Presentation and Stage-Specific Outcomes of Lifelong Never-smokers with Non-small Cell Lung Cancer (NSCLC)

Janakiraman Subramanian, MD, MPH, Vamsidhar Velcheti, MD,* Feng Gao, PhD,† and Ramaswamy Govindan, MD*‡*

Background: Tobacco smoking leads to lung cancer. Approximately 10% of patients with lung cancer are life long never-smokers. There are only limited data available on the clinical characteristics and outcomes of lung cancer in never-smokers from the Western hemisphere.

Methods: Demographic and survival information was collected on 254 never-smokers with a confirmed pathologic diagnosis of non-small cell lung cancer (NSCLC) by reviewing their medical records and the Social Security database.

Results: The study population consisted of 182 (71.6%) women and 72 (28.3%) men. The median age was 70 years (range: 31–91 years). Adenocarcinoma was the most common histology accounting for 60.8% of all patients, followed by NSCLC not otherwise specified (14.4%), bronchoalveolar carcinoma (13.6%), squamous cell carcinoma (8.8%), and large-cell type (2.4%). Majority of patients presented with stage III or IV disease (62.5%). We compared survival between never-smokers and smokers with NSCLC matched for gender, histology, tumor stage, and years of diagnosis. No significant difference in 5-year survival was seen between never-smokers (27.2%) and smokers with NSCLC (31.3%; $p = 0.73$).

Conclusions: Two thirds of patients with lung cancer who report no history of tobacco smoking are women. In the matched case–control analysis, we report no significant survival difference between lung cancer in never-smokers and those with history of tobacco smoking and lung cancer.

Key Words: Non-small cell lung cancer, Never-smoker, Outcomes, Presentation.

(*J Thorac Oncol.* 2007;2: 827–830)

Lung cancer is the leading cause of cancer related mortality in the United States, and tobacco smoking is the main risk factor for lung cancer.[1] It accounts for more than 90% of lung cancer in men and 75% to 85% in women in the United States and Northern Europe.[2,3] Nevertheless, 10% to 15% of all newly diagnosed patients with lung cancer are never-smokers.[1] This subgroup of lung cancer patients has higher response rates compared with those with history of tobacco smoking when treated with inhibitors of epidermal growth factor receptor tyrosine kinase (EGFR-TK), such as gefitinib and erlotinib.[4–7] The advent of EGFR-TK inhibitors in lung cancer chemotherapy has directed attention to lung cancer in never-smokers (LCINS) as never before. In addition, it has been reported that activating mutations in the EGFR-TK domain that predict treatment response is significantly higher in LCINS when compared with tobacco-associated lung cancer (TALC).[8,9]

Distinctive molecular features have been described in LCINS including 16p chromosomal aberration, variations in the mutational spectrum of p53, and lower methylation rates have been identified in LCINS.[8–15] These genetic markers indicate that the carcinogenesis pathway for LCINS may differ from TALC.[9,13,16] Several studies involving LCINS report predominance of adenocarcinoma subtype and a gender reversal with a higher proportion of women compared with TALC. Only very little is known about the clinical outcomes of patients with lung cancer who are life long never-smokers, particularly from the Western hemisphere.[17,18] Therefore, we conducted this retrospective study to identify the presenting features and stage specific outcomes in patients with LCINS. For survival analysis, we conducted a one to one matched case control analysis to compare survival between patients with LCINS and TALC.

MATERIALS AND METHODS

The study involved 2762 consecutive patients with non-small cell lung cancer NSCLC (all stages) diagnosed and treated at the Washington University School of Medicine (WUSM) Siteman Cancer Center from 1992 to 2002. The WUSM Siteman Cancer Center is a major tertiary referral center for cancer care and the patient population is predominantly from the midwestern United States. The case records on all these patients were retrieved. Of these 2762 patients, 254 were determined to be never-smokers with a confirmed pathologic diagnosis of NSCLC. Patients with NSCLC who were current or former smokers were excluded.

A never-smoker was defined as one who had never smoked and was stated as such in the attending physician's notes. The smoking status information was drawn from the

From *Department of Medicine, †Division of Biostatistics, and ‡Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri.

Disclosure: Please provide complete financial disclosure information.

