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What is This?
Poor Survival for American Indians with Head and Neck Squamous Cell Carcinoma

Sunshine M. Dwojak, MD, MPH1, Dianne M. Finkelstein, PhD2, Kevin S. Emerick, MD1, John H. Lee, MD3, Daniel G. Petereit, MD4, and Daniel G. Deschler, MD1

Abstract

Objective. To examine patient characteristics, treatment modalities, and human papillomavirus (HPV) prevalence to identify potential mediators of disparities that may lead to differences in outcomes for American Indians with head and neck squamous cell carcinoma (HNSCC).

Study Design. Historical cohort study.

Setting. Community cancer centers.

Patients and Methods. We reviewed all patients older than 18 years with a new diagnosis of HNSCC in South Dakota from 1999 to 2009. We assessed tissue samples from cases of oropharyngeal cancer for the presence of HPV DNA.

Results. In total, 474 white patients were compared with 32 American Indians. American Indians experienced significantly worse survival compared with whites (hazard ratio [HR], 0.59; P = .05), even after controlling for other factors such as age, sex, distance, Charlson comorbidity index, alcohol abuse, smoking, insurance, and disease stage. American Indians had a greater risk of alcohol abuse (68% vs 42%; P = .008), current smoking (67% vs 49%; P = .03), living more than 1 hour from a cancer center (81% vs 30%; P < .001), lacking private insurance (24% vs 68%; P < .001), and late-stage disease presentation (stages III and IV) (74% vs 55%; P = .04). There were no detected differences in age, sex, medical comorbidities, tumor site, tumor grade, HPV status, time to treatment, or type of treatment received.

Conclusion. American Indians in South Dakota with HNSCC have poorer survival compared with white patients. Once presented to a cancer center, American Indians received nearly identical treatment to white patients. Disparities in outcomes arise primarily due to sociodemographic factors and later stage at presentation.

Keywords

American Indians, head and neck cancer, disparities, human papillomavirus

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Racial and ethnic minorities with cancer have worse survival in the United States.1 Research into these disparities has focused primarily on African American and Hispanic minorities, with little data on the American Indian population. Yet American Indians have similar poor survival rates for all cancers.1 In fact, American Indians in some regions of the United States, such as the Northern Plains (North and South Dakota, Nebraska, and Iowa), have the highest cancer mortality rates in the nation.2

Research into the causes of this disparity is sparse, especially for head and neck squamous cell carcinoma (HNSCC). Data suggest that American Indians with HNSCC present with more advanced disease, receive different treatment, and have poorer survival.3,4 However, the American Indian population is diverse, and these studies did not include the many tribes in the Northern Plains. Overall, studies describing survival outcomes for American Indians with cancer and potential mediators of disparities are lacking.

Many factors may contribute to poorer cancer outcomes for American Indians. Smoking and alcohol use are 2 of the main risk factors for HNSCC and are very prevalent in this population.5,6 In addition, American Indians have high levels of poverty, less access to primary and specialty care, geographic isolation, and high rates of chronic diseases. This lack of resources reduces access and increases barriers

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This work was presented in poster format at the American Head and Neck Society Meeting; April 11, 2013; Orlando, Florida.

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Materials and Methods

Setting and Population
We used tumor registries from Rapid City Regional Hospital and Sanford Cancer Research Center to identify patients older than age 18 years diagnosed with HNSCC from January 1, 1999, to December 31, 2009. We included all patients reported as white or American Indian with a new diagnosis of HNSCC. Sites included in the analysis were nasopharyngeal, oropharyngeal, oral cavity, hypopharyngeal/laryngeal, and cervical metastasis with unknown primary. We then reviewed patients’ medical records at the 2 institutions to confirm and collect additional patient information. Approval for this study was obtained from the institutional review boards at Massachusetts Eye and Ear Infirmary, Rapid City Regional Hospital, and Sanford Cancer Research Center.

Patient Characteristics
We collected patient demographics, including race (self-reported), age at time of diagnosis, sex, history of tobacco and alcohol use, medical comorbidities, type of health insurance (public vs private), driving distance to a treatment facility, clinical presentation (tumor stage, tumor grade), and treatment patterns (surgery, radiation, chemotherapy, treatment start date.) When available, pathologic staging was reported according to American Joint Committee on Cancer (AJCC) historical guidelines; otherwise, clinical staging was reported. Distance to the nearest treatment center was calculated as the driving distance between the patient’s home address at the time of diagnosis and the address of the Rapid City Regional Cancer Care Institute or Sanford Medical Center by maps.google.com. We calculated the Charlson comorbidity index at the time of cancer diagnosis according to established methods. Vital status and date of death were confirmed by cross-reference with the Social Security Death Index.

