ORIGINAL ARTICLE

Epidemiologic factors in patients with advanced head and neck cancer treated with radiation therapy

Michael T. Brennan DDS, MHS[1] ⓘ | Nathaniel S. Treister DMD, DMSc[2,3] ⓘ |
Thomas P. Sollecito DMD[4,5] ⓘ | Brian L. Schmidt MD, DDS, PhD[6] |
Lauren L. Patton DDS[7] ⓘ | Yi Yang MS[8] ⓘ | Alexander Lin MD[9] |
Linda S. Elting DPH[10] | James S. Hodges PhD[8] | Rajesh V. Lalla DDS, PhD[11]

[1]Department of Oral Medicine, Atrium Health's Carolinas Medical Center, Charlotte, North Carolina

[2]Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, Massachusetts

[3]Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, Massachusetts

[4]Department of Oral Medicine, University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania

[5]Division of Oral Medicine, University of Pennsylvania Health System, Philadelphia, Pennsylvania

[6]Department of Oral & Maxillofacial Surgery and Bluestone Center for Clinical Research, New York University College of Dentistry, New York City, New York

[7]Division of Craniofacial and Surgical Care, Adams School of Dentistry, University of North Carolina, Chapel Hill, North Carolina

[8]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota

[9]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania

[10]Department of Health Services Research, Division of Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, Texas

[11]Section of Oral Medicine, University of Connecticut Health, Farmington, Connecticut

Correspondence
Michael T. Brennan, Department of Oral Medicine, Carolinas Medical Center, 1000 Blythe Blvd., Charlotte, NC 28203.
Email: mike.brennan@atriumhealth.org

Abstract

Background: Approximately 50% of patients with head and neck cancer (HNC) initially were seen with advanced disease. We aimed to evaluate the association of epidemiologic factors with advanced HNC at diagnosis.

Methods: The OraRad multicenter prospective cohort study enrolled HNC patients receiving curative-intent radiation therapy. Factors assessed for association with advanced HNC presentation at diagnosis included demographics, social and medical history, cancer characteristics, human papilloma virus (HPV) status, and dental disease measures.

Results: We enrolled 572 participants; 77% male and mean (SD) age of 61.7 (11.2) years. Oropharyngeal squamous cell carcinomas (88% HPV-related) were seen with smaller tumors, but more frequent nodal involvement. Private medical insurance and no Medicaid were associated with smaller tumors. A higher dental disease burden was associated with larger tumors.

Conclusions: Insurance status, cancer type/location, and dental disease are associated with advanced HNC and may represent potentially modifiable factors or factors to be considered in the screening process of new lesions.

KEYWORDS

baseline features, dental health, epidemiology, head and neck cancer, radiotherapy

1 | INTRODUCTION

Approximately 63 000 new cases of head and neck cancer (HNC) are diagnosed annually in the United States, with estimated 13 360 deaths each year and an overall 5-year survival rate of 65%.[1,2] About 50% of all HNC patients were seen with late-stage (advanced) cancer at diagnosis,[3] which is characterized as larger tumor size (T3 or T4) or nodal involvement ($\geq$ N1) in the HNC staging (tumor, node, metastases [TNM]) classification.[4] Numerous factors have been associated with more advanced HNC at diagnosis including demographics (age, sex, and race), socioeconomic status, insurance status, marital status, tumor location, and access to care.[3,5-8] Additionally, human papilloma virus (HPV)-related oropharyngeal carcinomas have been noted to involve smaller tumors, but more extensive nodal disease.[9]

The OraRad study (Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients) is a multicenter prospective study of 572 HNC patients receiving curative-intent radiation therapy (RT). The study was designed to address gaps in our knowledge of dental and oral outcomes and dental management strategies. This analysis evaluated the association of epidemiologic factors with more advanced cancers on presentation in the well-characterized OraRad cohort.

