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Authors

Zakeri, Kaveh
MacEwan, Iain
Vazirnia, Aria
et al.

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Race and competing mortality in advanced head and neck cancer

Kaveh Zakeri [a], Iain MacEwan [a], Aria Vazirnia [a], Ezra E.W. Cohen [b], Michael T. Spiotto [c], Daniel J. Haraf [c], Everett E. Vokes [b], Ralph R. Weichselbaum [c], Loren K. Mell [a,*]

[a] Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA, United States
[b] Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL, United States
[c] Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL, United States

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SUMMARY

Objectives: Black patients with head and neck cancer (HNC) have poorer survival and disease control compared to non-black patients, but disparities in death from non-cancer causes (i.e., competing mortality) are less well-studied.

Materials and methods: We conducted an analysis of 538 patients (169 black, 369 non-black) with stage III–IV HNC treated on one of six multi-institutional protocols between 1993 and 2004 involving multi-agent chemoradiotherapy with or without surgery. Competing mortality was defined as death due to intercurrent comorbid disease, treatment-related morbidity, or unknown cause in the absence of disease recurrence, progression, or second malignancy. Cox proportional hazards and competing risks regression were used to estimate the effect of black race on competing mortality.

Results: Black race was associated with increased rates of comorbidity, smoking, heavy alcohol use, advanced tumor stage, and poorer performance status ($p < .001$ for all). Compared to non-black patients, black HNC patients had a higher 5 year cumulative incidence of disease progression (31.4%; 95% CI, 24.4–38.5% vs 23.4%; 95% CI, 19.1–28.1%) and competing mortality (28.1%; 95% CI, 21.2–35.3% vs 14.5%; 95% CI, 11.0–18.5%). When adjusting for age, male sex, body mass index, distance traveled, smoking and alcohol use, performance status, comorbidity, and tumor stage, the black race was associated with death from comorbid disease (Cox hazard ratio 2.13; 95% CI, 1.06–4.28, $p = 0.033$).

Conclusions: Black patients with advanced HNC are at increased risk of both disease progression and death from competing non-cancer mortality, particularly death from comorbid disease. Improved strategies to manage comorbid disease may increase the benefit of treatment intensification in black patients.

Introduction

Racial disparities in treatment outcomes are a widely recognized problem in head and neck cancer (HNC). Studies have shown that black HNC patients have worse rates of overall survival, relative survival, HNC mortality, and disease recurrence compared to non-black HNC patients [1–5]. A better understanding of modifiable risk factors contributing to survival disparities is needed to design strategies to mitigate these disparities.

Previous studies have identified that lower socioeconomic status (SES), poorer access to health care, higher rates of comorbidity, later stage at presentation, and lower rates of surgical treatment are associated with both black race and poorer survival in HNC [3–8]. These studies have analyzed racial disparities in HNC using composite endpoints, such as overall survival or disease-free survival, which are comprised of both cancer-specific (e.g., disease recurrence) and non-cancer events (e.g., death from any cause). A limitation of composite endpoints is that they can obscure whether survival differences are due to cancer-specific events, non-cancer events, or both [9].

In addition to being undesirable events in their own right, deaths from competing causes diminish the clinical benefit of cancer therapies and reduce the efficiency of cancer clinical trials [9–13]. We have previously shown that black race is associated with increased risk of HNC specific mortality and non-cancer mortality in a population-based analysis [12], though the study did not directly compare black and non-black patients and lacked important prognostic data on tobacco and alcohol use, comorbidity, performance status, and treatment techniques. Therefore, with the addition of these covariates, we sought to determine the effect of race on competing mortality in advanced HNC using a multi-institutional cohort.

* Corresponding author. Address: Department of Radiation Medicine and Applied Sciences, 3855 Health Sciences Drive, MC0843, La Jolla, CA 92093, United States. Tel.: +1 (858) 246 0471; fax: +1 (858) 822 5568.
E-mail address: lmell@ucsd.edu (L.K. Mell).

