CSM died 6 months sooner than non-Appalachian patients with CSM (median 20 vs. 26 months, $p = 0.016$).

We compared diagnoses of pSCC in Appalachian Kentucky from 1995-2015 with data from the SEER database over the same time range with regards

TABLE 3. **Comparison of clinicopathologic characteristics in Appalachian and non-Appalachian patients diagnosed with penile squamous cell carcinoma**

	Kentucky Appalachian		p value
	Yes	No	
N	277 (39.6%)	423 (60.4%)	
Age (mean, yrs, STD)	62.2 (13.3)	65.3 (14.7)	0.005
Race			< 0.001
Caucasian	272 (99.6%)	384 (92.5%)	
African-American	1 (0.4%)	31 (7.5%)	
Tobacco use			0.257
Yes	150 (70.4%)	197 (65.7%)	
No	63 (29.6%)	103 (34.3%)	
Histologic differentiation			0.446
Well	48 (27.9%)	78 (33.5%)	
Moderate	83 (48.3%)	100 (42.9%)	
Poor	41 (23.8%)	55 (23.6%)	
Pathologic T stage			0.243
Ta-T2	208 (81.9%)	321 (85.4%)	
T3-T4	46 (18.1%)	55 (14.6%)	
Pathologic nodal involvement (N+)	24 (8.8%)	11 (2.7%)	< 0.001
Cancer-specific mortality (CSM)	41 (24.0%)	56 (23.7%)	0.954
Survival (median, mo) in patients with CSM	20	26	0.016

TABLE 4. **Comparison of clinicopathologic characteristics in Caucasian vs. African American diagnosed with penile squamous cell carcinoma**

	Caucasian	African American	p value
N	656 (93.7%)	32 (4.5%)	
Age (mean, yrs, STD)	64.4 (14.1)	62.6 (14.6)	0.506
Tobacco use			0.209
Yes	323 (67.2%)	22 (78.6%)	
No	158 (32.8%)	6 (21.4%)	
Histologic differentiation			0.526
Well	122 (31.4%)	4 (23.5%)	
Moderate	174 (44.8%)	10 (58.8%)	
Poor	92 (23.7%)	3 (17.6%)	
Pathologic T stage			0.041
Ta-T2	496 (84.2%)	21 (70%)	
T3-T4	93 (15.8%)	9 (30%)	
Pathologic nodal involvement (N+)	34 (5.4%)	1 (3.3%)	0.626
Cancer-specific mortality (CSM)	92 (21.7%)	5 (26.3%)	0.638
Survival (median, mo) in patients with CSM	23	12	0.023

to clinicopathologic factors (data not shown). The incidence of pSCC diagnosed in Kentucky Appalachia, Kentucky non-Appalachia and the national SEER database were 2.6, 1.6 and 0.9 per 100,000 persons, respectively. Compared to the national dataset, patients from Appalachian Kentucky presented with

TABLE 5. **Comparison of clinicopathologic characteristics by penile squamous cell carcinoma cancer-specific mortality**

	Survival	Death	p value
N	310	97	
Age (mean, yrs)	57.6	65.9	< 0.001
Appalachian			0.954
Yes	130 (41.9%)	41 (42.3%)	
No	180 (58.1%)	56 (57.7%)	
Race			0.635
Caucasian	286 (96.0%)	92 (94.8%)	
African-American	12 (4.0%)	5 (5.2%)	
Tobacco use			0.502
Yes	148 (65.2%)	48 (69.6%)	
No	79 (34.8%)	21 (30.4%)	
Histologic differentiation			< 0.001
Well	56 (36.6%)	12 (15.8%)	
Moderate	71 (46.4%)	32 (42.1%)	
Poor	26 (17.0%)	32(42.1%)	
Pathologic T stage			< 0.001
1-2	261 (90.0%)	46 (56.1%)	
3-4	29 (10.0%)	36 (43.9%)	
Pathologic N+	9 (3.0%)	14 (15.9%)	< 0.001

similar grade and stage at presentation. However, patients from Appalachian Kentucky exhibited higher rates of cancer-specific mortality compared to the SEER database (24.0% vs. 20.1%, p = 0.029).

