Long-term Survival Outcomes by Smoking Status in Surgical and Nonsurgical Patients With Non-small Cell Lung Cancer

Comparing Never Smokers and Current Smokers

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Background: Survival outcomes of never smokers with non-small cell lung cancer (NSCLC) who undergo surgery are poorly characterized. This investigation compared surgical outcomes of never and current smokers with NSCLC.

Methods: This investigation was a single-institution retrospective study of never and current smokers with NSCLC from 1975 to 2004. From an analytic cohort of 4,546 patients with NSCLC, we identified 724 never smokers and 3,822 current smokers. Overall, 1,142 patients underwent surgery with curative intent. For survival analysis by smoking status, hazard ratios (HRs) were estimated using Cox proportional hazard modeling and then further adjusted by other covariates.

Results: Never smokers were significantly more likely than current smokers to be women ($P < .01$), older ($P < .01$), and to have adenocarcinoma ($P < .01$) and bronchioloalveolar carcinoma ($P < .01$). No statistically significant differences existed in stage distribution at presentation for the analytic cohort ($P = .35$) or for the subgroup undergoing surgery ($P = .24$). The strongest risk factors of mortality among patients with NSCLC who underwent surgery were advanced stage (adjusted hazard ratio, 3.43; 95% CI, 2.32-5.07; $P < .01$) and elevated American Society of Anesthesiologists classification (adjusted hazard ratio, 2.18; 95% CI, 1.40-3.40; $P < .01$). The minor trend toward an elevated risk of death on univariate analysis for current vs never smokers in the surgically treated group (hazard ratio, 1.20; 95% CI, 0.98-1.46; $P = .07$) was completely eliminated when the model was adjusted for covariates ($P = .97$).

Conclusions: Our findings suggest that smoking status at time of lung cancer diagnosis has little impact on the long-term survival of patients with NSCLC, especially after curative surgery. Despite different etiologies between lung cancer in never and current smokers the prognosis is equally dismal.

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Abbreviations: aHR = adjusted hazard ratio; AJCC = American Joint Commission on Cancer; ASA = American Society of Anesthesiologists; BAC = bronchioloalveolar carcinoma; HR = hazard ratio; NSCLC = non-small cell lung cancer

Lung cancer is the leading cause of cancer death in the United States.¹ Although it is well known that lung cancer is associated with tobacco use, it is also apparent that never smokers are susceptible to the disease. Comparisons of genetic and epigenetic aberrations in non-small cell lung cancer (NSCLC) among smokers and never smokers have revealed marked differences in tumor biology that have resulted in clinicopathologic distinctions between smokers and

never smokers. Data have established that mutational differences in the active kinase domain of the epidermal growth factor receptor confer increased sensitivities of a subset of never smokers with lung cancer to tyrosine kinase inhibitors.^{2,3} Less well established is the actual natural history of NSCLC in never smokers compared with smokers. Emerging tumor biology data, especially recent reports highlighting fewer genomic alterations in never smokers, such as gene

copy number variations and somatic mutations, may imply that NSCLCs in never smokers are a less-aggressive malignancy.^{4,5} We examined whether patients with lung cancer caused by etiologies other than smoking have a better or worse prognosis than patients whose lung cancer was caused by smoking.

The current literature is equivocal. Whereas several studies report smoking to be a predictor of poor prognosis,⁶⁻¹² others have found no such association.¹³⁻¹⁹ One study reported smoking as a negative prognostic factor only in men,²⁰ whereas another found an association only in women.²¹ Even less is known about the survival of never smokers who undergo pulmonary resections with curative intent for NSCLC, with one recent study reporting a modest survival benefit of never smokers only in stage I patients with adenocarcinoma.²² One reason for the lack of clarity in the literature is that many large, epidemiology data sets lack the ability to adjust during their multivariate modeling for important comorbidities that contribute to reduced long-term survival. It is unclear whether these covariates were adequately controlled and whether the etiology of the NSCLC from either smoking or nonsmoking causes would be an independent predictor of long-term survival. Because we have available hospital records and clinically validated predictors of comorbidities, we reviewed our clinical outcomes over the past 30 years in a retrospective cohort study of 724 never smokers with NSCLC.

MATERIALS AND METHODS

Data Source

A retrospective analysis was performed using patient data collected from The Johns Hopkins Specialized Programs of Research

Excellence Lung Cancer Database, a single-institution database of patients with NSCLC who were clinically evaluated at The Johns Hopkins Hospital (Baltimore, MD). Data were obtained from cross-validated electronic and paper patient records. This study was approved by The Johns Hopkins institutional review board, which exempted the need for patient consent, and abides by Health Insurance Portability and Accountability Act compliance standards.