TABLE 1 Demographics of study cohort

Variable	All sites	BWH	UPENN	CMC	UConn	NYU	UNC	P-Value
N	572	158	146	104	53	80	31	
Sex								.1512
Male	440 (76.9%)	124 (78.5%)	119 (81.5%)	77 (74.0%)	44 (83.0%)	54 (67.5%)	22 (71.0%)	
Female	132 (23.1%)	34 (21.5%)	27 (18.5%)	27 (26.0%)	9 (17.0%)	26 (32.5%)	9 (29.0%)	
Age	61.7 (11.2)	63.1 (9.4)	61.0 (10.3)	61.4 (12.2)	60.9 (11.3)	62.1 (13.9)	58.7 (11.5)	.3322
Highest grade								.0014
≤High school	158 (27.6%)	26 (16.5%)	42 (28.8%)	34 (32.7%)	19 (35.8%)	31 (38.8%)	6 (19.4%)	
>High school	412 (72.0%)	131 (82.9%)	104 (71.2%)	70 (67.3%)	33 (62.3%)	49 (61.3%)	25 (80.6%)	
Decline	2 (0.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	
Marital status								.0010
Not married	173 (30.2%)	41 (25.9%)	32 (21.9%)	42 (40.4%)	20 (37.7%)	33 (41.2%)	5 (16.1%)	
Married	398 (69.6%)	117 (74.1%)	114 (78.1%)	62 (59.6%)	33 (62.3%)	46 (57.5%)	26 (83.9%)	
Decline	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	
Race								.0005
White only	474 (82.9%)	150 (94.9%)	134 (91.8%)	78 (75.0%)	47 (88.7%)	38 (47.5%)	27 (87.1%)	
African American only	45 (7.9%)	2 (1.3%)	6 (4.1%)	18 (17.3%)	3 (5.7%)	13 (16.2%)	3 (9.7%)	
Other	53 (9.3%)	6 (3.8%)	6 (4.1%)	8 (7.7%)	3 (5.7%)	29 (36.2%)	1 (3.2%)	
Ethnicity								<.0001
Hispanic	29 (5.1%)	2 (1.3%)	1 (0.7%)	6 (5.8%)	5 (9.4%)	15 (18.8%)	0 (0.0%)	
Non-Hispanic	543 (94.9%)	156 (98.7%)	145 (99.3%)	98 (94.2%)	48 (90.6%)	65 (81.2%)	31 (100.0%)	

Note: Table entries are n (%) except for age, which is average (SD).
Abbreviations: BWH, Brigham and Women's Hospital; CMC, Atrium Health's Carolinas Medical Center; NYU, New York University; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.

2 | METHODS

2.1 | Patient cohort

The OraRad study, which has been described in detail elsewhere,[10] enrolled HNC patients at six clinical centers: Brigham and Women's Hospital, University of Pennsylvania, Atrium Health's Carolinas Medical Center, University of Connecticut, New York University, and University of North Carolina with the Data and Coordinating Center at the University of Minnesota. IRB approval was obtained at all sites and participants were consented and enrolled before initiating curative-intent RT. Patients were eligible if age 18 or older; diagnosed with head and neck squamous cell carcinoma (SCC) or a salivary gland cancer (SGC), or with a non-SCC, non-