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Methods

Patients

The study design was a secondary analysis of 538 patients (168 black; 369 non-black) with American Joint Committee on Cancer stage III–IV HNC, treated on a series of six multi-institutional protocols between August 1993 and November 2004. Patients were treated at one of four institutions: University of Chicago, Northwestern Memorial Hospital, University of Illinois Chicago, and Weiss Memorial Hospital. Protocol treatment details have been previously described (Appendix Table A1) [10,14–17].

Treatment techniques

All patients were treated with concurrent multi-agent chemoradiotherapy (CRT). Select patients received induction chemotherapy with paclitaxel and carboplatin preceding CRT. Limited initial organ-sparing surgery was used in selected patients preceding CRT and was used at the primary site for persistent or recurrent disease after CRT. Neck dissection was recommended for patients with N2 or N3 disease.

CRT was given in five cycles on alternating weeks and RT was given in 1.5 Gy fractions twice daily. Gross disease was treated to total dose of 70–75 Gy, while postoperatively treated patients received 60–66 Gy. High-risk areas of the neck were treated to 51–60 Gy and standard-risk areas were treated to 36–45 Gy. Chemotherapy consisted of fluorouracil plus hydroxyurea concurrent with RT. Additional chemotherapy depended on the protocol and consisted of cisplatin, paclitaxel, or oral ZD1839 (Iressa; AstraZeneca, Wilmington, DE).

Patients were evaluated 1 month after the completion of CRT, every 3 to 4 months in the first year, every 6 months in the second and third year, and annually thereafter. Computed tomography of the head, neck, and chest, was obtained at each follow-up evaluation. All locoregional and distant recurrences were biopsy proven whenever possible and clinically indicated. Follow-up continued until November 2004.

Statistical analysis

Disease-free survival was defined as disease progression, second malignancy, or death due to any cause. Competing mortality was defined as death due to intercurrent comorbid disease, treatment-related morbidity, or unknown cause in the absence of disease recurrence, progression, or second malignancy. Examples of death from comorbid disease included stroke, myocardial infarction, arrhythmia, pneumonia, hepatic failure, and diabetic ketoacidosis. Treatment-related mortality included death from any cause within two months of treatment and death immediately after surgery or late complications. Examples included surgical complications, sepsis, and pulmonary embolism within two months of treatment, in accordance with previously described methods [18]. As the patients in this study were treated at tertiary referral centers on a set of multi-institutional protocols, cause of death ascertainment was collectively reviewed and confirmed in multidisciplinary tumor boards [10].

Chi-squared and *t*-tests were used to test differences in covariates for black and non-black patients. Cumulative incidence

Table 1
Patient Characteristics.

	Black (n = 169) No. (%)	Non-Black (n = 369) No. (%)	P value
Institution			
University of Chicago	113 (66.9)	225 (61.0)	
Northwestern Memorial Hospital	12 (7.1)	98 (26.6)	
University of Illinois Chicago	44 (26.0)	40 (10.8)	
Weiss Memorial Hospital	0	5 (1.4)	
Missing	0	1	
Age (mean)	56.1	57.1	0.33
Age > 65	37 (21.9)	100 (27.1)	0.24
Male sex	122 (72.2)	281 (76.2)	0.38
Body Mass Index (mean)	23.4	25.9	<.001
Smoking history > 20 pack years	134 (79.3)	225 (61.0)	<.001
Alcohol use > 1 drink per day	117 (69.2)	196 (53.1)	<.001
Distance traveled > 15 miles	30 (17.8)	237 (64.2)	<.001
Unknown	24 (14.2)	35 (9.5)	
Charlson comorbidity index			
0	100 (59.2)	233 (63.1)	0.016
1	16 (9.5)	37 (10.0)	
2	23 (13.6)	29 (7.9)	
⩾3	13 (7.7)	8 (2.2)	
Unknown	62 (3.7)	17 (4.6)	
ECOG performance status			<.001
0	53 (31.4)	196 (53.1)	
1	86 (50.9)	156 (42.3)	
2	30 (17.8)	17 (4.6)	
T stage 3/4	138 (81.5)	216 (58.5)	<.001
Unknown	7 (4.1)	9 (2.4)	
Nodal stage			
N2c	36 (21.4)	60 (16.3)	0.12
N3	31 (18.5)	50 (13.6)	0.17
Unknown	7 (4.1)	9 (2.4)	
Site			
Hypopharynx	16 (9.5)	43 (11.7)	
Larynx	42 (24.9)	44 (11.9)	
Oropharynx	67 (39.6)	167 (45.3)	