Patient Population

The study population consisted of 7,245 patients who were given a diagnosis of NSCLC between January 1, 1975, and December 31, 2004, and who received their primary medical and surgical treatment at The Johns Hopkins Hospital. From this study population of 7,245, an analytic cohort of 4,546 was derived after excluding patients lacking cancer stage information ($n = 59$); those with unknown smoking status ($n = 86$); those aged < 30 years ($n = 15$); those with tumor histology other than adenocarcinoma, squamous, adenosquamous, non-small cell not otherwise specified, large cell, or bronchioloalveolar carcinoma (BAC) ($n = 141$); and former-smokers ($n = 2,398$), who were excluded due to a lack of reliability about the timing of smoking cessation. Results are reported on this analytic cohort of 724 never smokers and 3,822 current smokers. Detailed smoking pack-year histories were available on 2,910 (76%) patients. Patients were identified as never or current smokers based on self-report, with never smokers defined as those who smoked 100 or fewer cigarettes during their lifetime. Current smokers were defined according to the 1992 National Health Interview Survey-Cancer Control and Epidemiology Supplements²³ and, in this article, refer to patients who had smoked at least 100 cigarettes at the time of their lung cancer diagnosis and who were still actively smoking (every day or intermittently) at the time of their lung cancer diagnosis.

As in another large US study, we compared never smokers with current smokers (the exposed group).¹⁰ Pack-year index was determined by multiplying the average number of cigarette packs smoked daily by the number of years smoked.

A subgroup analysis of 1,142 patients who underwent surgery with curative intent was performed. Staging was according to the American Joint Commission on Cancer (AJCC) TNM classification criteria²⁴ and reported as pathologic staging. Mediastinal lymph node sampling was performed as systematic sampling of levels 2, 4, 7, 8, 9, and 10 on the right side of the chest and 5, 6, 7, 8, and 9 on the left side.

Pathologic slides initially read as BAC were re-reviewed (W. H. W.) in accordance with the World Health Organization reclassification of BAC.²⁵ Those without the initial diagnosis of BAC were not re-reviewed. Surgical procedure type was classified as lobectomy, bilobectomy, pneumonectomy, wedge resection, segmentectomy, and lung resection not otherwise specified from the operative report. The American Society of Anesthesiologists (ASA) five-grade classification system, only available for patients seen since 1993 (683/1,142), was used as an index of preoperative comorbidity.²⁶⁻²⁸ At our institution, the ASA status is formulated as a composite score assigned by at least two anesthesiologists in the anesthesia records at the time of operative assessment.

Statistical Analysis

Comparison of continuous, categorical, and dichotomous variables was performed using the Student t test and χ^2 test for homogeneity, as appropriate. The association of factors with time to death was analyzed using the Cox proportional hazards model. Independent variables tested included age and year of diagnosis as continuous variables; sex, race, histology, AJCC stage, never- vs

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current-smoking status, performance of surgical treatment, surgical procedure type, and ASA classification as categorical variables; and pack-years smoked as a categorical variable based on quartiles. Crude and adjusted hazard ratios (aHRs) with 95% CIs are reported for all variables considered as potential risk factors for mortality. All hazard ratios (HRs) were presented as independent variables and then further adjusted for the previously stated covariates. AJCC stage and ASA classification variables presented in the regression model were treated as continuous variables when tested for trend. All comparisons with two-sided $P \leq .05$ were considered statistically significant. Analyses were performed using statistical software Stata, version 10 (StataCorp; College Station, TX).

RESULTS

Of 4,546 patients with NSCLC in the analytic cohort, 724 self-reported as never smokers vs 3,822 as current smokers (Table 1). Smokers had a median pack-year index of 50. Never smokers were significantly more likely than current smokers to have adenocarcinoma (47.4% vs 34.1%; $P < .01$) as well as the adenocarcinoma subtype of BAC ($P < .01$). No statistically significant difference existed in distribution of stage at presentation ($P = .35$) for the analytic cohort or between the proportions of never and current smokers who subsequently underwent surgery with curative intent ($P = .24$) (Table 2).

In the analytic cohort, women were statistically more likely than men to be never smokers (21.5% vs 12.4%; $P < .01$), and never smokers were more likely to be older in both sexes (Table 3). Female never smokers were more likely to have BAC histology than female current smokers, male current smokers, and male never smokers (9.5% vs 2.8%, 1.4%, and 4.9%, respectively; $P < .01$). Importantly, there was no difference between the sexes in stage at presentation of never and current smokers.

