Original Article

Characteristics of female lung cancer in Korea: analysis of Korean National Lung Cancer Registry

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Backgrounds: The present study evaluated Korean women with lung cancer and compared the clinical characteristics of ever-smoker and never-smoker groups using the National Lung Cancer Registry.

Methods: In affiliation with the Korean Central Cancer Registry, the Korean Association for Lung Cancer constructed a registry into which 10% of the lung cancer cases in Korea were registered. Female lung cancer patients with valid smoking history were evaluated.

Results: Among 735 female lung cancer patients, 643 (87.5%) were never-smokers and 92 (12.5%) were smokers. The median survival was significantly longer in the never-smoker group (28 *vs.* 14 months; P<0.001). Among 683 patients with non-small cell lung cancer (NSCLC), the never-smoker group showed significantly longer median survival (29 *vs.* 14 months; P=0.002) and a higher proportion of stage I cancer (40.3% *vs.* 25.7%; P<0.001). Survival analysis of the NSCLC patients showed that smoking status, receiving only supportive care, EGFR mutation status, lung cancer stage, and forced vital capacity (FVC) (%) were significantly associated with mortality in the multivariate analysis (P=0.025, HR 2.39, 95% CI: 1.12–5.11; P=0.017, HR 3.14, 95% CI: 1.22–8.06; P=0.033, HR 0.63, 95% CI: 0.41–0.96; P<0.001, HR 11.88, 95% CI: 5.79–24.38; P=0.002, HR 0.98, 95% CI: 0.96–0.99, respectively).

Conclusions: In Korean women with NSCLC, smoking status, not receiving active anticancer treatment, EGFR mutation status, lung cancer stage, and pulmonary function were significantly associated with mortality.

Keywords: Women; lung cancer; smoking; pulmonary function; mortality

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide (1,2). In the United States, lung cancer is one of the most common cancers and the leading cause of cancer-related mortality in women (3). In other countries, increases in lung cancer mortality have been observed in parallel with the prevalence of cigarette smoking (4). Lung cancer in women shows different clinical characteristics compared to men regarding pathophysiology, prognosis, and related risks (5-7). The differences may be due to the environment, hormones, and other factors (8,9), and lung cancer in females could be a distinct disease entity.

However, the clinical presentation of lung cancer in women can also differ depending on region and race. Asian women with lung cancer have distinct clinical characteristics compared to women in Western populations. The prevalence of smoking in women with lung cancer is less than 20% in Asian regions (10,11), whereas 70–85% of women with lung cancer in Western populations, including North America, northern Europe, and Australia/New Zealand, were reported to be smokers (12). In addition, it is widely known that the prevalence of epidermal growth factor receptor (EGFR) mutation is higher in Asian females than in Western populations (13,14).

The proportion of women in the lung cancer population has been increasing in Korea (15). Among women, we can speculate that the clinical characteristics of smokers would be less favorable compared to never-smokers among lung cancer patients. They would have poorer lung functions and the prevalence of EGFR mutation would be lower (13,16,17). Thus, it is also important to evaluate how smoking affects the prognosis of women with lung cancer. In this context, the real-life data of female lung cancer patients would provide useful clinical information.

In affiliation with the Korean Central Cancer Registry (KCCR), the Korean Association for Lung Cancer (KALC) built a registry (KALC-R) into which 10% of the lung cancer cases from all Korean nationals were registered after the survey of the patients. This registry was developed to construct an unbiased lung cancer database to represent the Korean lung cancer population.

Using data from the KALC-R for 2014, the present study evaluated Korean women with lung cancer and further compared the clinical characteristics of ever-smoker and never-smoker groups. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1671).

Methods

Study patient selection

In 2014, 24,253 patients with newly diagnosed lung cancer were registered in the KCCR. After excluding patients who were enrolled in more than one institution or did not fit the KCCR enrollment criteria, 21,960 patients from 13 regional cancer centers and 39 hospitals remained as the final study population. Based on the annual number of patients registered in each hospital, the sample size allocated to each hospital was decided after taking selection probability into account. After sorting patients by age, sex, date of the first diagnosis, and the Surveillance, Epidemiology, and End Results program (SEER) summary stage, 2,640 were selected from 52 hospitals using a systematic sampling method (18). After excluding 19 patients with multiple primary cancers, 745 female lung cancer patients were selected from the remaining 2,621 patients. Thus, after exclusion of male patients and those without valid smoking history, 735 female lung cancer patients with valid smoking history were evaluated retrospectively in the present study. The selection process is shown in *Figure 1*.

