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Lung Cancer Survival Disparities in Nevada

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LUNG CANCER SURVIVAL DISPARITIES IN NEVADA

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Abstract

Lung cancer is the leading cause of cancer death in both men and women in the United States. Nevada shows moderate incidence rates of lung cancer for men but high rates for women. Little is known about the lung cancer experience and survival characteristics of the nearly 2000 new cases occurring every year in the State. The purpose of this study was to measure the extent to which geographic area of residency, gender, race, health insurance, social economic status (SES) and stage at diagnosis were associated with survival in patients diagnosed with lung cancer in Nevada. This was a retrospective population-based cohort study utilizing the Nevada Central Cancer Registry (NCCR) database for incident cases of lung cancer diagnosed in the state from 2003-2010 and followed-up through December 2011. The study population included all patients with incident cases of invasive carcinoma of the lung and bronchus, site codes C34.0, C34.3, C34.8, C34.9 and morphology codes 8000–8576. Five year cumulative survival rates were computed using the life table method stratified by race and adjusted for age. Cox proportional hazards regression was performed adjusting for region, age, gender, SES, race, tumor stage, marital status, histology, and insurance types, to examine the influence of each of these determinants on lung cancer survival in Nevada. A total of 12,962 lung cancer cases were diagnosed in Nevada during 2003-2010. The fatality of this cancer was very high with 81.9 % of the cases deceased by the end of the follow-up period. The overall age-standardized 5 year survival rate for Nevada lung cancer patients was 16.44% (95%CI 15.74-17.14). Blacks had a lower combined, age adjusted 5 year survival rate of 13.63% (95% CI 10.24-16.48) compared to the rate of Whites, 16.55 % (95% CI 15.8-17.30). However, after adjustment for all confounders, Blacks did not show an increased risk of death compared to Whites, (HR 0.99, 95% CI 0.904-1.077).

Asians (HR 0.80, 95% CI 0.71-0.89) and Hispanics (HR 0.84, 95% CI 0.76-0.93) exhibited better lung cancer survival over time compared to Whites. Patients from Southern and Rural Nevada had an 8.5 % (p=0.001) and 11.3 % (p=0.008) higher risk of dying respectively, compared to patients from Northwestern Nevada. This study provides much needed baseline lung cancer survival data for Nevada. There was no lung cancer survival disparity between Blacks and Whites. The apparently better survival rates of Asians and Hispanics should be interpreted with caution as it may be due to death linkage artifacts. Disparities between different parts of the state warrants further study.

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To my dear parents, wife and son

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Chapter 1

Background and Significance

Introduction

Lung cancer is the leading cause of cancer deaths in both men and women in the United States. In year 2010, a total of 201,144 people in the United States were diagnosed with lung cancer, including 107,164 men and 93,980 women. In the same year 158,248 people in the United States died from lung cancer, including 87,698 men and 70,550 women (CDC WorkingGroup., 2011). Nationally, lung cancer survival rates continue to be very low (Siegel, Naishadham, & Jemal, 2013). Nevada has a significantly higher rate of lung cancer incidence and mortality compared to the rest of the Western US (Siegel et al., 2013). Pinheiro , Reid , Saccucci and Harris (2012) found that 1,310 deaths occurs every year from lung cancer in Nevada, more than breast cancer, colorectal cancer and prostate cancer combined.

Risk factors. A number of environmental and life-style factors have been associated with the subsequent development of lung cancer, of which cigarette smoking is the most important (Alberg & Samet, 2003). Other risk factors includes exposure to second-hand smoke, radon, arsenic, asbestos, radiation therapy to the breast or chest polycyclic aromatic hydrocarbons, other agents, and air pollution (Wingo et al., 1999).

Clinical features. Lung cancer symptoms and signs may result from the location of the primary local invasion, compression of adjacent chest wall structures, distant metastases, or by hormone like features. The most common symptoms at presentation are worsening cough or chest pain.

Screening. Screening for lung cancer has not been widely implemented. Previous studies of lung cancer screening with chest radiography and sputum cytology failed to demonstrate lower lung cancer mortality rates (Finigan & Kern, 2013). The only screening modality for early detection that has been shown to alter mortality, is low-dose helical CT scanning among high-risk patients such as heavy smokers (Aberle et al., 2011).

Histology types. According to the website of the National Cancer Institute (NCI, 2014), lung carcinomas are broadly classified into Non-Small Cell Lung Carcinoma (NSCLC) and Small Cell Lung Carcinoma (SCLC). NSCLC is a heterogeneous aggregate of histologies. The most common NSCLC histologies include squamous cell carcinoma (SCC), adenocarcinoma (ADK) and large cell carcinoma. These histologies are often classified together because of similar approaches to diagnosis, staging, prognosis, and treatment.

Treatment. In NSCLC, surgery offers the greatest chance of cure in appropriate cases, but results of standard treatment are poor except for the most localized cancers (Manser, Wright, Hart, Byrnes, & Campbell, 2005). SCLC is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer; however, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated at the time of diagnosis (Fry, Menck, & Winchester, 1996; Govindan et al., 2006; Jänne et al., 2002).

Survival. The stage at presentation in patients with NSCLC is the factor that has the greatest impact on prognosis (Harpole, Herndon, Young, Wolfe, & Sabiston, 1995; Pairolero et al., 1984). The most important prognostic factor in patients with SCLC is the extent of disease (stage) at presentation. For patients with limited stage disease, median survival range from 15 to 20 months and the reported five-year survival rate is 10 to 13%. In contrast, for patients with extended stage disease, the median survival is 8 to 13 months, and the five-year survival rate is extremely low at 1 to 2 % (Johnson et al., 1990).

Disparities

Like other major cancers, the disease burden of lung cancer is not shared equally in the US population. Minorities often have an increased incidence rate and a decreased overall survival rate (Siegel et al., 2013). Poor outcome in survival has been attributed to multiple reasons including age, gender, histological type, performance status, stage, socioeconomic status, and health disparities (Forrest, Adams, Wareham, Rubin, & White, 2013; Grivaux et al., 2011; Mulligan et al., 2006; Niu, Roche, Pawlish, & Henry, 2013).

Despite improving cancer mortality, health disparities in cancer survival including lung cancer continue to exist (Cheung et al., 2009; CDC working group., 2011; Pinheiro et al., 2012; Zheng et al., 2012). In a systematic review by Forrest et al., (2013), patients with lung cancer living in more socioeconomically deprived circumstances are less likely to receive any type of treatment, surgery, and chemotherapy. In the United States, uninsured and Medicaid insured patients with lung cancer have higher mortality or lower survival than patients with private insurance or Medicare, even after adjustment for other factors (Niu et al., 2013). Some studies have demonstrated that providing equal access to health care may eliminate racial disparities in lung cancer survival and improve the outcome of all cases (Zheng et al., 2012).

Cancer incidence and survival disparities have been reported in Nevada (Pinheiro et al., 2012). The report suggests existence of regional disparities in survival rates in Nevada for breast, colon, prostate, cervical, and skin (melanoma) cancers, possibly due to less accessibility to quality healthcare in Southern Nevada. However, lung cancer survival disparities in Nevada were not analyzed, although the study reported that in Nevada, only 16% of the cancers were detected in a localized stage, 19% in regional stage and 42% in distant stage, with 23% having an unknown stage of diagnosis.

