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Effects of Obesity and Smoking on Survival in Non-Small Cell Lung Cancer

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Abstract

Background: Obesity is an emerging leading cause of morbidity and mortality in the US and the relationship between obesity, tobacco, and survival in NSCLC is unclear. Methods: Data (n = 87,631) were obtained from linkage of the 1996-2007 Florida Cancer Data System to the Agency for Health Care Administration database providing procedure and diagnoses codes. Survival time was calculated from date of diagnosis to date of death. Smoking status was categorized as never, current, and former. Obesity (yes/no) = ICD9 code BMI > 30 kg/m², cachexia = ICD9 code "wasting syndrome", & non-obese = non-obese & non cachectic. Cox proportional regression models used to predict survival; demographic, clinical, treatment factors, & comorbidities were included in adjusted models with smoking status and obesity as the main factors. Results: The majority of patients (pts) were either former (49%) or current (40%) smokers, & non-obese (88%). 6.8% of pts were obese & 4.8% of pts were cachectic. There were significant differences between survival curves and median survival (months) for obese vs. non-obese vs. cachectic pts. (20 vs 10 vs. 7.9; P < 0.001). Former and current smokers had shorter median survival than never smokers (10.8 & 9.2 vs. 11.9; P < 0.001). Survival rates (%) at 1-yr (60.1 vs. 45.2 vs. 37.7; P < 0.001), 5-yr (30.3 vs. 15.4 vs. 9.5; P < 0.001), 10-yr (18.1 vs. 7.6 vs. 2.7; P < 0.001) were better for obese vs. non-obese and cachectic pts respectively. Independent predictor of worse survival in the unadjusted model was former (HR 1.08; P < 0.001) and current (HR 1.20; P < 0.001) smokers compared to never. Obese and non-obese pts had better survival vs. cachexia pts. (HR 0.52; P < 0.001 and HR 0.80, p < 0.001 respectively) and obese had better survival than Non-obese pts (HR 0.65, p < 0.001). In the adjusted model, controlling for extensive variables and comorbidities, former (HR 1.11; P < 0.001) and current (HR 1.19; P < 0.001) smokers still had significantly worse survival vs. never smokers. Obese patients still had better survival (HR 0.87; P < 0.001, and HR 0.88, p < 0.001) vs. cachexia patients and non-obese respectively, survival rate was not significantly different compare non-

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obese with cachexia. Conclusions: Our results show that being a former or current smoker worsens survival while obesity improved survival when compared with cachexia patients or Non-obese.

Keywords

Lung Cancer, Non-Small Cell Lung Cancer, Tobacco, Smoking, Obesity

1. Introduction

Tobacco, the leading cause of preventable death in the United States (US), has been linked to the development of many cancers, most notably lung cancer [1]. Other risk factors for lung cancer have been explored in the literature: radon gas [2], asbestos exposure [3], high-dose beta carotene [4], low dietary consumption of fruits and vegetables [5], and obesity [6]. Smoking not only increases the risk of developing lung cancer but is also associated with decreased survival after diagnosis [7]. Although obesity is a major cause of morbidity and mortality in the US, the impact of obesity on lung cancer survival is unclear. Furthermore, the interrelationship between obesity, tobacco, and survival time after diagnosis for patients with non-small cell lung cancer (NSCLC) is uncertain. We examined BMI and smoking as predictors of survival in patients with NSCLC using a population-based cancer registry in the state of Florida.

2. Methods

After institutional review board approval, data were obtained from linkage of the 1996-2007 Florida Cancer Data System (FCDS), a population-based cancer registry, to the Agency for Health Care Administration (AHCA) database which provides procedure and diagnoses codes, and the US census. We followed this cohort for an additional 3 years to allow for a determination of survival status through the year 2010.

2.1. Sample

Inclusion criteria were all adult patients 18 years or older diagnosed with NSCLC from 1996-2007 and residing in the state of Florida during 1996-2007 (n = 106,824). Exclusion criteria were patients with missing values on age of diagnosis, county of diagnosis, survival time, race, ethnicity, socioeconomic status (SES), smoking history, and obesity. Also, patients with carcinoma in situ were excluded. A total of 19,193 patients were excluded and 87,631 patients met full inclusion criteria.

2.2. Variables

Overall survival (OS) was defined as the time from diagnosis to death (information found in the FCDS database) from any cause with surviving patients censored at the date of last contact. Self-reported smoking status was categorized as never, current, and former. Obesity (yes/no) was determined by presence of an ICD9 diagnosis code for obesity indicating body mass index (BMI) of ≥30. Cachexia was determined by presence of ICD9 diagnosis code for "wasting syndrome". Non-obese patients were all non-obese and non-cachectic patients.

