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Determinants of Head and Neck Cancer Survival in Nevada for 1995-2008

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DETERMINANTS OF HEAD AND NECK CANCER SURVIVAL IN NEVADA FOR 1995-2008

By

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ABSTRACT

Determinants of Head and Neck Cancer Survival in Nevada for 1995-2008

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Head and neck cancer (HNC), also known as oral cavity and pharyngeal cancer, comprises a group of cancers that arise in the head or neck region, such as the nasal cavity, sinuses, lips, mouth, salivary glands, and pharynx. Use of tobacco, alcohol, or a combination of the two, are major risk factors for head and neck cancer. Approximately 75% of oral cancers are attributable to smoking and/or alcohol consumption. More recently, the human papilloma virus (HPV) has also been associated with the development of head and neck cancer.

The objective of the present study is to investigate head and neck cancer survival in Nevada and its potential determinants utilizing Nevada Central Cancer Registry data between 1995 and 2008. The life table method was used to calculate age-adjusted 5-year survival rates. The Kaplan-Meier method and Cox regression were adopted to identify significant determinants of head and neck cancer survival in Nevada.

A total of 2,522 new cases of head and neck cancer in Nevada were analyzed. Age, race/ethnicity, civil status, insurance status, site, and stage of diagnosis are all significant determinants for head and neck cancer survival in Nevada. The Surveillance,

Epidemiology, and End Results (SEER) Program reported a significant survival disparity between whites and blacks in 2013 for HNC. A significant disparity in survival, due to race, was observed in Nevada. Blacks tend to have the worst survival outcome after adjusting for select covariates (HR=1.35, 95% CI: 1.04-1.75), even though black males in Nevada were found to have a better 5-year overall age-adjusted survival rate (38.2%) than the national average (25.7%). The findings from this study also suggested a geographic disparity in survival between Northern (HR=0.89, 95% CI: 0.77-1.02) and Southern Nevada, possibly due to limited quality healthcare resources, different lifestyle factors, or inadequate access to care, in the south. The present study shows that insured individuals with private insurance or Medicare have significantly better chances at survival, after diagnosis of head and neck cancer, than uninsured individuals (HR=1.45, 95% CI=1.17-1.80), with a difference as much as half. Specific public health strategies, such as increasing oral screenings and persuading public officials to include dental care coverage as part of health insurance, are necessary to improve head and neck cancer survival and to diminish survival disparities in Nevada.

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CHAPTER 1

INTRODUCTION

Head and neck cancer (HNC), also known as oral pharyngeal cancer, includes cancers of the lip, oral cavity, oropharynx, hypopharynx, tonsil, salivary glands, nasopharynx, nose, paranasal sinus, and middle ear (Piccirillo, Costas, & Reichman, 2007). They are usually grouped together by epidemiologists based on their anatomical sites. The International Classification of Diseases (ICD, 10th revision) classifies head and neck cancer into malignant neoplasms of the lip, oral cavity (tongue, major salivary glands, gum, floor of the mouth, other parts of the mouth), and pharynx (oropharynx, nasopharynx, and hypopharynx).

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program is the only comprehensive population-based cancer registry that includes stage at diagnosis and patient survival data (SEER, 2014). It covers approximately 28% of the United States. SEER 17 areas are composed of SEER 13 plus Greater California, Kentucky, Louisiana, and New Jersey (SEER, 2014). The SEER registry is generally considered a good representation of the entire U.S. population (Reid et al., 2001).

The most frequent sites for head and neck cancer are tongue (21%), gum and other mouth sites (15%), tonsil (11%), and salivary glands (10%) [Piccirillo et al., 2007]. Almost all head and neck cancers begin as squamous cells that cover the moist mucosal surfaces of the oral cavity (National Cancer Institute [NCI], 2008). Globally, over 90% of head and neck cancers are squamous cell carcinomas (Johnson et al., 2011). However, malignant neoplasms of the salivary glands have mixed cell type origins. They are more likely to be

adenocarcinomas, which start in gland cells, rather than squamous cell carcinomas. As a result, salivary glands are often not included in head and neck cancer studies (Pulte, & Brenner, 2010; Shibosky, Schmidt, & Jordan, 2007). In addition, malignant neoplasms of the lip are not usually included either, due to their separate risk factors. The major risk factor for lip cancer is sun exposure, which is different from the epidemiologic risk factors associated with head and neck cancer (Piccirillo et al., 2007). Therefore, malignant neoplasms of the salivary glands and lip were excluded from the present study.

Background and Significance

Epidemiology

Head and neck cancer ranks as the sixth most common cancer in the world, probably due to heavy tobacco and alcohol consumption in the developing countries (Saman, 2012). Global figures show an estimated 482,300 new cases and 406,800 deaths in 2008; men are three times more likely to be diagnosed with head and neck cancer than women (Jemal et al., 2011). However, these figures include both adenocarcinomas (cancer originating from glands) and squamous cell carcinomas (cancer originating from epithelial cells) [Jemal et al., 2011]. The World Health Organization's International Agency for Research on Cancer show oral cavity cancer mortality rates to be: 66.9% in Asia, 16.6% in Europe, 0.7% in Oceania, 6.9% in Africa, 5.5% in Latin America & Caribbean, and 3.4% in North America (Globocan, 2012).

Head and neck cancer accounts for 2.3% of cancers in the United States (Saman, 2012). SEER incidence rates of the top 15 cancers, for 1992-2007, show that head and neck cancer is the eighth leading cancer for men and fourteenth leading cancer for women in

terms of incidence (Kohler, 2011). According to SEER data, the prevalence of head and neck cancer in the United States was 275,193 in 2012, with 41,380 new cases and 7,890 deaths in 2013 (SEER, 2013; Siegel, Naishadham, & Jemal, 2013). Head and neck cancer has an age-adjusted incidence rate of 10.8 per 100,000 men and women each year with a median diagnosis of 62 years of age (Howlader, 2013). Head and neck cancer is common in people 60 years of age and over; but, incidence has increased for people under 40 years of age, due to changing risk factors (Laronde, Hislop, Elwood, & Rosin, 2008). The lifetime risk of being diagnosed with head and neck cancer is 1 in 93 for men and women (Howlader et al., 2013).

Overall, head and neck cancer incidence in the United States has substantially decreased over the past few decades. The National Cancer Institute (NCI) estimated that three out of four people diagnosed with head and neck cancer have used tobacco, alcohol, or both (NCI, 2008). The declines are largely credited to a decrease in smoking prevalence beginning in the 1970s as tobacco use decreased in the United States as a result of public health efforts to reduce consumption of smoking since the Surgeon General's Report in 1964 (Kim, King, & Agulnik, 2010).

According to SEER data, between 1975 and 2007, head and neck cancer is on the top fifteen leading causes of cancer deaths in men, while absent from the same list for women (Kohler et al., 2011). The mortality rate for head and neck cancer has been decreasing for the last 30 years. The death rates were decreasing by 1.3% for men and 2.2% for women on an annual basis from 2005 to 2008 (American Cancer Society, 2013). However, the overall 5-year survival rate is less than 50% (Mehanna, West, Nutting, & Paleri, 2010).

