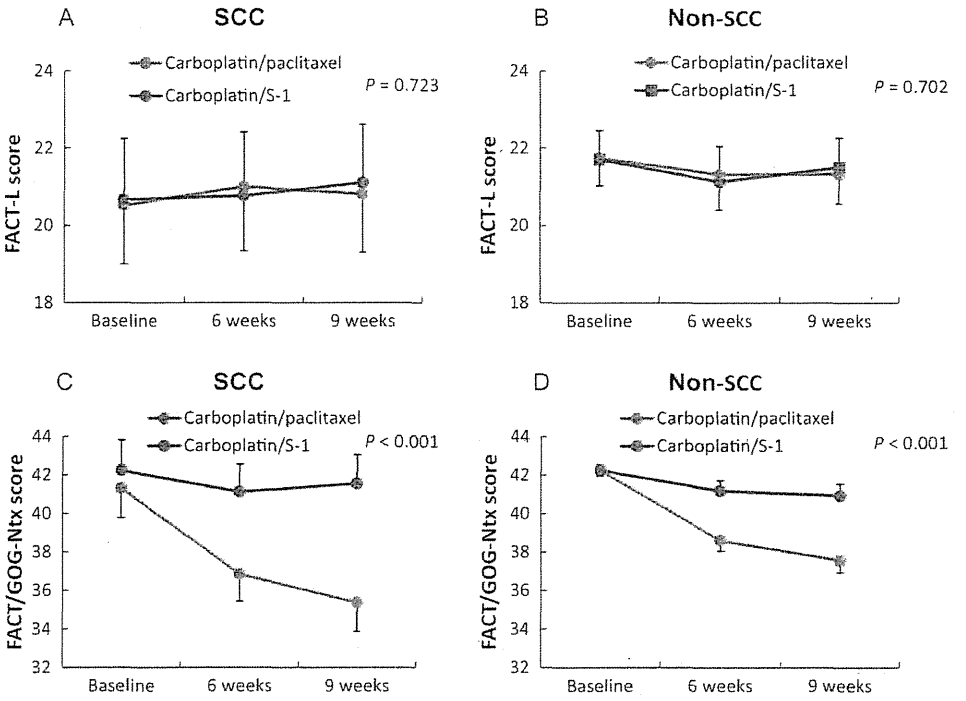

Figure 2. QOL assessments according to histological subtype of NSCLC. Assessments were carried out with the seven-item FACT-L (A and B) and 11-item FACT/GOG-Ntx (C and D) subscales for patients with SCC (A and C) or with non-SCC (B and D). Data are presented as least-square means and 95% CIs. Higher scores indicate a better QOL. *P* values were determined by analysis of variance.

Table 4. Post-treatment rate according to histological subtype of NSCLC

	Squamous			Nonsquamous		
	CBDCA–S-1 (*N* = 55)	CBDCA–PTX (*N* = 59)	*P*	CBDCA–S-1 (*N* = 227)	CBDCA–PTX (*N* = 223)	*P*
Second-line, *N* (%)	43 (78.2)	39 (66.1)	0.15	168 (74.0)	156 (70.0)	0.34
Docetaxel, *N* (%)	32 (58.2)	18 (30.5)	0.003	107 (47.1)	99 (44.4)	0.56
EGFR-TKI, *N* (%)	7 (12.7)	6 (10.2)	0.67	122 (53.7)	102 (45.7)	0.09

P values were determined by the chi-square test.

