

**Research Article** 



# Racial and Socioeconomic Disparities in Ocular Surface Squamous Neoplasia: A National Cancer Database Analysis

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## Abstract

**Objective:** A retrospective population-based study to investigate racial and socioeconomic disparities in patients diagnosed with ocular surface squamous neoplasia (OSSN).

**Methods:** Non-Hispanic white (NHW) and African American (AA) patients with OSSN with known age, insurance, gender, and zip code-level income and education were selected from the National Cancer Database. Patients were stratified based on race into two mutually exclusive groups, and unadjusted comparisons were made with the chisquareor Mann-Whitney tests. Survival was examined with the Kaplan-Meier method and a Cox regression model.

**Results:** Of the 2,402 identified patients from 2004 to 2015, 117 were African American. Unadjusted differences were found between groups in regard to age, histology, insurance, income, and education. African American patients in comparison to NHW patients were younger (mean age: 62 years vs. 70 years; p<0.001), represented a higher proportion of Medicaid use (10.3% vs. 3.2%) or uninsured (10.3% vs. 2.7%), and resided in areas with low educational attainment (32.5% vs. 16.1% of NHW). Multivariate analysis found higher risk of death for older African American males with no private insurance, and for those from areas of lowest level of income.

**Conclusion:** Disparities in socioeconomic factors were observed in African American patients with OSSN. Overall, OSSN occurs at a younger age in African Americans, who also are socioeconomically disadvantaged and face poorer prognoses. This association between social inequality and poor outcome warrant further investigation.

Keywords: Public health, Cancer research, Eye cancer, Racial disparities, Clinical characteristics

# Introduction

Persistent disparities in cancer care exist in the United States, which have been linked to racial classification, socioeconomic status, and educational attainment [1]. Although the adverse effects of socioeconomic deprivation on medical outcome and access to care have been extensively discussed in medical literature, the causes and patterns of health disparities among patients with ocular cancers remain poorly understood and understudied. The objective of this study was to examine disparities among OSSN patient populations characterized by race and socio economic indicators.

OSSN comprises of dysplasia, carcinoma in situ, and squamous cell carcinoma stemming from the conjunctiva and the cornea [2,3]. OSSN has an incidence rate of 0.03-1.9 cases per 100,000 person-years in the United States [4]. OSSN typically presents as unilateral vascularized nodules growing in sun-exposed surface of the eye, but can manifest bilaterally in immune compromised patients, who are also at higher risk overall for OSSN [5]. Metastatic OSSN can invade into the orbit and the adjacent sinuses in rare occurrences. Predisposing risk factors include advanced age, male gender, and exposure to chronic solar radiation (UVB) or cigarette smoke [6,7]. OSSN is usually managed with surgical resection with a 4mm clear margin while avoiding direct manipulation of the tumor, a so called "no touch technique" [8]. Postsurgical recurrence rate is 10% at 1 year and 17% at 5 years, and up to 52% if incompletely excised [9,10]. Nonsurgical treatments include topical chemotherapy, interferon immunotherapy, antiviral medications, or photodynamic therapy [11,12]. Benefits of topical chemotherapeutic agents include high bioavailability at the ocular surface and low systemic side effects. Topical therapies, usually in the form of an alkylating agent (mitomycin-C) or anti-metabolite (5-fluorouracil), can also be titrated based on the clinical response. These drugs are also used to achieve chemo reduction in invasive OSSN prior to surgery [13]. Both surgical and medical treatments of OSSN have shown similar efficacy [14]; however, medical treatments require frequent follow-up visits, whereas surgical treatment may be most expensive and subject to insurance coverage [15]. When considering the complexity of OSSN diagnosis and treatment options as well as the necessary serial followups, health care access may be integral to the successful management of this disease.

The analysis herein uses nationally representative data from the National Cancer Database (NCDB) to explore social and racial disparities that may affect clinical outcome in OSSN. Because of the robust sample size and uniform data collection in the NCDB, it is possible to pool data across survey years, allowing examination of multiple epidemiological factors in a large sample of adults diagnosed with OSSN.

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## Methods

**Data source:** The NCDB represents a joint data collection effort between the Commission on Cancer of the American College of Surgeons and the American Cancer Society, and includes de-identified patient data of over70% of all newly diagnosed cancer cases from more than 1,500 commission-accredited cancer programs in the United States [16]. This retrospective study encompassed demographic and clinical patient data (2004 to 2015)collected from the NCDB via participant user file. This study was deemed exempt by the Creighton University IRB.