Data collection

Using a standardized protocol, patient data including age; sex; treatment modalities; smoking status; histopathologic type; initial symptoms; Eastern Corporative Oncology Group (ECOG) score; cancer stage (according to the seventh edition of the TNM International Staging System); driver mutations, such as EGFR mutations and anaplastic lymphoma kinase (ALK) translocations; body mass index (BMI); and survival status were collected. Furthermore, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were also collected in the study. Choi's reference equation, the reference equation for the Korean population, was used to calculate the predicted FEV1% and predicted FVC% in the study

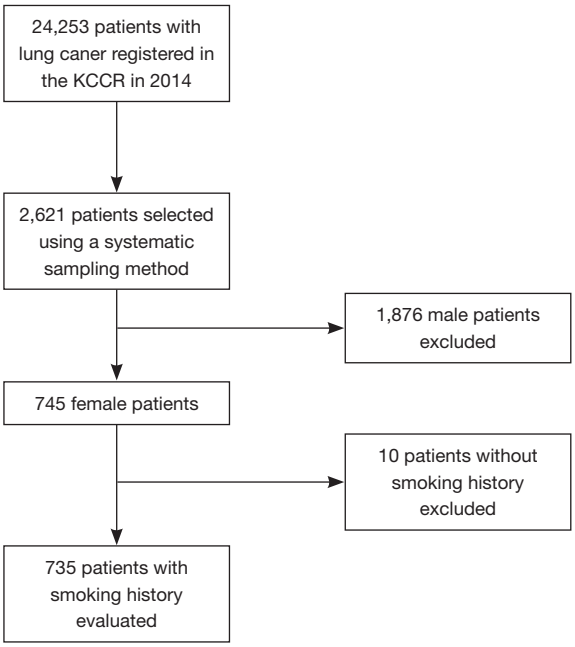

Figure 1 Selection process of the study patients.

patients (19). Regarding smoking status, ever-smokers were defined as patients with any history of smoking before a lung cancer diagnosis and never-smokers as those with no smoking history. The patients were followed-up until December 2017.

Statistical analysis

To compare the demographic and clinical characteristics between the two groups, we used the two-sample *t*-test for continuous variables and the chi-squared test for categorical variables. The overall survival (OS) of the patients was estimated from Kaplan-Meier survival curves and the statistical difference between the groups was tested by the log-rank test. OS was defined as the time from the lung cancer diagnosis to the date of death or the date of the last follow-up.

The Cox proportional hazard model was used to identify independent prognostic factors in the study and variables that were statistically significant in the univariate analysis were entered into multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated. A P value of <0.05 was considered statistically significant for all tests. Statistical analyses were performed using R (version 3.5.1; R Computing, Vienna, Austria).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Institutional Review Board at the National Cancer Center (NCC2018-0193), which waived the requirement for informed consent due to the retrospective nature of the study.

Results

Patients clinical characteristics

A total of 735 female lung cancer patients were selected and evaluated. There were 643 (87.5%) never-smokers and 92 (12.5%) smokers. Among 92 ever smokers, 61 (66.3%) were current smoker and 31 (33.7%) were former smokers. Mean pack years of the smoker group was 23.8±20.6. The clinical characteristics were compared between the two groups and are shown in *Table 1*. There was no significant difference in age and initial symptoms between the two groups. The never-smoker group had significantly higher BMIs than the smoker group (23.8 *vs.* 22.8; P=0.023), and had a higher proportion of patients with good performance (ECOG 0–2) with statistical significance (96% *vs.* 88.6% in the never-smokers *vs.* smokers, respectively; P=0.017). In addition, the never-smoker group showed significantly better lung function than the smoker group. The proportion of adenocarcinoma was significantly higher in the never-smoker group. Moreover, the median survival was significantly higher in the never-smoker group (28 *vs.* 14 months; P<0.001).