Racial disparities between Caucasian and African American patients in Kentucky were similarly investigated, Table 4. Statistical analysis was limited by the Caucasian predominance in cases of pSCC in Kentucky (93.7%). African American patients presented with more advanced stage at presentation and worse outcomes relative to Caucasian patients. In Kentuckians with CSM, Caucasian patients lived twice as long as African American patients (median 23 vs. 12 months, p = 0.023). Clinicopathologic characteristics between Kentucky patients who exhibited CSM were compared to pSCC survivors Table 5. Patients who experienced CSM were older, presented with higher grade disease, and advanced pTN stages compared with patients who survived (all statistically significant).

Discussion

This was the first study to investigate the incidence of penile squamous cell carcinoma specifically in an Appalachian population. There is a disproportionate amount of pSCC diagnosed in Kentucky. While prostate, bladder, renal cell and testis carcinomas exhibited a higher incidence in non-Appalachian regions in the state of Kentucky, the incidence of pSCC was notably higher in Appalachia. Patients in Appalachian Kentucky presented with similar histologic grade and pT stage relative to non-Appalachian patients, but exhibited higher rates of nodal metastases and worse cancer-specific outcomes compared to non-Appalachian Kentuckians. These findings were largely recapitulated when comparing the Kentucky Appalachian population to the national SEER database. Despite the relative underrepresentation of African Americans in Appalachia, these patients similarly presented with advanced pSCC with disparate clinical outcomes.

These data highlight the poor pSCC outcomes in underserved populations and further demonstrate disparities between African American and Caucasian patients with regards to stage/grade at presentation as well as clinical outcomes. Several prior studies investigated the degree of patient rurality with respect to the diagnosis, treatment and outcomes for pSCC. In a series of publications querying the NCDB from 1998-2012, patients who live in metropolitan areas were found to have lower pTN stages at presentation and superior overall survival compared to patients residing in urban and rural areas.[1,5] However, the classification of degree of rurality was not clearly defined by the authors and rural patient comprised < 3% of the total study population, making generalizations difficult.

The same authors used the NCDB from the same time period to investigate the utilization rates of regional lymphadenectomy without clinical adenopathy (cN0M0). There were no differences in the use of timely lymphadenectomy by degree of rurality in this patient population, and patients with cN0 disease had similar OS with regards to degree of rurality.[8] This study was similarly limited by the relative paucity of patients in rural areas. However, comparing the subanalysis of this clinically organ-confined cohort with the aforementioned studies, these data suggest similar oncologic outcomes among all organ-confined patients irrespective of the degree of rurality of their residence. Despite relatively equal stage and grade distribution between Appalachian and non-Appalachian regions in Kentucky in our study, there were still disparate oncologic outcomes. This could be explained by the higher rates of pN+ disease in Appalachian patients. While Chipollini et al found no difference in the utilization of early lymphadenectomy for cN0 disease between rural and non-rural patients, it is our experience that patients from underserved areas are difficult to surveil and are often lost to follow up, potentially making them optimal candidates for preemptive surgical intervention.[8]

The disparities in advanced stage/grade pSCC at presentation and poor oncologic outcomes in the non-white racial and ethnic populations has been well described in two other population-based studies. The NCDB investigations found that African-American patients presented with higher pT stage and had worse OS compared to Caucasian patients. Similarly, Hispanic patients more commonly presented with advanced pT stage and pN+ disease but similar survival compared to non-Hispanic patients.[1,5] An investigation of the Florida Cancer Data System also identified higher rates of locally advanced or metastatic disease as well as reduced overall survival in African Americans compared to Caucasians.[4] In our study we confirmed advanced pT stage in African American Kentuckians and identified shorter survival intervals in patients with CSM compared to Caucasians. Because there was only one African American patient residing in an Appalachian county in our dataset, this limited further sub-characterization of these phenomena based on rurality. Other identified risk factors for advance disease include lack of health insurance,[1,5] low education levels,[1,3] and low income.[3,5] A population-based Swedish study also identified history of divorce, having never been married, and living alone as risk factors for advanced pSCC.[3]