Given the high burden of morbidity and mortality associated with lung cancer and the lack of baseline data available to researchers, administrators and policy makers in the state of Nevada, the purpose of this thesis is to study lung cancer survival disparities and their determinants. Accurate estimation of lung cancer survival and its associated factors will better facilitate public health policies for allocating resources to people at highest risk which in turn will improve quality healthcare delivery and disease prevention.

Study Purpose and Hypotheses

Research questions. Given that lung cancer has a very poor prognosis in the population at large, the study sought to answer the following questions: do lung cancer survival disparities exist in Nevada, how large they are and what are the determinants associated with such disparities.

Goal and objectives. The purpose of this study was to measure the extent to which geographic residency, gender, race, health insurance, SES and stage at diagnosis are associated with survival over time in patients from Nevada diagnosed with lung cancer.

Hypotheses. To answer the research questions the following hypotheses will be tested:

H_1: Lung cancer patients in Northwestern Nevada show lower risk of death for lung cancer over time compared to those in Southern Nevada.

H_o: There is no difference in risk of death from lung cancer over time between Southern and Northwestern Nevada.

H_2: In Nevada, Blacks presenting with distant stage lung cancer are less likely to receive chemotherapy than Whites.

H_o: In Nevada, there is no difference in treatment with chemotherapy between Blacks and Whites with distant lung cancer.

H_3: In Nevada, lung cancer patients from low economic status exhibit higher risk of death overtime compared to higher SES.

H_o: In Nevada, there is no difference in risk of death over time between lung cancer patients from lower and higher socioeconomic status.

H_4: Patients from Rural Nevada with localized NSCLC lung cancer are less likely to receive surgery compared to those in Southern and Northwestern Nevada.

H_o: There is no difference in surgical treatment between Patients with localized NSCLC from Rural Nevada compared to Southern and Northwestern Nevada.

H_5: Overall, Nevada patients with SCLC have increased risk of death compared to those with SCC.

H_o: Overall, there is no difference in survival in Nevada, between patients with SCLC and SCC.

Ethical considerations. The study was approved by the University of Nevada, Las Vegas IRB; Protocol # 1403-4762M.

Chapter 2

Methodology

Study Design

Data source. Lung cancer data were obtained from the Nevada Central Cancer Registry (NCCR) through the Bureau of Health Planning and Statistics. The NCCR is a population-based registry that records and maintains data on all cancer patients within the State of Nevada. The Nevada statewide cancer registry achieved seven gold certifications with the North American Association of Central Cancer Registries in the last ten years. The details of NCCR case finding methodology and operations are described on its website (Nevada Division of Public and Behavioral Health, 2011). Death records came from the Office of Vital Records (OVR), also within the Bureau of Health Planning and Statistics. Out of state deaths were captured by manual search through the Social Security Death Index of all cases initially given out by the Registry as being alive (Boyle & Decouflé, 1990; Hill & Rosenwaike, 2001/2002). Comparison survival rates were obtained from Surveillance, Epidemiology, and End Results (SEER) Program. The SEER Program is a population-based cancer registration program coordinated by the NCI which identifies all primary cancers occurring in residents of defined geographic regions. Cancer registries of the SEER Program currently cover approximately 26% of the U.S. population. SEER collects detailed data on patient demographics, tumor characteristics, and initial therapy, and maintains follow-up of all registered patients for vital status in order to provide statistics on cancer patient survival (SEER Cancer Statistics Review 1975-2004 , 2007).

Study population. The study population in this study comprised men and women diagnosed with a first primary lung and bronchial cancer 2003 through 2010 identified through the NCCR and followed for vital status until December, 31 2011. The site codes included were C34.0–34.3, C34.8–34.9 while morphology codes included were 8000–8576 as described by Fritz et al., (2000) in International Classification of Diseases for Oncology, third edition (ICD-O-3). The Study went on with 12,962 cases out of the possible 13,653 cases that met the inclusion criteria.

Exclusion criteria. Patients only diagnosed at autopsy and by death certificate were excluded (687 cases). Also, patients with negative or missing survival period were also excluded (3 cases).

Outcome measure. The primary endpoint was observed survival. Survival time was measured in years from the date of diagnosis until the date of death, or the end of the study (December 31, 2011), whichever occurred first.

Variables

Lung cancer stage of diagnosis classification. SEER Program summary staging (localized, regional, and distant) was used to categorize the extent of the disease (Young Jr, Roffers , Ries & Fritz , 2001).

Age categorization. Age at diagnosis was categorized into the following 5 groups: 15-44, 45-54, 55-64, 65-74, 75+ based on the international age standard survival classification (Fritz A et al., 2000).

Lung cancer histology classification. Lung cancer was classified into 5 categories: Non Specific Lung Cancers/ Neoplasm (8000/3-8005/3,8010/3-8015/3 ,8020/3,8021/3), SCLC(8041/3-8045/3,8246/3), SCC (8050/3-8052/3, 8070/3-8076/3, 8078/3), ADK(8140/3, 8141/3, 8143/3, 8147/3, 8250/3- 8255/3,8260/3, 8310/3, 8320/3, 8323/3, 8480/3, 8481/3, 8490/3, 8510/3, 8550/3, 8551/3, 8570/3- 8574/3, 8576) and Others (all other codes not listed above).

Race/ Ethnicity. Race/ ethnicity was classified into the following mutually exclusive groups: White, Black, Hispanic, Asian/Pacific Islanders, Native Americans and Others.

Poverty level. SES information is not directly collected on individual patients by NCCR. SES was based on proportion of the population in poverty in the case's zip code based on 2011 US Census Bureau data (American Community Survey, 2011). The three categories of ecological SES considered were high SES (< 5 percent of population in poverty), middle SES (5-10 percent of population in poverty) and low SES (>10 percent of population in poverty).

Nevada geographical region classification. Nevada was classified into Southern, Northwestern and Rural regions. Clark County was referred to as Southern Nevada. Northwestern Nevada comprised of Douglas, Lyon, Storey, Washoe Counties and Carson City. The remainders of the counties (Humboldt, Pershing, Lander, Elko, Eureka, White Pine, Nye, Lincoln, Esmeralda, Mineral and Churchill) were classified as Rural Nevada.

Marital status. Marital status were classified according to the North American Association of Central Cancer Registries standards (The Florida Cancer Data System - Data Acquisition Manual, 2013). For analysis purpose, patients were described as single, married, widowed or divorced/separated.

Health insurance. Insurance types were classified according to the North American Association of Central Cancer Registries standards (The Florida Cancer Data System - Data Acquisition Manual, 2013.). For analysis purpose Insurance status were reclassified into uninsured, private and Medicaid. Veteran affairs (VA) and Medicare were included as part of private insurance. The Indian health insurance was grouped with Medicaid.

Statistical Analyses

All data were analyzed with SPSS (version 22, SPSS Inc., and Chicago, IL, USA). Statistical analyses were carried out using likelihood ratio chi-square tests to compare the demographics, tumor histology, stage and accessibility to healthcare for race and ethnicity groups. The cumulative 5-year survival rates/curves were computed by the life table method stratified by race and adjusted for age. Survival rates were calculated using the actuarial method. Univariate and multivariate Cox proportional hazards regression was performed using all variables of interest. Hazard ratios were computed adjusting for region, age, gender, SES, race, tumor stage, marital status, histology, and insurance status.

