ORIGINAL ARTICLE

Impact of smoking on mortality of patients with non-small cell lung cancer

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Abstract

Background: Cigarette smoking is one of the major causes of lung cancer. However, the correlation between smoking status and the survival of patients with lung cancer is uncertain. The present study aimed to evaluate the impact of smoking status on the mortality of patients with non-small cell lung cancer (NSCLC).

Methods: The medical records of 313 patients newly diagnosed with NSCLC between January 2005 and January 2006 were reviewed. Eligible patients were divided into ever-smokers (221 patients) and never-smokers (92 patients), and the overall survival and clinical characteristics of the two groups were compared. Predictors of survival were analyzed using Cox's proportional hazards regression.

Results: In ever-smokers, the mean age was higher, and male gender and squamous histology were predominant compared to never-smokers. The median survival time was longer in never-smokers (21.1 vs. 41.9 months, ever-smokers vs. never-smokers, respectively; P = 0.027). Overall survival estimates at 12, 24, and 60 months were 62.9 *versus* 82.6%, 43.4 *versus* 65.2%, and 31.2 *versus* 42.4%, in each group. Advanced age, advanced disease stage (stages III and IV), and coexistence of interstitial lung disease were analyzed as independent risk factors for shorter survival. Although ever-smoking was not an independent risk factor, current smoking was a risk factor for higher mortality.

Conclusions: The overall mortality of ever-smokers was higher than that of never-smokers in patients with newly diagnosed NSCLC, and current smoking was an independent risk factor for a poorer prognosis.

Introduction

Lung cancer accounted for 12.7% (1.61 million) of all new cancers in 2008 globally, and was the most common type associated with cancer-related deaths.[1,2] Cigarette smoking is a well-established cause of lung and many other types of cancer, including cancers of the oral cavity, pharynx, larynx, esophagus, stomach, colon, liver, pancreas, cervix, kidney, and lower urinary tract.[3,4] Both current and past smoking significantly increases the relative risk of lung cancer.[4] Furthermore, millions of deaths worldwide as a result of cardiovascular disease, chronic obstructive lung disease, and lung cancer, are attributable to cigarette smoking.[5]

Although a causal relationship between smoking and the incidence of lung cancer is clear, there have only been a few studies on the impact of smoking status on the mortality of patients with lung cancer, and the results have not always agreed. Ferketich *et al.* reported that current smokers at the time of diagnosis with non-small cell lung cancer (NSCLC) had poorer survival rates compared to never-smokers, in a population of 4200 patients who participated in the National Comprehensive Cancer Network project in the United States.[6] Nia *et al.* reported that non-smokers, former smokers, and recent quitters had better survival rates than current smokers in 311 surgical patients with NSCLC in Belgium.[7] Conversely, the study by Meguid *et al.* showed no difference in the long-term survival of patients with NSCLC between current- and never-smokers.[8]

In the present retrospective study, long-term mortality and the clinical characteristics of patients with NSCLC were

evaluated according to smoking status at the time of diagnosis. Additionally, risk factors for overall mortality in NSCLC patients were identified.

Methods

Data collection

Information concerning patients' baseline demographics and clinical characteristics was determined by reviewing the medical records of enrolled subjects. Age, gender, body mass index (BMI), smoking status, number of smoking pack-years, pulmonary function, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, symptoms at presentation, tumor node metastasis (TNM) stage, histologic type of lung cancer, serum level of carcinoembryonic antigen (CEA), and method of treatment were obtained from medical records. Smoking status was categorized into: (i) never-smokers, patients who had never smoked or had smoked fewer than 100 cigarettes in their entire lifetime; (ii) former-smokers, patients who had smoked at least 100 cigarettes in their lifetime and had stopped smoking at least one month before the diagnosis of lung cancer; (iii) current-smokers, patients who continued smoking upon diagnosis or stopped smoking less than one month before the diagnosis of lung cancer and had smoked more than 100 cigarettes during their lifetime. The stage of lung cancer was graded according to the 7th American Joint Committee on Cancer TNM classification. NSCLC histologic type was divided into adenocarcinoma, squamous cell carcinoma, NSCLC not otherwise specified, and others, which included large cell carcinoma, carcinoid tumor, signet ring carcinoma, and mucoepidermoid carcinoma. Review of medical records also identified the date of death. If the date of death could not be identified from medical records, data from the Korean Ministry of Public Administration and Security on 26 October 2012 was used. Follow-up for survival analysis was defined as the time in months from diagnosis of lung cancer to the date of death or the date of the last outpatient visit.