TABLE 2 Clinical characteristics

Measure	All sites	BWH	UPENN	CMC	UConn	NYU	UNC	*P*-Value
N	572	158	146	104	53	80	31	
Tobacco use								.5470
Never used	250 (43.7%)	76 (48.1%)	64 (43.8%)	42 (40.4%)	18 (34.0%)	35 (43.8%)	15 (48.4%)	
Ever used	322 (56.3%)	82 (51.9%)	82 (56.2%)	62 (59.6%)	35 (66.0%)	45 (56.2%)	16 (51.6%)	
Alcohol use in past 12 months								.0031
No/do not know/declined	190 (33.2%)	42 (26.2%)	40 (27.4%)	38 (36.5%)	20 (37.7%)	41 (51.2%)	9 (29.0%)	
Yes	382 (66.8%)	116 (73.4%)	106 (72.6%)	66 (63.5%)	33 (62.3%)	39 (48.8%)	22 (71.0%)	
Drinks per week in past 12 months	6.9 (10.4)	6.1 (6.1)	6.0 (6.5)	10.3 (19.6)	7.4 (9.1)	4.6 (3.4)	8.1 (10.6)	.0770
Type of cancer								.3293
SCC	469 (82.0%)	132 (83.5%)	120 (82.2%)	88 (84.6%)	44 (83.0%)	58 (72.5%)	27 (87.1%)	
SGC	66 (11.5%)	15 (9.5%)	19 (13.0%)	10 (9.6%)	7 (13.2%)	11 (13.8%)	4 (12.9%)	
Non-SCC/non-salivary	37 (6.5%)	11 (7.0%)	7 (4.8%)	6 (5.8%)	2 (3.8%)	11 (13.8%)	0 (0.0%)	
Primary tumor site								.0240
Oropharynx	266 (46.5%)	76 (48.1%)	82 (56.2%)	44 (42.3%)	25 (47.2%)	26 (32.5%)	13 (41.9%)	
Oral cavity	87 (15.2%)	26 (16.5%)	12 (8.2%)	21 (20.2%)	6 (11.3%)	19 (23.8%)	3 (9.7%)	
Larynx/hypopharynx	40 (7.0%)	10 (6.3%)	6 (4.1%)	9 (8.7%)	8 (15.1%)	5 (6.2%)	2 (6.5%)	
Salivary gland	56 (9.8%)	12 (7.6%)	18 (12.3%)	10 (9.6%)	6 (11.3%)	6 (7.5%)	4 (12.9%)	
Other	89 (15.6%)	24 (15.2%)	23 (15.8%)	15 (14.4%)	5 (9.4%)	19 (23.8%)	3 (9.7%)	
Unknown	34 (5.9%)	10 (6.3%)	5 (3.4%)	5 (4.8%)	3 (5.7%)	5 (6.2%)	6 (19.4%)	
Cancer classification								
T								.7570
1 or 2	343 (60.0%)	99 (62.7%)	94 (64.4%)	62 (59.6%)	29 (54.7%)	42 (52.5%)	17 (54.8%)	
3 or 4	178 (31.1%)	45 (28.5%)	46 (31.5%)	34 (32.7%)	21 (39.6%)	25 (31.2%)	7 (22.6%)	
M								.0005
0	536 (93.7%)	144 (91.1%)	146 (100.0%)	103 (99.0%)	50 (94.3%)	71 (88.8%)	22 (71.0%)	
1	10 (1.7%)	5 (3.2%)	0 (0.0%)	1 (1.0%)	2 (3.8%)	1 (1.2%)	1 (3.2%)	
X	26 (4.5%)	9 (5.7%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	8 (10.0%)	8 (25.8%)	
N								.4503
00	137 (24.0%)	32 (20.3%)	33 (22.6%)	24 (23.1%)	17 (32.1%)	23 (28.7%)	8 (25.8%)	
01/02/2a/2b/2c/03	427 (74.7%)	123 (77.8%)	112 (76.7%)	80 (76.9%)	36 (67.9%)	53 (66.2%)	23 (74.2%)	

Note: Table entries are n (%) or average (SD).

Abbreviations: BWH, Brigham and Women's Hospital; CMC, Atrium Health's Carolinas Medical Center; NYU, New York University; SCC, squamous cell carcinoma; SGC, salivary gland cancer; TNM, tumor, node, metastasis; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.

SGC malignancy of the head and neck region; receiving curative-intent RT of at least 4500 cGy to the head and neck region; had at least 1 natural tooth remaining after any pre-RT dental extractions; and had no prior curative-intent RT to the head and neck region. The baseline visit was scheduled before RT, after the pre-RT dental evaluation and after any recommended dental treatment was completed (eg, extractions). Participants underwent a baseline dental examination completed by calibrated examiners, and panoramic radiographic evaluation. A total of 572 participants were enrolled between April 2014 and October 2018 and eligible for follow-up post-RT. The current manuscript focuses on epidemiologic factors associated with presentation of advanced cancer (primary outcome).

2.2 | Primary outcome

The primary outcome was presentation with advanced cancer (based on American Joint Committee on Cancer [AJCC] seventh edition TNM staging) at diagnosis.[4] Participants were defined for this purpose to have advanced cancer based on presenting with larger tumor size (T3 or T4) or any nodal metastases (N1, N2, or N3), whereas patients presenting with smaller tumor sized (T1 or T2) and absence of nodal metastases (N0) were considered early-stage HNC.

2.3 | Epidemiologic factors of interest

Baseline characteristics collected from the medical record included demographics (sex, age, race, ethnicity, insurance status/type, and public assistance) and cancer characteristics (type, location, and TNM),[4] radiation dose and location, and chemotherapy used. Outcomes collected by interview and patient report included highest grade level of school completed, marital status, social history including tobacco and alcohol use, medications, oral hygiene status (routine dental care, frequency of brushing and flossing) and dental history. Information collected by