Cross tabulation tables were carried out to test the appropriate hypotheses. To further test some hypothesis in a multivariate way, logistic regression was done, adjusting for appropriate variables. Partial likelihood tests were used to estimate the regression coefficients. All statistical tests were two-sided with p-value of <0.05 reported as statistically significant.

Cox Models. A Cox model is a statistical technique for exploring the relationship between the survival of a patient and several explanatory variables. It allows the estimation of the hazard (or risk) of death or other event of interest. It assumes that the effects of the explanatory variables upon survival are constant over time and are additive in one scale. This is known as proportional hazard assumption. The hazard function is the probability that an individual or object will experience an event (such as death) within time interval, given that the individual has survived up to the beginning of the interval.(“ XLSTAT,” 2014).

Chapter 3

Results

Descriptive Analysis

A total of 12,962 diagnoses of lung cancer from 2003 through 2010 were included in the study. Of those diagnoses, 51.4 % [n=6656] were male and the remaining 48.6 % [n=6306] were female. Whites made up the largest proportion of the patients in Nevada, constituting 86.4 % [n=11193]. Other racial-ethnic groups included Blacks 5.2 % [n=680], Native Americans 0.5 % [n=67], Asian 3.3 % [n=423], and Hispanics 4.4 % [n=567]. A very small proportion of the population were unknown race or multiracial 0.2 % [n=32].

For the period 2003 through 2010, the mean age of Nevada patients diagnosed with lung cancer was 68.9 years with a standard deviation of 10.3. The most common (36 %) age group for lung cancer diagnosis was 65-74 years [n=4665]. Most of the lung cancers were unstaged (35.6 %). Distant or metastatic stage was 31.0 %. Only 17.5 % were diagnosed at localized stage. The remaining 15.9 % were diagnosed at a regional stage. Most of the patients, 73.9 %, had private health insurance or Medicare. A small proportion or2.9 % was covered with Medicaid. Uninsured patients constituted 3.4 % of the cases. The remaining 19.8 % had unknown health insurance at the time of their diagnosis. In terms of diagnosed histology, ADK was the largest proportion (33.1 %). SCC was diagnosed in 16.6 % of population studied. The rest were distributed as follows: SCLC (14.8 %), carcinomas NOS (14.3 %) and others (21.1 %). Predominantly, 69 % of the lung cancer patients resided in Southern Nevada. Rural Nevada contributed 7.8 % of the cases. Northwestern Nevada recorded 23.2 % of the cases. 48.4 %, of the Nevada lung cancer patients were married. The lower SES constituted a large proportion of the cases (45.2 %). Please see table 1 for the detailed demographic and clinical characteristics of the study population.

Table 1

Patients' Dermographic and Clinical Characteristics by Race/Ethnicity (N=12962)

Race	White n=11193	Black n=680	N.A n=67	Asian/PFI n=423	Hispanics n=567	Unknown n=32	Total N=12962	p value*
Age at diagnosis								<0.001
<45	129	22	1	10	21	2	185	
45-54	745	95	8	50	74	2	974	
55-64	2561	192	13	114	145	7	3032	
65-74	4084	222	24	153	168	14	4665	
75+	3674	149	21	96	159	7	4106	
Sex								<0.001
Male	5659	372	48	236	323	18	6656	
Female	5534	308	19	187	244	14	6306	
Stage at diagnosis								0.001
Localized	2005	104	15	60	75	6	2265	
Regional	1786	115	10	68	79	6	2064	
Distant	3405	236	31	143	194	12	4021	
Unstaged	3997	225	11	152	219	8	4612	
Marital status								<0.001
Married	5447	264	32	266	247	17	6273	
Single	1531	180	9	52	105	3	1880	
Separated/Divorced	1363	95	9	33	67	6	1573	
Widowed	2070	97	11	49	61	6	2294	
Unknown	782	44	6	23	87	0	942	
Insurance								<0.001
Private/Medicare	8318	501	48	324	356	29	9576	
Medicaid	279	36	6	15	36	2	374	
Uninsured	318	44	3	28	48	0	441	
Unknown	2278	99	10	56	127	1	2571	
Nevada Region								<0.001
Northwestern	2794	37	28	53	82	7	3001	
Rural	956	9	13	4	33	0	1015	
Southern	7443	634	26	366	452	25	8946	
Histology								<0.001
SCC	1861	128	11	64	86	7	2157	
SCLC	1713	75	7	42	81	3	1921	
ADK	3594	264	22	202	197	13	4292	
Carcinoma NOS	1644	63	14	45	81	5	1852	
Others	2381	150	13	70	122	4	2740	
Proportion in poverty								<0.001
<5 percent	2100	70	6	90	65	10	2341	
5-10 percent	3990	211	15	187	150	10	4563	
>10 percent	4923	390	44	143	346	12	5858	
Unknown	180	9	2	3	6	0	200	

Notes: Abbreviations: N.A, Native Americans; PFI, Pacific Islanders; SCC, Squamous Cell Carcin carcinoma
ADK, Adenocarcinoma; NOS, Not otherwise Specified; SCLC, ;SCLC,Small Cell Lung Cancer
*Likelihood ratio p value, significant at p<0.05.

There were 10619 (81.9 %) deaths in Nevada lung cancer patients by the end of the follow up period (2003 – 2011). Demographically, Blacks, Native Americans, Asians, and Hispanics tended to be diagnosed at a younger age (before 55 years) with proportions of 17.2 %, 13.4 %, 14.2 % and 16.8 % respectively versus 7.8 % of Whites. Hispanics had higher proportion of uninsured patients than other races/ethnicity at 8.5 % compared to Whites (2.5 %), Blacks (6.5 %), Native Americans (4.5 %) and Asians (6.6 %). At the time of diagnosis of lung cancer, lower proportion of Asians (33.8 %) had a low economic status compared to Whites (44 %), Blacks (57.4 %), Native Americans (65.7 %) and Hispanics (61 %). A higher proportion of Native Americans (48.4 %) were diagnosed at distant stage of lung cancer compared with other races as follows: Whites (30.4 %), Blacks (34.7 %), Asians (33.8 %) and Hispanics (34.2 %) respectively. Higher proportion of Whites were diagnosed with the more aggressive SCLC (15.3 %) compared to other races/ethnicities. Small cell histology was diagnosed in 11 % of Blacks, 10.5 % of Native Americans, 9.9 % of Asians and 14.2 % of Hispanics.

Survival Analyses

Lung cancer survival rates. In this particular study, it was found that the median overall survival for the entire cohort was 1.04 years. Age-adjusted survival rates were obtained using the international survival standards (Corazziari, Quinn, & Capocaccia, 2004) and compared with the general population derived from Surveillance Epidemiology and End Results (SEER) -17. The overall age-standardized observed 5 year survival rate for Nevada lung cancer patients was 16.44 % (95% CI 15.74-17.14). This was not statistically different from SEER overall lung cancer survival rate of 16.40 % (95% CI 16.20-16.50) (Table 2). When stratified by gender (Table 3), Nevada females had a significantly higher 5 year survival rate (19.65%, 95% CI 18.56-20.74) versus Nevada males (12.96%, 95% CI 12.07-13.85). This is similar to the SEER national findings. In addition, when Nevada males and females were compared with SEER males (13.60%, 95%CI 13.4-13.70) and females (19.60%, 95% CI 16.2-16.5), there were no difference

between Nevada and the rest of the nation (Tables 3& 4).