Study population

In total, 313 patients aged over 20 years and newly diagnosed with NSCLC histologically and/or cytologically between January 2005 and January 2006 at Seoul National University Hospital, Seoul, Korea were enrolled in the current study. Among them, 221 (70.6%) patients were ever-smokers, and 92 (29.4%) patients were never-smokers. Subjects were excluded if they had a malignant disease other than lung cancer that affected their survival (n = 2), the lung cancer presented as an incidentally found ground-glass nodule (GGN) (n = 4), or smoking status could not be verified (n = 46). The Seoul National University Hospital Institutional

Review Board approved the study (approval number IRB-H-1204-093-407). Eligible patients were divided into ever-smokers, including current and former smokers, and never-smokers. Demographic and clinical characteristics, as well as overall survival, were compared between the groups. Additionally, risk factors for mortality of NSCLC patients were analyzed.

Statistical analysis

Comparison of continuous variables, including age, BMI, number of smoking pack-years, pulmonary function, and serum CEA level, was performed by unpaired t-test between two groups or one-way analysis of variance (ANOVA) between three groups. Categorical variables, including gender, ECOG status, stage of lung cancer, histology, method of treatment, symptoms, and comorbidities were analyzed using Pearson's chi-squared test. The survival of patients was evaluated using Kaplan–Meier survival curves, and the difference was assessed by the log-rank test. The Cox proportional hazards model was used to estimate independent risk factors for the mortality of patients after adjusting for significant confounding factors. Variables with a $P < 0.05$ in a univariate analysis were entered into a multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Differences were deemed to be statistically significant at $P < 0.05$. Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics

Ever-smokers were significantly older than never-smokers (mean ages, 64.7 and 57.6 years, respectively; $P < 0.001$). Male patients accounted for 96.8% of ever-smokers, in contrast to the 85.9% female predominance in never-smokers. The ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) and predicted % of FEV_1 were significantly lower in ever-smokers. About 67% of ever-smokers and 62% of never-smokers had stage III or IV disease. Interestingly, the proportion of patients with stage IV lung cancer was higher in never-smokers than in ever-smokers (46.7% vs. 32.1%, respectively). Squamous cell was the most common histologic type in ever-smokers, whereas adenocarcinoma was the most common histologic type in never-smokers. Surgical resection was the most commonly performed treatment in both groups, followed by chemotherapy. BMI, ECOG performance status, and serum CEA level were comparable in the two groups (Table 1).

Cough was the most common symptom at presentation in both groups. Sputum and dyspnea were significantly more common in ever-smokers than in never-smokers. The

Table 1 Baseline characteristics of the study population

	Ever-smokers (n = 221)			
	Current-smokers (n = 96)	Former-smokers (n = 125)	Never-smokers (n = 92)	P-value
Age, year	62.7 ± 8.5	66.2 ± 10.1	57.6 ± 10.4	<0.001
Male% / female%	99.0/1.0	95.2/4.8	14.1/85.9	<0.001
BMI, kg/m^2	22.1 ± 3.4	22.5 ± 3.0	23.0 ± 3.0	0.095
Pack-years	39.0 ± 15.8	39.0 ± 19.9	0	<0.001
FEV_1/FVC, %	66.1 ± 12.7	67.5 ± 11.7	79.1 ± 5.2	<0.001
FEV_1, L	2.1 ± 0.6	2.3 ± 0.7	2.1 ± 0.6	0.167
FEV_1, %	77.3 ± 18.5	86.1 ± 22.2	96.9 ± 23.6	<0.001
FVC, L	3.2 ± 0.8	3.3 ± 0.8	2.6 ± 0.8	<0.001
FVC, %	82.8 ± 16.1	88.4 ± 15.9	89.8 ± 21.5	0.0127
ECOG status				0.692
0–1	91 (94.8)	118 (94.4)	88 (95.7)	
≥2	5 (5.2)	7 (5.6)	4 (4.3)	
Stage				0.001
I	18 (18.8)	26 (20.8)	27 (29.3)	
II	13 (13.5)	16 (12.8)	8 (8.7)	
III	35 (36.5)	42 (33.6)	14 (15.2)	
IV	30 (31.3)	41 (32.8)	43 (46.7)	
Histology				<0.001
Adenocarcinoma	23 (24.0)	46 (36.8)	75 (81.5)	
Squamous cell	47 (49.0)	49 (39.2)	2 (2.2)	
NSCLC, NOS	18 (18.8)	25 (20.0)	12 (13.0)	
Others	8 (8.3)	5 (4.0)	3 (3.3)	
Treatment				0.039
Surgery	40 (41.7)	52 (41.6)	43 (46.7)	
Chemotherapy	36 (37.5)	42 (33.6)	42 (45.7)	
Chemoradiation	4 (4.2)	8 (6.4)	0 (0)	
Radiation	5 (5.2)	5 (4.0)	2 (2.2)	
BSC	7 (7.3)	16 (12.8)	4 (4.3)	
Unknown	4 (4.2)	2 (1.6)	1 (1.1)	
Serum level of CEA, ng/ml	20.6 ± 137.4	74.9 ± 436.1	25.4 ± 114.8	0.477