A subset of 1,442 patients underwent surgery with curative intent (Table 2). The statistical differences observed in the larger analytic cohort persisted in the patients who underwent surgery. As in other large published surgical series,^{29,30} our surgical data set contained a proportion of patients with advanced-stage NSCLC, such as stages IIIB and IV, because in both of these stages, there is a significant subset of surgical candidates who we post, as part of our routine practice, for surgery with curative intent. Stage IIIB includes patients with T4 tumors who mainly underwent an anatomic lobectomy because of a satellite lesion in the same lobe as the primary tumor. The majority of stage IV patients who were resected represent those with a single cerebral metastasis who then underwent a subsequent pulmonary lobectomy of their lung cancer primary or who had a satellite pulmonary metastasis in an adjacent ipsilateral lobe to their primary tumor and underwent complete resec-

Table 1—Characteristics of the Analytic Cohort by Never and Current Cigarette Smoking Status (N = 4,546)

Characteristic	Never Smoker (n = 724)	Current Smoker (n = 3,822)	P Value ^a
Sex			< .01
Male	347 (47.9)	2,452 (64.2)	
Female	377 (52.1)	1,369 (35.8)	
Age, y	65 (56-73)	62 (54-68)	< .01
Race			< .01
White	533 (73.6)	2,556 (66.9)	
Black	166 (22.9)	1,235 (32.3)	
Other	25 (3.5)	31 (0.8)	
Histology			< .01
Adenocarcinoma	343 (47.4)	1,305 (34.1)	
Squamous cell	138 (19.1)	1,234 (32.3)	
NSCLC, nos	107 (14.8)	656 (17.2)	
Large cell	75 (10.4)	530 (13.9)	
BAC	53 (7.3)	73 (1.9)	
Adenosquamous	8 (1.0)	24 (0.6)	
Stage			.35
I	153 (21.1)	814 (21.3)	
II	56 (9.1)	360 (9.4)	
III	148 (20.4)	884 (23.1)	
IV	357 (49.4)	1,764 (46.2)	
Surgical treatment			.86
No surgery	544 (75.1)	2,860 (74.8)	
Surgery	180 (24.9)	962 (25.2)	
Pack-years smoked	...	50 (30-75)	n/a

Data are presented as No. (%) or median (interquartile range). BAC = bronchioloalveolar carcinoma; n/a = not applicable; nos = not otherwise specified; NSCLC = non-small cell lung cancer.

^aNonparametric median test and χ^2 test for homogeneity.

tion of both lesions. Also in this surgical group, women were more likely than men to be never smokers (23.1% vs 10.1%; $P < .01$). There was no significant difference between stage of the never and current smokers who underwent surgery or any significant differences between groups in type of surgical procedures performed. There also was no difference between the median time from diagnosis to surgery for the never and current smokers. Significant differences existed in ASA classification, with current smokers having a distribution toward higher ASA scores than never smokers ($P = .01$).

On univariate analysis of the analytic cohort, there was a weak trend toward current smokers having a 7% increased mortality over never smokers (HR, 1.07; 95% CI, 0.99-1.17; $P = .09$) (Table 4). However, after multivariate analysis, smoking status was not an important determinant of overall survival (Table 4). Female sex was associated with a 16% decreased mortality over male sex (aHR, 0.84; 95% CI, 0.78-0.91; $P < .01$). Black race was associated with an 11% increased mortality over white race (aHR, 1.11; 95% CI, 1.03-1.19; $P = .01$). Histologic diagnosis of BAC conferred a 27% reduction in risk of death over patients with predominately adenocarcinoma histology (aHR, 0.73; 95% CI, 0.57-0.94; $P = .01$). Increasing

Table 2—Characteristics of Patients Who Underwent Surgery by Never and Current Cigarette Smoking Status (N = 1,142)