frequently as a second-line treatment than did those in the carboplatin–paclitaxel arm (58.2% versus 30.5%, respectively, $P = 0.003$), possibly because the former patients were in better condition as a result of a better tolerated first-line regimen. The reduced toxicity of carboplatin–S-1, especially with regard to neuropathy and neutropenia, may thus have allowed for more frequent application of second-line treatment with docetaxel, which has been shown to improve survival over best supportive care for the second-line setting in phase III trials [18]. Kaplan–Meier survival curves for the patients with SCC began to diverge shortly after the end of the study treatment, suggesting that the higher percentage of active second-line treatment in the carboplatin–S-1 arm of the SCC cohort may have contributed to the improved survival outcome. Given the increasing number of active drugs available for second-line treatment, subsequent therapies instituted after disease progression can have a substantial impact on OS in advanced NSCLC [19]. If multiple drugs with no large differences in effectiveness are indicated for NSCLC, treatment strategies should take into account the overall treatment plan envisioned for a given patient, including second-line and subsequent therapies as well as first-line chemotherapy.

In conclusion, we have presented the results of updated survival analysis and subgroup analysis by histology for the first phase III study of the combination of carboplatin and S-1 for the treatment of chemotherapy-naïve patients with advanced NSCLC. This regimen is therapeutically beneficial and well tolerated in such patients with either SCC or non-SCC histology. Given its efficacy and favorable toxicity profile, the combination of carboplatin and S-1 is a feasible platinum-based option to which molecularly targeted agents can be added. We are currently conducting a phase II trial of carboplatin and S-1 in combination with bevacizumab for patients with previously untreated advanced non-SCC NSCLC [20]. Furthermore, on the basis of the promising results showing a survival advantage for

SCC patients, carboplatin and S-1 should be considered among first-line treatment options for NSCLC patients with SCC.

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disclosure

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Histology and Smoking Status Predict Survival of Patients with Advanced Non–Small-Cell Lung Cancer

Results of West Japan Oncology Group (WJOG) Study 3906L

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Introduction: Smoking status is one of the prognostic factors in advanced non–small-cell lung cancer (NSCLC). Currently, adenocarcinoma (Ad) histology is considered a predictive factor in advanced NSCLC. We investigated the correlation between histology or smoking status and survival of NSCLC patients receiving chemotherapy.

Methods: We retrospectively reviewed clinical data from stage IIIB or IV NSCLC patients who started first-line chemotherapy at affiliated institutions of West Japan Oncology Group from 2004 to 2005. We also collected information on pack-years of cigarette smoking and years since cessation. Overall survival was compared using log-rank test, and Cox regression analysis was used to identify independent prognostic factors.

Results: In total, 2542 consecutive patients were enrolled at 40 institutions. Of those, 71 were excluded because of unknown smoking history. The median overall survival of nonsmoking Ad patients (593 days) was longer than that of smoking Ad, nonsmoking non-Ad, and smoking non-Ad patients (384, 374, and 319 days, respectively; $p < 0.001$). In Cox regression with sex, age, stage, performance, and treatment as covariates, we found significant interaction ($p = 0.039$) between histology (Ad/non-Ad) and smoking status (smoker/non-smoker); smoking conferred a hazard ratio of 1.34 (95% confidence interval, 1.15–1.55) in Ad, but only 0.99 (0.75–1.31) in non-Ad. Higher pack-years and shorter period since cessation were significantly associated with poorer survival in Ad ($p < 0.001$), but not in non-Ad ($p \geq 0.434$).

Conclusion: Ad histology is associated with better prognosis, and only smoking status had a prognostic impact in Ad.

Key Words: Non–small-cell lung cancer, Histology, Adenocarcinoma, Smoking status.

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This study is registered with University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr/index.htm umin.ac.jp/ctr; identification number UMIN000001263).

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Lung cancer is the leading cause of cancer-related mortality in Japan, and the rest of the world, with more than one million people dying from it each year. Non–small-cell lung cancer (NSCLC), which accounts for nearly 80% of all lung cancers, comprises several histological types, including adenocarcinoma (Ad), squamous cell carcinoma (Sq), and large-cell carcinoma (La). NSCLC had been treated as a single disease because of similar therapeutic effects of conventional chemotherapeutic agents. In the last few decades, however, treatment with new drugs, such as epidermal

growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), bevacizumab, and pemetrexed revealed that tumor histology has profound impact on the benefits of a variety of chemotherapy or targeted-therapy regimens for advanced NSCLC.[1–4] Thus, histology came to be considered a predictive factor for the effectiveness of specific chemotherapy in patients with advanced NSCLC. However, there is no previous report on histology as a prognostic factor, that is, a variable determining survival irrespective of the chemotherapy regimen administered.