Values are presented as mean ± standard deviation or No. (%). P-values represent differences between ever- and never-smokers. BMI, body mass index; BSC, best supportive care; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; FEV_1 forced expiratory volume in 1 second; FVC, forced vital capacity; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

number of asymptomatic patients was greater in never-smokers (Table 2). Hypertension was the most common comorbid disease in both groups and was more common in ever-smokers (Table 2).

Comparison of survival between ever-smokers and never-smokers

Two hundred and twenty five out of 313 patients died and 88 patients survived during the study period. The median survival in the group of survivors was 84.0 months. The median survival time was 21.1 months in ever-smokers and 41.9 months in never-smokers (log-rank test; P = 0.027; Fig 1a). The median survivals for current and former smokers were 14.7 and 22.6 months, respectively. Kaplan-Meier survival estimates at 12, 24, and 60 months were 62.9 *versus* 82.6%,

43.4 *versus* 65.2%, and 31.2 *versus* 42.4%, in each group, respectively. Kaplan-Meier survival curves of current, former, and never-smokers are shown in Figure 1b.

Prognostic factors of survival in the study population

Univariate analysis showed that ever-smokers, advanced age, male gender, low BMI, advanced disease stage (stage III and IV), low FEV_1 (% predicted), low FVC (% predicted), a high serum CEA level, ECOG ≥ 2, the presence of cough, sputum, dyspnea, extra-thoracic pain, hoarseness, and neurologic symptoms, and the coexistence of diabetes and interstitial lung disease (ILD) were predictors of high overall mortality. Advanced age, advanced disease stage (stage III and IV), and the coexistence of ILD were still significant predictors of high

Table 2 Symptoms at presentation and comorbidities of enrolled patients

	Ever-smokers (n = 221)		Never-smokers (n = 92)	P-value
	Current-smokers (n = 96)	Former-smokers (n = 125)		
Symptoms				
Cough	42 (43.8)	54 (43.2)	37 (40.2)	0.599
Sputum	33 (34.4)	36 (28.8)	17 (18.5)	0.021
Dyspnea	13 (13.5)	29 (23.2)	19 (20.7)	0.737
Hemoptysis	17 (17.7)	26 (20.8)	8 (8.7)	0.019
Weight loss	8 (8.3)	9 (7.2)	4 (4.3)	0.281
Thoracic pain	14 (14.6)	11 (8.8)	10 (10.9)	0.910
Extra-thoracic pain	6 (6.3)	4 (3.2)	7 (7.6)	0.273
Hoarseness	5 (5.2)	3 (2.4)	3 (3.3)	0.875
Neurologic symptom	4 (4.2)	3 (2.4)	1 (1.1)	0.288
Others	2 (2.1)	2 (1.6)	0 (0)	0.194
Asymptomatic	19 (19.8)	35 (28.0)	34 (37.0)	0.025
Comorbidities				
COPD	50 (52.1)	61 (48.8)	0 (0)	<0.001
Hypertension	17 (17.7)	37 (29.6)	13 (14.1)	0.043
Diabetes	8 (8.3)	21 (16.8)	7 (7.6)	0.164
Cardiovascular disease	6 (6.3)	10 (8.0)	2 (2.2)	0.079
Malignant disease	4 (4.2)	10 (8.0)	9 (9.8)	0.287
ILD	3 (3.1)	6 (4.8)	2 (2.2)	0.406
Others	7 (7.3)	7 (5.6)	2 (2.2)	0.128
No comorbidities	64 (66.7)	60 (48.0)	66 (71.7)	0.010