ECOG = Eastern Cooperative Oncology Group.

Table 2
Five year unadjusted cumulative incidence of disease-specific and competing events in black and non-black head and neck cancer patients.

	Cumulative incidence in blacks at 5 years (95% CI)	Cumulative incidence in non-blacks at 5 years (95% CI)
Local failure	11.5% (7.2–17.0%)	10.5% (7.5–14.0%)
Distant failure	19.9% (14.2–26.3%)	13.0% (9.6–16.8%)
Death due to comorbidity	14.1% (9.1–20.1%)	5.5% (3.4–8.4%)
Death due to treatment toxicity	10.8% (6.7–16.1%)	5.9% (3.7–8.6%)
Secondary malignancy	3.0% (1.1–6.5%)	7.9% (5.1–11.6%)
Unknown death	3.2% (1.2–6.8%)	3.2% (1.7–5.5%)

CI = confidence interval.

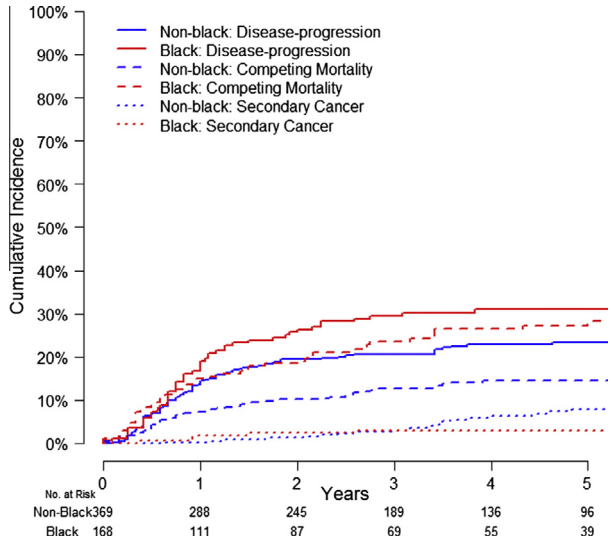

Figure 1. Cumulative incidence of disease progression, competing mortality, and secondary malignancies for black and non-black patients with head and neck cancer during a 5-year period.

functions were calculated to determine event probabilities [19,20]. For univariable and multivariable analysis of covariates, we used the Cox proportional hazards model and the Fine-Gray semi-parametric model for subdistribution hazards [21,22]. The cause-specific hazard ratio (CSHR) was obtained from the Cox proportional hazards model and was used to isolate the effect of black race to the event of interest, without regard to how race is related to the competing event. To determine the net effect of black race on the cumulative probability of competing mortality, we used the subdistribution hazard ratio (SDHR) from the Fine-Gray cumulative incidence model [23,24]. The effect of race on disease-free survival did not vary significantly between the six protocols. Statistical analysis was conducted using the R software, version 2.14.0.

Results

Median follow-up for surviving patients was 53 months. Overall, 110 competing mortality events and 135 local or distant failures were observed. Median disease-free survival in black patients was 24 months compared to 37 months in non-black patients. Black race was associated with smoking and heavy alcohol use, lower body mass index, higher comorbidities, poorer performance status, and advanced tumor stage (Table 1). Black patients were also less likely to travel greater than 15 miles for treatment. There was no difference in nodal status or tumor grade between blacks and non-blacks.