Sociodemographic variables for patients in our data included: race (Black, White, or Other), ethnicity (Hispanic/non-Hispanic), SES (derived from the US census using percent of households in a census tract living below the federal poverty line and categorized as lowest [≥20% below poverty line], middle low [<20 and >10%], middle high [≥5 and ≤10%], highest [<5%]), age at diagnosis, sex, marital status (married, never married, divorced/widowed/separated), treating facility type (academic vs. non-academic), treating hospital volume (low vs. high), insurance status (uninsured, private, Medicaid, Medicare, veteran/military).

Pathological and clinical characteristics included: number of co-morbid conditions (none, 1 - 2, 3 - 4, >4), Surveillance Epidemiology and End Results (SEER) stage at diagnosis (localized, regional with direct extension +/− lymph nodes, regional with lymph nodes only, distant, unknown/unstaged), grade (undifferentiated, poorly-differentiated, moderately-differentiated, well-differentiated, unknown), histologic type (adenocarcinoma, squamous cell carcinoma/combined complex, neuroendocrine, large cell and other), treatments of chemotherapy,

radiation therapy, and surgery (yes/no/unknown).

2.3. Statistical Analysis

Descriptive statistics of the demographic, pathological, and clinical characteristics were calculated for the overall sample as well as by smoking status and obesity status. Frequencies and percentages are shown for categorical variables and means, standard deviations, medians, first and the third quintiles for the continuous variables. The overall survival rates at 1-, 3-, 5-, and 10-years were calculated for the whole population, by smoking status, by presence of obesity status, and by smoking status x obesity status. Median overall survival was estimated and survival curves were plotted using the Kaplan-Meier methodology. Log-rank tests were used for the survival plots to compare overall survival by smoking status, and obesity status.

Cox proportional hazards regression models were used to determine the effect of potential factors on OS. Unadjusted and adjusted hazard ratios (HR), 95% confidence intervals (95% CI) and p-values were calculated from these models. We first performed univariate Cox regression to examine the association of OS with smoking, obesitystatus, and other factors such as race, ethnicity, and SES, respectively. Multivariate Cox regression models were then performed with the main predictors of smoking status and obesity. We adjusted for potential confounding variables using the sociodemographic variables in **Table 1**, the clinical characteristic variables in **Table 2**,

Table 1. Demographic characteristics of lung cancer stratified by smoking status and obesity status (column %).

Variable	Total patients		Tobacco use						Obesity					
			Never		History		Current		Cachexia		Non-obese		Obese	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total patients	87,631	100.0	9326	100.0	43,270	100.0	35,035	100.0	4175	100.0	77,526	100.0	5930	100.0
Tobacco use														
Never smoke	9326	10.6	9326	100.0	-	-	-	-	290	6.9	8308	10.7	728	12.3
History smoke	43,270	49.4	-	-	43,270	100.0	-	-	1611	38.6	38,350	49.5	3309	55.8
Current smoke	35,035	40.0	-	-	-	-	35,035	100.0	2274	54.5	30,868	39.8	1893	31.9
Obesity														
Cachexia	4175	4.8	290	3.1	1611	3.7	2274	6.5	4175	100.0	-	-	-	-
Non-obese	77,526	88.5	8308	89.1	38,350	88.6	30,868	88.1	-	-	77,526	100.0	-	-
Obese	5930	6.8	728	7.8	3,309	7.6	1893	5.4	-	-	-	-	5930	100.0
Race														
White	80,480	91.8	8336	89.4	40,571	93.8	31,573	90.1	3472	83.2	71,586	92.3	5422	91.4
Black	6492	7.4	792	8.5	2425	5.6	3275	9.3	668	16.0	5335	6.9	489	8.2
Other	659	0.8	198	2.1	274	0.6	187	0.5	35	0.8	605	0.8	19	0.3
Hispanic origin														
Non-hispanic	82,377	94.0	8372	89.8	41,096	95.0	32,909	93.9	3912	93.7	72,911	94.0	5554	93.7
Hispanic	5254	6.0	954	10.2	2174	5.0	2126	6.1	263	6.3	4,615	6.0	376	6.3
Age at diagnosis (yrs)														
Mean	68.9		71.1		71.6		64.9		66.9		69.1		67.7	
STD	10.9		12.5		9.6		10.7		11.4		10.9		10.0	
Median	70.0		73.0		73.0		66.0		68.0		70.0		69.0	
Q1, Q3	62.0	77.0	64.0	80.0	66.0	78.0	58.0	73.0	59.0	76.0	62.0	77.0	61.0	75.0
Min, Max	18.0	104.0	18.0	102.0	20.0	104.0	22.0	102.0	21.0	98.0	18.0	104.0	22.0	96.0
Sex														
Female	38,445	43.9	5801	62.2	17,648	40.8	14,996	42.8	1517	36.3	33,889	43.7	3039	51.2
Male	49,186	56.1	3525	37.8	25,622	59.2	20,039	57.2	2658	63.7	43,637	56.3	2891	48.8

Table 2. Pathological and clinical characteristics (column %).