Major Risk Factors

Many risk factors for causing head and neck cancer have been identified. The most common ones include tobacco, betel quid, alcohol, Human papillomavirus infection, poor diet, poor oral hygiene and dentition.

1. Substance use

The single most important risk factor for head and neck cancer is tobacco use. Smokers have a 5-25 fold risk of developing head and neck cancer compared to nonsmokers based on frequency, duration, and extent of smoking (Mehanna et al., 2010). In South and Southeast Asia, tobacco is popularly consumed in the form of betel quid, which is primarily composed of piper betel leaves rolled with areca nuts, tobacco, and other additives (Johnson et al., 2011). Tobacco use has been labelled as the world's most avoidable cause of cancer by the World Health Organization (Petersen, 2008). Heavy alcohol drinking is an independent risk factor for causing HNC even though there is no current evidence to suggest differences in risk due to different types of alcohol consumption (Kim et al., 2010). It is reported that never smokers who drink three or more alcoholic beverages per day had almost twice the risk for HNC as never drinkers (Hashibe et al., 2007). Alcohol and tobacco have a multiplicative effect. A dose-response relationship exists in both alcohol and tobacco consumption where the risk for head and neck cancer increased along with consumption (Mehanna et al., 2010). A study found that heavy smokers and heavy drinkers are 20.7 and 4.9 times more likely to have HNC than those who don't smoke and drink, but a combination of the two, elevates the risk to 48 times (Saman, 2012). Head and neck cancer due to alcohol and smoking exposure have a population attributable risk of 80% for men and 61% for women (Petersen, 2008).

2. Human papillomavirus (HPV)

Historically, tobacco and alcohol are the most important risk factors for head and neck cancers (Saman, 2012). However, oral HPV infection is now linked with an increasing proportion of head and neck cancer. Studies have shown that HPV-related head and neck cancer is more frequent in patients who do not smoke or drink (Argiris, Karamouzis, Raben, & Ferris, 2008). Although there are over 100 subtypes of HPV, only two subtypes, 16 and 18, far exceed the detection rate compared to other subtypes (Mehanna et al., 2010). HPV 16 has been singled out as the most common subtype found in head and neck cancer (Mehanna et al., 2010). HPV strain subtype 16 has been identified as the main causal factor in HNC with HPV16 DNA detected in up to 72% of head and neck cancers (Argiris et al., 2008). Mehanna (2010) reported that up to 90% of head and neck cancer carcinomas have identified HPV-16 DNA in them. While a recent multi-state study estimated that 70% of head and neck cancer is caused by HPV infection (Chaturvedi et al., 2011).

HPV has been implicated as a significant risk factor for head and neck cancer. HPV-related head and neck cancer occurs most commonly in the tonsils and oropharynx and least commonly in the oral cavity. HPV-positive head and neck cancer has increased from 16.3% in 1984 to 72.7% in 2004, partially due to increased oral sex and oral HPV exposure (Chaturvedi et al., 2011). A SEER analysis from 1973-2001 showed an increase of incidence in oral tongue, base of tongue, and tonsil cancers by 2.1%, 1.7%, and 3.9% in people aged 20-44 (Mehanna et al., 2010). HPV-negative head and neck cancer has declined, paralleling the decline in smoking in the United States (Chaturvedi et al., 2011).

Although smoking has been on the decline in the United States, the gains realized have been somewhat countered by a rise in head and neck cancer due to the HPV epidemic.

3. Others

Eating diets rich in vegetables, fruits, and vitamin C have been shown to have a protective effect against head and neck cancer (Laronde et al., 2008). High intake of meat and processed meat products are associated with higher risk for head and neck cancer. Poor oral hygiene and poor dentition are risk factors as well. It is believed that improper dentures or tooth repair causes tissue irritation that facilitates exposure to carcinogens. Oral microbes in alcohol drinkers convert alcohol into acetaldehyde, a carcinogen that increases risk for head and neck cancer. Lower social economic status due to occupation, income, or education is also a significant risk factor for head and neck cancer (Warnakulasuriya, 2008).

Diagnosis

Symptoms of head and neck cancer include a sore in the lip or mouth that doesn't heal, difficulty when swallowing, bleeding in the mouth, loose teeth, numbness in the lower lip and chin, to having white or red patches in the lips and mouth (NCI, 2008). The red patches are called erythroplakia while the white patches are called leukoplakia. They are precancerous lesions and are clinical terms with no association to histopathology (Mehanna et al., 2010). A biopsy of a tissue sample remains the gold standard for confirmation of malignant cells (NCI, 2008). A biopsy and histopathological exam are always necessary to establish a diagnosis of oral cancer (Bagan, Sarrion, & Jimenez, 2010).

Treatment and Prevention

Most head and neck cancers are diagnosed at late stage because symptoms are hard to notice. Stage at diagnosis also determines what treatment options are available for treating the patient (Shiboski et al., 2007).This contributes to a poor overall survival rate of 40-50% (Mehanna et al., 2010). It is reported that survival rate can be improved by 80-90% if head and neck cancer is detected at the early stage (Bagan et al., 2010). Treatment options for head and neck cancer are surgery, radiotherapy, chemotherapy, targeted therapy, or a combination of these depending on the stage at diagnosis (NCI, 2008). Radiotherapy and surgery are the most common treatment choices (Mehanna et al., 2010). Early stage cancers are treated with surgery or radiotherapy while more advanced stages are treated with surgery and chemoradiotherapy (Mehanna et al., 2010). It is estimated that one third of HNC patients have stage I (localized) or stage II (regional) cancer (Argiris et al., 2008). Surgery and radiation are used to cure these patients with a success rate of up to 90% for stage I patients and up to 70% for stage II presenting individuals (Argiris et al., 2008). Efficacy between surgery and radiation treatment is roughly equal. However, surgery is preferred over radiation treatment to avoid its more toxic cellular effects. Medical technology with robotic surgery and carbon dioxide lasers under microscope guidance has increased organ preservation during surgery. Two drugs used in chemotherapy, Cisplatin and Cetuximab, when used in combination with radiation were shown to increase overall survival and tumor control for later stages (Mehanna et al., 2010). However, more radical treatments decrease the quality of life for patients.

Literature reports that HPV-positive tumors are more responsive to radiation, chemotherapy, or both, than HPV-negative tumors (Argiris et al., 2008). The efficacy of HPV vaccination against cervical cancer shows potential prevention for head and neck cancer as well (Argiris et al., 2008). The FDA approved a vaccine against HPV subtypes 6, 11, 16, and 18 for both males and females between 9-26 years of age. It is believed that the vaccination will benefit head and neck cancer even though the vaccine was initially made to guard against genital warts and cervical cancer (Mehanna et al., 2010).