TABLE 3 Public assistance and insurance status

Variable	All sites	BWH	UPENN	CMC	UConn	NYU	UNC	*P*-Value
N	572	158	146	104	53	80	31	
Public assistance								.0005
No	521 (91.1%)	155 (98.1%)	138 (94.5%)	90 (86.5%)	42 (79.2%)	66 (82.5%)	30 (96.8%)	
Yes	49 (8.6%)	1 (0.6%)	8 (5.5%)	14 (13.5%)	11 (20.8%)	14 (17.5%)	1 (3.2%)	
Declined	2 (0.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Type of medical insurance								
No insurance								<.0001
No	552 (96.5%)	158 (100.0%)	145 (99.3%)	97 (93.3%)	53 (100.0%)	72 (90.0%)	27 (87.1%)	
Yes	20 (3.5%)	0 (0.0%)	1 (0.7%)	7 (6.7%)	0 (0.0%)	8 (10.0%)	4 (12.9%)	
Private insurance:								.0005
No	137 (24.0%)	23 (14.6%)	8 (5.5%)	37 (35.6%)	18 (34.0%)	44 (55.0%)	7 (22.6%)	
Yes	435 (76.0%)	135 (85.4%)	138 (94.5%)	67 (64.4%)	35 (66.0%)	36 (45.0%)	24 (77.4%)	
Medicare								.0092
No	428 (74.8%)	123 (77.8%)	119 (81.5%)	66 (63.5%)	43 (81.1%)	53 (66.2%)	24 (77.4%)	
Yes	144 (25.2%)	35 (22.2%)	27 (18.5%)	38 (36.5%)	10 (18.9%)	27 (33.8%)	7 (22.6%)	
Medicaid								<.0001
No	512 (89.5%)	149 (94.3%)	144 (98.6%)	96 (92.3%)	40 (75.5%)	52 (65.0%)	31 (100.0%)	
Yes	60 (10.5%)	9 (5.7%)	2 (1.4%)	8 (7.7%)	13 (24.5%)	28 (35.0%)	0 (0.0%)	
Dental insurance								<.0001
No	206 (36.0%)	43 (27.2%)	36 (24.7%)	56 (53.8%)	21 (39.6%)	37 (46.2%)	13 (41.9%)	
Yes	366 (64.0%)	115 (72.8%)	110 (75.3%)	48 (46.2%)	32 (60.4%)	43 (53.8%)	18 (58.1%)	

Note: Table entries are n (%).
Abbreviations: BWH, Brigham and Women's Hospital; CMC, Atrium Health's Carolinas Medical Center; NYU, New York University; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.

TABLE 4 Associations of characteristics with presentation of advanced head and neck cancer (defined as TNM values of T3/T4 and N ≥ 1)

Characteristic	T1/2	T3/4	P-Value	N0	N ≥ 1	P-Value
N*	343	178		137	427	
Education (≤ vs >high school)	254 (74.1%)	122 (68.5%)	.216	104 (75.9%)	307 (71.9%)	.379
Dental insurance	221 (64.9%)	111 (62.4%)	.701	80 (58.4%)	280 (65.6%)	.152
Routine dental care	256 (74.6%)	124 (69.7%)	.253	97 (70.8%)	312 (73.1%)	.660
Freq. of brushing (≤1×/day vs >1×/day)	256 (74.6%)	119 (66.9%)	.065	102 (74.5%)	306 (71.7%)	.584
Freq. of flossing (<1×/day vs ≥1×/day)	177 (51.6%)	90 (50.6%)	.854	73 (53.3%)	218 (51.1%)	.695
Enrollment sites			.757			.450
Married (vs not)	239 (67.0%)	121 (68.0%)	.764	88 (64.2%)	306 (71.7%)	.108
Ethnicity	12 (2.9%)	12 (6.7%)	.122	9 (6.7%)	20 (4.7%)	.379
Race			.469			.301
White	290 (84.5%)	143 (80.3%)		109 (79.6%)	360 (84.3%)	
African American	25 (7.3%)	16 (9.0%)		14 (10.2%)	28 (6.6%)	
Other	28 (8.2%)	19 (10.7%)		14 (10.2%)	39 (9.1%)	
Private insurance	272 (79.3%)	123 (69.1%)	.013	99 (72.3%)	331 (77.5%)	.207
Medicaid	29 (8.5%)	27 (15.2%)	.025	15 (10.9%)	44 (10.3%)	.873
Public assistance	25 (7.3%)	20 (11.2%)	.140	14 (10.2%)	34 (8.0%)	.384
Primary tumor site[a]			.003			<.0001
Oropharynx	193 (56.3%)	71 (39.9%)		22 (16.1%)	242 (56.7%)	
Oral cavity	55 (16.0%)	30 (16.9%)		33 (24.1%)	54 (12.6%)	
Larynx/hypopharynx	19 (5.5%)	20 (11.2%)		19 (13.9%)	20 (4.7%)	
Salivary gland	29 (8.5%)	24 (13.5%)		32 (23.4%)	23 (5.4%)	
Other	47 (13.7%)	33 (18.5%)		31 (22.6%)	54 (12.6%)	
Type of cancer[b]			.053			<.0001
SCC	290 (84.5%)	136 (76.4%)		80 (58.4%)	387 (90.6%)	
SGC	38 (11.1%)	27 (15.2%)		47 (34.3%)	18 (4.2%)	
Non-SCC/SGC	15 (4.4%)	15 (8.4%)		10 (7.3%)	22 (5.2%)	
Age	61.2 (60.0-62.4)	61.2 (59.6-62.8)	.983	61.5 (59.6-63.3)	61.6 (60.6-62.7)	.888
Whole mouth avg PD	2.3 (2.3-2.4)	2.4 (2.4-2.5)	.033	2.3 (2.2-2.4)	2.4 (2.3-2.4)	.381
Whole mouth avg CAL	1.8 (1.7-1.9)	2.1 (1.9-2.2)	.005	1.9 (1.7-2.0)	1.9 (1.8-2.0)	.367
% sites CAL >= 2 mm	0.50 (0.48-0.53)	0.57 (0.53-0.61)	.013	0.52 (0.48-0.57)	0.53 (0.51-0.56)	.678
% sites PD >= 4 mm	0.10 (0.09-0.12)	0.13 (0.11-0.15)	.416	0.11 (0.08-0.13)	0.11 (0.10-0.13)	.572
Number of teeth at baseline	23.6 (23.0-24.2)	21.8 (21.0-22.6)	.0007	22.6 (21.7-23.6)	23.0 (22.5-23.6)	.509
Tobacco use	189 (55.1%)	106 (59.6%)	.352	80 (58.4%)	241 (56.4%)	.766
Alcohol use	228 (66.5%)	124 (69.7%)	.491	88 (64.2%)	291 (68.1%)	.404
DMFS score	46.9 (43.8-50.1)	48.7 (44.3-53.2)	.515	47.5 (42.5-52.6)	48.4 (45.6-51.3)	.769

