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Disparate molecular, histopathology, and clinical factors in HNSCC racial groups

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Abstract

Objective—The causes of the differences in the higher incidence of and the mortality from head and neck squamous cell carcinoma (HNSCC) in African American (AA) versus Caucasian Americans (CA) lack a consensus. We examined a comprehensive array of risk factors influencing health and disease in an access to care, racially diverse, primary HNSCC cohort.

Study Design—Cross-sectional study.

Setting—Primary care academic health care system.

Subjects and Methods—The cohort of 673 comprised 391 CA and 282 AA (42%). Risk variables included demographic, histopathology, and clinical/epidemiologic factors. Tumor DNA was interrogated for loss and gain of 113 genes with known involvement in HNSCC/cancer. Logistic regression for univariate analysis was followed by multivariate modeling with determination of model predictability (c-index).

Results—Of the 39 univariate differences between AA and CA, multivariate modeling (c-index=0.81) retained seven ($p<0.05$). AA were less likely to be married, more likely to have tumor lymphocytic response, undergo radiation treatment, and smoke. Insurance type was a significant predictor of race. AA were more likely to have Medicaid, Medicare, and other HMO types. AA tumors were more likely to have loss of *CDKN2A* and gain of *SCYA3* versus CA.

Conclusions—Multivariate modeling indicated significant differences between AA and CA HNSCC for histopathology, treatment, smoking, marital status, type of insurance, as well as tumor gene copy number alterations. Our data reiterate that for HNSCC as in the case of other complex diseases, tumor genetics or biology is only one of many potential contributors to differences among racial groups.

Keywords

African American; Caucasian American; risk factor variables; tumor biology

INTRODUCTION

There is abundant epidemiological evidence that self-identified race/ethnicity is associated with differences in cancer incidence and mortality. The high mortality rate for HNSCC continues to be driven by the disparate unfavorable diagnosis and prognosis outcomes for African Americans (AA)^{1–3}. There is no consensus on the causes of the differences in the higher incidence of and the mortality from HNSCC for AA when compared to Caucasian Americans (CA), but they can include differences in access to care, stage at diagnosis, insurance, attitudes of health providers, as well as human papilloma virus (HPV) infection status^{3–8}. HPV is now regarded, in addition to tobacco and alcohol⁹, as a causative agent for some HNSCC¹⁰ and an independent risk factor for oropharyngeal cancer (OPSCC)¹¹.

Racial/ethnic difference such as genetic features, in combination with environmental factors can also influence carcinogenic mechanisms and lead to biologically important differences in the molecular profile of a tumor¹². Epidemiological and clinical studies using molecular markers indicate that racial differences in cancer types do exist¹², supporting a systematic evaluation of these issues.

The objective of this study was to gain insights into differences in the higher incidence of and the mortality from HNSCC in AA versus CA through the examination of a comprehensive array of risk factors influencing health and disease in an access to care, racially diverse, primary HNSCC cohort.

MATERIALS AND METHODS

Study design

Study Cohort—The study cohort of 673 primary HNSCC was drawn from a large, clinically well characterized multi-ethnic (40% AA), primary care patient population in the Detroit area. Patients, 21 years or older with a primary HNSCC diagnostic biopsy in the Henry Ford Health System with available tumor tissue blocks were identified through tumor registry and ENT clinic records between 1986 and 2005. The Henry Ford Health System Tumor Registry (HFHS-TR) is certified by the Commission on Cancer (CoC) of the American College of Surgeons and has been a division of the Department of Medical Records since the mid-1960s. All HFHS Tumor Registry registrars are Registered Health Information Technicians (RHIT) and have passed the National Exam for RHIT[®]. Follow-up spanned 4–23 years (through 9/25/2009). This study included only self-reported AA and CA HNSCC. Other ethnicities were excluded.