Variable	Total patients		Tobacco use						Obesity					
			Never smoke		History smoke		Current smoke		Cachexia		Non-obese		Obese	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total patients	87,631	100.0	9,326	100.0	43,270	100.0	35,035	100.0	4,175	100.0	77,526	100.0	5930	100.0
Co-morbidity														
None	4213	4.8	574	6.2	1874	4.3	1765	5.0	-	-	4213	5.4	-	-
1 - 2	2594	3.0	411	4.4	1155	2.7	1028	2.9	2	0.0	2585	3.3	7	0.1
3 - 4	6530	7.5	954	10.2	3001	6.9	2575	7.3	52	1.2	6412	8.3	66	1.1
>4	74,294	84.8	7387	79.2	37,240	86.1	29,667	84.7	4121	98.7	64,316	83.0	5857	98.8
SEER stage														
Localized	19,546	22.3	2,278	24.4	10,253	23.7	7015	20.0	715	17.1	16,964	21.9	1867	31.5
Regional, direct extension ± lymph nodes	13,140	15.0	1074	11.5	6613	15.3	5453	15.6	625	15.0	11,635	15.0	880	14.8
Regional, lymph nodes only	9123	10.4	801	8.6	4655	10.8	3667	10.5	366	8.8	8064	10.4	693	11.7
Distant	35,917	41.0	3824	41.0	16,688	38.6	15,405	44.0	1973	47.3	32,061	41.4	1883	31.8
Unknown/Unstaged	9905	11.3	1349	14.5	5061	11.7	3495	10.0	496	11.9	8802	11.4	607	10.2
Grade														
Undifferentiated	2822	3.2	206	2.2	1,295	3.0	1321	3.8	151	3.6	2538	3.3	133	2.2
Poorly-differentiated	27,782	31.7	2,186	23.4	13,320	30.8	12,276	35.0	1368	32.8	24,683	31.8	1731	29.2
Moderately-differentiated	15,981	18.2	1539	16.5	8299	19.2	6,143	17.5	681	16.3	14,094	18.2	1206	20.3
Well-differentiated	4437	5.1	814	8.7	2308	5.3	1315	3.8	159	3.8	3904	5.0	374	6.3
Unknown/not stated	36,609	41.8	4581	49.1	18,048	41.7	13,980	39.9	1816	43.5	32,307	41.7	2486	41.9
Regional Nodes Positive														
No	16,169	18.5	1,656	17.8	8400	19.4	6,113	17.4	523	12.5	14,101	18.2	1545	26.1
Yes	8568	9.8	816	8.7	4348	10.0	3404	9.7	295	7.1	7663	9.9	610	10.3
Unknown	62,894	71.8	6854	73.5	30,522	70.5	25,518	72.8	3357	80.4	55,762	71.9	3775	63.7
Histology														
Adenocarcinoma	38,684	44.1	5173	55.5	19,391	44.8	14,120	40.3	1650	39.5	34,509	44.5	2525	42.6
Squamous/combine complex	26,270	30.0	1675	18.0	13,080	30.2	11,515	32.9	1433	34.3	23,047	29.7	1790	30.2
Neoendocrine	2277	2.6	692	7.4	910	2.1	675	1.9	58	1.4	1899	2.4	320	5.4
Large cell	7038	8.0	608	6.5	3341	7.7	3089	8.8	338	8.1	6353	8.2	347	5.9
Other	13,362	15.2	1178	12.6	6548	15.1	5636	16.1	696	16.7	11,718	15.1	948	16.0
Chemotherapy														
No	55,362	63.2	6407	68.7	27,483	63.5	21,472	61.3	2512	60.2	49,063	63.3	3787	63.9
Yes	28,410	32.4	2544	27.3	13,976	32.3	11,890	33.9	1513	36.2	25,037	32.3	1860	31.4
Unknown	3859	4.4	375	4.0	1811	4.2	1673	4.8	150	3.6	3426	4.4	283	4.8
Radiation therapy														
No	47,544	54.3	6060	65.0	23,439	54.2	18,045	51.5	2086	50.0	41,883	54.0	3575	60.3
Yes	38,193	43.6	3091	33.1	18,977	43.9	16,125	46.0	2002	48.0	33,937	43.8	2254	38.0
Unknown	1894	2.2	175	1.9	854	2.0	865	2.5	87	2.1	1706	2.2	101	1.7
Surgery														
No	59,852	68.3	6304	67.6	28,936	66.9	24,612	70.2	3271	78.3	53,121	68.5	3460	58.3
Yes	26,836	30.6	2900	31.1	13,894	32.1	10,042	28.7	870	20.8	23,571	30.4	2395	40.4
Unknown	943	1.1	122	1.3	440	1.0	381	1.1	34	0.8	834	1.1	75	1.3