Black patients had higher 5 year cumulative incidence of distant failures, death due to comorbidity, and death due to treatment toxicity compared to non-black patients (Table 2). Consequently, black patients had a higher likelihood of both disease-progression and competing mortality (Fig. 1). The imbalance in the incidence of

Table 3
Univariable analysis.

	Disease-free survival				Competing mortality			
	SDHR (95% CI)	*P* value	CSHR (95% CI)	*P* value	SDHR (95% CI)	*P* value	CSHR (95% CI)	*P* value
Black race	1.56 (1.22–1.99)	<0.001	1.56 (1.22–1.99)	<0.001	1.65 (1.13–2.41)	0.009	1.82 (1.24–2.66)	0.0022
Age	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001	1.02 (1.00–1.04)	0.025	1.03 (1.01–1.05)	0.0017
Male sex	1.37 (1.06–1.79)	0.017	1.38 (1.06–1.79)	0.016	1.81 (1.23–2.66)	0.0025	1.85 (1.25–2.73)	0.0022
Body mass index (log)	0.22 (0.12–0.38)	<0.001	0.21 (0.12–0.37)	<0.001	0.37 (0.14–0.96)	0.04	0.23 (0.09–0.55)	0.0011
Distance traveled > 15 miles[a]	0.66 (0.51–0.86)	0.0016	0.66 (0.51–0.85)	0.002	0.56 (0.37–0.83)	0.004	0.49 (0.32–0.74)	0.0007
Smoke > 20 pack years	1.77 (1.35–2.33)	<0.001	1.78 (1.35–2.36)	<0.001	1.24 (0.82–1.87)	0.31	1.37 (0.90–2.09)	0.15
Alcohol use > 1 drink per day	1.16 (0.91–1.48)	0.22	1.17 (0.91–1.49)	0.22	1.08 (0.74–1.58)	0.70	1.06 (0.72–1.57)	0.77
Charlson comorbidity index	1.21 (1.10–1.33)	<0.001	1.21 (1.09–1.33)	<0.001	1.29 (1.11–1.49)	<0.001	1.33 (1.16–1.53)	<0.001
Performance status > 0	1.65 (1.37–1.99)	<0.001	1.65 (1.38–1.98)	<0.001	1.29 (0.98–1.68)	0.065	1.49 (1.12–1.98)	0.0056
T stage 3/4	2.13 (1.60–2.83)	<0.001	2.14 (1.60–2.88)	<0.001	1.86 (1.18–2.93)	0.0075	2.18 (1.37–3.50)	0.0011
	Death due to comorbidity				Disease-progression			
Black race	1.87 (1.06–3.29)	0.029	2.24 (1.27–3.96)	0.0056	1.45 (1.03–2.05)	0.033	1.62 (1.15–2.29)	0.0063
Age	1.02 (0.99–1.05)	0.17	1.04 (1.01–1.07)	0.021	1.02 (1.00–1.04)	0.015	1.03 (1.01–1.05)	0.0013
Male sex	1.27 (0.70–2.31)	0.44	1.47 (0.80–2.72)	0.22	1.02 (0.69–1.51)	0.91	1.14 (0.78–1.69)	0.50
Body mass index (log)	0.80 (0.20–3.24)	0.75	0.34 (0.09–1.31)	0.12	0.28 (0.13–0.61)	0.0013	0.22 (0.10–0.48)	<0.001
Distance traveled > 15 miles[a]	0.93 (0.51–1.70)	0.80	0.71 (0.38–1.33)	0.29	0.72 (0.49–1.05)	0.089	0.66 (0.45–0.98)	0.0367
Smoke > 20 pack years	0.91 (0.51–1.65)	0.76	1.04 (0.57–1.91)	0.89	1.01 (1.32–3.04)	0.001	2.12 (1.40–3.22)	<0.001
Alcohol use > 1 drink per day	0.94 (0.54–1.66)	0.84	0.88 (0.49–1.58)	0.67	1.15 (0.81–1.62)	0.43	1.17 (0.83–1.66)	0.36
Charlson comorbidity index	1.30 (1.04–1.63)	0.023	1.41 (1.16–1.71)	<0.001	1.08 (0.94–1.25)	0.28	1.12 (0.96–1.32)	0.15
Performance status > 0	1.53 (1.01–2.31)	0.044	1.88 (1.23–2.86)	0.0034	1.77 (1.37–2.28)	<0.001	1.90 (1.48–2.45)	<0.001
T stage 3/4	1.07 (0.58–1.97)	0.83	1.41 (0.75–2.64)	0.28	1.94 (1.28–2.94)	0.0019	2.14 (1.40–3.27)	<0.001