Comparison of NSCLC in the never- and ever-smoker groups

Among 735 patients, a total of 683 patients were categorized as NSCLC (92.9%). There were 613 (89.8%) never-smokers and 70 ever-smokers (10.2%). Mean pack years of the smoker group was 22.1±18.7. The never-smoker NSCLC patients showed significantly higher BMIs (25.1 *vs.* 22.5; P=0.017) and were significantly younger (66 *vs.* 69; P=0.048). No statistical differences were found between the initial symptoms and ECOG scores. The never-smoker NSCLC patients showed significantly longer median survival (29 *vs.* 14 months; P=0.002) (*Figure 2*), and a higher proportion of stage I cancer (40.3% *vs.* 25.7%; P<0.001). However, no significant difference was seen in

Table 1 Baseline clinical characteristics of the study patients

Characteristics	Total	Never smoker	Ever smoker	P value
Number of patients, n (%)	735	643 (87.5)	92 (12.5)	
Age (year)	66.6±12.0	66.4±11.9	68.2±12.7	0.173
BMI (kg/m^2)	23.6±3.7	23.8±3.7	22.8±4.0	0.023
Initial symptoms, n (%)				0.126
Asymptomatic	121 (14.7)	112 (17.4)	9 (9.8)	
Cough	233 (28.4)	200 (31.1)	33 (35.9)	
Sputum	117 (14.3)	96 (14.9)	21 (22.8)	
Dyspnea	153 (18.6)	123 (19.1)	30 (32.6)	
Hoarseness	6 (0.7)	5 (0.8)	1 (1.1)	
Hemoptysis	17 (2.1)	13 (2.0)	4 (4.3)	
Weight loss	32 (3.9)	25 (3.9)	7 (7.6)	
Pain	142 (17.3)	123 (19.1)	19 (20.7)	
ECOG, n (%)				0.017
0–2	520 (95.1)	458 (96.0)	62 (88.6)	
3–4	27 (4.9)	19 (4.0)	8 (11.4)	
Median survival time (months)	26.0 [8.0–34.0]	28.0 [9.0–35.0]	14.0 [5.0–30.0]	0.000
Pathology, n (%)				0.000
Adenocarcinoma	549 (74.7)	513 (79.8)	36 (39.1)	
Squamous cell	54 (7.3)	27 (4.2)	27 (29.3)	
Small cell	52 (7.1)	30 (4.7)	22 (23.9)	
Others	80 (10.9)	73 (11.4)	7 (7.6)	
FEV1 (liter)	1.9±0.7	2.0±0.7	1.6±0.6	0.000
FVC (liter)	2.5±0.6	2.5±0.6	2.3±0.7	0.004
FEV1 (%)	62.5±16.9	63.9±16.5	52.7±16.6	0.000
FVC (%)	71.3±16.4	72.0±16.2	65.9±16.6	0.004
FEV1/FVC ratio	0.8±0.1	0.8±0.1	0.7±0.1	0.000
FEV1/FVC <0.7	83/527	52/461	31/66	0.000
DLCO (absolute)	14.4±4.3	14.8±4.2	11.4±4.2	0.000
DLCO (%)	85.2±22.4	87.4±21.7	68.6±20.5	0.000

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

the prevalence of EGFR or ALK mutations. The treatment modalities and parameters related to pulmonary function were also compared between the two groups and are shown in *Table 2*.

Stage IV NSCLC

From 683 patients with NSCLC, 298 patients were categorized with stage IV cancer. There was no statistically

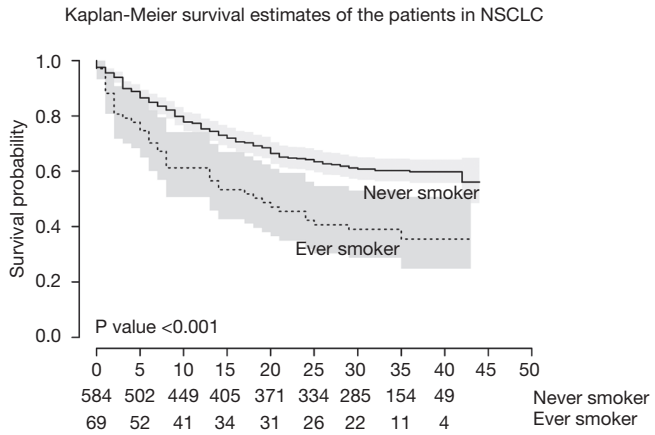

Figure 2 Kaplan-Meier survival curves for the ever and never smoker patients with non-small cell lung cancer.

significant difference between the two groups with respect to age, BMI, initial symptoms, ECOG, primary mass size or the proportion of driver mutations (EGFR and ALK). A significantly higher proportion of never-smoker patients received targeted therapy as an initial treatment compared to ever-smoker patients (28% *vs.* 8%; P=0.022), whereas diffusing capacity for carbon monoxide (DLCO) (%) was lower and the proportion of patients with FEV1/FVC <0.7 was higher in the smoker group with statistical significance (P=0.035 and P=0.028, respectively).