Appalachian regions have higher rates of malignancy and cancer-specific mortality.[6,7] This is likely multifactorial, potentially attributable to cultural beliefs, lower healthcare literacy and access, as well as lifestyle factors including dietary indiscretions and tobacco use. Appalachian patients utilize screening services at lower rates, have lower rates of healthcare insurance, and travel greater distances to access care than non-Appalachian regions.[7] The average age of our Appalachian cohort was 62 years, which is under the age of Medicare eligibility. Compounded with the fact that nearly 60% of Appalachian Kentuckians reported annual household income less than 50,000 dollars, access and affordability of subspecialty care may be limited.[6] Our data identified penile cancer as the only genitourinary malignancy with higher incidence in Appalachian compared to non-Appalachian counties. This largely confirms prior data utilizing the United States Cancer Statistics from 2011-2015, but this prior analysis excluded pSCC.[9] Access to screening services and advanced diagnostic imaging modalities, including PSA screening, may result in higher rates of prostate, renal and bladder cancer diagnoses in non-Appalachian regions. This is reflected in a recent study from our institution which concluded that Kentucky Appalachian patients diagnosed with prostate cancer presented with higher Gleason grades, advanced stage, higher PSA levels and exhibited worse disease-specific survival compared to non-Appalachian Kentuckians.[10] Further analysis showed that these trends were not related to geographic locations per se, but rather more statistically associated with higher poverty rates and lower educations levels endemic to the Appalachian region.

The increased incidence of penile cancer in Appalachia may be related to poor hygiene, lower circumcision rates, or increased incidence of HPV infection in rural Kentucky, although one study suggests that HPV infection is not related to socioeconomic status.[2] Additionally, pervasive negative attitudes exist towards preventative behaviors and cancer screening, as evidenced by lower rates of adherence to recommended cancer treatments. These negative attitudes and fatalistic beliefs regarding cancer were found to be most pervasive in the state of Kentucky in a recent population-based study of three Appalachian states.[6]

There are several fundamental limitations to this study, including its use of statewide and national databases with inherent limitations, such as reporting errors and selection bias. These databases were not designed for this study and allowed only secondary analysis. The rates of circumcision and HPV infections in the studied regions limit interpretation of penile cancer rates. Information regarding treatment modalities and other cancer-specific outcomes were limited in these databases. The SEER dataset includes Appalachian populations in Kentucky and Georgia only, which limits generalizability of conclusions based on rurality on a national level.

Conclusions

There is a disproportionately high rate of pSCC in Kentucky with relative predominance in Appalachian counties. Both Appalachian and African-American men exhibited more advanced disease at presentation and shorter survival intervals, highlighting socioeconomic and racial disparities which can be exploited to improve health literacy, timely diagnosis and access to care in high risk individuals. Future work will focus on investigating genomic and tumor biologic differences between individuals from difference socioeconomic and racial backgrounds. □

References

1. Attalla K, Paulucci DJ, Blum K et al. 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* 2018;36(1):14.e17-14.e24.
2. Hernandez BY, Goodman MT, Unger ER et al. Human papillomavirus genotype prevalence in invasive penile cancers from a registry-based United States population. *Front Oncol* 2014;5:4-9.
3. Torbrand C, Wigertz A, Drevin L et al. Socioeconomic factors and penile cancer risk and mortality; a population-based study. *BJU Int* 2017;119(2):254-260.
4. Ritch CR, Soodana-Prakash N, Pavan N et al. Racial disparity and survival outcomes between African-American and Caucasian American men with penile cancer. *BJU Int* 2018;121(5):758-763.
5. Sharma P, Ashouri K, Zargar-Shoshtari K, Luchey AM, Spiess PE. Racial and economic disparities in the treatment of penile squamous cell carcinoma: Results from the National Cancer Database. *Urol Oncol* 2016;34(3):122.e9-15.
6. Vanderpool RC, Huang B, Deng Y et al. Cancer-related beliefs and perceptions in Appalachia: findings from 3 states. *J Rural Health* 2019;35(2):176-188.
7. Yao N, Alcalá HE, Anderson R, Balkrishnan R. Cancer disparities in rural Appalachia: incidence, early detection, and survivorship. *J Rural Health* 2017;33(4):375-381.
8. Chipollini J, Tang DH, Sharma P, Baumgarten AS, Spiess PE. Patterns of regional lymphadenectomy for clinically node-negative patients with penile carcinoma: analysis from the National Cancer Database from 1998 to 2012. *Clin Genitourin Cancer* 2017;15(6):670-677.e1.
9. Wilson RJ, Ryerson AB, Singh SD, King JB. Cancer incidence in Appalachia, 2004-2011. *Cancer Epidemiol Biomarkers Prev* 2016;25(2):250-258.
10. Myint ZW, O'Neal R, Chen Q, Huang B, Vanderpool R, Wang P. Disparities in prostate cancer survival in Appalachian Kentucky: a population-based study. *Rural Remote Health* 2019;19(2):4989.
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65(1):5-29.