Characteristic	Never Smoker (n = 180)	Current Smoker (n = 962)	P Value ^a
Age, y	64.5 (57-74)	62 (56-68)	.05
Sex			< .01
Male	65 (36.1)	579 (60.2)	
Female	115 (63.9)	383 (39.8)	
Race			.20
White	145 (80.6)	733 (76.2)	
Black	35 (19.4)	229 (23.8)	
Histology			< .01
Adenocarcinoma	97 (53.9)	393 (40.9)	
Squamous cell	21 (11.7)	349 (36.3)	
NSCLC, nos	8 (4.4)	62 (6.4)	
Large cell	9 (5.0)	98 (10.2)	
BAC	41 (22.8)	53 (5.5)	
Adenosquamous	4 (2.2)	7 (0.7)	
Stage			.24
I	99 (55.0)	521 (54.2)	
II	38 (21.1)	194 (20.2)	
III	33 (18.3)	218 (22.6)	
IV	10 (5.6)	29 (3.0)	
Procedure			.49
Lobectomy	140 (77.8)	719 (74.7)	
Pneumonectomy	12 (6.7)	88 (9.2)	
Wedge resection	16 (8.9)	82 (8.5)	
Segmentectomy	5 (2.8)	24 (2.5)	
Bilobectomy	4 (2.2)	12 (1.3)	
Lung resection, nos	3 (1.6)	37 (3.8)	
ASA			.01
1	0 (0.0)	2 (0.2)	
2	36 (20.0)	96 (10.0)	
3	86 (47.8)	418 (43.4)	
4	4 (2.2)	41 (4.3)	
5	0 (0.0)	0 (0.0)	
Unavailable ^b	54 (30.0)	405 (42.1)	
Time from diagnosis to surgery, d	22 (6-51)	21 (5-43)	.78

Data are presented as No. (%) or median (interquartile range). ASA = American Society of Anesthesiology classification morbidity index. See Table 1 legend for expansion of other abbreviations.

^aNonparametric median test and χ^2 test for homogeneity.

^bASA classification only readily available starting in 1993.

AJCC stage was associated with progressively worse survival, with patients presenting with stage IV disease being 148% more likely to die than those with stage I disease (aHR, 2.48; 95% CI, 2.21-2.79; $P < .01$). A semiquantifiable smoking variable, such as the dose of tobacco exposure measured as pack-year history, was not a statistically significant predictor of outcome after adjusting for other variables (P for trend, .84).

Although the univariate analysis of never and current smokers who underwent surgery with curative intent (Table 5) showed a trend toward an elevated risk of death for current vs never smokers (HR, 1.20; 95% CI, 0.98-1.46; $P = .07$), this was completely obviated when the model was adjusted for other covari-

ates. Pack-year history was not a significant predictor of outcome after univariate (P for trend, .108) or multivariate analysis (P for trend, .957). As in the larger analytic cohort, BAC histology conferred a survival advantage with surgical patients over patients with predominately adenocarcinoma histology, even after multivariate adjustment (aHR, 0.72; 95% CI, 0.52-1.00; $P = .05$). Increasing AJCC stage also was associated with progressively worse survival, with patients presenting with stage IV disease being 243% more likely to die than those with stage I disease (aHR, 3.43; 95% CI, 2.32-5.07; $P < .01$). Of surgical procedure types, none had significantly different risk for mortality compared with lobectomy after adjustment for covariates. Patients classified with ASA grades 3 and 4 were at significantly greater risk of death compared with patients with ASA grade 1 classification ($P < .01$). The 30-day postoperative mortality rate for the never- and current-smoker cohorts was not significantly different (data not shown).

DISCUSSION

This study is one of the largest to examine outcomes of surgically treated never-smoker patients with lung cancer in the United States. We report that for 4,546 never and current smokers with NSCLC and a subset of 1,142 of these patients who underwent surgery with curative intent, tobacco smoking was not an independent predictor of reduced long-term survival. In both the larger analytic cohort and the subgroup of surgically resected patients, after adjusting for pertinent covariates in a multivariate analysis, those actively smoking cigarettes when given a diagnosis of lung cancer had no increase in the long-term risk of death over those who never smoked. In fact, despite the different etiologies of NSCLC and the known different tumor biology in smokers and never smokers, our data suggest that never smokers and current smokers do not differ in clinical stage at lung cancer diagnosis. This similarity in stage at presentation of never and current smokers translates into no difference in long-term survival rates.