**Patient selection and categorization:** Patients were selected based on the International Classification of Disease Oncology (ICD-O-3) coding specific to sites C69.0 (conjunctiva) and C69.1 (cornea, NOS) of the following histologic types: 8070 (squamous cell carcinoma, NOS), 8076 (squamous cell carcinoma, micro invasive), and 8720(malignant melanoma, NOS). A binary categorization of histology was created where 8070 and 8076 were designated as squamous cell carcinoma (SCC) and 8720 was designated as not SCC. Our primary variable of interest was a combined term of race where patients were classified as non-Hispanic white, Hispanic white, African American, or other race and ethnicity, and we selected African American and non-Hispanic white patients. Other racial classifications were omitted due to small sample size.

Variables of interest: Additional clinical and demographic variables selected include age, biological sex, Charlson/Deyo score, primary payer, income, education, tumor size, the number of days from diagnosis to definitive surgery, the number of days from diagnosis to receipt of systemic therapy and chemotherapy, laterality, tumor behavior, and facility type. The Charlson/Deyo score is a weighted value derived from numerous clinical conditions by assessing their predictive value of 1-year mortality. In each patient, every comorbid condition is given a score based on the relative risk of 1-year mortality, and the aggregate value of the comorbidity scores is an indicator of disease burden [17], and was recorded as 0, 1, 2, or  $\geq$  3. Primary payer was recorded at the time of diagnosis and/or initial treatment and categorized as none, private, Medicaid, Medicare, or other government insurance. Income was measured at the zip-code level and generated from the 2008 to 2012 American Community Survey. Income was subsequently adjusted for 2012 inflation and categorized into four quartiles: low (< \$38,000), moderate (\$38,000 to \$47,999), high (\$48,000 to \$62,999), and highest (≥ \$63,000). Education was also measured at the zip-code level as proportion of adults within that zip-code who did not receive a high school diploma, and was coded as low (≥ 21%),moderate (13% to 20.9%), high (7% to 12.9%), and highest (< 7%). Patients with any missing age, biological sex, Charlson/ Deyo score, primary payer status, income, education, time to definitive surgery, time to censoring or death, or vital status were excluded from the analysis.

# **Statistical Analysis**

Patients were stratified based on race and ethnicity into two mutually exclusive groups. Continuous variables of interest are presented as median and inter quartile range (IQR) whereas categorical variables are presented as frequencies and proportions. Unadjusted comparisons were made with the chi-square or Mann-Whitney tests for categorical and continuous variables, respectively. Our primary outcome of interest was all-cause mortality, which was initially examined in an unadjusted manner with the Kaplan-Meier method and associated logrank test. We examined the time between the date of diagnosis and date of patient contact or death, which was provided in months, in conjunction with vital status information. A multivariable Cox regression model was computed to assess causes of mortality. The proportionality of hazards assumption was examined with log-negative log survival plots as well as the creation of time dependent coefficients to determine if there was a time interaction for each variable of interest. We also investigated the functional form of continuous variables with plots of Martingale residuals and accommodated the clustering of patients within a facility with a robust sandwich covariance estimator. SAS version 9.4 was used for all analyses and clinical significance was set at p < 0.05.

# Results

The overall clinical and demographic characteristics as well as comparisons of AA and NHW patients regarding these characteristics are presented in Table 1. The overall median tumor size at diagnosis was 0.7cm, with 0.6cm in AA patients and 0.7cm in NHW patients. Tumor laterality indicated 48.7% arose from the right eye, and 50.9% from the left eye. In general, 46.8% of the diagnosed cases were carcinoma in situ, and 53.2% were confirmed to be invasive carcinoma. We did not observe evidence of a significant difference in tumor size, laterality, and tumor behavior between AA and NHW patients. However, it was found that AA patients had a higher proportion of squamous cell carcinoma (84.6% vs. 68.3%).