Table 2
Lung Cancer Age Standardized 5 Year Survival Rates for SEER and Nevada

	SEER			Nevada		
Race	Survival (%)	LLCI	ULCI	Survival (%)	LLCI	ULCI
Whites	16.6	16.4	16.8	16.55	15.8	17.3
Blacks	12.5	12.2	12.9	13.63	10.24	16.48
N.A	11.7	9.9	13.6	6.38	0.15	12.61
A/PFI	19.9	19.2	20.5	17.27	12.98	21.56
Hispanics	17.9	17.3	18.5	17.64	14.11	21.17
Overall	16.4	16.2	16.5	16.44	15.74	17.14

Notes : Abbreviations: NA, Native Americans, A/PFI, Asians/Pacific Islanders;
LLCI, Lower Limit of 95% Confidence Interval; ULCI, Upper Limit of 95% Confidence Interval
SEER, Surveillance Epidemiology and End Results

Table 3
Nevada Age Standardized 5 year Survival Rates of Lung Cancer by Gender

	Male			Female		
Race	Survival (%)	LLCI	ULCI	Survival (%)	LLCI	ULCI
Whites	13.1	12.14	14.06	19.67	18.52	20.82
Blacks*	8.02	4.41	11.63	19.47	14.29	24.65
N.A*	2.03	0.01	8.11	19.72	1.48	37.96
A/PFI	14.81	9.64	19.98	19.44	12.16	26.72
Hispanics	14.85	10.44	19.26	22.09	16.33	27.85
Overall*	12.96	12.07	13.85	19.65	18.56	20.74

Notes : Abbreviations: NA, Native Americans, A/PFI, Asians/Pacific Islanders;
LLCI, Lower Limit of 95% Confidence Interval; ULCI, Upper Limit of 95% Confidence Interval
* Significant compare to Whites

Table 4
SEER Age Standardized 5 year Survival Rates of Lung Cancer by Gender

	Male			Female		
Race	Survival (%)	LLCI	ULCI	Survival (%)	LLCI	ULCI
Whites	13.7	13.5	13.9	19.9	19.6	20.1
Blacks	10.6	10.1	11	15.2	14.6	15.8
N.A	10	7.7	12.6	13.3	10.7	16.2
A/PFI	16.6	15.8	17.5	24.3	23.2	25.4
Hispanics	14.9	14.2	15.7	21.4	20.4	22.4
Overall	13.6	13.4	13.7	19.6	19.4	19.9

Notes : Abbreviations: NA, Native Americans, A/PFI, Asians/Pacific Islanders;
LLCI, Lower Limit of 95% Confidence Interval; ULCI, Upper Limit of 95% Confidence Interval

When survival rates were broken down further by race/ethnicity and gender, Nevada females had consistently higher survival rates than their male counterparts (Table 3). These differences in male and female survival rates are comparable to the patterns seen in patients residing in the SEER regions (Table 4). Only Native Americans had a significantly lower overall survival rate (6.38 %, 95% CI 0.15-12.61) compared to Whites (16.55%, 95% CI 15.8-17.30). Blacks had lower but non-significant overall adjusted 5-year survival rate (13.63%, 95%CI 10.24-16.48) compared to Whites (16.55%, 95% CI 15.8-17.30). Once stratified by gender, Nevada Black males (8.02%, 95% CI 4.41- 11.63) and Native Americans (2.03%, 95% CI 0.01-8.11) exhibited a lower 5-year survival rate compared to White males (13.1%, 95% CI 12.14-14.06). There were no racial survival differences amongst Nevada females (Table 3).

Cox regression model

Proportional hazard assumption test. The proportional hazard assumption was tested for all the variables. All variables except radiotherapy and chemotherapy satisfied this assumption. Although surgery as a treatment modality satisfied the proportional hazard test it was excluded from the main model, alongside chemotherapy and radiotherapy, because it is only appropriate for early NSCLC. Univariate model was first performed to assess the impact of each variable alone on lung cancer survival. Multivariable model was performed next, to account for other covariates. In the multivariate model, adjusted hazard ratios (HR) and the corresponding 95 % confidence intervals (CI) were estimated using the Cox proportional hazards regression. The forward stepwise method was employed. Univariate analysis of all the variables of interest demonstrated significant contribution to lung cancer survival (Table 5). In the multivariate models, all variables of interest remained significant after simultaneously adjusting for other variables (Table 5).

Effect of race/ethnicity on survival. Race has been shown to be a determinant of cancer survivals. In our study, there was no difference between Blacks (HR 0.99, 95% CI 0.91-1.08, p=0.91) and Whites (reference) unadjusted for other factors. The lack of difference between Blacks and Whites remained in the multivariate model (Table 5) when simultaneously adjusted for age group, gender, stage, health insurance type, marital status, SES, tumor histology and geographical regions. Blacks had a HR 0.99, 95% CI 0.90-1.08, p=0.762; compared to Whites (the reference group). Surprisingly, this study result suggests that Asian (adjusted HR 0.80, 95% CI 0.71-0.89, p<0.001) and Hispanic (adjusted HR 0.84, 95% CI 0.76-0.93, p<0.001) lung cancer patients had lower risk of death compared to Whites whether adjusted or unadjusted for other confounders (Table 5 & Figure 1).

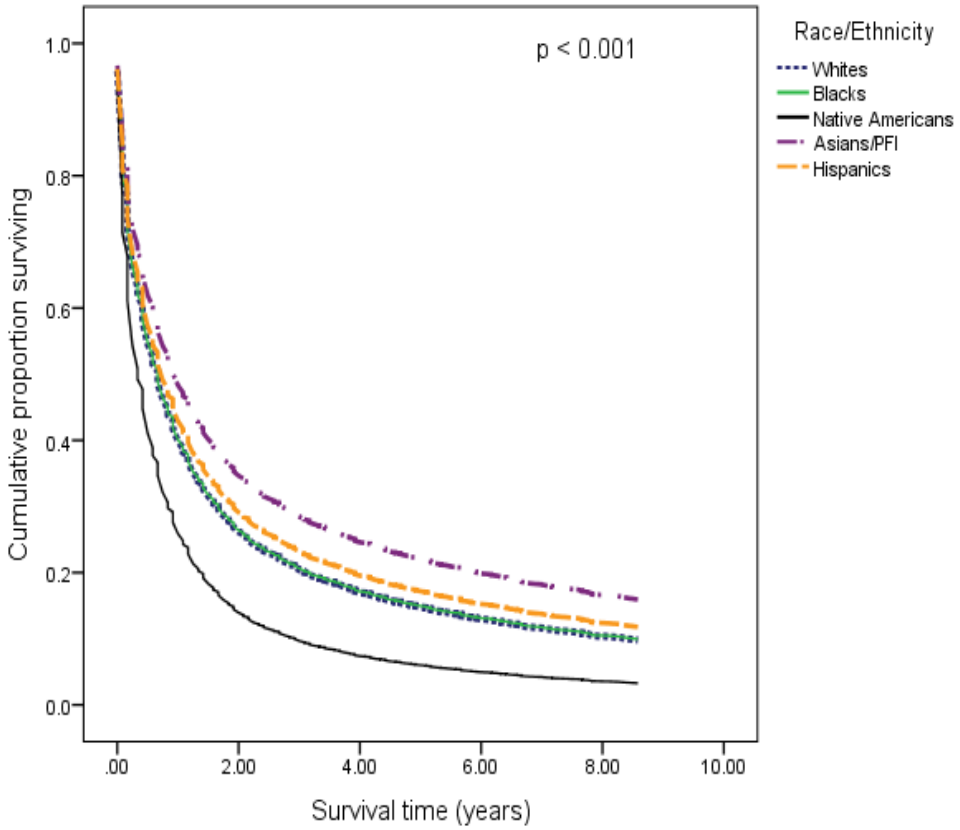

Figure 1. Univariate Cox regression survival function plot of Nevada lung cancer patients by race/ethnicity