In both our analytic and surgical cohorts, stage is by far the strongest predictor of overall patient survival (Tables 4, 5). Most patients in the analytic cohort have advanced-stage NSCLC on presentation, and thus, most patients, regardless of smoking status, have unresectable disease and poor long-term survival. In the subset of patients who underwent surgery also, never smokers and current smokers had similar pathologic stages. As in the analytic cohort, multivariate analysis in the surgical group showed no long-term survival difference according to smoking status (Table 5). Importantly, increasing dose of tobacco

Table 3—Characteristics of Male and Female Patients in the Analytic Cohort by Never and Current Cigarette Smoking Status (N = 4,546)

Characteristic	Male (n = 2,800)			Female (n = 1,746)			P Value ^b
	Never Smoker	Current Smoker	P Value ^a	Never Smoker	Current Smoker	P Value ^a	
Total ^c	347 (12.4)	2,453 (87.6)		377 (21.6)	1,369 (78.4)		
Age, y	64 (56-72)	62 (55-69)	.01	65 (54-73)	60 (52-67)	< .01	< .01
Race			< .01			.54	.02
White	263 (75.9)	1,598 (65.1)		270 (71.6)	958 (70.0)		
Black	84 (24.2)	855 (34.9)		107 (28.4)	411 (30.0)		
Histology			< .01			< .01	.17
Adenocarcinoma	145 (41.8)	761 (31.0)		198 (52.5)	544 (39.7)		
Squamous cell	88 (25.4)	917 (37.4)		50 (13.3)	317 (23.2)		
NSCLC, nos	50 (14.4)	387 (15.8)		57 (15.2)	269 (19.6)		
Large cell	40 (11.5)	341 (13.9)		35 (9.3)	189 (13.8)		
BAC	11 (4.9)	35 (1.4)		36 (9.5)	38 (2.8)		
Adenosquamous	7 (2.0)	12 (0.5)		1 (0.2)	12 (0.8)		
Stage			.07			.52	.16
I	59 (17.0)	487 (19.9)		94 (24.9)	327 (23.9)		
II	26 (7.5)	241 (9.8)		40 (10.6)	119 (8.7)		
III	74 (21.3)	580 (23.6)		74 (19.6)	304 (22.2)		
IV	188 (54.2)	1,145 (46.7)		169 (44.8)	619 (45.2)		
Surgical treatment			.05			.34	.03
No surgery	282 (81.3)	1,874 (76.4)		262 (69.5)	986 (72.0)		
Surgery	65 (18.7)	579 (23.6)		115 (30.5)	383 (28.0)		

Data are presented as No. (%) or median (interquartile range). See Table 1 legend for expansion of abbreviations.

^aNonparametric median test and χ^2 test for homogeneity within groups.

^bCochran-Mantel-Haenszel test for homogeneity between male vs female.

^cRow percentages.

exposure measured as increasing pack-year history was not associated with increased risk of long-term death. Thus, our data suggest that NSCLC diagnosed in a never smoker is equally as deadly over the long term as in a current smoker.

The important influence of stage in our data set is supported by the findings of Myrdal et al,³¹ who concluded that tumor stage is the best prognostic clinical indicator after surgical resection. Importantly, the distribution of staging within our single-institution data set is representative of national data. The American College of Surgery national survey of 40,909 patients with NSCLC found that 67% had stage III or IV disease,³² which mirrors the proportion of patients with advanced NSCLC in our data set. To account for possible stage migration over the 30 years of our study population due to improved diagnostic techniques, the diagnosis year was included in all of our multivariate models. Nonetheless, the impact of smoking status on long-term outcome in either the entire analytic population or in the surgical group was negligible.

Although our study was not designed to examine whether current or persistent smoking prolongs or shortens short-term survival after the diagnosis or treatment of lung cancer, our data from patients who underwent surgery suggest that both tumor staging and ASA classification were the most significant

determinants of overall survival. Because our current smokers who had surgery had a higher ASA classification, current smokers in our surgical group probably had more comorbidities and poorer performance status than the never smokers who underwent surgery. Baser et al¹⁸ showed a better performance status up to 1 year after surgery in patients with lung cancer who quit smoking at diagnosis. In a recent report by Mason et al,³³ the timing of smoking cessation preoperatively directly correlated with not only substantial improvements in short-term morbidity but also in short-term survival after lung cancer resection.

In contrast to the impact of smoking on short-term survival, the literature is equivocal about the impact of smoking status on long-term overall survival of patients with NSCLC. Most reports querying the impact of smoking status on long-term survival from NSCLC at the time of lung cancer diagnosis describe minimal to no effect, with reported aHRs ranging from 0.98 to 1.37.^{9,10,17,31,32,34} Moreover, whenever smoking status has been shown in the literature to have a large deleterious effect on the HR, it is usually limited to small patient subsets. Yoshino et al,²² for example, reported an aHR of 1.73 (95% CI, 1.01-3.04; $P = .0461$) of smoking on surgically treated patients with stage I adenocarcinoma only. Similarly, Hinds et al³⁵ reported an adjusted odds ratio of 1.74 ($P = .02$)