Values are presented as No. (%). *P*-values represent for differences between ever- and never-smokers. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

mortality after multivariate analysis (Table 3). Ever-smoking was a significant risk factor on univariate analysis, but ever-smokers had no increase in mortality over never-smokers after adjusting for covariates. Otherwise, current smoking remained a significant prognostic factor after multivariate analysis compared with current non-smoking, including former and never smoking (HR, 1.466; P = 0.032; Table 4).

Discussion

The present study was conducted to evaluate the impact of smoking status at the time of diagnosis on the long-term overall survival of patients with NSCLC. The mortality of ever-smokers, including current and former smokers, was higher than that of never-smokers. After adjusting for
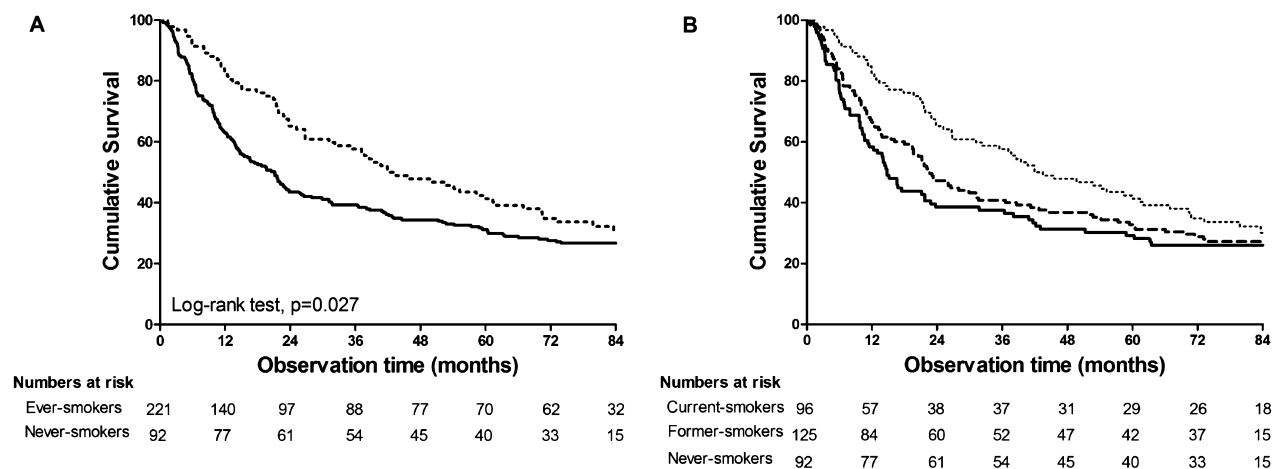

Figure 1 Overall survival of patients with non-small cell lung cancer (NSCLC) according to smoking status. (a) ▬, ever-smokers; ▪▪▪, never-smokers. (b) ▬, current-smokers.; ▬▬, former-smokers; ▪▪▪▪, never-smokers.