Risk Factor Variables—Risk variables included demographic, histopathology, and clinical/epidemiologic risk factors for a total of 23 non-gene variables and are described in Tables 1 & 2. Tumor DNA was interrogated for loss and gain of 113 genes with known involvement in HNSCC/cancer (gene panels p005, p006, p007, www.mlpa.com).

The Pathology Review Form recorded all squamous head and neck (SHN) diagnoses from a specific biopsy specimen (Table 2). The Squamous Head and Neck (SHN) Medical Record Abstraction Form captured a patient's clinical, demographical, and epidemiological information, including smoking, alcohol, and comorbidity. Overall comorbidity was determined using the Adult Comorbidity Evaluation 27 (ACE-27) index for cancer patients¹³. The ACE-27 categorizes specific diseases into one of three grades: grade 1 (mild), grade 2 (moderate), and grade 3 (severe), based on organ decompensation and prognostic impact. Comorbidity scores include none - 0; mild - 1; moderate - 2; or severe - 3 and are assigned based on the highest ranked/graded single ailment¹⁴. Collection of clinical, epidemiological and demographical data was conducted by experienced Medical Record

Abstractors trained in the use of study forms. Age cut-offs of < 50 yrs, 51–65 yrs and > 65 yrs were set to capture younger patients and those in the Medicare group.

Health insurance payors included Blue Cross, Medicare, Medicaid, Health Alliance Plan (HAP, a Health Maintenance Organization [HMO]), and other non-HAP HMO's (other HMO). Patients were categorized into treatment groups of surgery, radiation, and chemotherapy. This study was approved by the Henry Ford Health System Institutional Review Board committee.

Molecular Methods

Whole 5 micron tissue sections or microdissected tumor lesions and adjacent normal when present were processed for DNA extraction¹⁵. DNA was interrogated for gene copy number alterations (losses and gains) using the multiplex ligation-dependent probe amplification assay (MLPA) as previously described^{16–19}. MLPA is a high throughput assay allowing simultaneous interrogation of 41 genes using minute amounts (20 ng) of DNA. Validated using real-time PCR, it is ideally suited for DNA from formalin-fixed paraffin embedded tissues^{16–19}. Gene gain and loss by MLPA concurred with chromosomal aberrations, and provide a novel index to estimate the extent of genomic abnormality with disease progression.¹⁶. Three gene probe panels, p005, p006, and p007 (www.mlpa.com), comprising 113 unique genes were examined. The panels detects primarily oncogenes and tumor suppressor genes that are located at chromosomal segments that have been implicated in cancer and distributed throughout the genome^{16–19}.

Statistical Methods

All analyses were done using SAS 9.2. Logistic regression modeling was used to examine risk factor differences between AA and CA HNSCC. The analysis started with testing for individual variable effects followed by inclusion of variable(s) of $p < 0.10$ in the stepwise multivariable modeling process. Multivariable modeling is an analytical approach to increase model predictability (e.g., c-index) based on a set of risk factors rather than a single factor. The risk factors retained in the final multivariable model become independent predictors after adjusting for the other covariate factors. The final multivariate model included variable(s) of $p < 0.05$ with determination of the c-index estimation for goodness-of-fit. The c-index ranges from 0 to 1, where 1 indicates perfect fit and 0 none. The usual interpretation of the c-index is in context of prediction, but here it reflects the general amount of separation between AA and CA for the variables in the model.

RESULTS

Of the 673 primary HNSCC cohort, 391 were CA and 282 AA (42%); the mean age was 64 years (SD=12) with 14% 50 years or younger, 38% 51–65 years, and 48% >65 years of age. Demographic, histopathology, and clinical/epidemiological variables examined in this study for AA and CA patients are presented in Tables 1 & 2.

Of the 136 total variables (2 demographic, 11 histopathology, 10 clinical/epidemiology, 113 MLPA), univariate differences in race as AA and CA, were noted for 39 risk factors ($p < 0.10$). Of the 39 univariate factors, 25 were gene and 14 were non-gene variables.