The overall median age in the study group was 69 years, but AA patients were significantly younger at the time of diagnosis in

	Overall	African American	Non- Hispanic White	p value
Sample size	2,402	117	2,285	
	Median (IQR)	Median (IQR)	Median (IQR)	
Age (years)	69 (59-79)	62 (49-70)	70 (59-79)	<0.001
Biological Sex				
Female	699 (29.1)	39 (33.3)	660 (28.9)	
Male	1703 (70.9)	78 (66.7)	1625 (71.1)	
Days from Diagnosis to Systemic Therapy*	26 (0-67)	66 (19-79)	25 (0-64)	0.028
Days from Diagnosis to Chemotherapy*	19 (0-57)	79 (13-180)	18 (0-47)	0.036
Days from Diagnosis to Definitive Surgery	0 (0-16)	0 (0-19)	0 (0-16)	0.653
	Count (%)	Count (%)	Count (%)	
Squamous Cell Carcinoma	1682 (70.0)	99 (84.6)	1583 (68.3)	<0.001
Laterality				0.124
Right Primary Origin	1171 (48.7)	52 (44.4)	1119 (49.0)	
Left Primary Origin	1222 (50.9)	64 (54.7)	1158 (50.6)	
Bilateral Involvement	2 (0.1)	1 (0.9)	1 (0.1)	
Unknown	7 (0.3)	0 (0.0)	7 (0.3)	
Behavior				0.88
In Situ	1125 (46.8)	54 (46.2)	1071 (46.9)	
Invasive	1277 (53.2)	63 (53.8)	1214 (53.1)	
Charlson/Deyo Score				0.289
0	1972 (82.1)	94 (80.3)	1878 (82.2)	
1	332 (13.8)	15 (12.8)	317 (13.9)	
2	70 (2.9)	5 (4.3)	65 (2.8)	
≥ 3	28 (1.2)	3 (2.6)	25 (1.1)	

#### \*Substantial Missing Data

 Table 1: Clinical and demographic characteristics of ocular surface squamous neoplasia patients stratified by racefrom the National Cancer Database (2004-2015).

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comparison to NHW patients (62 years vs. 70 years; p<0.001). The average wait time between diagnosis and first treatment received was found to be significantly higher in AA patients as compared to NHW patients (66 days vs. 25 days; p<0.05).

Among AA patients, a higher proportion were uninsured (10.3% vs. 2.7%) or on Medicaid (10.3% vs. 3.2%; p < 0.001) relative to NHW patients as shown in Table 2. Additionally, a lower proportion of AA patients received Medicare compared to NHW patients (39.3% vs. 56.7%; p<0.001). Patient income levels measured based on residential zip code demonstrated higher proportions of AA patients living in neighborhoods with low household income compared to NHW patients (34.2% vs. 16.0%; p<0.001). Conversely, only 13.7% of AA patients were from neighborhoods with average income greater than \$63,000, compared to 32.4% of NHW patients living in the same income level neighborhoods. The same zip-code level analysis on education showed significantly higher proportion of AA patients living in neighborhoods with low levels of educational attainment (32.5% vs 16.1%; p<0.001).

Results from the multivariable Cox regression model found evidence of higher risk of death in AA compared to NHW patients (HR=1.57, 95% CI: 1.03 to 2.38) after adjusting for age, biological sex, Charlson/Deyo score, primary payer, income, education, histologic type, and time to definitive treatment as shown in Table 3. Risk of death increased in an accelerated trend for every additional year of age (59 years of age: HR=1.05, 95% CI: 1.04 to 1.06; 79 years of age: HR=1.08, 95% CI: 1.07 to 1.09). In comparison to females, male biological sex was associated with increased risk of death (HR=1.66, 95% CI: 1.37 to 2.01). A consistent trend in increasing risk of death was associated with increasing Charlson/Deyo scores in comparison to a score of zero (Charlson/Deyo score=1: HR=1.24, 95% CI: 1.03 to 1.50; Charlson/ Deyo score=2: HR=1.98, 95% CI: 1.37 to 2.85; Charlson/Deyo score ≥ 3: HR=3.63, 95% CI: 2.21 to 5.96). Finally, there was minimal statistical evidence that Medicare vs. private insurance was associated with increased risk of death (HR=1.25, 95% CI: >1.00 to 1.56).

## Discussion

We report a retrospective epidemiological analysis of 2,402 OSSN patients over a 12-year period, examining 15 epidemiological