Abbreviations: CAL, clinical attachment level; PD, probing depth; SCC, squamous cell carcinoma; SGC, salivary gland cancer; TNM, tumor, node, metastasis.

[a]Note that the percentages reflect the frequency based on all patients in each T or N category.

[b]T score and N score were available for 521 and 564 participants, respectively.

examination to establish dental disease characteristics included number of teeth; decayed, missing, and filled surfaces (DMFS); and clinical attachment loss (CAL) and probing depth (PD).[10] The burden of dental disease was based on the dental findings, with fewer teeth serving as a surrogate measure of prior dental disease resulting in tooth loss, while PD and CAL are indicators of periodontal disease and DMFS is an indicator of dental caries. HPV status was assessed and confirmed via p16 immunohistochemistry or HPV in-situ hybridization for patients presenting with SCC originating in the oropharynx.

2.4 | Statistical considerations

Differences between enrollment centers were tested using Fisher's exact test for categorical characteristics (eg, education) and one-way ANOVA for characteristics measured on continuous scales (eg, periodontal disease measures). Associations of tumor size and nodal metastases, and HPV status (all binary characteristics) with categorical characteristics were tested using Fisher's exact test, and associations with characteristics measured on continuous scales were tested using two-sample t-tests. We also performed multivariate logistic regression analysis separately for tumor size stage (T1/2 vs T3/4) and for nodal involvement (N0 vs any nodal involvement), with P-values from likelihood-ratio tests. Characteristics with $P < .05$ in the univariate analyses were included in the multivariate analyses. All analyses were performed using JMP (Pro version 14.0, SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

A total of 572 HNC patients were enrolled in this cohort, with 77% male and mean (SD) age 61.7 (11.2) years (Table 1). The most common race was white (83%), with the proportion of patients of Hispanic origin consistent with national surveillance data (5%).[11] Tobacco use (current or past) was reported by 56% of participants, 67% reported alcohol use in the past 12 months (Table 2). SCC was the most common histology (n = 469, 82%) with the oropharynx the most common primary location (n = 266, 47%). Most participants (60%) were seen with smaller tumors, while the majority (75%) had nodal metastases (Table 2).

The range of maximum RT dose that was delivered to the primary tumor site ranged from 636 to 7802 cGy with mean 6573 cGy; 7 out of 572 (1.22%) participants had ≤4500 cGy. The study enrolled 314 (54.9%) patients who had surgical resection before RT.