Table 3 Prognostic factors for higher overall mortality using univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	P-value
Smoking status						
Never-smokers	1			1		
Ever-smokers	1.387	1.037–1.857	0.028	0.810	0.458–1.403	0.470
Current-smokers	1.499	1.067	0.020	1.050	0.576–1.916	0.873
Former-smokers	1.311	0.951–1.809	0.098	0.665	0.367–1.205	0.179
Age, years	1.036	1.022–1.050	<0.001	1.044	1.026–1.061	<0.001
Gender						
Female	1			1		
Male	1.471	1.089–1.987	0.012	1.611	0.906–2.866	0.104
BMI, kg/m^2	0.944	0.904–0.986	0.009	0.957	0.912–1.005	0.076
Stage						
I	1			1		
II	1.555	0.853–2.838	0.150	1.199	0.635–2.266	0.576
III	3.636	2.313–5.716	<0.001	3.082	1.919–4.951	<0.001
IV	7.594	4.889–11.794	<0.001	7.573	4.654–12.323	<0.001
†Adenocarcinoma	0.808	0.621–1.051	0.111			
‡Squamous cell	0.807	0.603–1.081	0.150			
FEV_1, %	0.984	0.978–0.990	<0.001	0.991	0.976–1.006	0.224
FVC, %	0.981	0.974–0.989	<0.001	1.004	0.987–1.020	0.676
CEA, ng/ml	1.001	1.000–1.001	0.008	1.000	1.000–1.001	0.165
ECOG status						
0–1	1			1		
≥ 2	2.686	1.587–4.548	<0.001	1.387	0.708–2.717	0.340
Cough	1.313	1.009–1.709	0.042	1.020	0.683–1.523	0.924
Sputum	1.424	1.069–1.896	0.01	0.850	0.555–1.302	0.455
Dyspnea	2.134	1.574–2.894	<0.001	1.080	0.709–1.645	0.719
Hemoptysis	1.275	0.899–1.808	0.173			
Weight loss	1.611	0.982–2.643	0.059			
Thoracic pain	1.241	0.835–1.844	0.286			
Extra-thoracic pain	2.013	1.191–3.405	0.009	1.737	0.958–3.151	0.069
Hoarseness	2.210	1.170–4.173	0.015	1.669	0.838–3.325	0.145
Neurologic symptom	3.669	1.795–7.500	<0.001	2.216	0.925–5.309	0.074
COPD	1.371	1.046–1.797	0.022	0.985	0.590–1.647	0.955
Hypertension	1.162	0.854–1.581	0.341			
Diabetes	1.575	1.078–2.303	0.019	1.079	0.702–1.658	0.729
Cardiovascular disease	1.319	0.768–2.267	0.316			
Malignant disease	0.702	0.409–1.207	0.200			
ILD	2.783	1.506–5.143	0.001	2.529	1.272–5.030	0.008

†Referent histology for adenocarcinoma is non-adenocarcinoma. ‡Referent histology for squamous cell is non-squamous cell carcinoma. CEA, carcino-embryonic antigen; CI, confidence interval; body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; FEV_1 forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; ILD, interstitial lung disease.

confounding variables, ever-smoking was not an independent prognostic factor. Current smoking increased mortality compared to current non-smoking, including never and former smoking, even after adjustment. Ever-smokers were significantly older, predominantly male, and had a higher frequency of squamous cell histology, whereas never-smokers were younger, predominantly female, and had a higher frequency of adenocarcinoma.

It is well established that smoking is a major cause of mortality from diverse medical diseases.[5,9,10] Of these, lung cancer is the third most common cause of death attributable to smoking (0.85 million deaths), with the highest fraction attributable to smoking (71%) in the year 2000.[10] With respect to these deleterious impacts of smoking, there is a growing body of literature that evaluates the correlation between smoking and the survival of patients with lung cancer.

It seems obvious that smoking cessation improves the survival of patients with lung cancer.[11–14] However, there is controversy concerning the impact of smoking status at the time of diagnosis on the survival of patients with lung cancer. The impact of smoking is usually assessed in terms of two aspects: (i) the difference in overall survival according to smoking status and (ii) the importance of smoking status as a prognostic factor after adjusting for confounders. The results of

Table 4 Independent prognostic factors for higher mortality after multi-variate analysis

	HR	95% CI	P-value
Smoking status			
Current non-smoking	1		
Current smoking	1.466	1.034–2.079	0.032
Age, years	1.044	1.028–1.061	<0.001
Stage			
I	1		
II	1.189	0.630–2.246	0.593
III	3.000	1.869–4.816	<0.001
IV	8.149	4.980–13.334	<0.001
ILD	2.591	1.306–5.138	0.006

CI, confidence interval; HR, hazard ratio; ILD, interstitial lung disease.