Multivariate modeling retained seven variables ($p < 0.05$) with a c-index of 0.81 (Table 3). Type of insurance such as HAP (Health Alliance Plan), Blue Cross, Medicaid, Medicare, and other HMO was a significant predictor of race. Insurance type (including Medicaid) was noted for 87% CA (339/391) and 88% AA ((249/282). A larger proportion of the CA group (87%, 336/391) had private insurance (HAP, Medicare, Blue Cross, other HMO) as

compared to 81% (228/282) of AA patients. With HAP as reference, AA were more likely to have Medicaid (OR=24.5), Medicare (OR=3.69) and other HMO (OR=3.99). Insurance status by stage was not significant. AA were more likely to be unmarried (OR=2.44). AA were more likely to be current and past smokers (OR=2.83 and OR=3.89, respectively). AA were more likely to have a tumor lymphocytic response, whether continuous rim or patchy infiltrate (OR=6.12, OR=7.83, respectively). Of the treatment types (surgery, radiation, chemotherapy), radiation ($p=0.020$) and chemotherapy ($p=0.010$) were univariate predictors of race as AA. Radiation remained in the final model; AA were more likely to receive radiation treatment than CA (OR=2.23). Radiation by stage was not significant ($p=0.09$).

With regard to tumor genetic alterations, AA tumors were more likely to have gain of *SCYA3* (OR=2.81) and less likely to have loss of *SCYA3* (OR=0.58) than CA tumors. For the *CDKN2A* gene, AA tumors were more likely to have loss of *CDKN2A* (OR=1.47) when compared to CA tumors.

DISCUSSION

There is considerable evidence to support the disproportionate increase in HNSCC incidence and mortality in AA as compared to CA^{1-3,20}. The age-adjusted incidence of head and neck cancers of the larynx and oral cavity and pharynx in African Americans in the US between 2003–2007 was higher than whites²¹. For the period 1975–2007, the death rates for all cancers combined continued to be substantially higher among African Americans than whites with improving rates for women²¹

The ability to dissect out factors that contribute to racial disparities, while gaining ground continues to be challenging. Some reasons for this include a dearth of large multi-ethnic studies of primary HNSCC cohorts with sizable AA patients. Also, a majority of studies have examined HNSCC outcomes in narrower contexts of a limited number of pathologic and clinical risk factors. This large multi-ethnic Detroit HNSCC study with 42% AA took a broader more inclusive approach by examining many intertwined variables influencing health and disease.

Access to Care

Much of the disparities in HNSCC outcomes for AA, as in other cancers, are likely due to access to care barriers that prevent timely and high-quality medical care, resulting in later stage at diagnosis as well as inequalities in treatment^{3,22,23}. In this study, though a majority of patients had some form of medical insurance, insurance type was a significant predictor of race. The primary health care environment of the Henry Ford Health System (HFHS) is dominated by Health Alliance Plan (HAP), a non-profit health maintenance organization (HMO) serving more than 2,800 Detroit area employers and more than 580,000 members. Nearly half of the cohort (287/588) had Medicare, reflecting the age distribution of the two groups. When compared to CA, AA were significantly more likely to have Medicaid (8% AA, 1% CA), Medicare (58% AA, 42% CA), and other HMO types (13% AA, 6% CA). Stage at diagnosis, a significant univariate predictor ($p=0.003$) for race (late stage: 66% AA, 54% CA) did not remain in the final multivariate model as an independent factor for race. The latter is likely due to the primary care environment of the Henry Ford Health system and access to some form of insurance for the majority of cohort subjects.

Marital Status

Quality of life and survival rates for head and neck cancer patients are better for married persons and those not living alone compared with unmarried persons and those living alone²⁴. In our study, marital status was an independent predictor of race as AA versus CA

(OR=2.44) and a likely underlying contributing social factor for the observed disparate outcomes for AA as compared to CA with HNSCC in reported studies.