Address for correspondence: Ramaswamy Govindan, MD, Division of Oncology, 4960 Childrens' Place, St Louis, MO 63110. E-mail: rgovinda@im.wustl.edu

ISSN: 1556-0864/07/0209-0827

medical oncology charts and was verified from additional sources when possible. The information collected on the 254 patients included demographic information, histopathology, staging information, treatment, response to treatment, date of last follow-up or date of death. Mortality data were collected from several sources including tumor registry data, physician's office charts, and the Social Security database. Overall survival was determined as the duration from the date of diagnosis to the date of death. Patients who were disease free were censored at the date of last clinical contact.

We had complete presentation and outcomes information on 221 LCINS. For survival analysis, we matched these 221 patients with LCINS (cases) to patients with confirmed smoking status (controls). The controls were also drawn from the WUSM tumor registry and included all smokers with NSCLC seen between 1992 and 2002. The two groups were matched for gender, histology, tumor stage, and time of diagnosis. The time of diagnosis for each control had to be within four years (arbitrarily chosen) from the time of diagnosis for the corresponding case. Overall survival in the two groups was estimated using Kaplan–Meier product limit method and compared with a Cox proportional hazards model for clustered survival data.[19]

RESULTS

This study population consisted of 254 patients with LCINS, of whom 182 (71.6%) were women and 72 (28.3%) were men (Table 1). The median age was 70 years (range: 31–91 years). The study group had 215 Caucasians (84.9%), 32 (12.6%) African Americans, and 6 (2.4%) of Asian descent. Adenocarcinoma was the most common histologic subtype, with 152 (60.8%) patients; bronchoalveolar, 34 (13.6%); squamous cell carcinoma, 22 (8.8%); and large-cell, 6 (2.4%). Histologic subtype determination was unavailable in 36 (14.4%) patients and was classified as NSCLC.

Staging information was available for 248 of the 254 patients with LCINS; 72 (28.3%) had stage I disease, 17 (6.7%) had stage II disease, 66 (25.9%) had stage III disease, and 93 (36.6%) had stage IV disease at the time of presentation. The most common site of metastasis was to the bone in 37 (35.6%) patients, followed by the central nervous system in 31 (29.8%) patients, the lung and pleura in 31 (29.8%) patients, and solid organs in 23 (22.1%) patients. Information on treatment with chemotherapy and radiation was available in 220 patients; 88 (34.6%) had received chemotherapy, and 84 (33.1%) had received radiation therapy as a part of their first-line treatment. None of the patients included in this study received EGFR-TK inhibitors.

The 5-year survival estimate for the cases (221 patients with LCINS) was 27.2% compared with 31.3% for the controls (221 patients with TALC); the difference was not statistically significant ($p = 0.73$; Figure 1) The results did not change after adjusting for age at diagnosis for the two groups. The stagewise distribution of 5-year survival between the two groups did not show any significant differences. (Table 2) To validate the results of the case–control analysis we compared the 5-year survival of the patients with LCINS against a one-to-one matched unique second control group, and no significant survival difference was detected.

We also reviewed the presentation characteristics and outcomes of all NSCLC seen at our institution from 1992 to 2002. We compared the characteristics of the LCINS group and the control group against the entire NSCLC patient cohort (Tables 1 and 2). Our comparison identified a clear predominance of women and adenocarcinoma subtype in patients with LCINS.

TABLE 1. Characteristics of Study Population

	All Patients	LCINS
Total subjects	2762	254
Median age (yr)	66.5	70
Gender		
Female	1197 (43.3%)	182 (71.6%)
Male	1564 (56.6%)	72 (28.3%)
Race		
Caucasian	2198 (79.6%)	215 (84.9%)
African American	540 (19.5%)	32 (12.6%)
Asian	13 (0.5%)	6 (2.4%)
Other/unknown	11 (0.4%)	—
Histology		
Adenocarcinoma	1226 (44.4%)	152 (60.8%)
Squamous cell carcinoma	1177 (43.2%)	22 (8.8%)
Bronchoalveolar carcinoma	134 (4.9%)	34 (13.6%)
Large-cell carcinoma	72 (2.6%)	6 (2.4%)
NSCLC	137 (4.9%)	36 (14.4%)
Stage		
Stage I	853 (30.9%)	72 (28.3%)
Stage II	261 (9.4%)	17 (6.7%)
Stage III	870 (31.5%)	66 (25.9%)
Stage IV	707 (25.6%)	93 (36.6%)
Unknown	71 (2.6%)	

LCINS, lung cancer in never-smokers; NSCLC, non-small cell lung cancer.