and 31 individual Elixhauser comorbidity conditions entered as yes/no variables. We examined the models for violations of the proportional hazards assumptions, and found no violations. We also found no significant interactions between obesity status and smoking status in the adjusted models. The outcomes of patients treated at individual facilities are not independent, and therefore, we used robust standard errors to adjust for this clustering of patients in facilities. Statistical analyses were conducted using SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina).

3. Results

The majority of patients were former (49.4%) or current (40%) smokers, and not obese (88.5%) (**Table 1**). 6.8% of patients were obese and 4.8% of patients were cachectic. The median age at diagnosis was 70 years old with a range of 18 to 104 years old. Most patients were male (56.1%), White (91.8%) and non-Hispanic (94%) patients. The mean age at diagnosis of current smokers was substantially younger (64.9 years) than that of former smokers (71.6 years) or never smokers (71.1 years). A higher percentage of never smokers were female (62.2%) than male (37.8%); whereas more current smokers were male (57.2%) than female (42.8%).

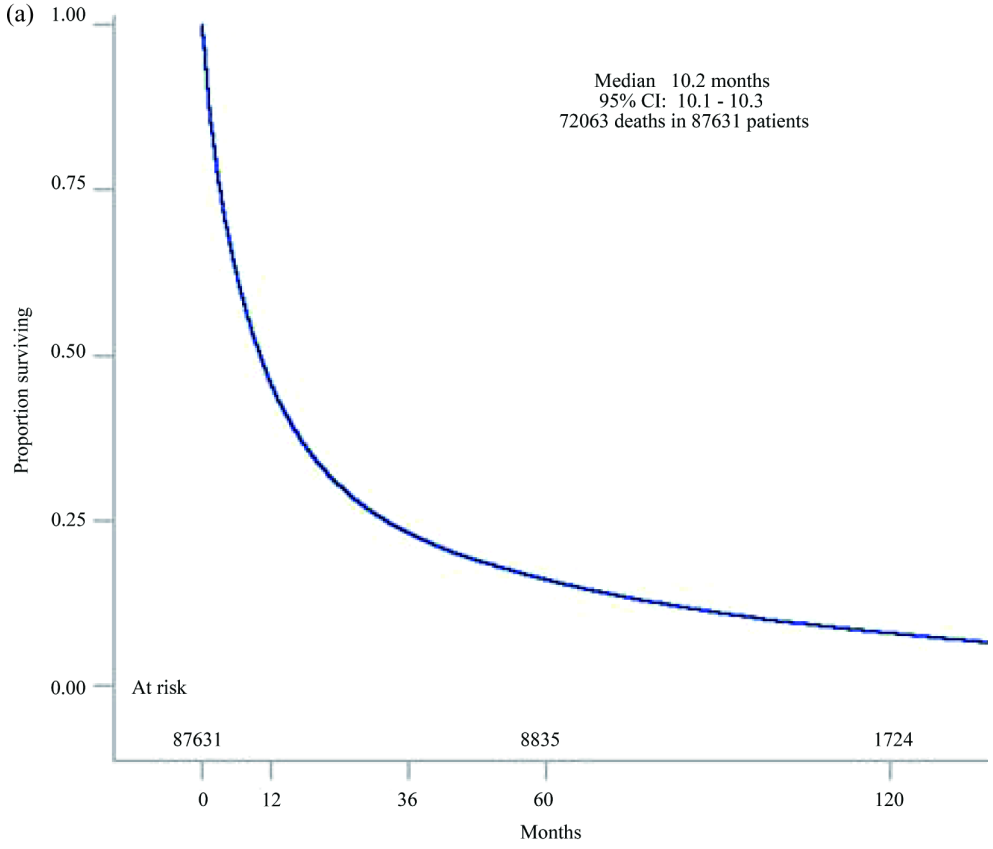
Table 2 shows clinical characteristics of patients. There was a high rate of comorbidities in this population, with 84.8% overall having 4 or more comorbidities. The most common comorbidities include congestive heart failure, cardiac arrhythmia, hypertension, diabetes, and depression. More current (84.7%) and former (86.1%) smokers had 4 or more comorbidities than did never smokers (79.2%); and a much higher percentage of obese patients (98.8%) and cachectic patients (98.7%) had 4 or more comorbidities than did non-obese patients (83.0%). Conversely, obese patients were more likely to be diagnosed with localized disease (31.5%) than were non-obese patients (21.9%) and cachectic patients (17.1%). Also obese patient were less likely to be diagnosed with distant disease (31.8%) compared with non-obese (41.4%) and cachectic patients (47.3%). The majority of patients who never smoked had adenocarcinoma (55.5%) compared with 44.8% of former smokers and 40.3% of current smokers (**Table 2**). In terms of treatments, 40.4% obese patients vs. 30.4% of non-obese patients vs 20.8% of cachectic patients had surgery (**Table 2**). 31.4% of obese patients vs. 32.3% of non-obese patients vs. 36.2% of cachectic patients had chemotherapy. 38% of obese patients had radiation vs. 43.8% of non-obese patients vs. 48% of cachectic patients.