Smoking

Smoking is responsible for about 30% of all cancer deaths and is associated with increased risk of at least 16 types of cancer including HNSCC²⁵. Unlike past decades where the rate of adult smoking has been higher in AA than CA, in recent years these rates are more comparable²¹. Tobacco is an etiologic agent in some HNSCC and in this study, smoking status as past (OR=2.83) or current (OR=2.44) was significantly associated with race as AA.

Radiation treatment

In this cohort, radiation treatment was an independent predictor of race. AA were 2.2 times more likely to receive radiation than CA. Fewer AA (43%) received surgery than CA (49%) and chemotherapy was a univariate predictor of race ($p=0.010$: 28% AA received chemotherapy vs 19% of CA). This observation is interesting from two aspects. **First**, it suggests that treatment was likely not a barrier given that 87% of AA had some type of insurance, similar to that of the CA group (86%). Second, though radiation by stage was not significant ($p=0.09$), it remains suspect that late stage disease contributed to chemo-radiation and less surgery and requires validation in a larger 1:1 matched case (AA) and control (CA) study.

Tumor lymphocytic response

In HNSCC, studies of lymphocytic response, a histologic parameter has been based on the subjective observation of lymphocyte infiltration on H&E (hematoxylin and eosin) tissue sections. These earlier studies have indicated an inverse correlation between lymphocytic infiltrate, local recurrence²⁶, potential for lymph node metastasis²⁷, as well as survival²⁸. In this study, presence of a lymphocytic response as continuous rim or patchy infiltrate was an independent predictor of race. AA tumors were 6–7 times more likely than CA tumors to present with a lymphocytic response. The latter suggests a growing support for the dual roles of immune system cells, on one hand being summoned as first responders in local host defenses against tumors²⁹ and on the other hand being maneuvered into behaving as if they were healing a wound³⁰, emitting growth factors that embolden the tumor into activities such as stimulating angiogenesis³¹. Molecular insights into these responses would greatly aid in our understanding of HNSCC pathogenesis and is further discussed in the section below.

Tumor molecular characteristics

Genetic alterations provide means of identifying tumor cells as well as defining changes that presumably determine biological differences from their normal counterparts. Molecular genetic prognosticators can influence prevention, diagnosis, appropriateness of adjuvant chemotherapy, and, possibly, the chemotherapeutic regimen of cancer patients. Dissecting out processes specific to the pathogenesis of malignancy can distill key genetic biomarkers of HNSCC etiology, transformation, and progression.

In this study, the AA tumors were 1.4 times more likely to have loss of the *CDKN2A* gene as compared to CA tumors. The *CDKN2A* *p14ARF*, *p16INK4a* locus at 9p21, which generates two gene products, p16 and p14^{32,33}, has been linked to malignant progression in HNSCC^{34,35}. Loss of p16 expression by deletion, mutation, or hypermethylation is common in HNSCC^{17,36} and is associated with worse prognosis³⁷. Also, tobacco/alcohol-associated HNSCC appears to be associated with p16 downregulation (as an early event) and the *TP53* gene mutation resulting in p53 overexpression³⁸.

SCYA3, otherwise known as macrophage inflammatory protein-1 α (MIP-1-alpha) or CCL3, belongs to the CC (beta) subfamily of chemokines that recruit a variety of cells to sites of inflammation³⁹. In oral squamous cell carcinoma, CCL3/CCR1 appears to have dual roles of tumor lymph node metastasis and local host defense against tumor²⁹. This was also demonstrated in hepatocellular carcinoma progression⁴⁰, and support multiple and opposite functions in tumorigenesis for the CCL3/CCR1 system.

In our study, the lack of fidelity of the *SCYA3* gene with respect to loss and gain was an independent factor for race. AA tumors were almost three times more likely to have gain of *SCYA3* and 57% less likely to have loss when compared to CA tumors. This observation suggests a tantalizing connection to the finding that AA tumors were almost 6–7 times more likely to have presence of lymphocytic response, when presenting as a patchy infiltrate or as a continuous rim, when compared to CA tumors.