DISCUSSION

The well-known reversal in gender distribution, with a higher proportion of women in LCINS (unlike the more common TALC), was observed once again in our study.[2,3,20] In North America and Europe, more than 90% of all men with lung cancer are tobacco smokers, whereas in women it ranges from 75% to 85%.[2] The prevalence of tobacco smoking among men with newly diagnosed lung cancer in the Asian population is similar to that of North America and Europe. Nevertheless, the prevalence of tobacco smoking among Asian women with newly diagnosed lung cancer is much lower compared with their Western counterparts, ranging between 25% and 56%.[3,21–23] The predominance of adenocarcinoma (61%) reported in our study is consistent with results reported in other published studies, ranging from 76% to 47%.[3,18,24–28] It has been reported that the incidence of adenocarcinoma is more or less uniform among never-smoker women of different geographical regions.[3]

It is unclear whether patients with lung cancer who are lifelong never-smokers present with metastatic disease at presentation more often than those with history of tobacco

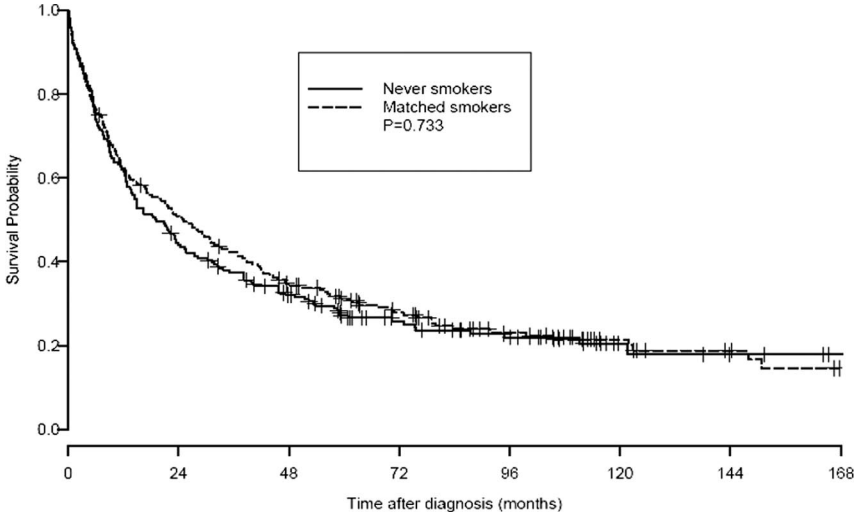

FIGURE 1. Kaplan–Meier survival curve for lung cancer in never-smokers (LCINS; cases) versus tobacco-associated lung cancer (TALC; controls).

TABLE 2. Five-year Survival by Stage

Stage	All Patients (%)	LCINS (%)	TALC (%)
I	51.3	63.5	62.8
II	38.8	33.3	42.4
III	13.6	12.4	26.6
IV	2.8	3.8	5

LCINS, lung cancer in never-smokers; TALC, tobacco-associated lung cancer.

smoking. In our study, there was a slight predominance in stage IV disease (36.6%) in patients with LCINS versus all patients with NSCLC (25.6%) at presentation. In a chart review of consecutive patients ($n = 654$) with adenocarcinoma of the lung, there was no significant difference in the proportion of stage IV disease between never-smokers (35%) and smokers (39%).[17] In an Asian study, the proportion of stage IV disease at presentation was higher in patients with LCINS versus patients with TALC (51.8% versus 42%; $p = 0.002$).[22] The study by Dibble and colleagues[18] reported a greater proportion of distant-stage disease in LCINS than in patients with TALC (71% versus 56%). Thus, it is unclear whether a greater proportion of patients with LCINS present with metastasis than patients with TALC. It may be that this difference is more prominent in the Asian population than in Caucasians. It is unknown whether there is any distinct pattern of metastasis in LCINS. In our study, bone is the most common site of metastasis, followed by brain and lung, and then pleura.