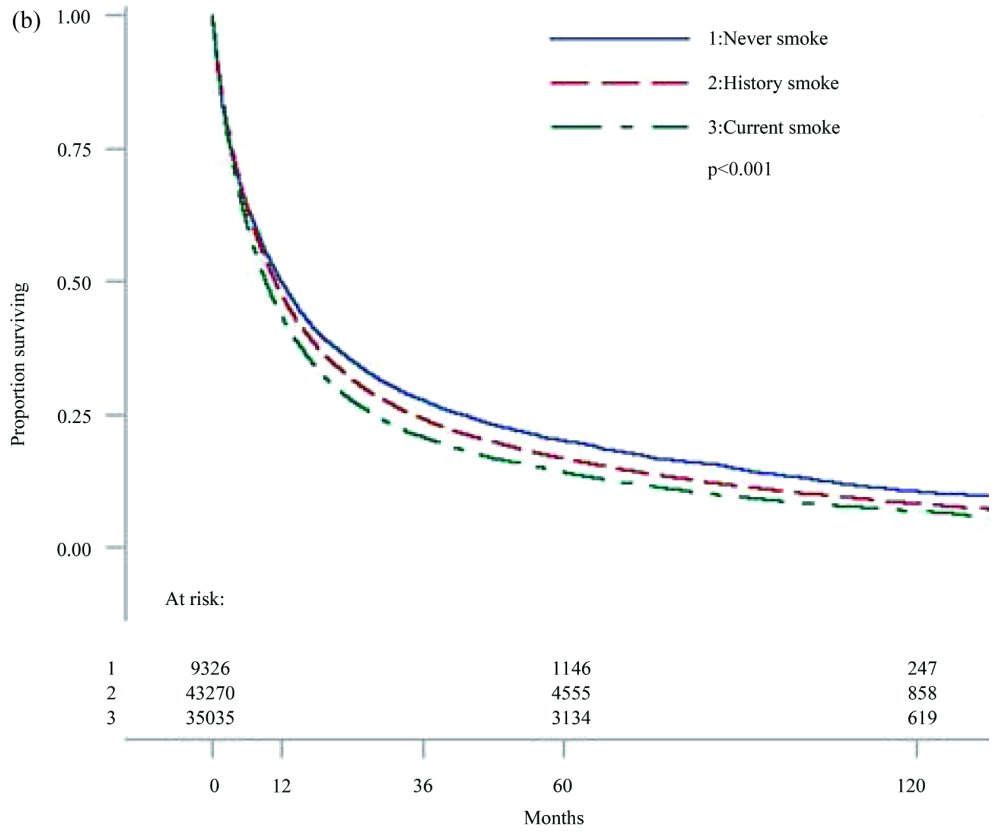
The overall median survival time (MST) of patients was 10.2 months (**Table 3**). Median survival was 20.0 vs. 10.0 vs. 7.9 months for obese vs. non-obese vs. cachectic, respectively ($p < 0.001$). Survival rates (%) were better for obese vs. non-obese vs. cachectic patients: 1-year (60.1 vs. 45.2 vs. 37.7; $p < 0.001$), 5-year (30.3 vs. 15.4 vs. 9.5 $p < 0.001$), and 10-year (18.1 vs. 7.6 vs. 2.7 $p < 0.001$). Median survival times by smoking status were 9.2 (current), 10.8 (former) and 11.9 (never) months (**Table 3**). Survival rates (%) were worse for current and former smokers vs. never smokers at 1, 3, 5, and 10 years.

Figure 1 shows Kaplan-Meier survival curves for the entire population, by smoking status, and by obesity status. There are significant differences in overall survival by obesity status, with patients who are obese having significantly better survival than non-obese and cachectic patients (log rank test, $p < 0.001$). Also, significant differences in overall survival by smoking status, with survival lowest for current smokers and highest for never smokers (log rank test, $p < 0.001$).