Comparison between EGFR mutation-positive and wild-type NSCLC groups

Among 481 patients who underwent EGFR tests, 248 (51.6%) were EGFR wild-type and 233 (48.4%) were EGFR mutation-positive. There was no significant difference between the two groups in BMI, age, smoking status, ECOG or pulmonary function parameters. The EGFR mutation group showed significantly longer survival time (29.0 *vs.* 23.5 months; P=0.001) (*Figure 3*), and a higher proportion of stage I cancer (39.8% and 29.7%; P=0.009). In addition, a higher proportion of the EGFR mutation group underwent targeted therapy as an initial treatment (30.3% *vs.* 1.7% in EGFR mutation-positive *vs.* EGFR wild-type, respectively; P<0.001) (*Table S1*).

Survival analysis in NSCLC

Table 3 shows both univariate and multivariate survival analyses in all NSCLC patients. Smoking status, receiving only supportive care for treatment, EGFR mutation status, lung cancer stage, and FVC (%) showed significant associations with mortality in multivariate analysis (P=0.025, HR 2.39, 95% CI: 1.12–5.11; P=0.017, HR 3.14, 95% CI: 1.22–8.06; P=0.033, HR 0.63, 95% CI: 0.41–0.96; P<0.001, HR 11.88, 95% CI: 5.79–24.38; P=0.002, HR 0.98, 95% CI: 0.96–0.99, respectively).

Discussion

The present study described the clinical characteristics of female lung cancer patients in Korea and focused on comparing the clinical presentation between ever-smoker and never-smoker groups. The strength of this study was the use of national cancer registry data, which are data representing all Korean patients with lung cancer.

Asian women with lung cancer show distinct clinical characteristics compared to European populations. First, the proportion of ever-smokers is low compared to Western populations (12). A previous study of Korean lung cancer patients showed that the proportion of ever-smokers was about 10% (10). In contrast, a study from Spain showed that about 60.5% of the female lung cancer patients were either current or former smokers (20). In addition, the prevalence of smokers in women with lung cancer was 70–85% in another Western population studied (12). This difference in the proportions is presumably due to demographic differences. We assume that the elderly female population in Asia may be a relatively smaller group of smokers compared to other global regions, and the culture of social disapproval of women's smoking may have contributed to the difference in prevalence. Secondly, the prevalence of EGFR mutations was much higher in an Asian female population than in other regions (13,17). The present study also showed that about 48% had positive EGFR mutations. This proportion is higher than that reported in a European population (14,21). With respect to pathologic subtype, the ever-smoker group had a significantly higher proportion of squamous and small cell lung cancer than the never-smoker group and this difference in the pathologic types regarding smoking status was seen in previous studies, including a study in a Korean population (11,18,20).

The prevalence of smoking experience in our study was about 12.5%, which was relatively low when compared to European women with lung cancer (22), and it is comparable to the smoking rate among general female population of Korea (23). Looking from a different perspective, it is possible that a considerable proportion of