Determinants of Cancer Survival

Risk factors that are significantly associated with the development of head and neck cancer may not be significant determinants of survival for head and neck cancer, because survival determinants and risk factors for head and neck cancer are disparate entities for pathogenesis of head and neck cancer. Also information on most risk factors for head and neck cancer are not collected by the majority of cancer registries. Therefore, the majority of cancer research focuses on a variety of available variables, such as age, gender, race/ethnicity, stage at diagnosis, treatment, insurance status, civil status, and geographic location. However, there are no set prognostic variables that researchers can agree on as being the definitive variables to independently predict survival.

1. Stage of diagnosis

Stage at diagnosis is the most important determinant of survival for most cancers, including head and neck cancer. Head and neck cancer has a successful cure rate of as high as 90% if it is diagnosed in the early stages (Bagan et al., 2010). The sooner an

individual is diagnosed and treated for head and neck cancer, the better their chances of attaining a high cure rate and an increased survival outcome.

A strong correlation between stage of diagnosis and relative survival has been well established (Piccirillo, Costas, & Reichman, 2007). SEER showed that 31% of cases were diagnosed at localized stage with a 5-year survival rate of 82.7% while 47% of cases were diagnosed at regional stage with a 5-year survival rate of 59.2% (Howlader et al., 2013).

2. Race

Literature has shown that there are significant disparities in survival between blacks than whites in the United States (Saman, 2012). The 5-year relative survival rates for white men and women were 63.6% and 64.6% while those for black men and women were 38.6% and 53.0%, respectively (Howlader et al., 2013). There are various reasons proposed for these differences between racial groups. They range from lower educational attainment, social economic status, occupational status, access to care, and likelihood of being insured, to more advanced stages at time of diagnosis (Ragin et al., 2010). Minorities who are associated with lower socioeconomic status and less insurance choices are also presented with less preventative and treatment options accessible to them.

3. Others

Health insurance status has been found to impact the stage at diagnosis and survival (Saman, 2012). A study by Kwok (2010) found that Medicaid and uninsured patients were three times more likely to present with advanced stages of head and neck cancer

(stage III and IV) than private insurance or Medicare. Individuals without insurance or had Medicaid were found to have up to 50% lower survival (HR=1.50, 95% CI=1.07-2.11) than individuals with private insurance. Married individuals have also been shown to have better survival outcomes due to better quality of life that leads to a protective effect. Married individuals and individuals living together had better survival and lower mortality rates than divorced individuals, or those not living together (De Graeff et al., 2000). The better survival is attributed to better health habits and social support related to marriage.

Researchers have been looking at various independent variables that could be used as prognostic factors for head and neck cancer survival time. By finding strong and independent indicators for survival time, clinicians and health professionals can lower disparities in the survival time of diseased patients, and improve survival rates of individuals by targeting individuals known to have lower survival outcomes through education, screening, and early diagnosis of patients.

Relevance to Public Health

Head and neck cancer has a relatively low incidence and low mortality rate in the United Sates. However, the gains seen in smoking cessation through the decades and a lowering in head and neck cancer incidence has been offset by increases in HPV-related head and neck cancer. While, there is no definitive exact cause for head and neck cancer, the major risk factors are preventable. Smoking and alcohol remain the largest risk factors for head and neck cancer with socioeconomic status being a contributing factor.

Public health should strive to mediate these risk factors as much as possible. Early diagnosis, treatment, and prevention of head and neck cancer lead to higher survival rates. Advanced treatment usually requires surgery, radiotherapy and chemotherapy, or a combination of all three which also tends to lower the quality of life for affected patients. The differences between incidence rates for race are minor but the mortality rates between whites and blacks show a significant disparity. From 2002-2006, the mortality rate for black men was 6.5 per 100,000 versus 3.7 per 100,000 for white men with head and neck cancer (Ragin, Langevin, Marzouk, Grandis, & Taioli, 2011).

Other potential disparities such as insurance status have been found to lead to late stage diagnosis and lower survival (Kwok et al., 2010). To provide better head and neck cancer outcomes for all segments of the population, public health should enhance programs that encourage smoking and alcohol cessation in low income areas, promoting HPV vaccination, and practicing safe oral sex in young adults, as well as lobbying for policies that result in healthier outcomes for all, by increasing access to care, screenings, and oral health insurance.

In Nevada, head and neck cancer survival outcomes have never been studied. Traditionally, Nevada has low access to healthcare and poor social service programs, due to the lack of a state income tax as well as low business tax rates, which limit adequate public social investments in Nevada. The Centers for Disease Control & Prevention (CDC; 2014) Health of the United States 2012 report ranks Nevada as the second state with the most uninsured persons in 2008-2011. In addition, Nevada ranks eighteen for having the lowest number of doctors per 10,000 people. This retrospective cohort study will look for differences and disparities in outcome by examining the determinants of

head and neck cancer survival in Nevada utilizing data from the Nevada Central Cancer Registry (NCCR) for years 1995-2008.

Purpose of the Study

To understand the disparities in head and neck cancer survival in Nevada and compare with the national trends, the objectives of the present study are (1) to calculate age-adjusted 5-year survival rates of head and neck cancer in Nevada by race/ethnicity and (2) to identify determinants of head and neck cancer survival in Nevada.

Research Question and Hypotheses

Research Question:

What are the determinants of survival for patients with head and neck cancer in Nevada?

Hypothesis 1: Gender

H_0: There is no association between head and neck cancer survival and gender.

$H_{A:}$ There is an association between head and neck cancer survival and gender.

H_{A1}: Women have better head and neck cancer survival than men.

Hypothesis 2: Race

H_0: There is no association between head and neck cancer survival and race.

$H_{A:}$ There is an association between head and neck cancer survival and race.

H_{A1}: Whites have higher head and neck cancer survival than blacks.

Hypothesis 3: Insurance Status

H_0: There is no association between head and neck cancer survival and insurance status.

$H_{A:}$ There is an association between head and neck cancer survival and insurance status.

H_{A1}: Having insurance will result in higher head and neck cancer survival than people without insurance.

Hypothesis 4: Civil status

H_0: There is no association between head and neck cancer survival and civil status.

$H_{A:}$ There is an association between head and neck cancer survival and civil status.

H_{A1}: Married individuals have higher head and neck cancer survival than single individuals.

Hypothesis 5: Geographic Region

H_0: There is no association between head and neck cancer survival and geographic region.

$H_{A:}$ There is an association between head and neck cancer survival and geographic region.

H_{A1}: Northern Nevada will have higher head and neck cancer survival than Southern Nevada.