Effect of geographical region on survival. There was no difference in crude survival between Northwestern Nevada (reference group) and Southern Nevada (HR 1.01, 95% CI 0.97-1.06, p =0.63). However, In the multivariate model, after simultaneously adjusting for age group, gender, stage, health insurance type, marital status, SES, tumor histology and race/ethnicity, Southern Nevada lung cancer patients had a 9 % higher risk of dying compared to Northwestern Nevada (HR 1.09,95% CI 1.04-1.14, p =0.001). Rural Nevada patients, on the other hand, had significantly increased risk of death unadjusted and adjusted for confounders compared to Northwestern Nevada (Table 5).

Table 5
Cox Regression Model

Type		Univariate (N=12962)				Multivariate (N=12962)			
		HR	LLCI	ULCI	P value*	HR	LLCI	ULCI	P value*
Sex					<0.001				<0.001
	Male	1.00				1.00			
	Female	0.81	0.78	0.84	<0.001	0.81	0.78	0.85	<0.001
Age at diagnosis					<0.001				<0.001
	<45	1.00				1.00			
	45-54	1.60	1.31	1.95	<0.001	1.59	1.31	1.94	<0.001
	55-64	1.62	1.35	1.96	<0.001	1.75	1.45	2.11	<0.001
	65-74	1.75	1.45	2.11	<0.001	2.04	1.69	2.46	<0.001
	75+	2.26	1.87	2.72	<0.001	2.63	2.17	3.18	<0.001
Race/Ethnicity					<0.001				<0.001
	White	1.00				1.00			
	Black	0.99	0.91	1.08	0.91	0.99	0.90	1.08	0.762
	N.A	1.47	1.14	1.89	0.003	1.38	1.07	1.78	0.012
	Asian/PFI	0.79	0.71	0.88	<0.001	0.80	0.71	0.89	<0.001
	Hispanics	0.92	0.84	1.01	0.09	0.84	0.76	0.93	<0.001
	Unknown	0.77	0.51	1.18	0.23	0.88	0.58	1.34	0.564
Stage at diagnosis					<0.001				<0.001
	Localized	1.00				1.00			
	Regional	1.62	1.51	1.74	<0.001	1.63	1.51	1.75	<0.001
	Distant	3.65	3.43	3.89	<0.001	3.65	3.42	3.89	<0.001
	Unstaged	2.35	2.21	2.50	<0.001	2.13	1.99	2.27	<0.001
Marital status					<0.001				<0.001
	Married	1.00				1.00			
	Single	1.23	1.16	1.30	<0.001	1.20	1.13	1.27	<0.001
	Separated/Divorced	1.13	1.07	1.21	<0.001	1.11	1.04	1.18	0.001
	Widowed	1.23	1.17	1.30	<0.001	1.11	1.05	1.17	<0.001
	Unknown	0.96	0.89	1.04	0.33	0.81	0.75	0.88	<0.001
Insurance					<0.001				<0.001
	Private/Medicare	1.00				1.00			
	Medicaid	1.18	1.05	1.32	0.004	1.13	1.01	1.28	0.036
	Uninsured	1.36	1.22	1.51	<0.001	1.20	1.08	1.34	0.001
	Unknown	1.45	1.38	1.52	<0.001	1.32	1.25	1.39	<0.001
Nevada Region					0.003				0.002
	Northwestern	1.00				1.00			
	Rural	1.14	1.05	1.23	0.001	1.11	1.03	1.20	0.008
	Southern	1.01	0.97	1.06	0.63	1.09	1.04	1.14	0.001
Histology					<0.001				<0.001
	SCC	1.00				1.00			
	SCLC	1.53	1.43	1.64	<0.001	1.28	1.20	1.37	<0.001
	ADK	0.94	0.89	1.00	0.06	0.91	0.86	0.97	0.003
	Carcinoma NOS	2.15	2.01	2.30	<0.001	1.68	1.57	1.81	<0.001
	Others	1.23	1.15	1.31	<0.001	1.09	1.02	1.16	0.008
Proportion in poverty					<0.001				<0.001
	<5 percent	1.00				1.00			
	5-10 percent	1.17	1.11	1.24	<0.001	1.15	1.09	1.22	<0.001
	>10 percent	1.28	1.22	1.36	<0.001	1.22	1.16	1.29	<0.001
	Unknown	1.24	1.06	1.45	0.01	1.10	0.94	1.28	0.257

Notes: Abbreviations: N.A, Native Americans; PFI, Pacific Islanders; SCC, Squamous Cell Carcinoma ADK, Adenocarcinoma; NOS, Not otherwise Specified; SCLC, Small Cell Lung Cancer; HR; Hazard Ratio; LLCI, Lower Limit of 95% Confidence Interval of HR; ULCI, Upper Limit of 95% Confidence Interval of HR ; * p value, significant at p<0.05.

Effect of gender on survival. Both univariate and multivariate analyses showed that female gender was advantageous. When simultaneously adjusted for age group, race, stage, health insurance type, marital status, SES, tumor histology and geographical regions, females were 19 % less likely (HR 0.81, 95% CI 0.78-0.85, p<0.001) to die from lung cancer over the study period compared to males (Table 5 & Figure 2).

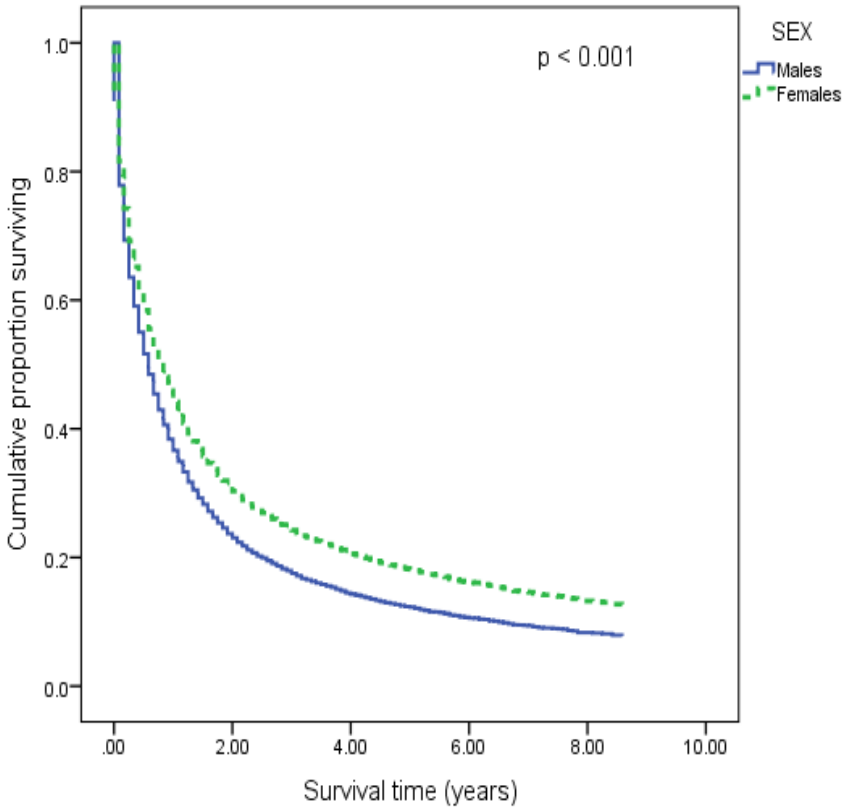

Figure 2. Univariate Cox regression survival function plot of Nevada lung cancer patients by gender