HPV Typing of Oropharyngeal Samples

DNA extraction from paraffin. Three 15- to 20-μm sections were extracted in an 800-μL volume of CitriSolv (Fisher Scientific, Pittsburgh, Pennsylvania) for 5 minutes. Microcentrifuge tubes were spun for 5 minutes at 5000 rpm in a Sorvall Legend Micro 17 Microcentrifuge (Fisher Scientific) and CitriSolv removed. A second extraction was repeated with 400 μL of CitriSolv. Samples were further processed by adding 200 μL 70% ethanol, spun and dripped in a 50°C heating block. A Qiagen DNA Blood & Tissue Kit (Qiagen, Valencia, California) was then used to extract DNA as per protocol. Briefly, 180 μL ATL buffer and 20 μL protease K were added and incubated at 56°C with mixing; after this, 200 μL AL buffer and 200 μL 96% to 100% ethanol were added and mixed and placed on DNease mini spin columns in a 2-mL collection tube and centrifuged at 8000 rpm for 1 minute. Flow-through was discarded. Columns were rinsed with 500 μL AW1 buffer and then with 500 μL AW2 buffer. Samples were eluted from the column in 200 μL of deionized water.

Polymerase Chain Reaction

Standard polymerase chain reaction (PCR) was performed to check for the expression of HPV16 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in each sample. Then, 50 ng DNA was added to a master mix containing 200 μM dNTP mix (Promega, Madison, Wisconsin), 1× GoTaq Reaction Buffer (Promega), 450 nM E6/E7 forward primer 5′-CAAAACCGTTGTGGATTGTTAATTAGGA-3′ and 450 nM E6/E7 reverse primer 5′-GCTTTTTGTCCAGATGTC-3′, and 13U GoTaq DNA Polymerase (Promega) in a 25-μL volume. A separate PCR reaction was run using identical master mix components substituting primers GAPDH forward 5′-GG-GAAAGGTGAAGGTCGGAGTTGAGCA-TGTTTGC-3′, and 13U GoTaq DNA Polymerase (Promega) in a 25-μL volume. A separate PCR reaction was run using identical master mix components substituting primers GAPDH forward 5′-GG-GAAAGGTGAAGGTCGGAGTTGAGCATTTC-3′ and GAPDH reverse 5′-TTGGAAGATGGTATGGGATTTC-3′ at 450 nM. Preincubation was 94°C for 10 minutes. Cycling conditions were 94°C for 40 seconds, 55°C for 40 seconds, and 72°C for 1 minute for a total of 30 cycles using an Eppendorf Mastercycler gradient thermocycler (Fisher Scientific).

Sequencing
The PCR products were sequenced to check for HPV type. Then, 50 ng DNA was added to a master mix containing 200 μM dNTP mix (Promega), 1× GoTaq Reaction Buffer (Promega), 400 nM GP5+ forward primer 5′-TTGTGTACTGTTAGATACACTAC-3′ and 400 nM GP6+ reverse primer 5′-GAAAATAAAGCTGAAATCATAAT-3′, and 13U GoTaq DNA Polymerase (Promega) in a 25-μL volume. Then PCR was performed at 94°C for 10 minutes, 94°C for 30 seconds, 45°C for 60 seconds, 72°C for 1 minute, and 72°C for 10 minutes for a total of 30 cycles
using an Eppendorff Mastercycler gradient thermocycler (Fisher Scientific). The PCR products were gel purified using a Thermo Scientific GeneJET Gel Extraction Kit (Fisher Scientific) and sent to Eurofins MWG Operon (Huntsville, Alabama) for sequencing using the GP+ primers above. Sequence results were put through a BLAST (http://www.ncbi.nlm.nih.gov) search to check for HPV typing.

Statistical Methods

Patient demographics and clinical characteristics were compared using the Fisher exact test, Wilcoxon rank sum, and Kruskal-Wallis test. Patients were stratified by stage grouping (I-II vs III-IV) and compared with respect to receipt of surgery, radiation, and chemotherapy using a Fisher exact test. Time to treatment was calculated as time from presentation to the cancer center to time of first cancer-directed treatment, either surgery or radiation. Survival time was measured from date of diagnosis to date of death. All patients without a confirmed date of death were censored at the time of last follow-up visit.