CHAPTER 2

METHODOLOGY

Data Collection

Data Sources

Data were obtained from the Nevada Central Cancer Registry (NCCR). NCCR is a population based registry that collects data on all patients diagnosed with cancer in the state of Nevada. NCCR is administered through the Office of Public Health Informatics and Epidemiology of the Department of Health and Human Services Nevada Division of Public and Behavioral Health. NCCR is part of the National Program of Cancer Registries (NPCR) which is administered by the Centers for Disease Control and Prevention (CDC). The data obtained from the NCCR meet the completeness and quality standards set by NPCR and the North American Association for Central Cancer Registries (NAACCR) for 2000-2006 and 2008. Data were obtained from the National Cancer Institute's SEER Program to generate survival tables. SEER is used as the representative national population when comparing to Nevada in this study.

Study Population

The study population is patients diagnosed with head and neck cancer from 1995 to 2008 and registered in the NCCR. The total patient cases in the database were initially 3,091. Among them, 9 cases were excluded in the age range of 0-14 years because head and neck cancer is extremely rare in ages younger than 15 years. One case was excluded due to unknown gender. The subsite categories of lips (n=172) and salivary glands (n=336) were excluded. An additional 51 cases were excluded due to incomplete data on survival

time. After exclusions, the sample size was reduced to 2,522 cases that made up our analytical file.

Study Design and Institutional Review Board (IRB)

The study design is a retrospective cohort study using secondary de-identified cancer registry data. IRB exempt approval was granted for the study of existing data by the Office of Research Integrity at the University of Nevada Las Vegas on July 19, 2013.

Head and Neck Cancer Classification

Head and neck cancer site topography and morphology variables were coded with the SEER site recodes for International Classification of Disease for Oncology, Third Edition, morphology codes C000-C148, and histology codes 8000-9990. The site category variables were classified using the following sub sites: tongue (C019-C029), floor of mouth (C040-C049), gums (C030-C039, C050-C059, C060-C069), nasopharynx (C110-C119), tonsils (C090-C099), oropharynx (C100-C109), hypopharynx (C129, C130—C139), and other oral cavity and pharynx (C140, C142-C148).

Stage of Diagnosis Classification

Both TNM and SEER historic staging are available in the NCCR dataset. Considering the completeness and reliability of the data, SEER historic staging was used in the present study. SEER is a summary staging system used for all types of cancers. SEER staging was classified as localized, regional, distant, or unknown. Localized refers to cancer that is limited to the organ it originated from. Regional refers to cancer that has spread from the primary site to nearby tissues, nodes, or organs. Distant refers to cancer that has

spread from the primary site to distant tissues, nodes, or organs. Unknown refers to cancer that was not assigned a stage due to various reasons.

Demographics

Demographic variables included gender, geographical location, race/ethnicity, insurance status, age at diagnosis, and civil status. Gender was categorized as male or female. Nevada is comprised of 17 counties. Clark County, Washoe County, and Carson City make up the 3 urban areas of the state (Department of Health and Human Services [DHHS], 2013). In this study, geographic location was aggregated into Southern Nevada, Northern Nevada, or rural Nevada. Southern Nevada is comprised of Clark County. Northern Nevada is comprised of Washoe, Douglas, Lyon, Storey counties, and Carson City. The rest of the counties comprise rural Nevada (Pinheiro, Reid, Saccucci, Harris, & Guinan, 2012). Race/ethnicity was categorized into mutually exclusive groups as white, black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown. American Indians/Alaskan Natives were excluded from the survival analysis due to the small number of patient cases found in the dataset. Non-Hispanic whites are referred to as whites in this paper. Insurance status was classified as having private insurance, Medicare, uninsured, Medicaid, or unknown. Private insurance and Medicare patients were recoded into one variable. Age groups were classified as 15-44, 45-54, 55-64, 65-74, or 75 years old and above. Civil status was classified as married, single, divorced/separated, or widowed.

Head and Neck Cancer Survival Time

Vital status was determined from in-state death certificates. Survival time was measured from the date of diagnosis until December 31st, 2008 (the last date for linkage with the in-state death certificates), or date of death whichever came first. Cases not reported as dead on December 31, 2008 were censored as alive on that date. Censoring refers to when a subject is followed from the date of diagnosis but the event (death) is not observed or the subject is lost to follow-up. The overall observed survival rate is used in this study.

Statistical Analysis

Descriptive statistics were calculated, including frequency counts for each of the predictors, and percentages from predictor variables.

Univariate analysis for 5-year survival rate estimates was performed using the life table, also known as actuarial method by race/ethnicity. We standardized for age using international age standards (Corazziari, Quinn, & Capocaccia, 2004). Five-year overall survival proportions were estimated for both males and females combined, males only, in Nevada, 1995-2008. These were then compared to SEER proportions for the same years. Kaplan Meier was used to analyze survival and plot overall survival curves. The log-rank test was used to compare the survival curves for significance.

The Cox proportional hazards model was used for multivariate analysis and to estimate hazard ratios for survival for each of the predictors. Cox is a semi-parametric model. The covariates were adjusted to each other to address confounding that may result due to age, gender, race, insurance status, civil status, stage, site, and region.

Statistical analysis was performed using SPSS version 20. P-values below 0.05 were considered statistically significant.

CHAPTER 3

RESULTS

Patient characteristics

There were a total of 3,091 cases of head and neck cancer in the NCCR from 1995 to 2008. After excluding the lip, salivary glands, unknown gender, and deaths with deficient survival data, the total number of cases used in this study was 2,522. The characteristics of the study population are summarized in Appendix B.

Univariate analysis

Survival Rates for Each Category of the Predictor Variables

The 5-year overall age-adjusted survival rates, for both males and females combined, by race in Nevada are 46.7% for white, 29.7% for black, 47.1% for Hispanic, and 46.4% for Asian and Pacific Islander (Table 1). The 5-year age-adjusted survival rates by race from SEER are 46.6% for white, 29.2% for black, 43.2% for Hispanic, and 51.2% for Asian and Pacific Islander (Table 2).

Table 1. 5-year overall age-adjusted survival rate for males and females combined in Nevada, 1995-2008

Race/ethnicity	Survival Rate (%)	95% CI	
White	46.7	44.4	49.0
Black	29.7	19.4	39.9
Hispanic	47.1	36.7	57.5
Asian/PI	46.4	34.1	58.6

**Age standardized to Corazziari age standards

Table 2. 5-year overall age-adjusted survival rate for males and females combined, SEER, 1995-2008

Race/ethnicity	Survival Rate (%)	95% CI	
White	46.6	46.1	47.2
Black	29.2	27.8	30.6
Hispanic	43.2	41.5	45.0
Asian/PI	51.2	49.5	52.9

The Nevada survival rates when compared to the rates from SEER show similar survival rates for whites and blacks in Nevada. However, the survival rates between Hispanic and Asian suggest some difference compared to SEER's Hispanic and Asian population, although this is not statistically significant. Hispanics in Nevada have better survival than Asians when compared to SEER rates which show Asians have a higher survival rate.