Effect of socioeconomic status on survival. After simultaneously adjusting for gender, age group, race, stage, health insurance type, marital status, tumor histology and geographical regions, lung cancer patients of low SES were 22.3 % more likely (HR 1.22, 95%CI 1.16-1.29, p<0.001) to die from lung cancer over study period compared to those of higher SES (reference group). There was a clear gradient effect of SES on survival as patients of the middle SES had a 15.4 percent greater adjusted risk (HR 1.15, 95% CI 1.09-1.22, P<0.001) compared to SES.

Effect of insurance on survival. Uninsured patients (HR 1.20, 95%CI 1.08-1.34, P<0.001) and those with Medicaid (HR 1.13, 95%CI 1.01-1.28, p<0.036) were at higher risk of death compared to those with Private insurance or Medicare before (Figure 3) and after (Table 5) adjusting for other factors.

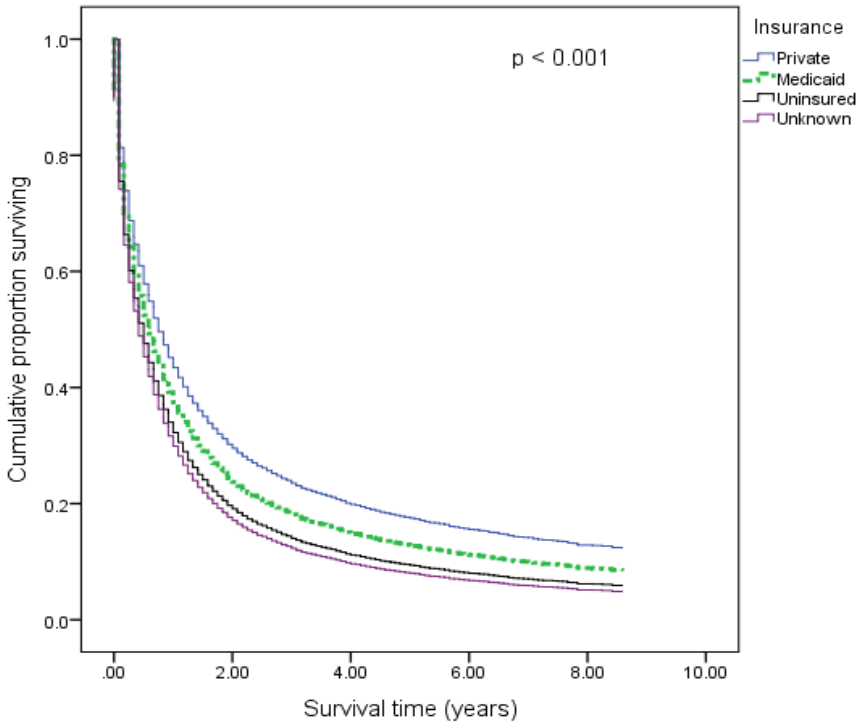

Figure 3. Univariate Cox regression survival function plot of Nevada lung cancer patients by insurance

Effect of histology on survival. Surprisingly, patients with ADK of the lung (HR 0.91, 95%CI 0.86-0.97, p= 0.003) had better survival compared to SCC after multivariate adjustment. As expected, patients with SCLC were 28.1 % more likely to die (HR 1.28, 95%CI 1.20-1.37, p <0.001) compared to those with SCC after adjusting for gender, age group, race, stage, health insurance type, marital status, geographical regions, and SES.

Effect of marriage on survival. Single patients had a higher risk of death compared to married patients (HR 1.20, 95%CI 1.13-1.27, p< 0.001) after simultaneously adjusting for all other factors.

Effect of age on survival. Increasing age at diagnosis showed a clear increase in risk of death from lung cancer. Patients less than 45 years old demonstrated the least risk of death. Patients more than 75 years old were at highest risk of death (HR 2.63, 95% CI 2.17-3.18, p<0.001 compared to the reference) (Table 5).

Effect of stage on survival. Stage at diagnosis proved to be the single most important factor in our model. Prior to adjusting for other factors (Figure 4) there was a clear separation of survival curves based on stage of lung cancer. This advantage was maintained after simultaneously adjusting for adjusting for all other factors. Those with distant disease were 3.65 times (HR 3.65, 95%CI 3.42-3.89, and p < 0.001) more likely to die over time compared to those with localized lung cancer.

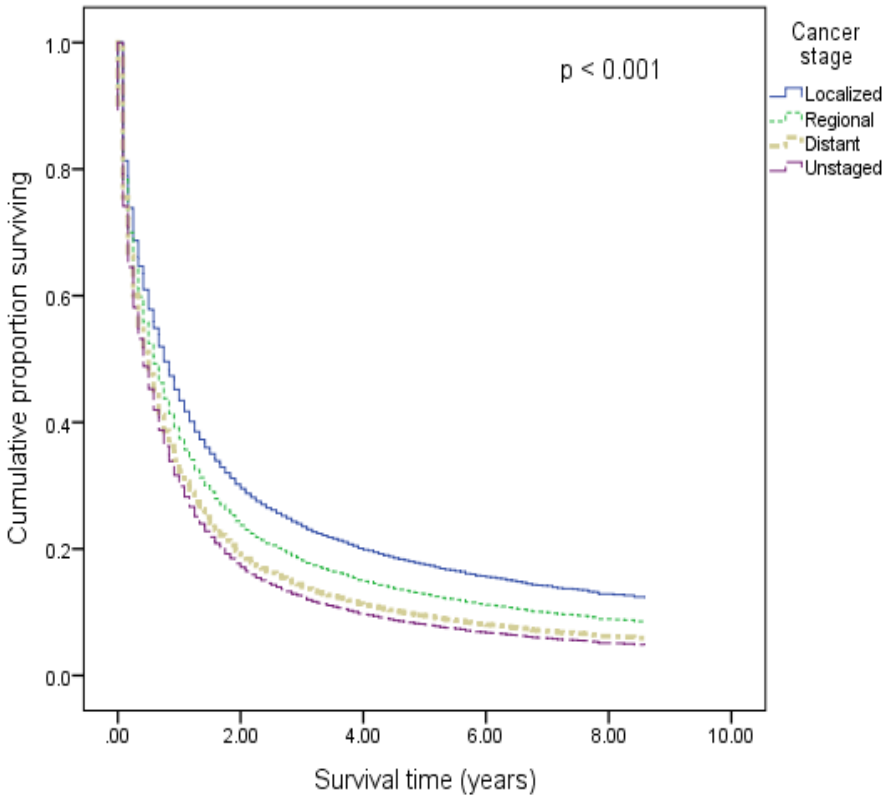

Figure 4. Univariate Cox regression survival function plot of Nevada lung cancer patients by stage

Hypotheses Testing

Hypothesis 1. Univariately, there was no difference in survival between Northwestern Nevada (reference group) and Southern Nevada (HR 1.01, 95%CI 0.97-1.06, p =0.63) (Table 5). However, after multivariate adjustment for age group, gender, stage, health insurance type, marital status, SES, tumor histology and race/ethnicity, Southern Nevada Lung cancer patients had 8.5 percent higher risk of dying compared to Northwestern Nevada (Table 5). Thus, the null hypothesis was rejected.