The presentation characteristics of the entire cohort of 2762 patients with NSCLC are different from the LCINS group (Table 1). In patients with NSCLC seen at WUSM Siteman cancer center, there has been a significant increase in the number of stage IV patients after January 1, 2000 (37% versus 30%; $p < 0.0001$).[29] In addition, there has been a decrease in squamous cell cancer histology after January 1, 2000 (24% versus 34%; $p < 0.001$) and an increase in women with NSCLC (46% versus 42%; $p = 0.005$; unpublished data).

On the basis of our literature review, we identified four studies comparing survival between LCINS and TALC. Of these four studies, three reported better survival in LCINS versus TALC. Nordquist and colleagues[17] conducted an institutional retrospective study comparing survival between never-smokers and smokers with adenocarcinoma (all stages). They reported better 5-year survival in never-smokers ($n = 132$) compared with current smokers ($n = 522$; 23% versus 16%; $p = 0.004$). Multivariate analysis identified smoking status as an independent prognostic factor ($p = 0.0245$). Toh and colleagues[22] reported the risk of death to be higher in patients with TALC than patients with LCINS after adjusting for sex, Eastern Cooperative Oncology Group status, AJCC stage, comorbidities, weight loss, and treatment received (hazards ratio 1.3; 95% CI, 1.04–1.62). The Utah study reported a 3-year survival of 9.3% in never-smokers versus 3.2% in smokers with NSCLC for all stages (no p value given).[18] Nevertheless, it is not known whether the authors had controlled for the effect of confounding from gender, stage, and histology. Another study, from Singapore, has reported no significant difference in median overall survival between never-smokers and smokers.[30]

In our survival analysis, we did not find a significant difference in survival between LCINS and TALC. By using a matched case–control approach, we were able to eliminate the confounding effects of stage, gender, and histology. We did not control for treatment and comorbidities, because these data were unavailable on many of the patients. Nevertheless, we believe the inclusion of the year of diagnosis and using a second unique control significantly minimizes the risk of confounding from those variables. While our study findings indicate that the presentation characteristics of patients are different from patients with TALC, we did not find any significant survival difference between these two groups.

Current evidence suggests that LCINS and TALC have significant biological differences, although with conventional therapy alone there might be no difference in survival between the two groups. It is well known that treatment with EGFR-TKIs results in significantly better outcomes in LCINS.[4,6] On the basis of current evidence, it has been proposed that the EGFR and K-ras mutations are mutually exclusive to each other in lung cancer. The EGFR-gene mutation may play a key role in the carcinogenesis pathway in a significant proportion of LCINS, whereas in smokers K-ras mutation might have a similar role.[31] Other studies have also identified significant differences in the molecular genetics of LCINS and TALC.[16,19,32–33] Therefore, a targeted approach based on a better understanding of the molecular pathways, such as first-line treatment with EGFR-TKIs in never-smokers, may yield better results than would conventional chemotherapy alone. The CALGB 30406 study is currently evaluating the role of erlotinib in treatment naïve patients with NSCLC who are never-smokers/light former smokers. It is likely that in future the systemic therapy for LCINS may be distinctly different compared with TALC. Further investigations are required to characterize the molecular genetic differences between LCINS and TALC and to identify potential therapeutic targets and prognostic markers.[34]