To get more accurate survival rates, we separated the data by gender. The 5-year survival rates were calculated separately for each gender to minimize confounding from one another. The survival estimates for females are too unstable to report due to a small population sample size. After selecting cases for males only, the 5-year survival rates for each race in Nevada are as follows: white 44.3%, black 38.2%, Hispanic 51.0%, and Asian/Pacific Island 51.6% (Table 3). The SEER data revealed: white 45.3%, black 25.7%, Hispanic 40.0%, and Asian/Pacific Island, 48.8% (Table 4).

Table 3. 5-year overall age-adjusted survival rate for males in Nevada, 1995-2008

Race/ethnicity	Survival Rate (%)	95% CI	
White	44.3	41.5	47.1
Black	38.2	25.8	50.6
Hispanic	51.0	38.6	63.3
Asian/PI	51.6	36.4	66.8

**Age standardized to Corazziari age standards

Table 4. 5-year overall age-adjusted survival rate for males, SEER, 1995-2008

Race/ethnicity	Survival Rate (%)	95% CI	
White	45.3	44.7	46.0
Black	25.7	24.1	27.4
Hispanic	40.0	37.8	42.1
Asian/PI	48.8	46.6	51.0

Kaplan-Meier Method

The Kaplan-Meier method was used to estimate survival and produce survival curves. Univariate analysis looks at one independent variable at a time to ascertain whether it affects survival time and whether there is significance in the survival rate of the different groups. Significance between Kaplan-Meier survival curves was tested using the log-rank test. Kaplan-Meier curves show that blacks had significantly worse overall survival than the other race/ethnicity groups (Figure 1). Five year survival was less than 40% for the group. Civil status showed that widowed cases had worse survival followed by divorced/separated, single, and unmarried cases (Appendix C). Univariate analysis suggests whether a variable is a significant independent predictor of survival but it does not take into account other confounding variables that may mask the true value. To investigate confounding variables, multivariate analysis with Cox regression was used.

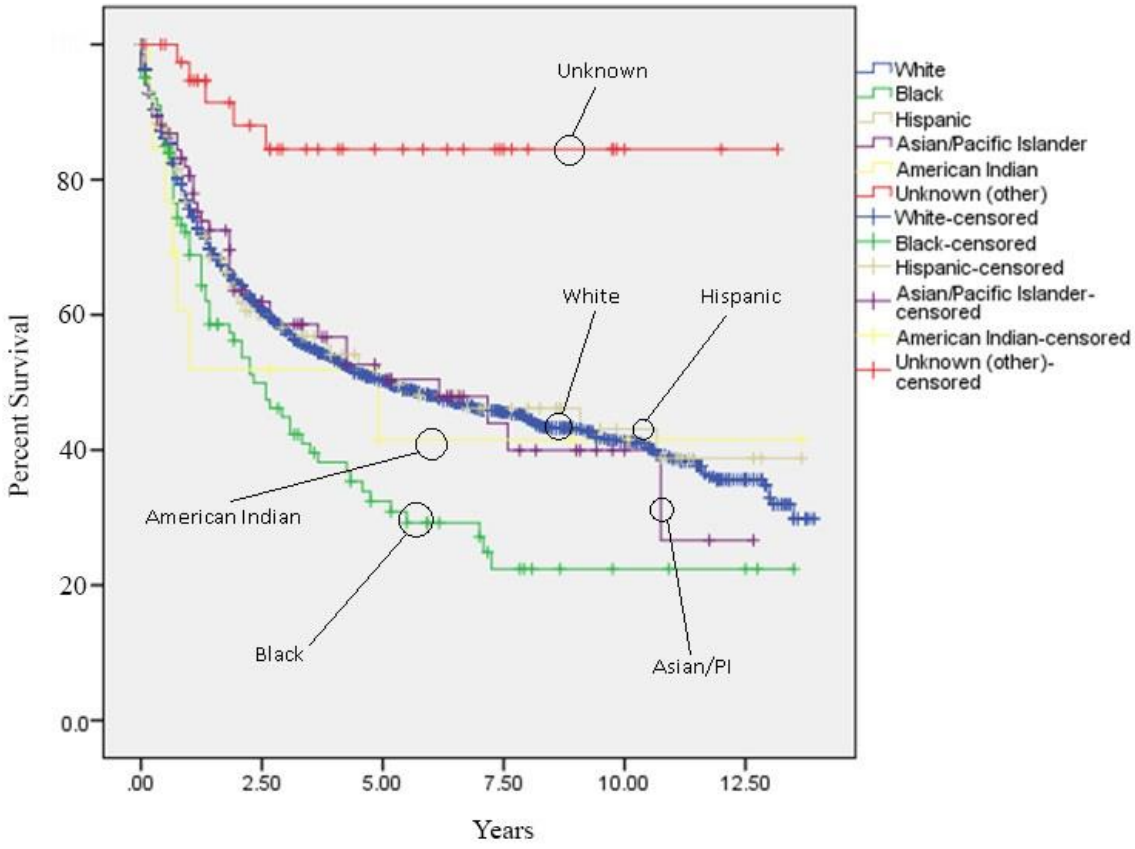


Figure 1. Kaplan-Meier overall survival by race, 1995-2008

Multivariate analysis

Multivariate analysis was performed using Cox regression model. Cox regression was used to examine differences in survival after adjusting for other confounder variables. Disparities in survival with significant results were calculated and adjusted for each co-variable (Appendix D). The reference group is the first category for each variable.

Age

Individuals progressively showed a higher risk of death as age increased. Individuals who were 75 years old and older were 3.8 times more likely to die than those who were

between 15 and 44 years old. Individuals who were between 65 and 74 years old were 2.6 times more likely to die than those who were between 15 and 44 year old. Individuals who were between 55 and 64 years old were 1.7 times more likely to die than those who were between 15 and 44 years old.

Gender

Females had better survival than males (HR: 0.945, 95% CI: 0.83-1.08). However, this was not found to be significant (p=0.40).

Site

Oral cancer of the hypopharynx had the worse prognosis overall, with those individuals being 1.38 times more likely to die than those with tongue cancer (95% CI: 1.13-1.69).

Race/Ethnicity:

Blacks were 1.35 times more likely to die than whites (95% CI: 1.04, 1.75).

Insurance Status:

Uninsured individuals were 1.45 times more likely to die than those with private or Medicare insurance (95% CI: 1.17-1.80).

Stage

Individuals diagnosed at the distant stage were 2.94 times more likely to die, and regional stage were 1.71 times more likely to die than those diagnosed at the localized stage (95% CI: 2.41-3.60; 95% CI: 1.46-2.00).

Civil Status

Married individuals showed better outcomes for head and neck cancer survival. Divorced or separated individuals were associated with the worst prognosis. Individuals who were divorced or separated were 1.47 times more likely to die than married individuals (95% CI: 1.24-1.75).

Geographic Region

Geographic region showed an interesting pattern but it was not found to be significant (p=0.10). Individuals who reside in Northern Nevada are 11% less likely to die than those who reside in Southern Nevada (95% CI: 0.77-1.02).