SDHR = subdistribution hazard ratio, CSHR = cause-specific hazard ratio, CI = confidence interval.
[a] Subset analysis of 479 patients for which these data were available.

Table 4
Multivariable analysis.

	Disease-free survival				Competing mortality			
	SDHR (95% CI)	*P* value	CSHR (95% CI)	*P* value	SDHR (95% CI)	*P* value	CSHR (95% CI)	*P* value
Black race	1.08 (0.81–1.46)	0.60	1.09 (0.82–1.44)	0.57	1.18 (0.74–1.87)	0.49	1.19 (0.76–1.87)	0.46
Age	1.03 (1.01–1.04)	<0.001	1.03 (1.01–1.04)	<0.001	1.02 (1.00–1.04)	0.062	1.03 (1.01–1.05)	0.0072
Male sex	1.31 (1.01–1.70)	0.041	1.31 (1.01–1.72)	0.046	1.76 (1.18–2.63)	0.0061	1.76 (1.17–2.64)	0.0066
Body mass index (log)	0.40 (0.23–0.72)	0.0021	0.40 (0.23–0.73)	0.0024	0.49 (0.20–1.18)	0.11	0.40 (0.16–0.97)	0.044
Distance traveled > 15 miles	0.78 (0.59–1.03)	0.078	0.78 (0.59–1.03)	0.076	0.77 (0.50–1.18)	0.23	0.70 (0.44–1.10)	0.12
Smoke > 20 pack years	1.34 (1.01–1.77)	0.041	1.34 (1.00–1.80)	0.050	1.01 (0.66–1.52)	0.98	1.06 (0.68–1.65)	0.80
Alcohol use > 1 drink per day	0.97 (0.75–1.26)	0.83	0.98 (0.75–1.27)	0.85	1.13 (0.75–1.71)	0.56	1.02 (0.68–1.55)	0.91
Charlson comorbidity index	1.08 (0.96–1.22)	0.20	1.08 (0.97–1.20)	0.16	1.21 (1.02–1.44)	0.028	1.21 (1.03–1.41)	0.017
Performance status > 0	1.28 (1.06–1.56)	0.012	1.28 (1.06–1.56)	0.012	0.95 (0.70–1.29)	0.73	1.09 (0.80–1.50)	0.57
T stage 3/4	1.49 (1.11–2.00)	0.0074	1.50 (1.11–2.02)	0.0078	1.42 (0.91–2.24)	0.13	1.60 (0.99–2.58)	0.055
	Death due to comorbidity				Disease-progression			
Black race	2.06 (1.03–4.10)	0.040	2.13 (1.06–4.28)	0.033	0.94 (0.63–1.41)	0.77	1.06 (0.71–1.59)	0.76
Age	1.02 (0.99–1.05)	0.20	1.04 (1.00–1.07)	0.025	1.02 (1.00–1.03)	0.079	1.02 (1.01–1.04)	0.0075
Male sex	1.15 (0.62–2.14)	0.65	1.24(0.64–2.41)	0.52	0.95 (0.64–1.41)	0.81	1.07 (0.72–1.59)	0.75
Body mass index (log)	0.89 (0.26–3.06)	0.85	0.57 (0.15–2.21)	0.42	0.57 (0.24–1.34)	0.20	0.49 (0.21–1.14)	0.10
Distance traveled > 15 miles	1.52 (0.79–2.95)	0.21	1.21 (0.61–2.40)	0.59	0.70 (0.46–1.05)	0.084	0.68 (0.46–1.01)	0.057
Smoke > 20 pack years	0.72 (0.36–1.42)	0.34	0.78 (0.40–1.47)	0.44	1.61 (1.03–2.50)	0.035	1.59 (1.03–2.46)	0.037
Alcohol use > 1 drink per day	0.95 (0.49–1.84)	0.88	0.82 (0.43–1.56)	0.55	0.89 (0.62–1.28)	0.53	0.87 (0.60–1.27)	0.46
Charlson comorbidity index	1.24 (0.97–1.57)	0.082	1.24 (0.99–1.55)	0.060	0.98 (0.84–1.15)	0.83	0.99 (0.83–1.16)	0.86
Performance status > 0	1.39 (0.84–2.32)	0.20	1.61 (1.01–2.56)	0.043	1.41 (1.07–1.86)	0.016	1.48(1.12–1.96)	0.0057
T stage 3/4	0.89 (0.48–1.65)	0.72	1.08 (0.55–2.11)	0.83	1.35 (0.88–2.06)	0.17	1.44 (0.94–2.20)	0.095