Table 3. Median and survival rates, n = 87,631.

	Median survival (months)	Survival rates (%) at time (yrs) after diagnosis			
		1 yr	3 yrs	5 yrs	10 yrs
Overall	10.2	45.8	23.2	16.1	8.0
Tobacco use					
Never	11.9	49.6	27.7	20.1	10.6
History	10.8	47.2	24.2	16.8	8.3
Current	9.2	43.1	20.8	14.2	6.9
Obesity					
Cachexia	7.9	37.7	15.0	9.5	2.7
Non-obese	10.0	45.2	22.5	15.4	7.6
Obese	20.0	60.1	38.6	30.3	18.1


(a)
1.00
0.75
0.50
0.25
0.00
Proportion surviving
Median 10.2 months
95% CI: 10.1 - 10.3
72063 deaths in 87631 patients
At risk
87631
8835
1724
0
12
36
60
120
Months


(b)
1.00
0.75
0.50
0.25
0.00
Proportion surviving
1:Never smoke
2:History smoke
3:Current smoke
p<0.001
At risk:
1 9326 1146 247
2 43270 4555 858
3 35035 3134 619
0
12
36
60
120
Months

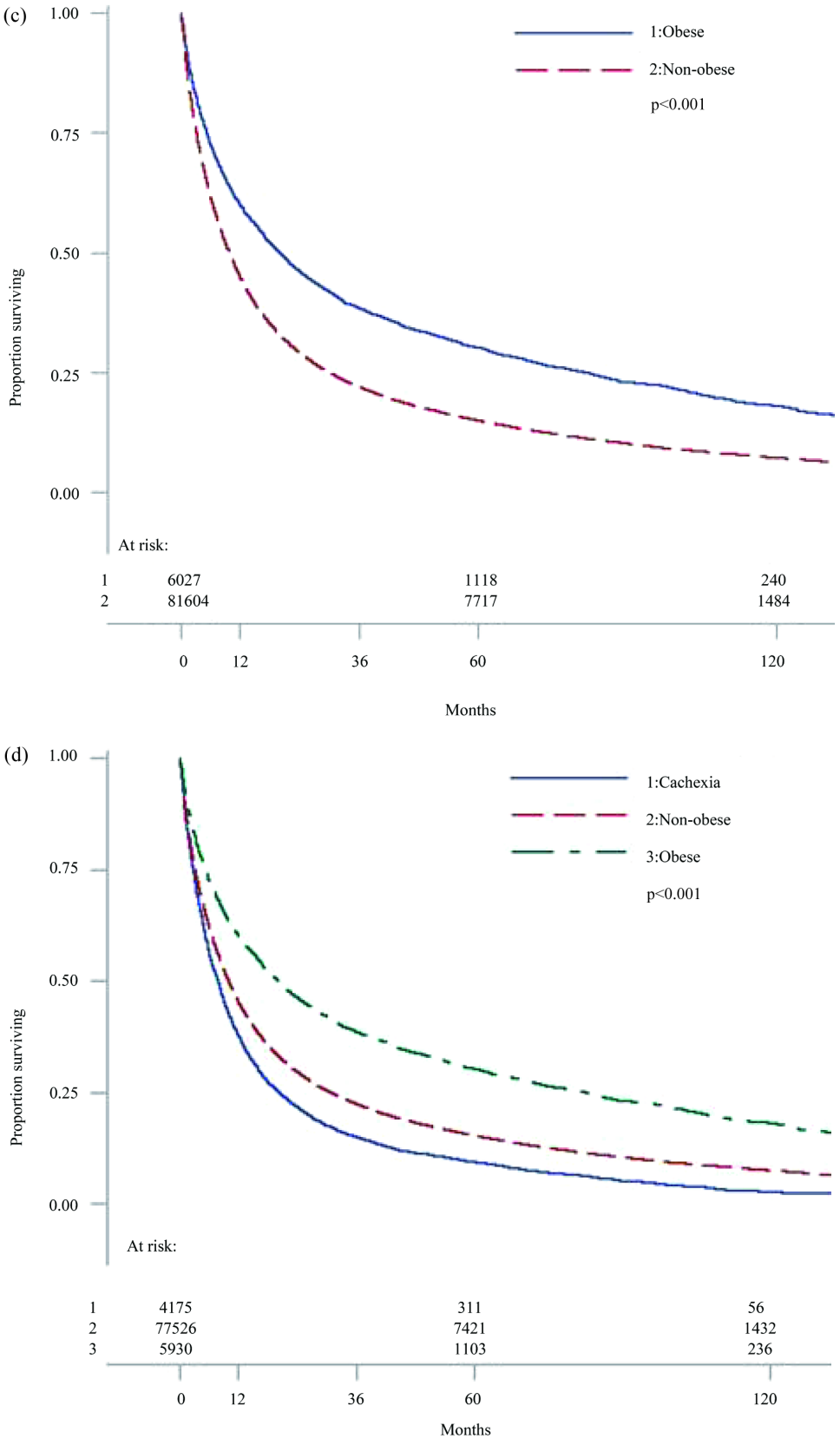


Figure 1. Survival plots.