Table 4—Crude and Multivariable Adjusted Hazard Ratios Assessing the Association Between NSCLC and Mortality for All Patients (N = 4,546)

Characteristic	Crude HR	95% CI	P Value	Adjusted HR ^a	95% CI	P Value
Smoking status						
Never smoker	1.00	Referent	...	1.00	Referent	...
Current smoker	1.07	0.99-1.17	.09	1.08	0.95-1.22	.25
Age, y	1.01	1.00-1.02	< .01	1.01	1.01-1.03	< .01
Sex						
Male	1.00	Referent	...	1.00	Referent	...
Female	0.78	0.74-0.84	< .01	0.84	0.78-0.91	< .01
Race						
White	1.00	Referent	...	1.00	Referent	...
Black	1.22	1.14-1.30	< .01	1.11	1.03-1.19	.01
Year of diagnosis	0.99	0.98-1.00	< .01	1.00	1.00-1.02	.25
Histology						
Adenocarcinoma	1.00	Referent	...	1.00	Referent	...
Squamous cell	1.10	1.02-1.19	.01	1.05	0.97-1.15	.24
NSCLC, nos	1.46	1.34-1.60	< .01	1.07	0.97-1.18	.19
Large cell	1.26	1.15-1.39	< .01	1.07	0.96-1.21	.08
BAC	0.41	0.33-0.51	< .01	0.73	0.57-0.94	.01
Adenosquamous	1.05	0.73-1.51	.80	1.03	0.68-1.56	.89
Stage						
I	1.00	Referent	...	1.00	Referent	...
II	1.42	1.25-1.60	< .01	1.26	1.10-1.46	< .01
III	2.01	1.83-2.22	< .01	1.42	1.27-1.60	< .01
IV	4.22	3.86-4.61	< .01	2.48	2.21-2.79	< .01
P for trend			< .001			< .001
Surgical treatment						
Surgery	1.00	Referent	...	1.00	Referent	...
No surgery	4.22	3.89-4.57	< .01	2.70	2.42-3.02	< .01
Pack-years smoked						
Never smoked	1.00	Referent	...	1.00	Referent	...
< 30	1.01	0.89-1.15	.84	0.98	0.85-1.14	.82
30-59	1.04	0.94-1.14	.44	1.03	0.92-1.16	.56
60-89	1.05	0.95-1.18	.35	1.02	0.90-1.16	.73
≥ 90	1.14	1.01-1.28	.04	...	...	...
P for trend ^b	...	...	.101	...	...	.844

HR = hazard ratio. See Table 1 for expansion of other abbreviations.

^aCox regression model adjusted for age (continuous), sex, race, diagnosis year, histology, stage, smoking status, pack-years, and surgical treatment.

^bTest for trend for pack-years smoked excludes never smokers.

of smoking for women but not for men with lung cancer.

It is important to consider that it is methodologically difficult in large patient cohorts to adjust well for patient comorbidities. For example, Zell et al³⁴ analyzed 11,969 patients with lung cancer for overall survival due to smoking status but were unable to adjust in their multivariate model for comorbidity and determined a modest HR of 1.09 for reduced survival in ever-smokers. In our analytic cohort of 4,546 patients with lung cancer treated both medically and surgically, we also were unable to adjust for comorbidity in our multivariate model, and the effect of current smoking on reduced overall survival (HR, 1.08) is similar to that of Zell et al³⁴ (Table 4). Unlike Zell et al,³⁴ however, we were able to analyze a subgroup of patients who underwent surgery and had available hospital records with the ASA classifications that we could use as a surrogate

for comorbidity. By univariate analysis, the HR for the effect of current smoking on long-term survival of this surgically treated group was 1.20, but when we adjusted for ASA classification in this group, the effect of smoking status on the HR was completely eliminated (0.97). This finding highlights not only the importance of including comorbidities as a covariate in models of long-term lung cancer survival but also the lack of survival differences in NSCLC tumors originating from smoking and non-smoking etiologies.