previous studies have varied widely. Nia *et al.* and Tammemagi *et al.* reported that current smokers had shorter survival rates than never- and former-smokers, and current smoking was an independent predictor of a poor prognosis.[7,15] Similarly, in the recent report by Ferketich *et al.*, current smokers had significantly poorer survival than never-smokers and current smoking was a poor prognostic factor.[6] According to the report of Hanagiri *et al.*, ever-smokers had worse survival than never-smokers; however, ever-smoking was not a prognostic factor in a multivariate analysis.[16] In contrast, Toh *et al.* reported no difference in survival between ever-smokers and never-smokers; moreover, smoking status was not a significant prognostic factor.[17] Furthermore, other reports found no survival difference between current and never smokers, and current smoking was not a significant prognostic factor.[8,18] The results of the present study show overall poor survival among ever-smokers compared to never-smokers; however, ever-smoking did not have prognostic significance after adjusting for covariates. Current smoking, rather than ever-smoking, was an independent risk factor of a poor prognosis. Several reasons for these discrepancies exist. Among them, demographic differences in the study population, including ethnicity and stage of lung cancer, are important. The prognosis of surgical and non-surgical patients according to smoking status is expected to differ. In fact, most studies of surgical patients report a poor prognosis of smokers or smoking as a significant prognostic factor.[7,16,19–21] Otherwise, studies that reported no impact of smoking included all stages of lung cancer, with more than 70% of patients with stage III or higher disease.[8,17] The methods of determining and adjusting for various confounding factors also differed among the many studies.

Lung cancer in never-smokers accounts for about 10–15% of all cancers.[22,23] Adenocarcinoma is the predominant histologic type, and females are more affected than males.[24–27] In the present study, more than 80% of the subjects had the adenocarcinoma histological type, and females accounted for 85.9% of the never-smokers with lung cancer. Exposure to

biomass or passive smoke may contribute to the high percentage of never-smoking women with adenocarcinoma. It is unclear why the proportion of never-smokers with stage IV disease was almost half of all never-smokers, and why never-smokers were significantly younger than ever-smokers in the present study population. We excluded lung cancer presenting as GGN, which was mostly adenocarcinoma in never-smokers, because the tumor biology is thought to be different in these cases. Despite the high proportion of patients with stage IV disease and the exclusion of GGN, the overall survival of never-smokers was significantly better.

Sputum was the only symptom more common at presentation in ever-smokers. Irrespective of other symptoms being comparable between the groups, never-smokers were significantly more asymptomatic. Considering this phenomenon, together with the advanced disease stage in never-smokers, a method of detecting asymptomatic lung cancer earlier in never-smokers is needed to improve the prognosis.

Lung cancer is a common comorbidity and a major cause of death in patients with chronic obstructive pulmonary disease (COPD).[28,29] Among subjects in the present study, COPD coexisted with NSCLC in 35.5% of all enrolled patients and 50.2% of ever-smokers. The high incidence of COPD in ever-smokers is thought to be the reason for the predominance of male, lower FEV_1 (% predicted), and a relative paucity of stage I disease and adenocarcinoma histology compared to never-smokers.

Previous studies of the impact of ILD on the survival of patients with lung cancer found that patients with both ILD and lung cancer had shorter overall survival rates than those without ILD. Furthermore, ILD was a significant predictor of a poor prognosis.[30–32] In the present study, ILD was present in 11 patients (3.5%) at the time of diagnosis, and was a poor prognostic factor after multivariate analysis, as in previous reports. Thus, the presence of ILD should be considered an important factor at the time of diagnosis and treatment.

Limitations of this study are as follows: (i) the cause of death could not be identified, thus the cause specific mortality could not be evaluated because this is a retrospective study; (ii) the number of enrolled patients was relatively small as many patients with NSCLC were excluded because of unidentifiable smoking history; and (iii) a history of exposure to the passive cigarette smoke and biomass smoke could not investigated.

Conclusion

In conclusion, ever-smokers had poorer survival rates than never-smokers, and current smoking was a significant prognostic factor of a poor prognosis in the present study population. Further efforts towards smoking cessation are needed, not only to decrease the incidence of lung cancer, but also to increase the survival of patients with NSCLC.

Disclosures

No authors report any conflict of interest.

References

1   Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer J Int Cancer* 2010; **127**: 2893–917.

2   Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. (Erratum in *CA Cancer J Clin* 2011; **61**: 134.) *CA Cancer J Clin* 2011; **61** (2): 69–90.

3   Agudo A, Bonet C, Travier N *et al.* Impact of cigarette smoking on cancer risk in the European prospective investigation into cancer and nutrition study. *J Clin Oncol* 2012; **30**: 4550–7.