	Overall	African American	Non- Hispanic White	p value
	Count (%)	Count (%)	Count (%)	
Primary Payer				< 0.001
Not Insured	74 (3.1)	12 (10.3)	62 (2.7)	
Private Insurance	860 (35.8)	46 (39.3)	814 (35.6)	
Medicaid	86 (3.6)	12 (10.3)	74 (3.2)	
Medicare	1341 (55.8)	46 (39.3)	1295 (56.7)	
Other Government	41 (1.7)	1 (0.8)	40 (1.8)	
Household Income (2012US Dollars)				
Low (< \$38,000)	407 (16.9)	40 (34.2)	367 (16.0)	
Moderate (\$38,000 to \$47,999)	560 (23.3)	33 (28.2)	527 (23.1)	
High (\$48,000 to \$62,999)	679 (28.3)	28 (23.9)	651 (28.5)	
Highest (≥ \$63,000)	756 (31.5)	16 (13.7)	740 (32.4)	
Education (% No High School Diploma)				< 0.001
Low (≥ 21%)	406 (16.9)	38 (32.5)	368 (16.1)	
Moderate (13.0% to 20.9%)	562 (23.4)	48 (41.0)	514 (22.5)	
High (7.0% to 12.9%)	825 (34.3)	24 (20.5)	801 (35.1)	
Highest (< 7.0%)	609 (25.4)	7 (6.0)	602 (26.3)	

 Table 2: Insurance, income, and education level in patients with ocular surface squamous neoplasia from theNational Cancer Database (2004-2015).

Variable of Interest	Hazard Ratio	95% CI	p value
Age (Years)			
59 Years	1.05	1.04-1.06	<0.001
70 Years	1.06	1.06-1.07	<0.001
79 Years	1.08	1.07-1.09	<0.001
Biological Sex			
Female		reference	
Male	1.66	1.37-2.01	<0.001
Race			
Non-Hispanic White		reference	
African American	1.57	1.03-2.38	0.034
Charlson/Deyo Score			
0		reference	
1	1.24	1.03-1.50	0.024
2	1.98	1.37-2.85	<0.001
≥ 3	3.63	2.21-5.96	<0.001
Primary Payer			
Private		reference	
Medicaid	1.59	0.96-2.64	0.073
Medicare	1.25	1.01-1.56	0.046
None	1.64	0.92-2.93	0.095
Government	2.03	0.95-4.36	0.068
Median Household Income (2012 US Dollars)			
Highest (≥ \$63,000)		reference	
High (\$48,000 to \$62,999)	0.99	0.79-1.25	0.957
Moderate (\$38,000 to \$47,999)	1.13	0.92-1.39	0.231
Low (< \$38,000)	1.07	0.80-1.42	0.658
Education (2008-2012, %No High School Diploma)			
Highest (<7.0%)		reference	
High (7.0% to 12.9%)	1.07	0.84-1.36	0.596
Moderate (13.0% to 20.9%)	1.1	0.90-1.35	0.339
Low (≥ 21%)	1.1	0.83-1.46	0.501
Squamous Cell Carcinoma			
No		reference	
Yes	1.15	0.95-1.38	0.151
Time to Definitive Surgery	10 Days	0 99-1 01	1 02

Model was adjusted for age, biological sex, Charlson/Deyo score, primary payer, income, education, histologic type, and time to definitive treatment.

 Table 3: Results of Cox regression model for ocular surface squamous neoplasia

 patients from the National CancerDatabase (2004-2015).

risk factors. Existing literature describing racial and socioeconomic risk factors for this uncommon malignant cancer is limited. To our knowledge, this is the first and the largest study to examine the epidemiology of OSSN in the United States using cancer registries, demonstrating racial bias in risk of death in patients with OSSN.

The overall clinical characteristics of OSSN as well as racial and sex distributions were consistent with previously reported data on immune competent populations worldwide [6,18,19]. However, we observed a stark difference in the average age at diagnosis between the NHW and AA patients, in which NHW patients presented

with OSSN almost a decade later in life than the AA patients in our study. One possible explanation may be that population-specific risk to infectious agents such as HPV or HIV that compromise host immune system leading to earlier development of OSSN [20-22]. However, we speculate that infectious agents are unlikely the major driver of earlier disease onset in the AA patients, since the average age of OSSN in the immune compromised or virally infected population is usually under 50 years old [23,24]. Alternatively, it is possible that the delayed onset in NHW patients may be related to higher rate of

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preventive or maintenance care received, since the late presentation in NHW was not associated worse clinical features that may suggest neglected screening. AA patients in our study presented with more severe comorbid conditions compared to NHW patients, as measured by their Charlson/Deyo scores. Although the NCDB does not specify the comorbid conditions each individual patient has, it does provide the Charlsonomorbidity Score Mapping Table as a reference to understanding the overall disease burden. The comorbid conditions that have higher weighted values include chronic diabetes, renal disease, severe liver disease, and AIDS, all of which are associated with a weakened immune system [25], and can be predisposing risk factors for developing OSSN. Recent advances in statistical methods and electronic medical records have revealed that comorbidities tend to cluster into multimorbidity, and that people of lower socioeconomic status are more likely to acquire multiple diseases [26,27]. Higher rates of comorbidities in AA have also been shown to be associated with a lack of access to screenings and treatment [28]. Although it remains unclear the extent of various comorbid conditions have on OSSN outcome, this finding raises the concern that managing OSSN may require more holistic care.