CHAPTER4

DISCUSSION

Summary of Findings

To our knowledge this is the first study to investigate the determinants of head and neck cancer survival in Nevada. Publications on head and neck cancer survival in the United States are sparse and there is no agreement on the best set of determinants for head and neck cancer survival. The present study builds on previous research by examining a pool of potential determinants suggested by the literature. The multivariate technique was adopted to adjust for multiple confounding effects to determine survival outcomes for patients with head and neck cancer.

1. Age, site, and stage of diagnosis

Age, site, and stage of diagnosis are three classic determinants in cancer survival. As people get older, they are more likely to die as a result of the natural process of aging and being less tolerant to aggressive cancer treatments.

Hypopharyngeal cancer is rare with about 3,400 cases in the United States each year (American Cancer Society, 2014). Hypopharyngeal cancer has one of the highest mortality rates of any head and neck cancer because it does not cause symptoms early and most of them are at an advanced stage when they are diagnosed (Piccirillo et al., 2007). In addition, malignant cells grow in the hypopharynx which is close to the cervical lymph node, increasing the risk of spreading regionally. Our study indicated that hypopharyngeal cancer is the most fatal subtype of head and neck cancer in Nevada.

Stage is the most important predictor of survival for most cancers. The sooner a cancer is treated, the less chance it spreads further away from the point of origin. In Nevada, the differences found in survival due to age and stage of diagnosis mimic the national trends (Pulte et al., 2010; Goldenberg, Brooksby, & Hollenbeak, 2009; and Goodwin et al., 2008).

2. Gender

In general, females have better survival than males in most cancers. Surprisingly, the multivariate model suggested that gender is not a significant determinant for head and neck cancer survival in Nevada. The impact of gender on head and neck survival is not conclusive. Saba (2011) found no discernable difference in relative survival between males and females, without further analysis separated by race.

3. Race

Both univariate and multivariate analysis showed that there is a racial disparity in survival of head and neck cancer in Nevada. Similar to the national trends, blacks had significantly worse survival than whites based on race alone. Less than 30% of blacks survive five years after diagnosis, which is significantly lower than whites. The racial disparity in head and neck cancer survival has been well established in previous research (Morse et al., 2006; Goodwin et al., 2008; Moore et al., 2001). However, the degree of disparity varies slightly with the sample populations and study durations. The results from Goodwin (2008) are similar to ours, in that blacks have a lower 5-year relative survival rate than whites using SEER data from 1996 to 2002. Another study found a 5-year survival rate of 51.4% for whites and 29.3% for blacks using SEER data from 1973

to 2008, which suggested that the survival rate for whites become worse over time while survival rate for blacks remain stable (Saba et al., 2011).

Despite similar survival rates compared with the national average, black males in Nevada seem to survive much longer than blacks reported in SEER. Black males in Nevada have a 5-year survival rate of 38.2% versus a national average of 25.7%. The estimates for black females were suppressed due to a small sample size, but it is logical to picture a much lower survival rate for black females in Nevada given an overall 5-year survival rate of 29.7% for blacks. This finding is unique in Nevada and opposite to the literature. Morse et al., (2006) found that black males had the lowest 5-year survival rate at 34%, with black females at 52% using SEER data from 1995 to 2001. Shiboski (2007) also found that black females had a better 5-year survival rate of 39 percent.

It has been reported that cancer rates among blacks in Nevada are significantly lower than the national average by up to 9% (Pinheiro et al., 2012). The better survival in black males may be attributed to the local employment opportunities, lifestyle, and culture endemic in Nevada, especially in Southern Nevada. The Minority Health in Nevada 2010 report showed that poverty percentages for blacks, and whites were lower than the national average. The difference in per capita income by race/ethnicity between whites and blacks is lower in Nevada compared to other states. Additionally, 9% of blacks were uninsured in Nevada compared to 15% in the U.S.

The Nevada Cancer Report in 2012 shows that minorities affected by cancer are more likely to live in areas of low economic income. Hispanics are more likely to be uninsured

whereas blacks are more likely to be Medicaid beneficiaries (Pinheiro et al., 2012). Therefore, the racial disparity in the form of 5-year survival rates might be blurred by other confounding variables. However, racial disparity between blacks and whites persists after adjusting for select confounding variables in this study. Blacks were 1.35 times more likely to die than whites. A similar conclusion was also reached in a previous study (Saba et al., 2011). This highlights the urgent public health interventions needed to improve head and neck survival in black Nevadans.

4. Civil status

Civil status has been studied in cancer research which indicates that marriage, in general, is a protective factor in cancer incidence and associated with better survival outcomes, especially for married men (Wang, Wilson, Stewart, & Hollenbeak, 2011). The protective effect of marriage on cancer survival has been observed in most cancer studies, such as bladder, breast, cervical, prostate, and lung cancer (Wang et al., 2011). Aizer (2013) studied ten cancers including head and neck cancer, using SEER data from 2004 to 2008, and found that married patients were less likely to die after adjustment for covariates of demographics, stage, and treatment, (HR=0.80, 95% CI=0.79, 0.81). Widowed individuals also had lower survival versus married individuals. Head and neck cancer patients who were married had the greatest relative reduction in cancer death (Aizer et al., 2013). There does not appear to be any studies that specifically address the relationship between civil status and survival in head and neck cancer in spite of the fact that civil status is conventionally included as an important covariate (Du, & Liu, 2010). The present study found that married individuals had significantly better survival than their counterparts. Overall, the worst survival was observed in divorced individuals. This result

differs from Aizer (2013) and Wang (2011) where single and widowed individuals have the worse prognosis.

Traditionally, married individuals tend to have better prognosis when they enter cancer treatment after diagnosis compared to single individuals (Jatoi, 2007). We are unable to provide conclusive evidence on why marriage has a protective effect against cancer due the limitation of the study design, although this study clearly demonstrates that civil status is a significant determinant for head and neck cancer survival. Social behavioral research has demonstrated that social factors that accompany marriage can positively modify individuals' behavior, such as healthy diet and lifestyle, regular screening, and compliance with treatment regimens, leading to improved cancer survival (Aizer et al., 2013; and Wang et al., 2011).

5. Geographic region

Geographical disparities on cancer survival have been observed among regions of Nevada. Northern Nevada has a similar survival rate to the national average on all cancers combined. On the other hand, Southern Nevada, where 70% of all cancers in the state are diagnosed, has systematically lower survival rates (Pinheiro et al., 2012). This study was not able to demonstrate a significant geographic disparity on head and neck cancer survival between Southern and Northern Nevada, possibly due to a small sample size. However, our results suggested that individuals who reside in Northern Nevada had better head and neck survival than those who reside in Southern Nevada.