Hypothesis 2. There was no difference in receipt of chemotherapy for Blacks with distant lung cancer compared to Whites (chi square 0.02, p=0.902) (Table 6). Non significance persisted after logistic regression was performed adjusting for sex, age, region, payer, marital status, morphology and poverty level (OR 1.11, 95% CI 0.80-1.54, p< 0.524). Thus, the null hypothesis could not be rejected.

Table 6

Chi Square Hypothesis Test for Chemotherapy Treatment for Advanced Lung Cancer, Whites vs. Blacks

		Chemotherapy		Total
		Yes	No	
Race	Whites	1135 (45.7%)	1350 (54.3%)	2485
	Blacks	80 (45.2%)	97 (54.8%)	177
Total		1215	1447	2662

Notes: Pearson's Chi square test is 0.015, p =0.902, n= 2662

Hypothesis 3. There was no significant difference in receipt of surgery in patients with localized NSCLC of the lung from Rural Nevada compared to Urban Nevada (Southern Nevada and Northwestern combined) with chi square of 0.59, p=0.442 (Table 7) and logistic regression (OR 1.14, 95% CI 0.80-1.62, p=0.467) adjusting for sex, race, age, poverty level, payer, and marital status.

Table 7

Chi Square Hypothesis Test for Likelihood of Receiving Surgery for a Localized NSCLC Urban vs. Rural Nevada

		Surgical treatment		Total
		Yes	No	
Region	Rural	86 (57%)	65 (43%)	151
	†Urban	1123 (60.2%)	744 (39.8%)	1867
Total		1209	809	2018

Notes: Pearson's Chi Square Value is 0.590, p=0.442, n=201

†Urban= Southern and Northwestern Nevada Combined

Hypothesis 4. Lung cancer patients of low SES were more likely to die from lung cancer over the study period compared to those of higher SES (Univariate HR 1.28, 95%CI 1.22-1.36, p<0.001: Multivariate HR 1.22, 95%CI 1.16-1.29 p<0.001). (Table 5). The null hypothesis was rejected.

Hypothesis 5. After reclassifying lung cancer into two broad groups of SCLC versus NSCLC. Patients with SCLC were at higher risk of death overtime compared to those with NSCLC, before and after adjusting for other factors (Univariate HR 1.43, 95%CI 1.35-1.50, p<0.001: Multivariate HR 1.26, 95%CI 1.20-1.33, p<0.001) (Table 8). The null hypothesis was therefore rejected.

Table 8

Univariate and Multivariate Cox Regression Hypothesis Test of NSCLC vs. SCLC Survival

	Univariate (N=12962)				†Multivariate (N=12962)			
	HR	LLCI	ULCI	P value*	HR	LLCI	ULCI	P value*
Histology				<0.001				<0.001
ŧ NSCLC	1.00				1.00			
SCLC	1.43	1.35	1.50	<0.001	1.26	1.20	1.33	<0.001
Unknown	2.63	2.46	2.81	<0.001	2.10	1.95	2.26	<0.001

Notes: Abbreviations: NSCLC, Non Small Cell Lung Cancer which includes ADK, SCC, and Others.
SCLC, Small Cell Lung Cancer; HR; Hazard Ratio; LLCI, Lower Limit of 95% Confidence Interval of HR;
ULCI, Upper Limit of 95% Confidence Interval of HR ; * p value, significant at p<0.05.
†multivariate analysis adjusting for †multivariate analysis adjusting for age, sex, race, region, SES, marital status, stage and insurance

Sub Analysis

Further analysis of hypothesis 3 was performed with the Chi square test (Table 9), a difference was detected in receipt of surgical treatment by patients with localized NSCLC between Southern Nevada and Northwestern Nevada. Logistic regression indicated that Southern Nevada patients with localized NSCLC were 32 % less likely to receive surgical treatment compared to similar patients in Northwestern Nevada adjusting for age, poverty level, sex, race, gender, marital status and insurance status (OR 0.68, 95% CI 0.55-0.85, p< 0.001).

Table 9

Chi Square Test for Likelihood of Receiving Surgery for Localized NSCLC Northwestern vs. Southern Nevada

		Surgical treatment		Total
		Yes	No	
Region	Northwestern	370 (67%)	182 (33%)	552
	Southern	753 (57.3%)	562 (42.7%)	1315
Total		1123	744	1867

Notes: Pearson's Chi Square Value is 15.695, p<0.001, n=1867

Chapter 4

Discussion

This study demonstrated that lung cancer is indeed a very deadly cancer, as 82 % of the patients were dead by the end of the fifth year of follow-up. This corresponds to a survival rate of 16 % after 5 years. Lung cancer survival rate, therefore, contrasts sharply with other cancers such as breast and colorectal cancer with 5-year survival rates of 89 % and 65 % respectively (SEER Cancer Stat Fact Sheets, 2014). In this study, Nevada lung cancer patients demonstrated comparable observed age standardized 5-year survival with patients residing in the SEER region. To the best of the author's knowledge, this was the first time lung cancer survival direct comparison had been documented between Nevada and SEER. Studies had been conducted to evaluate lung cancer survival disparities (Forrest et al., 2013; Mulligan et al., 2006; Niu et al., 2013) although none of these studies were specific to Nevada. Some studies showed overall poorer survival for African Americans and other minorities compared to Whites (Gadgeel et al., 2001; Schwartz & Swanson, 1997). In this study, although Blacks had lower 5-year unadjusted lung cancer survival rate, both univariate and multivariate Cox analysis failed to show any statistically significant difference between Blacks and Whites. This findings matched that of Mulligan et al.(2006) where no racioethnic differences in survival were observed under equal access to healthcare. That study had suggested that inequality in medical care access could have been responsible for a large proportion of racioethnic differences in lung cancer survival. The reason for absence of lung cancer survival disparity between Blacks and Whites in Nevada is likely complex and multifactorial. As demonstrated in the Mulligan study, it might be a reflection of similar healthcare access in White and Black lung cancer patients in Nevada. Unlike other cancers, due to the fatality of lung cancer, the nature of the disparities may be different. The usual prognostics factors associated with other cancers may be attenuated here. It is also plausible, that some unaccounted confounders affected the findings despite adequacy of study design and size.