We noted in our study that AA patients had a significantly higher rate of being uninsured and lower rate of being on Medicare compared to NHW patients. We suspect the uninsured status is associated with prohibitively high cost of care leading to lower ocular health care utilization [29]. Cost is often the most cited barrier to receiving eye care [30], thus insurance status and coverage implicate the out-of-pocket cost to patients [31,32]. Having health insurance coverage increases the odds of having regular health care provider and of receiving diagnostic tests [33], thus insurance status can influence timely access to screening and subsequent management of OSSN. Insurance coverage and outof-pocket cost are particularly important in the management of OSSN, and it is up to both the physician and the patient to balance the potential side effects from surgical therapy and the financial cost of long term medical treatment. One study examined cost of surgical versus medical treatment for OSSN at a large academic center and found that the cost for the surgical group over the course of treatment was approximately \$12,725 higher than that for the medically treated group, which on average cost \$3,058 [14]. These staggering figures may represent the out-of-pocket expense for the uninsured patients, thus medical treatment may be favored among these individuals. When the study calculated cost based on Medicare reimbursement, it found no significant difference between the total cost in the surgical and medical groups. This may be due to Medicare covering most if not all of the hospital charges required for surgical intervention, making surgical treatment an equally preferable option to medical treatment in patients with Medicare. As treatments for OSSN become increasingly complex, disparities in patients' ability to pay may widen. Lastly, one important consideration is that medically treated patients would require additional clinic visits with strict adherence to avoid treatment delays. Vulnerable populations that face financial barriers such as extra travel cost, lack of medical leave, and lack of childcare are at greater risk of compliance failure. Thus, patient insurance status affects both medical decision as well as nonmedical financial burden, and studies aimed at understanding these disparities and narrowing outcome gaps should be prioritized.

We reported that AA patients were more likely to reside in neighborhoods with lower median income. These findings are consistent with prior reports highlighting correlations between lowresourced neighborhoods and poor health outcomes [34,35]. Accessing eye health services can be a major challenge for those living in resource restricted areas, and social deprivation has been linked to significantly decrease ocular health screening with subsequent poor outcomes [36]. Interestingly, one study examined patients in impoverished regions of Nairobi and found that the main barriers to utilization of eye clinics were a lack of perceived need for treatment and lack of financial resources [37]. Additionally, one survey found the major impediments to cancer care include lack of awareness and social stigma of cancer [38]. Taken together, more research is needed to better understand the impact of patients' social, psychological, and emotional functioning, in addition to financial burdens, in their ophthalmologic care and outcomes.

Although we did not identify a significant correlation between education levels and risk of death due to OSSN, existing literature suggests an inverse relationship between patient education level and risk of OSSN. One study found patients with lower educational attainment were at higher risk of OSSN and presented with larger tumors than those with higher education [39,40]. Of note, the same authors found associations between low education level and outdoor occupations, suggesting greater sun exposure as a possible confound in explaining higher rate of OSSN in patients with lower education. We should point out that these studies were conducted in Kenya, which may present with different educational and occupational stratifications than the United States, thus contributing to the difference in our results. Nonetheless, occupational and related environmental risk may be mediating factors between educational attainment and clinical outcome that warrant further study.

Lastly, although we did not observe a significant risk of death due to insurance status and average household income in our multivariable Cox proportional hazard model, the fact that these variables are disproportionately represented in the AA patient population and that AA race is an independent risk factor suggest that racial disparity may be partly driven by mediating factors that our study could not examine. The main limitation of this study is its retrospective design, which was not truly population based. The electronic medical records in the database were limited to hospitals that participate in the NCDB registry [41]. Findings need to be interpreted in the context of the drawbacks of registry data that extrapolate population level statistics measured by zip code which may not be representative of individual patients.

## Conclusion

This study on the impact of racial and socioeconomic factors led to the identification of populations at risk for disparate outcomes in OSSN. The results from our study highlight that African American patients were more likely to have adverse outcomes when diagnosed with OSSN. Factors that increased risk of poor prognosis in African Americans with OSSN were significantly related to socioeconomic factors including being uninsured and residing in disadvantaged neighborhoods.

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