SDHR = subdistribution hazard ratio; CSHR = cause-specific hazard ratio; CI = confidence interval.

competing mortality was largely mediated by a nearly 3-fold higher incidence of death due to comorbid disease in black patients.

In the univariable analysis, black race, age, male sex, smoking, comorbidity, performance status, and *T* stage were all statistically significant predictors of disease-free survival (Table 3). Body mass index (BMI) and distance traveled greater than 15 miles were associated with lower incidence of disease-free survival and competing mortality. In the multivariable analysis, the effect of black race on disease-free survival and competing mortality was not significant (Table 4). However, black race had a significant effect on death due to comorbid disease, even after adjusting for age, sex, body mass index, distance traveled, smoking and alcohol use, performance status, comorbidity, and *T* stage.

Discussion

This study contributes to the understanding of racial disparities between black and non-black HNC patients. While previous studies have focused specifically on disparities in cancer-specific events, comparatively less attention has focused on disparities in death from non-cancer causes. We found that the incidence of competing mortality events, particularly death from comorbidities, were higher in black HNC patients and that consequently, these patients have significantly worse survival. Deaths from competing causes diminish the clinical benefit of cancer therapies and reduce the efficiency of cancer clinical trials [12,13]. Thus, improved strategies to manage comorbid disease would increase the benefit of intensive treatment in black patients and help reduce the health disparity between blacks and non-blacks.

There are several reasons to suspect that rates of competing mortality would be higher in black compared to non-black patients. Many studies have indicated that chronic disease is more prevalent in the black community [24-27]. In addition, black patients with HNC have a higher likelihood of having multiple comorbidities [6]. Optimizing treatment of comorbidities in HNC patients could be a potential strategy to prolong survival, but specific strategies to achieve this goal have not yet been developed. In addition, stratifying patients according to competing mortality risks may help in (1) selecting patients for more intensive medical treatment, (2) counseling of patients on their prognosis, and (3) designing more effective as well as cost-efficient clinical trials for patients with competing risks [12,13].

Strengths of this study include large sample size, homogeneity of treatment techniques, high incidence of competing events, long follow up, and detailed demographic data. Unique to this study was information regarding the cause of competing mortality, which allowed us to identify the large racial disparity in death due to comorbid disease. Limitations include retrospective design and lack of information on HPV status, which is an important prognostic factor for head and neck cancer. Additionally, the study lacked a direct measurement of socioeconomic status, though distance traveled is considered a surrogate and has been shown to predict survival in oncology clinical trials [28].

In conclusion, black patients with advanced HNC are at increased risk of death from competing non-cancer mortality, particularly death from comorbid disease. Improved strategies to manage comorbid disease could increase the marginal benefit of intensive treatment in black patients.

Conflict of Interest

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2013.09.012.

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