Table 2 Comparison between ever and never smokers in NSCLC

Characteristics	Total	Never smoker	Ever smoker	P value
Number of patients, n (%)	683	613 (89.8)	70 (10.2)	
Age (year)	66.5±12.1	66.2±12.0	69.2±12.6	0.048
BMI (kg/m^2)	24.8±20.8	25.1±21.9	22.5±4.2	0.017
Initial symptoms, n (%)				0.359
Asymptomatic	120 (17.6)	112 (18.3)	8 (11.4)	
Cough	208 (30.5)	185 (30.2)	23 (32.9)	
Sputum	107 (15.7)	93 (15.2)	14 (20.0)	
Dyspnea	133 (19.5)	111 (18.1)	22 (31.4)	
Hoarseness	6 (0.9)	5 (0.8)	1 (1.4)	
Hemoptysis	16 (2.3)	13 (2.1)	3 (4.3)	
Weight loss	28 (4.1)	24 (3.9)	4 (5.7)	
Pain	131 (19.2)	118 (19.2)	13 (18.6)	
ECOG, n (%)	n=506	n=455	n=51	0.098
0–2	484 (95.7)	438 (96.3)	46 (90.2)	
3–4	22 (4.3)	17 (3.7)	5 (9.8)	
Median survival time (months)	28.0 [10.0–35.0]	29.0 [10.0–35.0]	14.0 [5.0–32.0]	0.002
Clinical stage, n (%)	n=676	n=606	n=70	
I	262 (38.8)	244 (40.3)	18 (25.7)	
II	44 (6.5)	38 (6.3)	6 (8.6)	
III	72 (10.7)	56 (9.2)	16 (22.9)	
IV	298 (44.1)	268 (44.2)	30 (42.9)	0.072
EGFR mutation	n=481	n=442	n=39	
Number (%)	233 (48.4)	220 (49.8)	13 (33.3)	
ALK mutation (IHC)	n=321	n=294	n=27	0.000
Number (%)	24 (7.5)	23 (7.8)	1 (3.7)	
Initial treatment, n (%)	n=629	n=568	n=61	
Surgery only	216 (34.3)	202 (35.6)	14 (23.0)	
Surgery + adjuvant	95 (15.1)	89 (15.7)	6 (9.8)	
Conventional chemotherapy	125 (19.9)	111 (19.5)	14 (23.0)	
CCRT	17 (2.7)	14 (2.5)	3 (4.9)	
Targeted therapy	75 (11.9)	73 (12.9)	2 (3.3)	
Radiotherapy only	34 (5.4)	30 (5.3)	4 (6.6)	
Supportive care only	67 (10.7)	49 (8.6)	18 (29.5)	
Target agent usage (ever), n (%)	154 (22.5)	147 (24.0)	7 (10.0)	0.012
EGFR inhibitor ever	143 (20.9)	136 (22.2)	7 (10.0)	0.026
ALK inhibitor ever	16 (2.3)	16 (2.6)	0 (0.0)	0.342

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Total	Never smoker	Ever smoker	P value
FEV1 (liter)	1.9±0.7	2.0±0.7	1.6±0.6	0.001
FVC (liter)	2.5±0.6	2.5±0.6	2.3±0.7	0.017
FEV1 (%)	63.2±16.7	64.3±16.3	53.4±17.0	0.000
FVC (%)	71.9±16.2	72.5±16.0	66.6±16.8	0.013
FEV1/FVC ratio	0.8±0.1	0.8±0.1	0.7±0.2	0.003
FEV1/FVC <0.7	72/499	48/447	24/52	0.000
DLCO (absolute)	14.5±4.3	14.9±4.1	11.4±4.4	0.000
DLCO (%)	85.8±22.3	87.7±21.6	68.8±22.0	0.000

ALK, anaplastic lymphoma kinase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FEV1, forced expiratory volume in 1 s; FVC; forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

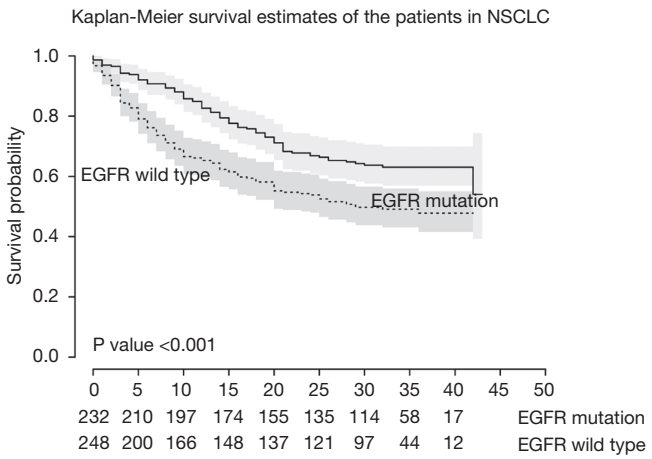

Figure 3 Kaplan-Meier survival curves for the epidermal growth factor receptor (EGFR) positive and wild-type patients with non-small cell lung cancer.

patients who were reported as never smoker, may have been exposed to passive smoking. In the previous study of Korean women with lung cancer (23), the passive smoking rate was 7.9% in non-smoking women. However, this survey was made in 2016, and we assume that the actual passive-smoking rate would have been higher in the past time, during which a large number of our study patients could have been exposed to. Unfortunately, no data on passive smoking were present in the current study. In addition, the smoking status was based on self-reporting, and the statistics on Korean women showed that smoking rate was about 6% which was also based on self-reporting (23), but we suspect that the actual rate is much higher. Thus, it is possible that disparity in actual number of ever smokers could be present due to the limitation of a self-reporting method.