Table 4 shows results from the univariate and multivariate Cox regressions. In the univariate model, compared to never smokers, former (HR 1.08; 95% CI 1.06 - 1.11, P < 0.001) and current smokers (HR 1.20; 95% CI 1.16 - 1.23, P < 0.001) had significantly worse survival. Obese and non-obese patients had better survival when compared with cachectic patients (HR 0.52; 95% CI 0.49 - 0.54, P < 0.001 & HR 0.80; 95% CI 0.77 - 0.82 respectively). Furthermore obese patients had better survival compared with non-obese patients (HR 0.65; 95% CI 0.63 - 0.67). Blacks had significantly worse and patients in higher SES categories had significantly better survival in univariate models.

In the multivariate model, controlling for all confounding variables and individual co-morbidities, former (HR 1.11; 95% CI 1.08 - 1.14, P < 0.001) and current (HR 1.19; 95% CI 1.15 - 1.23, P < 0.001) smokers still had significantly worse survival compared with never smokers. Obese patients still maintained better survival (HR 0.87; 95% CI 0.81 - 0.92, P < 0.001 & HR 0.88; 95% CI 0.85 - 0.91 P < 0.001) than non-obese patients. After controlling for demographic and clinical characteristics, Blacks no longer had worse survival than Whites. However, Hispanics now showed significantly better survival compared with non-Hispanics (HR 0.94; 95% CI 0.88 - 1.00, P < 0.001) and other race had better survival compared to White (HR 0.89; 95% CI 0.81 - 0.96, P = 0.005). Patients with highest (HR 0.88; 95% CI 0.84 - 0.91, P < 0.001) and middle-high (HR 0.92; 95% CI 0.89 - 0.95, P < 0.001) SES maintained better survival compared with lowest SES.

There were no significant interactions between smoking status and obesity in the adjusted model.

4. Discussion

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males in 2008 globally [1]. Among females it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death [1]. In the US, there will be an estimated 228,000 new cases of lung cancer and 159,500 deaths in 2013 [8]. Cigarette smoking has been positively correlated with lung cancer (both small-cell and non-small cell) in North America and Europe [3] and has been shown to increase mortality from lung cancer when compared with never-smoking patients [7] [9]. The results of our study confirm this relationship: never smokers had better survival compared with former and current smokers.

The relationship between obesity and NSCLC is not as obvious as that of smoking. While studies show that obesity is a strong risk factor for many cancers including colon, breast, endometrial, stomach, pancreas, gallbladder, and liver cancer [6] [10] [11], there is evidence that obesity may be protective against lung cancer risk [12]-[21]. There are studies, however, that show null [22]-[24], mixed [25] or opposite [26] results for the protective effect of obesity. A meta-analysis by Yang *et al*. found that excess body weight was inversely associated with incidence of NSCLC [27]. This study, however, was criticized for large heterogeneity of results, lack of-formal evaluation of study quality, and confounding by smoking [28].

The association of increased BMI and NSCLC survival is not as well defined in the literature as the data on BMI and risk of developing NSCLC. Calle *et al.* conducted a prospective cohort analysis of different cancer types including lung cancer patients and concluded that increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites [6]. In this study there was a significant inverse association between BMI and death from lung cancer in the total populations with greater effect at larger BMI categories. However, these investigators did not separately analyze NSCLC and small-cell lung

Table 4. Cox proportional hazard regression models, n = 87,631.

		Univariate		Multivariate	
Prognostic factors	**Category**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
FCDS tobacco use	Never	1.00		1.00	
	History	1.08 (1.06, 1.11)	<0.001	1.11 (1.08, 1.14)	<0.001
	Current	1.20 (1.16, 1.23)	<0.001	1.19 (1.16, 1.23)	<0.001
Obesity	Cachexia	1.00		1.00	
	Non-obese	0.80 (0.77, 0.82)	<0.001	0.99 (0.94, 1.04)	0.548
	Obese	0.52 (0.49, 0.54)	<0.001	0.87 (0.81, 0.92)	<0.001
	Obese vs. Non-obese (1.00)	0.65 (0.63, 0.67)	<0.001	0.88 (0.85, 0.91)	<0.001

cancer. [6]. When subgroup analyses were performed on patients who were never smokers, the inverse association was present, but not statistically significant. The lack of significance might be due to the relatively small sample size in that analysis (n = 156 males, n = 476 females). In another study Attaran *et al.* performed a propensity-matched analysis showing for the first time that following resection for lung cancer, survival was significantly higher in patients with a BMI ≥ 30 compared with those with BMI < 30 [29].