Immunohistochemistry to correlate CCL3/CCR1 and *SCYA3* copy number with presence or absence of lymphocytic response in AA and CA in this cohort is a next step.

Conclusion

Understanding and accounting for factors contributing to differences in HNSCC racial groups should provide much needed insights into disparities of incidence and mortality in AA. The contribution of HPV and p16 involvement was not evaluated, and this was a study limitation. Major strengths of this study include the large multi-ethnic primary HNSCC cohort with 42% AA and a comprehensive examination of patient and tumor variables influencing health and disease. We found significant differences between AA and CA HNSCC for histopathology, treatment, smoking, marital status, type of insurance, as well as tumor gene copy number alterations. Our data reiterate that for HNSCC as in the case of other complex diseases, tumor genetics or biology is only one of many potential contributors to differences among racial groups.

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Table 1

Demographic and clinical variables by race

Variable	Response	White (N= 391)	Black (N= 282)	p-value
Demographics				
Age category	<=50	49 (13%)	44 (16%)	0.516
	51–65	150 (38%)	106 (38%)	
	>65	192 (49%)	132 (47%)	
Gender	Male	286 (73%)	212 (75%)	0.553
	Female	105 (27%)	70 (25%)	
Clinical/Epidemiologic				
Marital Status	No	116 (31%)	140 (53%)	<.001
	Yes	257 (69%)	122 (47%)	
Insurance Type	Hap	127 (38%)	38 (15%)	<.001
	Other HMO	21 (6%)	32 (13%)	
	Blue Cross	44 (13%)	15 (6%)	
	Medicare	144 (42%)	143 (58%)	
	Medicaid	3 (1%)	21 (8%)	
Allergy	No	341 (87%)	247 (88%)	0.885
	Yes	50 (13%)	35 (12%)	
Overall Comorbidity	0. None	83 (21%)	21 (7%)	<.001
	1. Mild	175 (45%)	132 (47%)	
	2. Moderate	79 (20%)	78 (28%)	
	3. Severe	54 (14%)	51 (18%)	
Pneumonia	No	341 (87%)	237 (84%)	0.244
	Yes	50 (13%)	45 (16%)	
Hyperthyroid Disease	No	359 (92%)	270 (96%)	0.042
	Yes	32 (8%)	12 (4%)	
Family History of Cancer	No	68 (39%)	58 (47%)	0.160
	Yes	108 (61%)	66 (53%)	
Cigarette Smoking Category	0:Never Smk	61 (16%)	17 (7%)	<.001
	1:Past Smk	150 (40%)	84 (32%)	
	2:Current Smk 1–15	17 (5%)	31 (12%)	
	3:Current Smk 15–25	73 (20%)	98 (38%)	
	4:Current Smk 25–35	30 (8%)	16 (6%)	
	5:Current Smk >35	41 (11%)	15 (6%)	
Cigarette Smoking Category Collapsed	Never	61 (17%)	17 (7%)	<.001
	Current	150 (40%)	84 (32%)	
	Past	161 (43%)	160 (61%)	
Alcohol	No	27 (8%)	8 (3%)	0.007
	Yes	294 (92%)	252 (97%)	

Variable	Response	White (N= 391)	Black (N= 282)	p-value
Radiation	No	162 (41%)	92 (33%)	0.020
	Yes	229 (59%)	190 (67%)	
Chemotherapy	No	316 (81%)	204 (72%)	0.010
	Yes	75 (19%)	78 (28%)	
Surgery	No	198 (51%)	160 (57%)	0.118
	Yes	193 (49%)	122 (43%)	