The number of the never smoker group is about 8.5 times that of the smoker group in NSCLC, and the proportion of stage I cancer is about 40.3%, which is higher than 25.7% of the smoker group. In early stage lung cancer, it is difficult for patients to be aware of presenting symptoms (24,25), and the screening by simple chest X-ray is not as effective as in advanced cancer. Thus, a more effective screening tool, such as low dose chest CT may increase the chance of a curative treatment for the early stage lung cancer in the never smoker female population. Considering both the number and proportion of early stage lung cancer, our study results support the necessity of a more vigorous screening strategy using low dose CT in never smoker female population with risk factors for cancer development.

The reason why smoking experience was found to be an independent factor for shorter survival is not clear. It is possible that smoking results in decreased lung function, which further contributes to the poor prognosis of lung cancer patients. In the present study, the ever-smoker group had significantly lower FEV1, FVC, and DLCO in both the overall patient group and the NSCLC subgroup. The impact of decreased lung functions on prognosis will be discussed in a later section. A study by a French group showed that patients with positive cotinine during chemotherapy showed poorer overall response rates compared to never-smokers (26). Gemine *et al.* showed that after adjusting for various factors, smokers with NSCLC were more likely to die within one year compared to

Table 3 Survival analysis in NSCLC

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.04	1.03–1.05	0.000	1.01	0.99–1.03	0.373
BMI	1	0.99–1.01	0.434	0.96	0.89–1.02	0.181
ECOG						
0–2	1			1		
3–4	6.72	3.99–11.31	0.000	2.75	1.05–7.22	0.04
Smoking experience						
Never smoker	1			1		
Ever smoker	1.95	1.4–2.72	0.000	2.39	1.12–5.11	0.025
1st line treatment						
Active treatment	1			1		
Supportive treatment	5.93	4.31–8.16	0.000	3.14	1.22–8.06	0.017
EGFR mutation						
–	1			1		
+	0.60	0.45–0.8	0.000	0.63	0.41–0.96	0.033
Clinical Stage						
I/II	1			1		
III/IV	15.49	9.99–24.02	0.000	11.88	5.79–24.38	0.000
Histopathology						
Non-squamous	1			1		
Squamous	1.9	1.33–2.73	0.000	0.33	0.09–1.17	0.085
FVC (%)	0.95	0.94–0.96	0.000	0.98	0.96–0.99	0.002

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FVC, forced vital capacity.

never-smokers (27). It is possible that smoking has more detrimental effects in female lung cancer patients compared to male patients because they have relatively smaller lung volumes than men, and therefore, tobacco smoke can damage a larger proportion of the lung. Ryu *et al.* showed that among Korean patients with lung cancer, the unfavorable effects of smoking on pulmonary function were greater in women compared to men and suggested that the higher susceptibility might be attributed to lower lung volume (28).

We also investigated whether pulmonary function parameters were independent factors associated with overall survival. Mean FEV1 and FVC values of the never smoker groups were relatively low, considering the absent effect of smoking. However, in case of early-stage NSCLC, mean values of FEV1 (%) and FVC (%) were much higher than the mean values of all never smoker patients with NSCLC. Decreased FVC (%) was predictive of shorter survival in our study. Few studies showed that FVC (%) predicted worse prognosis in NSCLC patients. Low FVC (%) was shown to be associated with cytotoxic chemotherapy-related acute exacerbation of interstitial lung disease in lung cancer (29). We assume that FVC (%) not only reflected lung function but also lung volume indirectly. A study by Vandevoorde *et al.* showed that reduced FVC was highly correlated with reduced total lung capacity in female patients (30). However, further studies using plethysmography are necessary to confirm how pulmonary

function has prognostic value in female NSCLC.