Previous studies showed that cigarette smoking is an independent prognostic factor in patients with NSCLC,[2,5–7] but a dose–response relationship between the quantity of smoking and survival has not been established. Although Yelena et al.[6] noted that patients who had smoked up to 15 pack-years had a longer survival than those with more than a 15 pack-year history, other cutoff points for the amount of cigarette smoking have not been considered. In addition, the relationship between smoking and survival was not investigated with respect to differences in NSCLC histological subtypes, and the studies that did evaluate survival in Sq versus non-Sq patients did not reach a firm conclusion.[7,8] However, Kawaguchi et al.[8] showed that Ad had better prognosis than Sq in never-smokers, but not in ever-smokers, suggesting that the prognostic impact of cigarette smoking may differ among histologic subtypes in NSCLC.

We hypothesized that Ad histology and lower smoking status would result in better overall survival (OS) in advanced NSCLC. To test this hypothesis, we investigated the impact and possible interaction of histology and smoking status on survival of advanced NSCLC patients receiving chemotherapy in the clinic.

PATIENTS AND METHODS

Study Patients

We sent case report forms to 40 affiliated institutions of West Japan Oncology Group, and requested them to provide demographic and clinical data from medical records for all patients with stage IIIB or IV NSCLC, who started first-line systemic chemotherapy between January 1, 2004 and December 31, 2005. Patients who had a relapse after surgery or radiotherapy were excluded. The case report forms were submitted by the participating institutions during the period from September 2008 to January 2009. This study was approved by the institutional review board of each participating institution.

Demographic and Clinical Variables

We obtained the following baseline demographic and clinical information from the case report forms: age, sex, histology, disease stage, Eastern Cooperative Oncology Group performance status (PS), smoking status, type of first-line chemotherapy, number of treatment regimens, and the year in which first-line chemotherapy was started. Disease stage was determined according to the tumor, node, metastasis system.[9] Staging classification was performed by physical examination, chest–abdominal computed tomography, brain magnetic resonance imaging, bone scan, and positron emission tomography if necessary. Patients were categorized into nonsmokers and smokers according to smoking status. Nonsmokers were defined as those who had smoked less than 100 cigarettes. Among smokers, exsmokers were defined as those who had quit smoking 1 year or more before diagnosis, and current smokers as those who continued their smoking habit at diagnosis. Pack-years of smoking were calculated by multiplying the number of packs (20 cigarettes in one pack) smoked per day by the number of years smoked, and categorized as less than 10, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 or more. Years of smoking cessation were categorized as 1 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 or more. Type of first-line chemotherapy was categorized into platinum-based combination, nonplatinum combination, and single-agent chemotherapy. Because the only approved EGFR-TKI for the treatment of inoperable or recurrent NSCLC in Japan before October 2007 was gefitinib, we collected information on gefitinib usage during the observation period and noted the starting day of gefitinib treatment. OS was calculated from the start of first-line chemotherapy to the date of death. Patients still alive were censored as of the last known follow-up.