TABLE 5 Multivariate analyses for association between stages and patient characteristics

Outcome	Predictor	Effect estimate (log odds ratio)	SE	P-Value
T1/2 vs T3/4	Private insurance	−0.27	0.29	.37
	Medicaid	0.33	0.38	.38
	Whole mouth avg. PD	0.29	0.20	.15
	Whole mouth avg. CAL	0.02	0.12	.85
	# of teeth at baseline	−0.045	0.021	.029
N0 vs N1	Primary tumor site	—[a]	—[a]	<.0001
	Type of cancer	—[a]	—[a]	<.0001

[a]The cross-tab of primary tumor site and type of cancer has many cells with small counts, in many of which either all or none of the participants have nodal involvement. Thus, some coefficients in this multivariate logistic regression are estimated to be plus or minus infinity. The likelihood-ratio tests are nonetheless feasible and give the P-values in the table.

Seventy-six percent of participants had private primary medical insurance, 25% had Medicare and 11% had Medicaid; some participants had more than one type of insurance. Most participants (n = 366, 64%) had dental insurance (Table 3).

Several factors were associated with tumor size and nodal involvement. A total of 272 of 343 (79%) participants presenting with smaller tumors had private medical insurance compared to 123 of 178 (69%) participants with larger tumors ($P = .012$), whereas patients with Medicaid coverage tended to present with larger tumors ($P = .025$). Participants presenting with larger tumors also tended to present with a higher burden of dental disease including fewer teeth at baseline and more advanced periodontal disease measures (Table 4).

Few characteristics were associated with nodal involvement. Participants with SCC were more likely to have nodal involvement than participants with SGC or other non-SCC/SGC. This was especially the case for participants with oropharyngeal SCC, with the highest rate within the cohort presenting with nodal involvement (92%), but more frequently were seen with smaller tumors (73%) (Table 4). Dental disease measures were not associated with nodal involvement.

For tumor size stage (T1/2 vs T3/4), five characteristics that had $P < .05$ in the univariate analysis were included in the multivariate analysis as predictors: private insurance, Medicaid, whole mouth average PD,

TABLE 6 Associations of HPV status with patient characteristics

	HPV-positive oropharyngeal cancer	HPV-negative oropharyngeal and non-oropharyngeal cancer	P-Value
N[a]	236	323	
Sex (male)	210 (89.0%)	219 (67.8%)	<.0001
Education (>high school)	181 (77.4%)	222 (68.7%)	.0273
Age	62.6 (61.1-64.0)	61.0 (59.8-62.2)	.1113
Ethnicity	9 (3.8%)	18 (5.6%)	.4257
Race			<.0001
White	219 (92.8%)	245 (75.9%)	
African American	7 (3.0%)	35 (10.8%)	
Other	10 (4.2%)	43 (13.3%)	
Married (vs not)	185 (78.4%)	204 (63.4%)	.0001
Tobacco use	119 (50.4%)	192 (59.4%)	.0386
Alcohol use	176 (74.6%)	198 (61.3%)	.0010
Private insurance	205 (86.9%)	222 (68.7%)	<.0001
Medicaid	11 (4.7%)	46 (14.2%)	.0002
Public assistance	9 (3.8%)	38 (11.8%)	.0006
Dental insurance	162 (68.6%)	197 (61.0%)	.0739
Routine dental care	179 (75.9%)	227 (70.3%)	.1509
Freq. of brushing (≤1×/day vs >1×/day)	167 (70.8%)	238 (73.7%)	.4453
Freq. of flossing (<1×/day vs ≥1×/day)	120 (50.9%)	165 (51.1%)	1.0000
Whole mouth avg PD	2.4 (2.3-2.4)	2.3 (2.3-2.4)	.3340
Whole mouth avg CAL	1.8 (1.7-1.9)	2.0 (1.9-2.1)	.0735
% sites CAL > =2 mm	0.50 (0.46-0.53)	0.55 (0.52-0.58)	.0232
% sites PD > = 4 mm	0.12 (0.10-0.13)	0.10 (0.09-0.12)	.3167
N teeth at baseline	23.8 (23.1-24.5)	22.3 (21.7-23.0)	.0032
DMFS score	47.3 (43.5-51.1)	48.1 (44.8-51.4)	.7443
Enrollment sites			.0020

Note: Table entries are n (%) or group averages (95% confidence intervals).