Southern Nevada, which is comprised of only Clark County, houses 73% of the state population. Of this population, 40% are minorities with higher uninsured rates and lower

educational attainment. Minority populations who have lower education levels tend to have higher morbidity and mortality. The geographic disparity in Nevada may be partially due to the high minority population in Southern Nevada. However, the estimates in the present study have adjusted for race/ethnicity and insurance status. The Nevada Cancer Report 2012 stated that disparities in survival or prognosis for cancer in Nevada are more directly related to access to quality healthcare. With the School of Medicine, based in Reno, it is possible that Northern Nevada possesses more healthcare facilities and resources than Southern Nevada. Unequal quality healthcare access may be the main source leading to the geographic disparity in Nevada. Further research is needed to investigate the unequal availability of quality healthcare facilities across the state.

6. Insurance status

Insurance status must be taken into account to address cancer survival disparities because cancer treatment can be very expensive and patients often need long-term treatment and follow-up. Previous studies found that uninsured and Medicaid-insured patients with breast, cervical, colorectal, head and neck, lung, prostate or uterine cancer have lower survival than patients with private insurance or Medicare, even after adjustment for other factors (Subramanian, & Chen, 2013). The present study shows that insured individuals with private insurance or Medicare have significantly better chances at survival after diagnosis of head and neck cancer than uninsured individuals and the difference is as large as 50 percent.

Limitations

There are limitations in this study that must be addressed. The survival numbers in Nevada are very likely overestimated. Up until now, only in-state death linkages were performed. Other state registries, including SEER, matched their cases to both the Social Security Administration Master File and the National Death Linkage. Survival for Hispanics and Asians have to be interpreted with caution, since a proportion of these cases are undocumented and often impossible to match with death certificates in the absence of a workable social security number (Pinheiro, Morris, Liu, Bungum, & Altekruse, in press). The Pew Hispanic Center reports that Nevada had the highest share of unauthorized immigrants in the labor force with 12.2% in 2008 (Passel, & Cohn, 2009). A recent state report estimated that 47% of Nevadans without health insurance were Hispanic (DHHS, 2013). Most undocumented workers do not have insurance and are prone to have worse cancer survival. NCCR data used in this study are not complete. Data from the years 1996 to1999 were uncertified by the NPCR. Data for the years 2001 to 2003 contained incomplete information due to deficient in-state follow-up procedures. By default, these cases are automatically presumed alive. Data for year 2007 contained incomplete information and were not certified (Pinhiero et al., 2012). In addition, risk factors, such as tobacco use, alcohol use, and HPV status cannot be adjusted for in this study due the nature of the study design.

Conclusions

Cancer survival is related to a complex set of demographic and clinical factors. The present study showed that age, race/ethnicity, civil status, insurance status, site, stage of diagnosis are significant determinants for head and neck cancer survival in Nevada. Based on the findings of this analysis, in order to improve head and neck cancer survival in Nevada, I suggest the following three aspects on which public health interventions should focus.

1. Reduce the racial disparity on head and neck cancer survival in Nevada

The present study showed a significant disparity in survival due to race in Nevada. Blacks tend to have worse survival outcome even after adjustment for selected covariates. This suggests that insurance status, and socioeconomic status, may not be the solution to reduce disparities in survival. Other factors, such as having equal access to care, quality of care, better treatment options, and improved social support, may play a more significant role in reducing the survival disparities found in this study. Better outreach to inform and educate the black community about head and neck cancer survival risk factors and the positive effects of early screening may prevent advanced stage at diagnosis of HNC and lead to better survival. Reducing the number of individuals without insurance and increasing insurance coverage via enrollment with the newly implemented Patient Protection and Affordable Care Act (Obamacare), in 2014, is another avenue to increasing survival among blacks in Nevada. Future analysis with larger sample sizes and better quality data are needed to further evaluate survival disparities in the state to clarify the true reasons for this disparity.

2. Improve early diagnosis rate in Nevada

It is important to diagnose head and neck cancer at the early stage where it is more treatable and results in better prognosis. Although there is no cure for head and neck cancer, survival rates can be greatly improved if the cancer is caught at the early stage of diagnosis. Increased education and outreach can improve screening rates in the minority population, and thereby increase their survival rates. Through implementation of the Patient Protection and Affordable Care Act, more uninsured minorities in this state should be encouraged to apply for insurance coverage and reduce the disparity found in access to care.

3. Create equal access to quality healthcare across the state of Nevada

The present study suggested a geographic disparity in survival is starting to emerge between Northern and Southern Nevada. Although geographic region was not shown to be significant in this study, there is a suggestion that shows Northern Nevada to have better survival outcomes than Southern Nevada where most of the state population resides. A future study with a larger sample size may show that a statistically significant geographic disparity exists between the North and South for head and neck cancer. Quality of care may be an issue between Southern and Northern Nevada. Over 70% of the population live in the south but the state's only medical school remains in Reno, Nevada. Medical schools often attract more doctors, researchers, and clinics to local areas. As a result, they provide better quality of care to the local population due to having a larger supply of skilled professionals and bringing in more research money into the local economy which attracts more health professionals. Currently, Northern Nevada possesses more healthcare resources with possibly more ease at access. For example, the

2008 Nevada legislature found that Southern Nevada had 530 registered nurses per 100,000 population while Northern Nevada had 702 registered nurses per 100,000 population. Access to care is a contributing factor to better survival. Northern Nevada may have more public transportation options available to local residents than Southern Nevada. Cancer patients with inadequate transportation may miss more appointments with health professionals or miss filling their prescriptions in a timely manner. Fewer medical specialists may be located in the large urban areas of Southern Nevada compared to Northern Nevada. Since Southern Nevada's population is more diverse with a larger population than Northern Nevada, more resources should be proportionately diverted to the region to reduce the survival disparity seen between the two geographic regions.

APPENDIX A. INSTITUTIONAL REVIEW BOARD APPROVAL

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

Biomedical IRB – Exempt Review
Deemed Exempt

DATE: July 19, 2013

TO: **Dr. Paulo Pinheiro,** Environmental & Occupational Health

FROM: Office of Research Integrity – Human Subjects

RE: Notification of IRB Action
Protocol Title: The Determinants of Oral Cancer Survival Disparities
Protocol # 1307-4500M

This memorandum is notification that the project referenced above has been reviewed as indicated in Federal regulatory statutes 45CFR46 and deemed exempt under 45 CFR 46.101(b)4.

Any changes to the application may cause this project to require a different level of IRB review. Should any changes need to be made, please submit a **Modification Form**. When the above-referenced project has been completed, please submit a **Continuing Review/Progress Completion report** to notify ORI – HS of its closure.