TABLE 1. Patient Characteristics

Parameter	Ad ($n = 1731$)	Non-Ad ($n = 740$)	p
Men/women	1056/675	641/99	<0.001
Smoking status			<0.001
Nonsmoker	659	79	
Exsmoker	300	165	
Current smoker	772	496	
Stage IIIB/IV	444/1287	271/469	<0.001
PS			0.002
0	546	206	
1	873	402	
2	191	96	
3	90	25	
4	31	11	
Histology			—
Sq	—	516	
La	—	71	
Others	—	153	
Chemotherapy			0.181
Single-agent	354	137	
P doublet	1306	571	
Non-P doublet	71	32	
Regimen			<0.001
1	536	285	
2	445	201	
3	322	115	
≥4	428	139	
Gefitinib Y/N	959/772	146/594	<0.001

Ad, adenocarcinoma; PS, performance status; Sq, squamous cell; La, large cell; P, platinum; Y, yes; N, no.

Statistical Analysis

Demographic and clinical variables were compared among groups according to lung cancer histology, using the χ^2 test. The primary endpoint of this study was OS. Survival curves were calculated by the Kaplan–Meier method and compared using the log-rank test. Prognostic importance of histology and smoking status were analyzed using the Cox regression analysis adjusted for sex, age, disease stage, PS, type of first-line chemotherapy, and the year in which first-line chemotherapy was started. For detection of possible interaction between histology and smoking status, the terms of interaction of the two variables were evaluated by the likelihood ratio test. Because gefitinib was the preferred choice in patients with Ad, another Cox regression analysis was performed, in which patients were censored at the start of gefitinib administration, and the results were compared with the original Cox analysis. Significance level was set at a p value of 0.05. Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

Between January 1, 2004 and December 31, 2005, 2542 consecutively treated patients were enrolled at 40 institutions. Of these, 71 were excluded because of unknown smoking history. The characteristics of the study population, categorized into Ad and non-Ad, are listed in Table 1. There were 1731 Ad and 740 non-Ad patients (29.9% and 70.1%, respectively). Among them, we confirmed 1346 and 599 deaths in Ad and non-Ad patients, respectively. There were significantly more women (39.0% in Ad versus 13.4% in non-Ad) and nonsmokers (38.1% in Ad versus 10.7% in non-Ad) in the Ad group than in the non-Ad group. Patients who received single-agent chemotherapy accounted for approximately 20% of the study population. Compared with combination regimens, single-agent chemotherapy was associated with old age (63.6 years for combination regimens versus 71.1 years for single-agent chemotherapy), high proportions of female patients (29.3% versus 40.0%), nonsmokers (27.8% versus 34.0%), stage IV (69.4% versus 78.3%), and PS 0 to 1 (60.9% versus 87.1%). The proportion of Ad histology was not significantly different between single-agent and combination regimens (72.1% and 69.5%, respectively). The OS was 464 days in Ad compared with 326 days in non-Ad ($p < 0.001$; Fig. 1*A*). Between Ad and non-Ad, which was divided into Sq and La, Ad had significantly better survival than the other two histological groups (Sq, 341 days; La, 254 days; $p < 0.0001$; Fig. 1*B*). With regard