To evaluate the simultaneous impact of sociodemographic factors (including race), stage, and treatment on overall survival, a multivariate Cox proportional hazards model was constructed using a stepwise backward elimination process. All variables were placed into the model and then removed sequentially until only significant variables remained. A total of 55 (54 whites, 1 American Indian) patients without information on tumor stage or alcohol use were excluded from the multivariate analysis. All hypothesis tests were 2-sided, with statistical significance defined as having a P value less than or equal to .05. All results are based on univariate tests unless otherwise noted.

Results

Study Subjects

Our final cohort consisted of 474 white patients and 32 American Indians. Compared with white patients with HNSCC, American Indian patients were more likely to have a history of alcohol abuse (68% vs 42%; P = .008), to be current smokers (67% vs 49%; P = .03), and to live more than 1 hour from a cancer treatment center (81% vs 30%; P < .001) and less likely to have private insurance (24% vs 68%; P < .001). There were no significant differences in age at presentation (63 vs 64 years; P = .54), sex (78% vs 73% male; P = .68), and Charlson comorbidity index (1 vs 1; P = .54) (Table 1).

Table 1. Baseline Patient Characteristics.a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White</th>
<th>American Indian</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>474 (94)</td>
<td>32 (6)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>348 (73)</td>
<td>25 (78)</td>
<td>.68</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>180 (42)</td>
<td>21 (68)</td>
<td>.008</td>
</tr>
<tr>
<td>Current smoker</td>
<td>230 (49)</td>
<td>22 (67)</td>
<td>.03</td>
</tr>
<tr>
<td>Private insurance</td>
<td>263 (68)</td>
<td>6 (24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Distance from cancer center &gt;60 miles</td>
<td>144 (30)</td>
<td>26 (81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>64 (22-98)</td>
<td>63 (37-82)</td>
<td>.54</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (range)</td>
<td>1 (0-7)</td>
<td>1 (0-6)</td>
<td>.48</td>
</tr>
</tbody>
</table>

aValues are presented as number (%) unless otherwise indicated.

Clinical Presentation and Treatment

There were no differences detected in tumor site distribution between American Indians and whites (P = .64). The most common tumors were in the larynx/hypopharynx (44% vs 39%), followed by oral cavity (28% vs 32%), and oropharynx (19% vs 23%). Both groups had primarily well- to moderately differentiated tumors (69% vs 66%; P = .84). American Indians had significantly more advanced (stage III and IV) disease (74% vs 55%; P = .04). Eighty-four patient samples were available for HPV DNA analysis. There were no differences detected in the percentage of HPV-positive oropharyngeal carcinomas between American Indians and whites (67% vs 59%; P = .40) (Table 2).

Median time to first treatment was not significantly different (22 vs 25 days, P = .35) between American Indian and white patients. For patients with early stage disease, 25% vs 53% (P = .15) received surgery, 75% vs 55% (P = .47) received radiation, and 0% vs 5% (P = .99) received chemotherapy. For patients with advanced stage disease, 52% vs 45% (P = .52) received surgery, 87% vs 88% (P = .99) received radiation, and 52% vs 57% (P = .66) received chemotherapy. There were no significant differences detected in receipt of chemotherapy, radiation, or surgery when stratified by stage (Table 2).

Survival

Unadjusted survival rates between American Indians and whites were 62% vs 72% (P = .34) at 2 years and 39% vs 52% (P = .34) at 5 years. American Indians experienced a significantly higher mortality risk compared with whites, after adjusting for demographic and clinical variables (hazard ratio [HR], 0.59; P = .05) (Table 3). Additional variables that were included in the Cox model were sex (HR, 0.61; P = .001), Charlson comorbidity index greater
than zero (HR, 0.58; \(P < .001\)), stage III to IV disease (HR, 0.46; \(P < .001\)), current smoking (HR, 0.71; \(P = .02\)), history of alcohol abuse (HR, 0.71; \(P = .02\)), driving distance greater than 1 hour (HR, 0.63; \(P = .002\)), and lack of private insurance (HR, 0.62; \(P < .001\)) (Table 3). Tumor site, tumor grade, and receipt of radiation or surgery had no additional effect on the hazard ratio and therefore were left out of the model. Chemotherapy was significantly correlated with late-stage disease and was not included in the final model.