4   Gandini S, Botteri E, Iodice S *et al.* Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008; **122**: 155–64.

5   Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003; **362** (9387): 847–52.

6   Ferketich AK, Niland JC, Mamet R *et al.* Smoking status and survival in the national comprehensive cancer network non-small cell lung cancer cohort. *Cancer* 2013; **119** (4): 847–53.

7   Sardari Nia P, Weyler J, Colpaert C, Vermeulen P, Van Marck E, Van Schil P. Prognostic value of smoking status in operated non-small cell lung cancer. *Lung Cancer* 2005; **47**: 351–9.

8   Meguid RA, Hooker CM, Harris J *et al.* Long-term survival outcomes by smoking status in surgical and nonsurgical patients with non-small cell lung cancer: comparing never smokers and current smokers. *Chest* 2010; **138**: 500–9.

9   The Surgeon General's 1989 Report on Reducing the Health Consequences of Smoking: 25 Years of Progress. *MMWR Morb Mortal Wkly Rep* 1989; **38** (Suppl 2): 1–32.

10 Ezzati M, Lopez AD. Regional, disease specific patterns of smoking-attributable mortality in 2000. *Tob Control* 2004; **13**: 388–95.

11 Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ* 2010; **340**: b5569.

12 Ebbert JO, Williams BA, Sun Z *et al.* Duration of smoking abstinence as a predictor for non-small-cell lung cancer survival in women. *Lung Cancer* 2005; **47**: 165–72.

13 Wakai K, Marugame T, Kuriyama S *et al.* Decrease in risk of lung cancer death in Japanese men after smoking cessation by age at quitting: pooled analysis of three large-scale cohort studies. *Cancer Sci* 2007; **98**: 584–9.

14 Zhou W, Heist RS, Liu G *et al.* Smoking cessation before diagnosis and survival in early stage non-small cell lung cancer patients. *Lung Cancer* 2006; **53**: 375–80.

15 Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. *Chest* 2004; **125**: 27–37.

16 Hanagiri T, Sugio K, Mizukami M *et al.* Significance of smoking as a postoperative prognostic factor in patients with non-small cell lung cancer. *J Thorac Oncol* 2008; **3**: 1127–32.

17 Toh CK, Wong EH, Lim WT *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**: 1750–6.

18 Subramanian J, Velcheti V, Gao F, Govindan R. Presentation and stage-specific outcomes of lifelong never-smokers with non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007; **2**: 827–30.

19 Chen J, Jiang R, Garces YI *et al.* Prognostic factors for limited-stage small cell lung cancer: a study of 284 patients. *Lung Cancer* 2010; **67**: 221–6.

20 Yoshino I, Kawano D, Oba T, Yamazaki K, Kometani T, Maehara Y. Smoking status as a prognostic factor in patients with stage I pulmonary adenocarcinoma. *Ann Thorac Surg* 2006; **81**: 1189–93.

21 Fujisawa T, Iizasa T, Saitoh Y *et al.* Smoking before surgery predicts poor long-term survival in patients with stage I non-small-cell lung carcinomas. *J Clin Oncol* 1999; **17**: 2086–91.

22 Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**: 212–36.

23 Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers – a different disease. *Nat Rev Cancer* 2007; **7**: 778–90.

24 Govindan R. Lung cancer in never smokers: a new hot area of research. *Lancet Oncol* 2010; **11**: 304–5.

25 Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers – a review. *Eur J Cancer* 2012; **48**: 1299–311.

26 Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007; **25**: 561–70.

27 Samet JM, Avila-Tang E, Boffetta P *et al.* Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res* 2009; **15**: 5626–45.

28 Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; **142**: 233–9.

29 Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012; **379** (9823): 1341–51.

30 Miyazaki K, Satoh H, Kurishima K *et al.* Interstitial lung disease in patients with small cell lung cancer. *Med Oncol* 2010; **27**: 763–7.

31 Miyazaki K, Satoh H, Kurishima K *et al.* Impact of interstitial lung disease on survival for patients with non-small cell lung cancer. *Anticancer Res* 2009; **29**: 2671–4.

32 Togashi Y, Masago K, Handa T *et al.* Prognostic significance of preexisting interstitial lung disease in Japanese patients with small-cell lung cancer. *Clin Lung Cancer* 2012; **13**: 304–11.