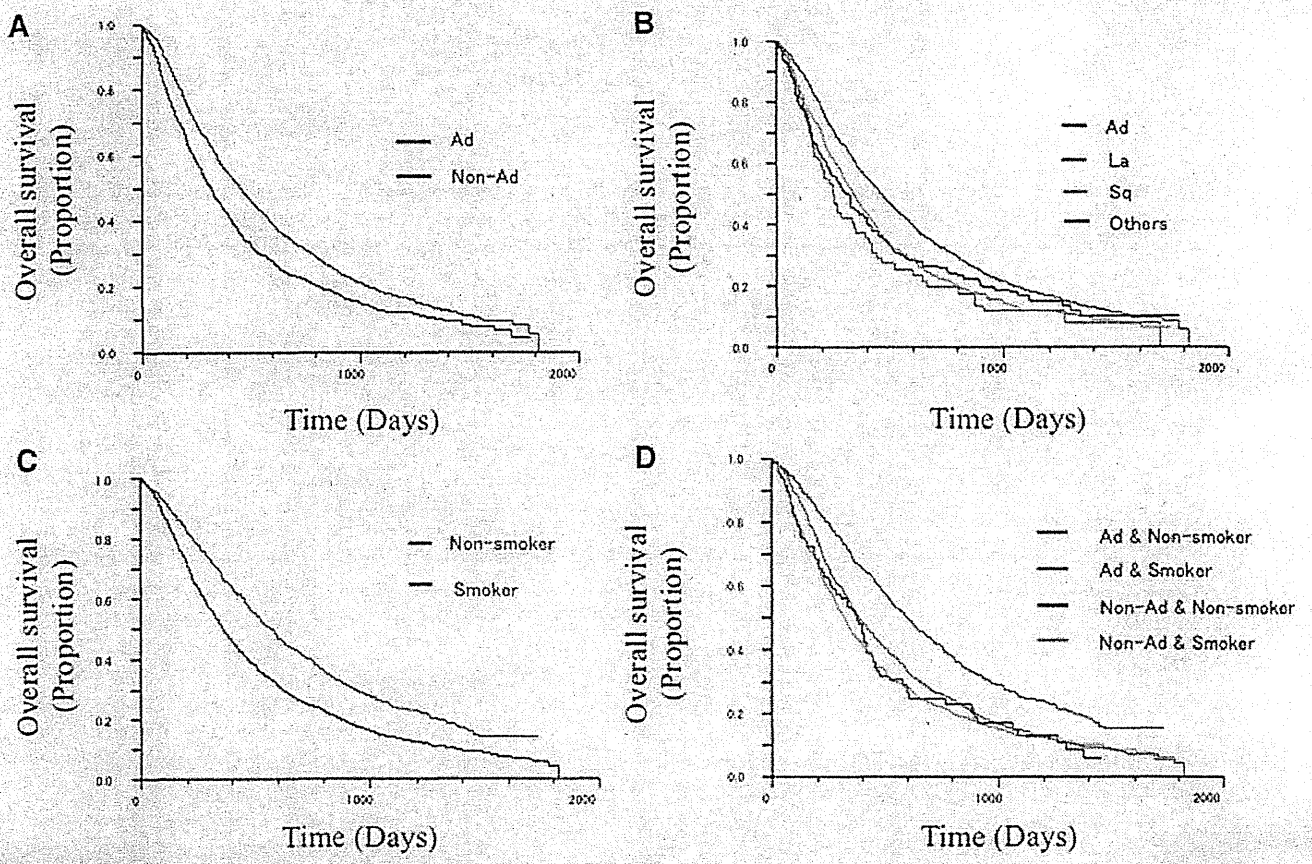

FIGURE 1. Kaplan–Meier plots of overall survival for patients classified according to histology type as (*A*) Ad and Non-Ad; histologic subtype as (*B*) Ad, La, Sq, and others; smoking status as (*C*) smokers and nonsmokers; and combination of smoking status and histology as (*D*) Ad and nonsmoker, Ad and smoker, Non-Ad and nonsmoker, and Non-Ad and smoker. Ad, adenocarcinoma; La, large cell; Sq, squamous cell.

TABLE 2. Survival Analysis by Cox Proportional Hazards Model ($n = 2471$)

Parameter	HR	95% CI	p
Sex			
Women	1		
Men	1.342	1.168–1.541	<0.001
Age yrs	1.007	1.002–1.012	0.005
Smoking status			
Nonsmoker	1		
Exsmoker	1.178	0.997–1.391	0.054
Current smoker	1.335	1.155–1.543	<0.001
Clinical stage			
Stage IIIB	1		
Stage IV	1.505	1.358–1.669	<0.001
PS			
0	1		
1	1.609	1.446–1.790	<0.001
2	2.229	1.910–2.601	<0.001
3	3.048	2.455–3.785	<0.001
4	5.487	3.864–7.790	<0.001
Histology			
Ad	1		
Sq	1.143	1.015–1.286	0.028
La	1.542	1.182–2.011	0.001
Others	1.397	1.159–1.683	<0.001
Chemotherapy			
Single-agent	1		
Non-P doublet	0.842	0.657–1.080	0.175
P doublet	0.793	0.699–0.899	<0.001