### Table 2. Clinical Presentation and Treatment Patterns.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White, No. (%)</th>
<th>American Indian, No. (%)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown primary</td>
<td>16 (3)</td>
<td>1 (3)</td>
<td>.63</td>
</tr>
<tr>
<td>Larynx/hypopharynx</td>
<td>184 (39)</td>
<td>14 (44)</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>152 (32)</td>
<td>9 (28)</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>111 (23)</td>
<td>6 (19)</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>11 (2)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well/moderately differentiated</td>
<td>275 (66)</td>
<td>20 (69)</td>
<td>.84</td>
</tr>
<tr>
<td>Poor/undifferentiated</td>
<td>140 (34)</td>
<td>9 (31)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>205 (45)</td>
<td>8 (26)</td>
<td>.04</td>
</tr>
<tr>
<td>III-IV</td>
<td>249 (55)</td>
<td>23 (74)</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV+</td>
<td>46 (59)</td>
<td>4 (67)</td>
<td>.40</td>
</tr>
<tr>
<td>HPV−</td>
<td>32 (41)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>Treatment stages I-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>108 (53)</td>
<td>2 (25)</td>
<td>.15</td>
</tr>
<tr>
<td>Radiation</td>
<td>112 (55)</td>
<td>6 (75)</td>
<td>.47</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>10 (5)</td>
<td>0</td>
<td>.99</td>
</tr>
<tr>
<td>Treatment stages III-IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>112 (45)</td>
<td>12 (52)</td>
<td>.52</td>
</tr>
<tr>
<td>Radiation</td>
<td>217 (88)</td>
<td>20 (87)</td>
<td>.99</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>144 (57)</td>
<td>12 (52)</td>
<td>.66</td>
</tr>
</tbody>
</table>

**Abbreviation:** HPV, human papillomavirus.

### Table 3. Hazard Ratios for Overall Survival.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>B Estimate</th>
<th>HR</th>
<th>SE</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian</td>
<td>−0.53</td>
<td>0.59</td>
<td>0.28</td>
<td>.05</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.49</td>
<td>0.61</td>
<td>0.15</td>
<td>.001</td>
</tr>
<tr>
<td>Distance (&gt;60) miles</td>
<td>−0.46</td>
<td>0.63</td>
<td>0.15</td>
<td>.002</td>
</tr>
<tr>
<td>Charlson comorbidity index (&gt;0)</td>
<td>−0.55</td>
<td>0.58</td>
<td>0.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of alcohol abuse</td>
<td>−0.34</td>
<td>0.71</td>
<td>0.15</td>
<td>.02</td>
</tr>
<tr>
<td>Age (&gt;65) y</td>
<td>−0.66</td>
<td>0.52</td>
<td>0.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No private insurance</td>
<td>−0.48</td>
<td>0.62</td>
<td>0.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>−0.34</td>
<td>0.71</td>
<td>0.15</td>
<td>.02</td>
</tr>
<tr>
<td>Stage III-IV disease</td>
<td>−0.78</td>
<td>0.46</td>
<td>0.15</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR, hazard ratio; SE, standard error.

### Discussion

We examined a cohort of American Indian and white patients with HNSCC over a 10-year period and evaluated the effects of biologic, sociodemographic, and treatment-related factors on overall survival. We found significant disparities in the overall survival of American Indians compared with whites with HNSCC, even after controlling for demographic and clinical factors. We also identified possible mediators for this disparity. American Indians were
more likely to be current smokers, have a history of alcohol abuse, lack private insurance, and live more than an hour from a treatment facility. They were also more likely to present with advanced stage disease. We did not find significant differences in biologic or treatment-related factors such as medical comorbidities, HPV status, time to treatment, or type of treatment received.

This study is the first to report on decreased survival outcomes for American Indians with HNSCC in the Northern Plains. It builds on our work showing decreased survival for American Indians/Alaska Natives with HNSCC residing in the Southwest and Alaska. In our previous study, differential survival outcomes were related to late stage at presentation and less surgery for cancer of the oral cavity. In addition to those treatment-related factors, this is the first and only study in the medical literature to highlight additional mechanisms by which these disparities occur. Current smoking is known to decrease the effectiveness of radiation therapy and increases the risk of recurrent and persistent disease. The addition of alcohol abuse synergistically portends poorer prognosis. Greater distance to a cancer center is correlated with later stage disease presentation and missed appointments, likely due to the personal time and cost associated with getting to each appointment. Lack of private insurance is associated with less routine and preventative care, delays in presentation, and a higher rate of death for all cancers. Seeing these mediators at work in this population creates an opportunity to design targeted interventions to improve outcomes.