Table 2

Histopathology variables by race

Variable	Response	White (N= 391)	Black (N= 282)	p-value
Histopathology				
Overall Grade	Well Differentiated	117 (30%)	65 (23%)	0.097
	Moderately Differentiated	177 (46%)	135 (48%)	
	Poorly Differentiated	94 (24%)	82 (29%)	
Tumor Type: Keratinizing	No	139 (36%)	98 (35%)	0.793
	Yes	250 (64%)	184 (65%)	
Tumor Type: Basaloid	No	385 (99%)	275 (98%)	0.143
	Yes	4 (1%)	7 (2%)	
Tumor Type: Adenocarcinoma	No	388 (100%)	282 (100%)	0.394
	Yes	1 (0%)	0 (0%)	
Lymphocytic Response	Continuous rim	182 (47%)	120 (43%)	0.003
	Patchy Infiltrate	177 (46%)	154 (55%)	
	Absent	25 (7%)	5 (2%)	
Desmoplastic Response	Prominent & Diffuse	176 (46%)	135 (48%)	0.282
	Patchy & Irregular	151 (39%)	117 (42%)	
	Focal	30 (8%)	16 (6%)	
	Absent	26 (7%)	11 (4%)	
Pattern Invasion	Pushing Cohesive Borders	71 (19%)	32 (11%)	0.092
	Solid Cords	192 (50%)	153 (55%)	
	Thin Irregular Cords	98 (26%)	74 (27%)	
	Single Cell	22 (6%)	20 (7%)	
Vascular Invasion	Identified	30 (8%)	21 (7%)	0.886
	Not Identified	356 (92%)	260 (93%)	
Perineural Invasion	Identified	27 (7%)	15 (5%)	0.374
	Not Identified	358 (93%)	267 (95%)	
Mitotic Index :Mitoses Per10 High Power Field (HPF)	Frequent<=5/10HPF	5 (1%)	4 (1%)	0.885
	Frequent>5/10HPF	383 (99%)	278 (99%)	
Tumor Necrosis.	Extensive	49 (13%)	32 (11%)	0.003
	Minimal	50 (13%)	65 (23%)	
	None	289 (74%)	185 (66%)	
Location of Primary Tumor	Oral cavity	110 (28%)	49 (17%)	0.025
	Larynx	112 (29%)	97 (34%)	
	Oropharyngeal	67 (17%)	49 (17%)	
	Hypopharyngeal	30 (8%)	26 (9%)	
	Other	72 (18%)	61 (22%)	
Stage	Early (1 & 2)	165 (46%)	88 (34%)	0.003
	Late (3 & 4)	195 (54%)	172 (66%)	

Table 3

Multivariate Model: c-index=0.81

Variable	Beta	Standard Error	Wald Chi-Square	P Value	Odds Ratio	95% Confidence Limits
Insurance Type	0.2286	0.4402	0.2697	0.6035	1.257	0.530 2.978
Insurance Type	3.1995	0.7294	19.2411	<.0001	24.521	5.870 102.427
Insurance Type	1.3063	0.2656	24.1945	<.0001	3.693	2.194 6.214
Insurance Type	1.3838	0.4044	11.7127	0.0006	3.990	1.806 8.814
Lymphocyte Response: Continuous rim vs Absent	1.8111	0.7159	6.4010	0.0114	6.117	1.504 24.883
Lymphocyte Response Patchy Infiltrate vs Absent	2.0587	0.7129	8.3395	0.0039	7.835	1.938 31.686
Married	0.8932	0.2222	16.1582	<.0001	2.443	1.580 3.776
Smoking	1.0426	0.3898	7.1523	0.0075	2.837	1.321 6.090
Smoking	1.3588	0.3807	12.7402	0.0004	3.892	1.845 8.207
Radiation	0.8002	0.2336	11.7339	0.0006	2.226	1.408 3.519
CDKN2A	-1.0190	0.6783	2.2569	0.1330	0.361	0.096 1.364
CDKN2A	0.3837	0.2210	3.0152	0.0825	1.468	0.952 2.263
SCYA3	1.0350	0.2856	13.1342	0.0003	2.815	1.608 4.927
SCYA3	-0.5521	0.2504	4.8597	0.0275	0.576	0.352 0.941