Although it was not shown in the results of the present study, each FEV1 (%) or fixed airway obstruction defined as FEV1/FVC <70% was entered into survival analyses in place of FVC (%) in other Cox regression models. In NSCLC, FEV1 (%) also showed a significant association with survival, consistent with the results of a previous study (31). However, FEV1/FVC <70% was not an independent prognostic factor. This statistical insignificance was shown in a study by Lee *et al.* (32) and is contrary to the results of a previous study on patients with chronic obstructive pulmonary disease (COPD) and NSCLC (33).

There were some limitations to the present study. First, data on second-hand smoke was not obtained in this study. Considering that many never-smokers are exposed to passive smoking in their households, a future study accounting for this factor is necessary. Second, the TNM classification of the 7th edition was used to define cancer stages in the patients, so this should be taken into account when applying the results of our study to other lung cancer populations. Third, comorbidities including interstitial lung disease were not evaluated in our study. Lastly, our data were retrospectively collected from the randomly sampled patients group representing whole newly diagnosed lung cancer population in 2014, however, not all patients with newly diagnosed lung cancer were evaluated in this study. We believe that limitation of relatively small number of study patients were overcome by careful sorting sampling process, but it should be taken into account for interpretation of results.

Conclusions

In conclusion, in women with NSCLC, smoking was associated with worse prognosis and decreased lung function was significantly associated with mortality. Further studies are necessary to clarify the underlying mechanisms of the association between smoking and unfavorable outcomes in Korean women with lung cancer.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1671). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Institutional Review Board at the National Cancer Center (NCC2018-0193), which waived the requirement for informed consent due to the retrospective nature of the study.

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Supplementary

Table S1 Comparison between EGFR mutation *vs.* EGFR wild type subgroups in NSCLC

Characteristics	Total	EGFR-wild type, n (%)	EGFR-mutation, n (%)	P value
Number of patients, n (%)	481	248 (51.6)	233 (48.4)	
Age (year)	65.8±11.8	66.1±11.6	65.6±12.0	0.678
BMI (kg/m^2)	24.5±17.1	25.3±23.6	23.6±3.2	0.276
Ever smoker, n (%)	39 (8.1)	26 (10.5)	13 (5.6)	0.072
ECOG, n (%)	n=374	n=192	n=182	0.343
0–2	359 (96.0)	182 (94.8)	177 (97.3)	
3–4	15 (4.0)	10 (5.2)	5 (2.7)	
Median survival time (months)	26.0 (10.0–34.0)	23.5 (6.0–32.5)	29.0 (14.5–34.5)	0.001
Stage, n (%)	n=477	n=246	n=231	0.009
I	165 (34.6)	73 (29.7)	92 (39.8)	
II	25 (5.2)	15 (6.1)	10 (4.3)	
III	51 (10.7)	36 (14.6)	15 (6.5)	
IV	236 (49.5)	122 (49.6)	114 (49.4)	
Initial treatment, n (%)	n=457	n=229	n=228	0.000
Surgery	134 (29.3)	64 (27.9)	70 (30.7)	
Surgery + adjuvant	74 (16.2)	32 (14.0)	42 (18.4)	
Conventional chemotherapy	106 (23.2)	80 (34.9)	26 (11.4)	
Targeted therapy	73 (16.0)	4 (1.7)	69 (30.3)	
CCRT	12 (2.6)	10 (4.4)	2 (0.9)	
Radiotherapy only	26 (5.7)	15 (6.6)	11 (4.8)	
Supportive care	32 (7.0)	24 (10.5)	8 (3.5)	
FEV1 (liter)	1.9±0.6	1.9±0.6	2.0±0.6	0.173
FVC (liter)	2.5±0.6	2.4±0.6	2.5±0.6	0.254
FEV1 (%)	62.9±16.6	61.8±17.0	64.0±16.2	0.216
FVC (%)	71.4±16.3	70.7±16.2	72.2±16.4	0.364
FEV1/FVC ratio	0.8±0.1	0.8±0.1	0.8±0.1	0.163
FEV1/FVC <0.7	56/372	33/192	23/180	0.297
DLCO (absolute)	14.5±4.2	14.0±4.3	14.9±4.2	0.059
DLCO (%)	85.5±22.6	84.7±20.1	86.4±24.9	0.510

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.