Abbreviations: CAL, clinical attachment loss; DMFS, decayed, missing, filled surfaces; HPV, human papilloma virus; N, number; PD, probing depth.

[a]Although 572 patients were included in this cohort, data regarding HPV assessment of oropharyngeal SCC vs all other HNC was available for 559 patients.

whole mouth average CAL, and the number of teeth at baseline. We did not include percent of sites with CAL ≥2 mm because of its extremely high correlation with whole mouth average CAL. After adjusting for other predictors, only the number of teeth at baseline was significantly associated with the tumor size stage (Table 5).

For the nodal involvement stage (N0 vs any other N), two characteristics with $P < .05$ in the univariate analysis were included in the multivariate analysis as predictors: primary tumor site and type of cancer. Both characteristics were significantly associated with nodal involvement stage after adjusting for each other ($P < .0001$ for both; Table 5).

Numerous epidemiologic factors differed in the HPV-positive vs HPV-negative oropharyngeal SCC groups (Table 6). In the HPV-positive group, a number of factors were more common including higher education level and higher likelihood of private medical and dental insurance, and lower likelihood of Medicaid insurance or receipt of public assistance. Participants in the HPV-positive group were also more likely to be white and married, to use tobacco less, and to use alcohol more frequently. The HPV-positive group had less dental disease burden with more teeth at baseline and fewer sites with CAL ≥2 mm.

4 | DISCUSSION

Prior studies have found numerous factors associated with presenting with advanced HNC such as demographics (age, sex, and race), socioeconomic status, insurance status, marital status, tumor location, and access to care.[3,5-8] In the present cohort, we identified three main factors: insurance status, type/location of cancer, and dental disease measures. Lebo et al. identified Medicaid insurance and lack of medical insurance as key predictors in severity of disease presentation in patients with laryngeal cancer.[8] Lack of medical insurance is often considered a surrogate measure for lack of routine screening and, perhaps, poor health. The findings from OraRad support this, with lack of medical insurance associated with more advanced HNC.

Adrien and colleagues[3] found a higher rate of T3/T4 presentation in the hypopharynx vs the oral cavity, suggesting that cancers at anatomical sites that are not easily observed may be seen with larger tumors. In the present cohort, a higher rate of advanced cancer presentation was associated with larynx/hypopharynx (51%) compared to oral cavity (35%) and oropharyngeal region (27%), which is consistent with prior findings. The lower rate of advanced cancer presentation with tumors located with the oropharyngeal region and the oral cavity may be due to HNC in this area being more clinically observable as compared to laryngeal/hypopharyngeal cancers.

Patients presenting with larger tumors had higher dental disease burden. The association of oral health with stage of cancer presentation has not been reported in prior studies, though poor oral health as a risk factor for presentation of any HNC has been evaluated. In a large case-control study of HNC patients from the International Head and Neck Cancer Epidemiology Consortium, daily tooth brushing, absence of gum disease, annual dental visits and missing fewer than five teeth were associated with lower risk of HNC.[12] A smaller case-control study of HNC patients from Taiwan found lack of regular dental visits, brushing teeth <2 times a day, gum bleeding and loss of more than 20 teeth were associated with higher risk of HNC.[13] A Brazilian case-control study of HNC identified less than daily tooth brushing and sores caused by dentures as risk factors for HNC.[14] A Swedish case-control study of oral and oropharyngeal SSCs identified poor oral hygiene, more than 5 defective teeth, more than 20 missing teeth and defective or malfunctioning dentures as risk factors for HNC.[15] We did find that measures of oral health (fewer teeth and periodontal disease) were associated with advanced HNC presentation. The findings suggest that poor oral health (fewer teeth and periodontal disease) may be associated with advanced cancer at presentation, so routine dental care and increased screening among people with poor oral health are recommended. Multivariate analysis of the present cohort identified that number of teeth at baseline was the key predictor of presentation with larger tumors (T3/T4) vs smaller tumors (T1/T2). We did not find significant associations with other factors previously found to be associated with more advanced HNC such as older age, male sex, African American race, and not being married.[3,5-8] The lack of associations with these factors in the present study may be related to inherent differences in study populations sampled and differences in sample size with prior studies.