Furthermore, the disparity in survival between American Indians and whites arose after controlling for sociodemographic and clinical variables. Additional causal factors may include a higher degree of smoking and alcohol use, contributing to poorer functional status prior to treatment. American Indians in this region have worse radiation toxicities, which may result in more treatment interruptions. In addition, 53% of the American Indians in this study identified the Indian Health Service (IHS) as their source of primary care. The IHS is a direct service provider financed by the US government. On the whole, it suffers from chronic underfunding, staffing shortfalls, high turnover, and problems accessing specialty care. This environment contributes to delays in presentation to tertiary care centers. Our results show that American Indians with HNSCC are an especially at-risk population with limited resources and significant barriers to care that all contribute to poorer outcomes.

Contrary to prior research in this field, we did not detect significant differences in type of treatment received. Our previous work showed that American Indians received less cancer-directed surgery for oral cavity cancer. In this current study, it appears that fewer American Indians with early-stage cancers received surgery; however, the difference did not meet statistical significance. Given the relatively few American Indians in our study with early-stage cancer, this difference is difficult to interpret and warrants further study. Several authors have published on American Indians’ mistrust of the medical system, which may lead to avoidance and as a result different treatment choices. Our study did not reveal any variations in treatment patterns or treatment delay that would suggest different patient choices or provider bias. This may be a result of programs over the past decade aimed at reducing cancer disparities for American Indians. These results suggest that future efforts to improve access to cancer care would result in equitable treatment for American Indians with HNSCC.

In examining potential biologic causes of cancer disparity, we did not detect significant differences in the rate of HPV-associated oropharyngeal carcinoma. Studies of American Indian women in the Northern Plains show increased risk factors for HPV infection, such as low age at first intercourse and multiple sexual partners. They also have high rates of cervical HPV infection. Therefore, American Indians in the Northern Plains are at risk for HPV-related oropharyngeal infection and resultant carcinoma. While our findings should be considered in light of our small numbers, it is possible that differential rates of HPV infection may not play a role in outcome disparities between American Indians and whites as they do for African Americans.

There are several limitations to our work. First, the population of American Indians is small, limiting our power to detect potentially important differences in outcomes such as survival. However, our cohort is representative of the state population distribution. Second, the retrospective nature of this study prevented us from collecting known mediators of disparity such as income and education level. We were unable to measure time from presentation at a primary care office to referral and treatment interruptions. Third, we were only able to provide data on 84 patients with oropharyngeal cancer for the HPV analysis due to insufficient sample or DNA degradation from some tumor blocks. Larger studies are needed to thoroughly assess the role that HPV infection plays in differential outcomes. Fourth, we encountered 55 subjects with missing data (on alcohol or tumor stage) who had to be removed from the multivariate analysis, raising the possibility for bias. Finally, this study is geographically restricted to the American Indian population of South Dakota and the surrounding region. The inherent diversity of the American Indian/Alaska Native population will need to be considered when applying these results to disparate American Indian populations.

Future work should seek to clarify how and when American Indians present to their primary care providers, the role of treatment interruptions, and access to surgical care, as well as address the mediators of disparities that we identified. Studies have shown that smoking and alcohol cessation programs can be effective when the message is culturally tailored and adequate resources are provided. Partnerships with tribal communities to create culturally appropriate programs should be implemented and studied. Comprehensive programs aimed at improving cancer education, cancer screening, and cancer treatment through patient navigation have been successful in this community. Funding to continue and expand these programs is critical.
Finally, targeted screening efforts and increased funding within rural and IHS clinics can help improve early detection and timely referral for patients with head and neck cancer.\textsuperscript{11,32}

**Conclusions**

This study is the first to establish possible root causes of disparities in outcomes for American Indians with HNSCC. It demonstrates that higher rates of preventable risk factors make American Indians particularly vulnerable to HNSCC. American Indians with HNSCC also face significant barriers to receiving cancer care such as poorer insurance and greater geographic distance. However, once they present to a cancer center, they receive equal treatment. Interventions to reduce this disparity need to target prevention, timely referral, and access to the cancer care system.

**Author Contributions**

Sunshine M. Dwojak, designed study, collected data, analyzed data, wrote manuscript; Dianne M. Finkelstein, analyzed data, drafted and revised manuscript; Kevin S. Emerick, designed study, interpreted data, revised manuscript; John H. Lee, designed study, acquired data, drafted and revised manuscript; Daniel G. Petereit, designed study, acquired data, drafted and revised manuscript; Daniel G. Deschler, designed study, interpreted data, revised manuscript.

**Disclosures**

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