As others have shown consistently throughout the literature,^{10,34,36,37} our findings demonstrate a biologic difference in the increased rate of adenocarcinomas in never smokers vs current smokers, in general, and BACs, in particular (Table 1). Others also have found on multivariate analysis that BAC is a significant favorable risk factor for overall NSCLC survival.³⁴ It is important, then, to consider carefully the proportion

Table 5—Crude and Multivariable Adjusted HRs Assessing the Association Between NSCLC and Mortality for Patients Who Received Surgical Treatment (N = 1,142)

Characteristic	Crude HR	95% CI	P Value	Adjusted HR ^a	95% CI	P Value
Smoking status						
Never smoker	1.00	Referent	...	1.00	Referent	...
Current smoker	1.20	0.98-1.46	.07	0.97	0.69-1.32	.79
Age, y	1.02	1.01-1.03	< .01	1.02	1.01-1.03	< .01
Sex						
Male	1.00	Referent	...	1.00	Referent	...
Female	0.75	0.65-0.86	< .01	0.83	0.71-0.98	.03
Race						
White	1.00	Referent	...	1.00	Referent	...
Black	1.10	0.94-1.29	.24	1.05	0.88-1.26	.57
Year of diagnosis	1.00	0.99-1.01	.52	1.01	1.00-1.03	.05
Histology						
Adenocarcinoma	1.00	Referent	...	1.00	Referent	...
Squamous cell	1.23	1.06-1.44	.01	1.08	0.90-1.30	.39
NSCLC, nos	1.03	0.76-1.40	.86	1.19	0.85-1.67	.32
Large cell	1.23	0.97-1.55	.09	1.12	0.85-1.47	.42
BAC	0.61	0.45-0.82	< .01	0.72	0.52-1.00	.05
Adenosquamous	1.43	0.71-2.88	.32	1.38	0.60-3.15	.45
Stage						
I	1.00	Referent	...	1.00	Referent	...
II	1.48	1.24-1.76	< .01	1.38	1.13-1.68	< .01
III	1.70	1.44-2.00	< .01	1.85	1.51-2.26	< .01
IV	3.31	2.35-4.67	< .01	3.43	2.32-5.07	< .01
P for trend	...	...	< .001	...	...	< .001
Surgical procedure						
Lobectomy	1.00	Referent	...	1.00	Referent	...
Pneumonectomy	1.56	1.25-1.94	< .01	1.16	0.91-1.47	.24
Bilobectomy	1.19	0.94-1.51	.15	1.16	0.59-2.27	.66
Wedge resection	1.37	0.93-2.03	.11	1.24	0.98-1.56	.07
Segmentectomy	1.46	0.76-2.83	.26	1.29	0.90-1.84	.16
Lung resection, nos	1.20	0.83-1.73	.34	1.15	0.78-1.69	.49
ASA						
1	1.00	Referent	...	1.00	Referent	...
2	1.71	0.24-12.36	.59	...	...	...
3	3.12	0.44-22.25	.28	1.59	1.20-2.11	< .01
4	5.42	0.74-39.62	.11	2.18	1.40-3.40	< .01
Unavailable ^b	3.11	0.44-22.13	.26	1.73	1.27-2.35	< .01
P for trend	...	...	< .001	...	...	.001
Pack-years smoked						
Never smoked	1.00	Referent	...	1.00	Referent	...
< 30	0.94	0.69-1.28	.68	...	...	...
30-59	1.23	0.98-1.53	.07	1.19	0.90-1.58	.22
60-89	1.25	0.98-1.59	.08	1.16	0.85-1.57	.35
≥ 90	1.28	0.97-1.70	.08	1.10	0.78-1.55	.59
P for trend ^c	...	...	.108	...	...	.957

See Table 1, 2, and 4 legends for expansion of abbreviations.

^aCox regression model adjusted for age (continuous), sex, race, diagnosis year, histology, stage, surgical procedure, ASA classification, smoking status, and pack-years smoked.

^bASA classification only readily available starting in 1993.

^cTest for trend for pack-years smoked excludes never smokers.

of this histologic subtype in populations of never-smokers of any one particular study.

In our analytic population of 4,546 current smokers and never smokers, the proportion of BAC is 2.8% (126/4,546), which is consistent with 3.53% (1,446/40,909) in the aforementioned American College of Surgeons' survey³² and the 3% to 4% proportion of BAC histology observed in the similarly large Sur-

veillance Epidemiology and End Results database study.³⁸ In our analytic cohort, 7.3% of never smokers had BACs, which, again, is similar to the 12.6% prevalence found in a large analysis of data from the Cancer Surveillance Programs of Orange County, Imperial County, and San Diego County, California.³⁴

Interestingly, studies that show overall survival benefit of never smokers often have very high prevalence

rates of adenocarcinoma subtypes, especially BAC, which also can translate into more patients with earlier-stage tumors.^{6,10,37} For example, an often-referenced US study of 132 never smokers and 522 current smokers from the H. Lee Moffitt Cancer Center found a prevalence of BAC of 24% and 10% in their never-smoker and current-smoker patients, respectively.¹⁰ High prevalence rates of adenocarcinoma histologic subtypes in never-smoker populations also is often observed in the Japanese literature,^{6,8,16,17,22,37} which may be partially related to their cultural propensity for population-based chest CT scan screening for lung cancer.^{39,40}