Patients with HPV-positive oropharyngeal cancers have been shown to have risk factors and presentation differing from non-HPV-related HNCs, including younger age, higher socioeconomic status, white race,[16] less tobacco exposure,[17] less alcohol use,[18] with smaller primary tumors and more nodal involvement.[19] We found similar associations in the present cohort with a similar demographic presentation and measures consistent with higher socioeconomic status including private medical insurance, dental insurance, less public assistance, and less Medicaid. The association of insurance status with cancer presentation in the present study may not generalize beyond the United States as many industrialized countries have more universal health care systems. Some key differences in the OraRad study from prior publications included more alcohol use in the HPV-positive oropharyngeal group and no age difference between patients with HPV-positive oropharyngeal cancer vs all other HNC. This may represent the aging cohort of HPV-related cancers compared to non-HPV-related HNC as OraRad is a more recent cohort of HNC, compared to prior publications finding that HPV-related cancers are represented by a younger age range.

The current study identified several factors associated with presentation of more advanced HNC such as insurance status, type/location of cancer, and dental disease measures. Recognition of these factors associated with presentation of more advanced cancers offers potentially modifiable factors and actions such as improving poor oral health, whereas other factors (such as socioeconomic status factors and lesion site) can be considered in the screening process of new lesions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Michael T. Brennan https://orcid.org/0000-0003-0638-4335

Nathaniel S. Treister https://orcid.org/0000-0002-5596-7222

Thomas P. Sollecito https://orcid.org/0000-0003-0569-7743

Lauren L. Patton https://orcid.org/0000-0002-8253-4588

Yi Yang https://orcid.org/0000-0002-1471-4026

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2017*. Atlanta, GA: American Cancer Society; 2017.

2. Choi SH, Terrell JE, Fowler KE, et al. Socioeconomic and other demographic disparities predicting survival among head and neck cancer patients. *PLoS One*. 2016;11(3):e0149886.

3. Adrien J, Bertolus C, Gambotti L, Mallet A, Baujat B. Why are head and neck squamous cell carcinoma diagnosed so late? Influence of health care disparities and socio-economic factors. *Oral Oncol*. 2014;50(2):90-97.

4. American Joint Committee on Cancer. In: Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. Chicago, IL: American Joint Committee on Cancer; 2010 https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC7thEdCancerStagingManual.pdf.

5. Farquhar DR, Tanner AM, Masood MM, et al. Oral tongue carcinoma among young patients: an analysis of risk factors and survival. *Oral Oncol*. 2018;84:7-11.

6. Simpson MC, Challapalli SD, Cass LM, et al. Impact of gender on the association between marital status and head and neck cancer outcomes. *Oral Oncol*. 2019;89:48-55.

7. Gourin CG, Podolsky RH. Racial disparities in patients with head and neck squamous cell carcinoma. *Laryngoscope*. 2006;116(7):1093-1106.

8. Lebo NL, Khalil D, Balram A, et al. Influence of socioeconomic status on stage at presentation of laryngeal cancer in the United States. *Otolaryngol Head Neck Surg*. 2019;161(5):800-806.

9. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83(4):489-501.

10. Lalla RV, Long-Simpson L, Hodges JS, et al. Clinical registry of dental outcomes in head and neck cancer patients (OraRad): rationale, methods, and recruitment considerations. *BMC Oral Health*. 2017;17(1):59.

11. National Cancer Institute. Cancer Stat Facts: Oral Cavity and Pharynx Cancer. https://seer.cancer.gov/statfacts/html/oralcav.html

12. Hashim D, Sartori S, Brennan P, et al. The role of oral hygiene in head and neck cancer: results from international head and neck cancer epidemiology (INHANCE) consortium. *Ann Oncol*. 2016;27(8):1619-1625.

13. Chang JS, Lo HI, Wong TY, et al. Investigating the association between oral hygiene and head and neck cancer. *Oral Oncol*. 2013;49(10):1010-1017.

14. Velly AM, Franco EL, Schlecht N, et al. Relationship between dental factors and risk of upper aerodigestive tract cancer. *Oral Oncol*. 1998;34(4):284-291.

15. Rosenquist K, Wennerberg J, Schildt EB, Bladström A, Göran Hansson B, Andersson G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol*. 2005;125(12):1327-1336.

16. Smith EM, Ritchie JM, Summersgill KF, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer*. 2004;108(5):766-772.

17. Hong AM, Martin A, Chatfield M, et al. Human papillomavirus, smoking status and outcomes in tonsillar squamous cell carcinoma. *Int J Cancer*. 2013;132(12):2748-2754.

18. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst*. 2008;100(6):407-420.

19. O'Sullivan B, Huang SH, Perez-Ordonez B, et al. Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation. *Radiother Oncol*. 2012;103(1):49-56.