To the best of our knowledge, this is the largest study that has demonstrated a positive association between BMI and survival in NSCLC. There are several explanations as to how obesity is associated with survival benefit, including genetic, endocrine, and nutritional components. Brennen *et al*. recently reported that one allele of the fat mass and obesity-associated (FTO) gene, which has been linked with increased BMI, was associated with a decreased risk of lung cancer [30]. The mechanism for this protective effect, however, is not clear [30].

Adipose tissue is considered an active and functional endocrine organ that may play a central role in explaining why obesity is protective in NSCLC. Abdul-Ghafar *et al.* demonstrated that expression of Adiponectin Receptor 1 (adipo R1) is indicative of a favorable prognosis in NSCLC [11]. Adiponectin may have a protective role in carcinogenesis as it has anti-angiogenic [31], anti-proliferative [32], proapoptotic effects, and also arrests cell growth [33] [34].

Females have lower incidence and higher survival rates in NSCLC when compared with males across all races [35]. It seems reasonable to hypothesize that females might have improved outcomes because of a protective effect from hormones such as estrogen. In fact, a recent retrospective analysis conducted by Katcoff *et al.* showed that the combination of estrogen plus progesterone plus the use of long term hormone therapy were associated with significant improvements in women with NSCLC [36]. Like women, obese individuals have higher levels of estrogens which might play a role in increased survival in NSCLC.

Consumption of phytochemicals and antioxidant-rich foods, such as fruit and vegetables, has a known protective effect on lung cancer risk [37]; accordingly, this protection may also be afforded to those with a diagnosis of NSCLC. It could therefore be hypothesized that obese individuals have higher intake of fruits and vegetables (or other unknown protective compounds) as a result of increased overall food intake and portion sizes thereby receiving more protective nutrients than those with a smaller total dietary intake.

Nutritional reserve may provide some explanation as to why obesity is protective in NSCLC survival. Cachexia which is commonly seen in NSCLC may not be as devastating in obese individuals because there is an ample energy supply in adipose tissue and supporting musculature of obese individuals. This may not provide an adequate explanation, however, given that increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites [6].

In our study obese patients had 31.5% localized presentations compared with 21.9% in non-obese and 17.1% of cachectic patients. 31.8% of obese patients had distant disease vs. 41.4% of non-obese patients and 47.3% of cachectic patients which would give this cohort of obese patients a survival advantage. Furthermore 40.3% of obese patients received surgery vs. 30.4% of non-obese and 20.8% of cachectic patients. Given that surgery is a curative modality this could increase the survival of the obese patients compared to non-obese patients. However, our multivariate regression analyses included variables for both stage at diagnoses and treatment; therefore, our adjusted results controlled for these confounders. Therefore, additional non-measured clinical or treatment factors, e.g., quality of the surgery, would need to be at work for these type of factors to play a role in survival. Interestingly, the fact that obese patients present with more limited disease and less distant disease than non-obese and cachectic patients may represent a distinct less aggressive biologic entity.

We acknowledge some potential limitations in our study. Most notable was the usage of ICD-9 coding to identify the obesity status of patients. The inability to utilize actual height and weight data could have caused variability in the three categories: obese, non-obese, cachexia. However, this is a limitation of using a population-based cancer registry that is difficult to overcome.

On the other hand, our study presented a number of advantages. First, it included a large sample size (n = 87,631) which is important in providing adequate power to detect significant differences even when performing subgroup analysis by smoking status and obesity (**Figure 1**). Second, the broad time span from 1996-2007 plus 3 years of follow up time allowed adequate years to perform survival analysis (**Figure 1**). Third, we were able to control for many clinical and demographic factors, and comorbidities, thus minimizing many potential confounding variables. Fourth, we were able to include a “cachexia” arm with a significant number of patients (n = 4,175) which eliminated possible confounder of this subgroup on the non-obese population survival statistics. Last, we included only NSCLC patients whereas many previous studies combined both small-cell lung cancer

and NSCLC which are different disease entities.

5. Conclusion

Obese individuals with NSCLC survived longer than non-obese and cachectic patients. As expected, current or former smokers had worse survival compared to never smokers. Obesity may have a protective effect and provide a survival advantage. Further investigation to determine the mechanism of this benefit, *i.e.*, hormonal, metabolic, nutrition-related, is warranted. Alternately obesity may merely be an indicator of less advanced and/or less aggressive disease.

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