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10–30.
2. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
3. Koo LC, Ho JH. Worldwide epidemiological patterns of lung cancer in non smokers. *Int J Epidemiol* 1990;19:s14–s23.
4. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:1103–1109.
5. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353: 123–132.
6. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23:5892–5899.
7. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366: 1527–1537.
8. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339–346.
9. Gazdar AF. Lung cancer in never smokers—a different pathway. In MC Perry (Ed.), American Society of Clinical Oncology Educational Book. Alexandria, VA: American Society of Clinical Oncology, 2005. Pp 619–621.
10. Ahrendt SA, Decker PA, Alawi EA, et al. Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. *Cancer* 2001;92:1525–1530.
11. Hashimoto T, Tokuchi Y, Hayashi M, et al. Different subtypes of human lung adenocarcinoma caused by different etiological factors: evidence from p53 mutational spectra. *Am J Pathol* 2000;157:2133–2141.
12. Hainaut P, Olivier M, Pfeifer GP. TP53 mutation spectrum in lung cancers and mutagenic signature of components of tobacco smoke: lessons from the IARC TP53 mutation database. *Mutagenesis* 2001;16: 551–553.
13. Wong MP, Lam WK, Wang E, et al. Primary adenocarcinomas of the lung in nonsmokers show a distinct pattern of allelic imbalance. *Cancer Res* 2002;62:4464–4468.
14. Toyooka STT, Adi F. Gazdar: the TP53 gene, tobacco exposure, and lung cancer. *Hum Mutat* 2003;21:229–239.
15. Shinichi Toyooka RM, Kiyomi O, Toyooka Dale McLerran, et al. Smoke exposure, histologic type and geography-related differences in the methylation profiles of non-small cell lung cancer. *Int J Cancer* 2003;103:153–160.
16. Wong MP, Lai-Fan Fung, Elaine Wang, et al. Chromosomal aberrations of primary lung adenocarcinomas in nonsmokers. *Cancer Epidemiol Biomarkers Prev* 2003;97:1263–1270.
17. Nordquist LT, Simon GR, Cantor A, et al. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. *Chest* 2004;126:347–351.
18. Dibble R, Langeburg W, Bair S, et al. Natural history of non-small cell lung cancer in non-smokers. *J Clin Oncol* 2005;23:7252.
19. Lee E, Wei L, Amato D. Cox-type regression analysis for a large numbers of small groups of correlated failure time observations, in Klein JP, Goel PK (eds): *Survival Analysis: State of the Art.* Netherlands, Kluwer Academic Publishers, 1992, pp711–743.
20. Tyczynski JE, Bray F, Parkin DM. Lung cancer in Europe in 2000: epidemiology, prevention, and early detection. *Lancet Oncol* 2003;4:45–55.
21. Gürsel G, Levent E, Öztürk, et al. Hospital based survey of lung cancer in Turkey, a developing country, where smoking is highly prevalent. *Lung Cancer* 1998;21:127–132.
22. Toh CK, Gao F, Lim WT, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *J Clin Oncol* 2006; 24:2245–2251.
23. Lee C, Kang KH, Koh Y, et al. Characteristics of lung cancer in Korea, 1997. *Lung Cancer* 2000;30:15–22.
24. Fontham ET, Correa P, Reynolds P, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA* 1994;271:1752–1759.
25. Brownson RC, Alavanja MC, Caporaso N, et al. Epidemiology and prevention of lung cancer in nonsmokers. *Epidemiol Rev* 1998;20:218–236.
26. Kreuzer M, Kreienbrock L, Müller KM, Gerken M, Wichmann E. Histologic types of lung carcinoma and age at onset. *Cancer* 1999;85: 1958–1965.
27. Kabat GC, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984;53: 1214–1221.
28. Kubik AK, Zatloukal P, Tomasek L, Petruzelka L. Lung cancer risk among Czech women: a case-control study. *Prev Med* 2002;34:436–444.
29. Goodgame B, Morgensztern D, Grove L, Govindan R. Non-small cell lung cancer in the new millennium: the effect of FDG-PET on stage distribution *J Clin Oncol* 2006;18(suppl):7205.
30. Toh C-K, Wong E-H, Lim W-T, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis. *Chest* 2004;126:1750–1756.
31. Gazdar AF, Shigematsu H, Herz J, et al. Mutations and addiction to EGFR: the Achilles 'heal' of lung cancers? *Trends Mol Med* 2004;10: 481–486.
32. Powell CA, Spira A, Derti A, et al. Gene expression in lung adenocarcinomas of smokers and nonsmokers. *Am J Respir Cell Mol Biol* 2003;29:157–162.
33. Sanchez-Cespedes M, Ahrendt SA, Piantadosi S, et al. Chromosomal alterations in lung adenocarcinoma from smokers and nonsmokers. *Cancer Res* 2001;61:1309–1313.
34. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007;25:561–570.