Growing evidence comparing differences in tumor biology between smokers and never smokers has mainly focused on differences in susceptibility to chemotherapeutic agents rather than on prognostic differences in survival.^{36,41-43} We did not include analysis of chemotherapy or radiotherapy, and our patient population predates the era of maximal targeting of chemotherapeutic agents such as tyrosine kinase inhibitors for never smokers. Although genomic and epigenomic differences in tumor biology between smokers and never smokers may exist,^{4,5,44} our data suggest that cancer developing as a result and independent of smoking produce patients who present for treatment with the same staging (Table 1) and, thus, the same overall survival. In both smokers and never smokers, the majority of patients presented with advanced disease, suggesting that these tumors are similarly aggressive independent of biologic development and chemosensitivity. In the absence of targeted therapy, the natural history of the disease in smokers and never smokers appears to be similar and to be independent of smoking status at the time of lung cancer diagnosis.

This cohort constitutes one of the largest published studies of never-smoker outcomes with lung cancer in the United States, but limitations exist. Although the database was collected retrospectively, we engaged in careful quality control of data collection, with auditing and correlating data between online and paper charts. However, the retrospective nature of the study prevents us from evaluating which active-smokers persisted in their cigarette smoking. It is known that approximately 6% of current smokers may refrain from smoking while under treatment, and these patients may have, in the short term, lower risks of hospital death and pulmonary complications after lung cancer resection than patients who persist in smoking.³³ It is unknown whether these current smokers who persist in smoking would have a higher incidence of death than patients who cease smoking from causes such as smoking-induced comorbidities, second malignancies, or even from less-favorable responses to chemotherapy.

It is a limitation of this study that no objective verification of smoking status in any patient was performed by nicotine metabolite testing. Possible bias effects due to self-underreporting would underestimate the true effect. We suspect, however, that smoking misclassification rates are low in the database examined due to its single-institution nature and to regular data auditing²⁷ and because other investigations of self-reporting smoking status have revealed low rates of smoker misclassification.^{45,46} In addition, it is a limitation that the various etiologies for NSCLC in never smokers were not carefully documented. If a high proportion of never smokers were exposed to secondhand smoke, for example, it could suggest that similar biologic pathways to primary smoke are causative in these patients, thus driving the stage at presentation and, ultimately, overall survival.

This database has incomplete pulmonary function testing data, ASA records, and postoperative complications for surgical patients as well as lacks detailed information on definitive treatment plans, functional status and comorbidities for nonoperative patients. Information on environmental exposures is incomplete for both the analytic and surgical groups. Finally, the database lacks cancer-specific mortality data, which would help to define further the effect of smoking on cancer-induced mortality vs competing causes of death.

Our results show that the determinants of survival are complex. Others have shown that for short-term survival, especially after surgery, current smokers may be at increased risk of perioperative death.³³ For long-term survival, however, our data suggest that the etiology of NSCLC from smoking or other causes is not an independent prognostic factor in either our larger analytic cohort of medically and surgically treated patients with NSCLC or in the subgroup that underwent surgery. NSCLC in never smokers is not intrinsically a less-aggressive tumor. Instead, we found that the observed detrimental impact on long-term survival after surgery of current-smoking status by univariate analysis is completely off set on multivariate analysis after adjustment for covariates, including tumor stage, histology, and ASA classification. In particular, cancer stage and the existence of comorbidities assessed directly or estimated through performance status measures appear superior to preoperative smoking status as indicators for estimating the long-term prognosis of patients with NSCLC. This lack of improved long-term survival in never-smokers with NSCLC relative to current smokers is clinically relevant and if corroborated in larger cohorts, may prove valuable in explaining disease outcomes to our patients, particularly those who have never smoked.

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Dr Harris: contributed to the examination of individual paper charts to verify database records.
Ms Xu: contributed as the database manager and designer.
Dr Westra: contributed the review of all patient bronchioloalveolar carcinoma slides.
Dr Sherwood: contributed to the study design and the provision of critical patient follow-up data.
Dr Sussman: contributed to the design and planning of the manuscript.
Dr Cattaneo: contributed to the design of the manuscript and the provision of critical follow-up patient data.
Mr Shin: contributed to the examination of individual paper charts to verify database records.
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Ms Zhang: contributed to the examination of individual paper charts to verify database records.
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