More studies are warranted in this area to fully explain lung cancer (or lack thereof) disparity in Nevada. Native Americans had significantly lower overall survival rates compared to Whites. This was in keeping with previous findings (Lanier, Day, Kelly, & Provost, 2008.; Plescia, Henley, Pate, Underwood, & Rhodes, 2014). This result confirms that Nevada Native American patients with lung cancer, like their counterparts across United States, are experiencing more mortality, likely due to disparities. However, it should be put in proper context during interpretation. The small number of Native American cancer patients means one person could easily influence the result.

As with other studies such as that by Tannenbaum et al., (2014), this study suggested that the Hispanics and Asians/PFI had better lung cancer survival rates compared to Whites. However, there have been questions raised over the accuracy of these findings due to inherent death linkage problems for foreign-born populations (Pinheiro , Morris , Liu & Bungum , 2014).

Females did better than their male counterparts across all racial/ ethnicity classes. This was in keeping with previous study findings that showed women have greater survival rates regardless of stage, histology, treatment modality or smoking status, even after adjusting for gender-specific life expectancy (Fu, Kau, Severson, & Kalemkerian, 2005; Thomas, Doyle, & Edelman, 2005). This study was not designed to tease out the reason for this difference. It may also be related to the fact that more men were smokers. Nonsmoking status predicts better survival and may possibly predict better response to therapy (Sun, Schiller, & Gazdar, 2007). The etiology behind these observations is theorized to be related to genetic and molecular differences (Berardi et al., 2009). Better survival in older women may be related to higher prevalence of co-morbidities among men of the same age (Fu et al., 2005).

There have been conflicting views in terms of survival between SCC and ADK (Gail et al., 1984; L. cancer study Group, 1987). Lung cancer study group found that lung cancer recurrences are histopathologically dependent in Stage I NSCLC, with higher rates occurring among patients with non SCC. In contrary, this study found that patients with ADK of the lung had better survival compared to SCC after multivariate adjustment. As expected, the study showed that patients with SCLC were at higher risk of dying compared with SCC.

This study was able to show significant survival difference between Southern Nevada and Northwestern Nevada. This was in keeping with regional disparities noted for other cancers described previously (Pinheiro et al., 2012). Although the reason for this regional disparity is not clear, it may be related to fewer surgeries being done on localized NSCLC in Southern Nevada. The study found that localized NSCLC patients in Southern Nevada were less likely to receive surgical treatment compared to similar patients in Northwestern Nevada. Surgery has been shown to be the single most important treatment and best chance for cure in localized NSCLC. If this result is true and does not correspond to a data artifact, such as a disproportionate lack of completeness in recording of treatments of lung cancer cases by NCCR for Southern Nevada, then this is a very important finding for lung cancer disparities in the State.

Stage at diagnosis was proven to be the strongest factor affecting lung cancer survival in this study. Early diagnosis increases the chances of successful curative surgical treatment. Those with distant disease were three and half times more likely to die over period of study after simultaneously adjusting for all other factors. Blacks and other racial groups were more likely to present late.

Inequalities in access to and receipt of quality health care had been reported as a possible determinant of lung cancer survival disparities. This study found that uninsured and Medicaid patients were at higher risk of death compared to patients with Private insurance or Medicare after adjusting for other factors. This was expected as previous studies had reported similar findings (Niu et al., 2013). Forrest et al., (2013) looked at SES as a determinant of lung cancer survival disparity amongst race/ethnicity groups. They found that patients with lung cancer living in more socioeconomically deprived circumstances are less likely to receive any type of treatment, surgery, or chemotherapy. Like the Forrest study, this study found that lung cancer patients of low SES were at higher risk of death compared to higher and middle SES. This could be due to lack of receipt of treatment or lack of access to health care.

This study also found that married patients with lung cancer had better 5 year survival. Marital status has been cited as an important determinant of lung cancer survival outcomes (Jatoi et al., 2007; Saito-Nakaya et al., 2008). The positive effects of marriage on lung cancer survival have been linked to good social networks, which in turn influence positively neuroendocrine or neuroimmune pathways, health behaviours, access to health care systems and assistance with navigating its complexities, the likelihood of receiving vigorous and aggressive, and active cancer treatment (Pinquart & Duberstein, 2010).

Age at diagnosis is also an important predictor of survival for patients with lung cancer survival (Howlader N, et al., 2014). This study showed increasing risk of death with aging. Aging is generally associated with a decrease in many bodily functions. Consequently elderly patients do not have as much physical reserve to combat a serious illness such as cancers as do younger people. In this study, all racial minorities had a higher proportion of their population presenting at younger age compared to Whites.

Strengths

This study provides an examination of survival disparities among individuals with lung cancer for the first time in the state of Nevada. The NCCR data provided a large study population with fairly representative proportions of race and ethnic groups allowing for the study of lung cancer survival disparities. Matching vital status with SSDI improved accuracy of the assessment through complete capture of deaths.

Limitations

The quality (completeness) of the data on key variables such as stage of diagnosis and histology for which many cancers have an unspecified morphology or stage could have influenced the results of this study. The quality of treatment data in cancer registries has not been thoroughly assessed across the United States(Bray & Parkin, 2009; Cress et al., 2003; Inwald, Klinkhammer-Schalke, Koller, & Ortmann, 2014; Parkin & Bray, 2009; Sinclair et al., 2012; Smith-Gagen, Cress, Drake, Felter, & Beaumont, 2005). Also, SES of the study population was based on proportion of population under poverty level. This is an ecological measure, which might be subject to some degree of ecological fallacy.

Chapter 5

Conclusion

This study provides much needed baseline lung cancer survival data for Nevada. Lung cancer is a very fatal cancer. Nevada's survival rate is comparable to SEER regions. All variables of interest contributed significantly to patients' survival even after simultaneously adjusting for other variables. There was no lung cancer survival disparity between Blacks and Whites after adjustment for other confounders. The better survival profile of Hispanics and Asian/PFI should be interpreted with caution. There is survival disparity across regions, and this may be explained in part by lower receipt of surgery at early stage when surgery could impact survival. This finding in particular needs to be further studied in order to determine the true cause of regional and racial lung cancer disparities in Nevada.

Appendix

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Biomedical IRB – Exempt Review
Modification Approved

NOTICE TO ALL RESEARCHERS:
Please be aware that a protocol violation (e.g., failure to submit a modification for any change) of an IRB approved protocol may result in mandatory remedial education, additional audits, re-consenting subjects, researcher probation, suspension of any research protocol at issue, suspension of additional existing research protocols, invalidation of all research conducted under the research protocol at issue, and further appropriate consequences as determined by the IRB and the Institutional Officer.

DATE: July 14, 2014

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

FROM: Office of Research Integrity - Human Subjects

RE: Notification of IRB Action
Protocol Title: Lung Cancer Survival Disparities in Nevada
Protocol #: 1403-4762M

The modification of the protocol named above has been reviewed and deemed exempt.

Modifications reviewed for this action include:
- Addition of Chima Osuoha to the research team.

This IRB action does not change your exempt status.

Should there be *any* change to the protocol, it will be necessary to notify ORI - Human Subjects. No changes may be made to the existing protocol until modifications have been reviewed and a determination has been made by the ORI-HS and/or the IRB. Modified versions of protocol materials must be used upon final determination. Unanticipated problems, deviations to protocols, and adverse events must be reported to the ORI – HS within 10 days of occurrence.

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

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