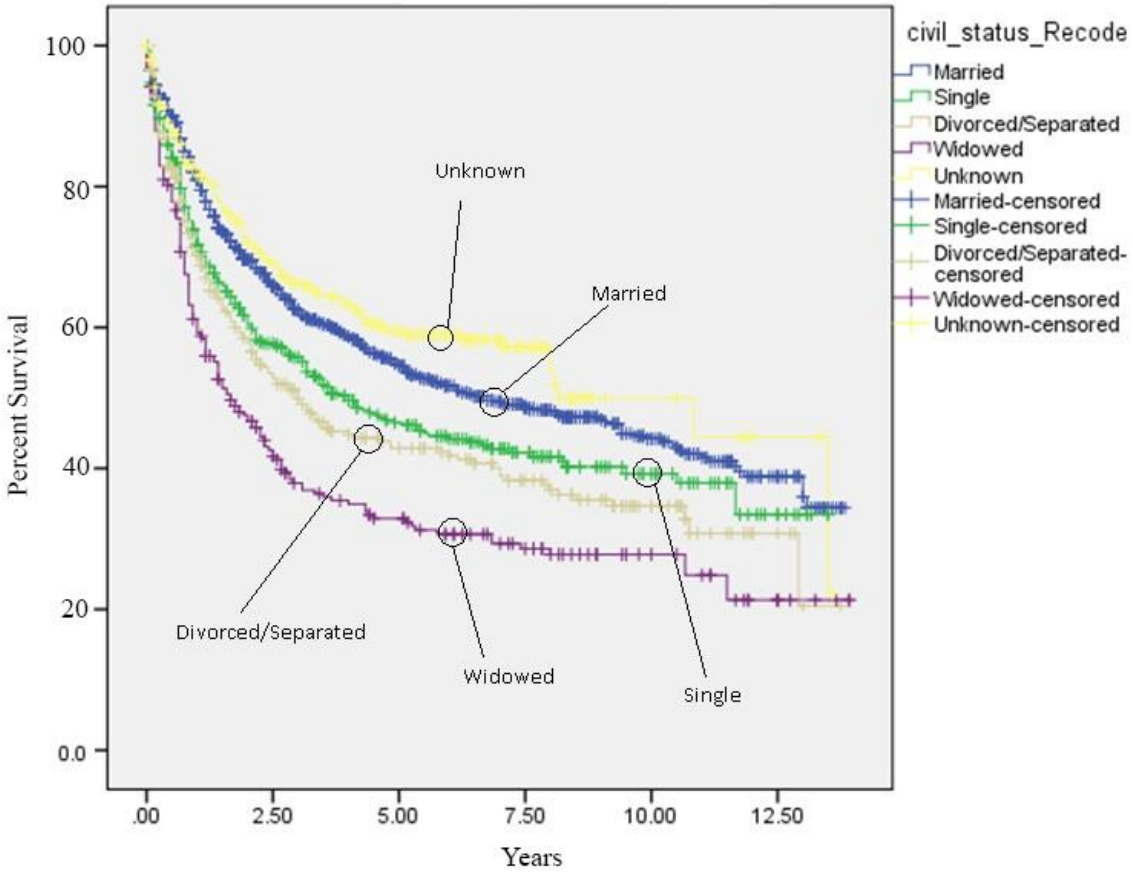
If you have questions or require any assistance, please contact the Office of Research Integrity - Human Subjects at IRB@unlv.edu or call 895-2794.

Office of Research Integrity – Human Subjects
4505 Maryland Parkway • Box 451047 • Las Vegas, Nevada 89154-1047
(702) 895-2794 • FAX: (702) 895-0805

APPENDIX B. CHARACTERISTICS AMONG 2,522 PATIENTS WITH HEAD AND NECK CANCER

Variable		No.	%
Region			
	Southern	1760	69.8
	Northern	602	23.9
	Rural	160	6.3
Tumor location			
	Tongue	899	35.6
	Floor of mouth	232	9.2
	Gums/other	341	13.5
	Nasopharynx	160	6.3
	Tonsil	421	16.7
	Oropharynx	139	5.5
	Hypopharynx	206	8.2
	Other	124	4.9
Race/ethnicity			
	White	2164	85.8
	Black	103	4.1
	Hispanic	114	4.5
	Asian	86	3.4
	AI/AN	13	0.5
	Unknown	42	1.7
Insurance status			
	Private/Medicare	1680	66.6
	Uninsured	178	7.1
	Medicaid	112	4.4
	Unknown	552	21.9
Age group (years)			
	15-44	178	7.1
	45-54	493	19.5
	55-64	786	31.2
	65-74	676	26.8
	75+	389	15.4
Stage			
	Local	709	28.1
	Regional	1035	41.0
	Distant	287	11.4
	Unknown	491	19.5
Civil status			
	Married	1194	47.3
	Single	439	17.4
	Divorced/Separated	327	13.0
	Widowed	263	10.4
	Unknown	297	11.8
Gender			
	Male	1750	69.4
	Female	772	30.6

APPENDIX C. KAPLAN-MEIER OVERALL SURVIVAL BY CIVIL STATUS, 1995-2008



APPENDIX D. COX HAZARD RATIOS (HR), HEAD AND NECK CANCER SURVIVAL, IN NEVADA, 1995-2008

Variable		N	HR	95% CI		p-value
Region						
	Southern	1760	Ref	-	-	-
	Northern	602	0.89	0.77	1.02	0.10
	Rural	160	1.08	0.86	1.36	0.50
Gender						
	Male	1750	Ref	-	-	-
	Female	772	0.95	0.83	1.08	0.40
Tumor location						
	Tongue	899	Ref	-	-	-
	Floor of mouth	232	1.15	0.94	1.41	0.18
	Gums	341	0.94	0.78	1.13	0.53
	Nasopharynx	160	0.99	0.77	1.27	0.93
	Tonsil	421	0.88	0.73	1.05	0.16
	Oropharynx	139	0.93	0.72	1.20	0.57
	Hypopharynx	206	1.38	1.13	1.69	<0.001
	Other	124	0.97	0.76	1.25	0.83
Race/ethnicity						
	White	2164	Ref	-	-	-
	Black	103	1.35	1.04	1.75	0.02
	Hispanic	114	0.93	0.70	1.23	0.59
	Asian/PI	86	1.14	0.82	1.60	0.44
	Unknown	42	0.23	0.10	0.57	<0.001
Insurance status						
	Private/Medicare	1680	Ref	-	-	-
	Uninsured	178	1.45	1.17	1.80	<0.001
	Medicaid	112	1.21	0.91	1.62	0.20
	Unknown	552	1.25	1.05	1.49	0.01
Age group (years)						
	15-44	178	Ref	-	-	-
	45-54	493	1.32	0.97	1.79	0.08
	55-64	786	1.69	1.26	2.26	<0.001
	65-74	676	2.63	1.94	3.57	<0.001
	75+	389	3.87	2.81	5.33	<0.001
Stage						
	Local	709	Ref	-	-	-
	Regional	1035	1.71	1.46	2.00	<0.001
	Distant	287	2.94	2.41	3.59	<0.001
	Unknown	491	2.14	1.79	2.56	<0.001
Civil status						
	Married	1194	Ref	-	-	-
	Single	439	1.23	1.05	1.45	0.01
	Divorced/Separated	327	1.47	1.24	1.75	<0.001
	Widowed	263	1.38	1.15	1.66	<0.001
	Unknown	297	0.77	0.62	0.95	0.02

Abbreviations: Ref, reference; HR, hazard ratio.

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