HR, hazard ratio, CI, confidence interval; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell; La, large cell; P, platinum.

to smoking status, nonsmokers (568 days) had significantly longer survival than smokers (358 days; $p < 0.0001$; Fig. 1*C*). In a combined analysis of smoking status and histology, the median OS of Ad in nonsmokers was longer than that of Ad in smokers, non-Ad in nonsmokers, and non-Ad in smokers (593, 384, 374, and 319 days, respectively; $p < 0.001$; Fig. 1*D*). In Cox regression analysis, sex, age, smoking status, disease stage, PS, histology, and chemotherapy showed a statistically significant prognostic impact on survival (Table 2). When the interaction between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker) was included in the Cox model, significant interaction was observed ($p = 0.039$); smoking conferred a hazard ratio (HR) of 1.34 (95% confidence interval [CI], 1.15–1.55) in Ad, in contrast to 0.99 (0.75–1.31) in non-Ad. In detailed analyses that excluded the 104 patients (current smokers, 89; unknown, 15) with unknown amount of cigarette smoking, shorter period since cessation showed a significant trend for poorer survival in the whole population ($p < 0.001$). This trend was also observed in Ad ($p < 0.001$; Table 3), but not in non-Ad ($p \geq 0.434$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.534 in Sq and 0.165 in La or others. The prognosis became significantly worse with higher pack-years of cigarette smoking in the whole population and Ad ($p < 0.001$; Table 3), but no significance was not achieved for the non-Ad group ($p = 0.519$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.798 in Sq and 0.380 in La or others. The prognostic impact of histology and smoking status remained significant in the Cox regression analysis, in which patients were censored at the start of gefitinib administration; positive smoking history, Sq histology, and La or other histology conferred an HR of 1.51 (95% CI, 1.21–1.88), 1.22 (95% CI, 1.06–1.41), and 1.59 (95% CI, 1.32–1.93), respectively. The negative prognostic impact of shorter period since cessation and pack-years of cigarette smoking was also essentially unchanged ($p < 0.001$ in both).

DISCUSSION

The consensus report of prognostic factors in NSCLC at the 1990 International Association for the Study of Lung Cancer Workshop showed that histology was not a prognostic factor for advanced NSCLC.[10] Our study is the first report to reveal that histology is a significant prognostic factor for advanced NSCLC. Importantly, we showed that Ad patients have the longest survival of all three histological groups (Ad, Sq, and La). Ad is the most common histological subtype of lung cancer in nonsmokers,[11] who have been reported to have a better prognosis than smokers.[12–14]

Smoking has been described as a prognostic factor in lung cancer. Although multiple studies have demonstrated the negative effects of smoking in patients with NSCLC, most included a heterogeneous population comprising patients with all stages and types of lung cancer.[5] In contrast, our study cohort consisted exclusively of patients with advanced NSCLC treated with first-line chemotherapy. We showed that smoking status is an independent prognostic factor for survival in those patients. Similar data have been shown in former studies.[2,5] However, those reports did not show whether smoking conferred any survival impact for advanced NSCLC irrespective of histological subtypes. In our study, only Ad histology had significant interaction with smoking status or smoking index and prognosis. A higher level of smoking was related to shorter survival in Ad patients, whereas smoking level and survival were not associated in non-Ad patients. Although the proportion of non-Ad patients was 29.9% of the total, the observed number of deaths in this study yielded a statistical power of more than 80% for detecting an HR of 1.5 at the 5% significance level in both Ad and non-Ad patients. Others have found that Ad histology is a significant prognostic factor in separate multivariate analysis for never-smokers in advanced NSCLC.[8] Yelena et al.[6] showed that high cigarette smoking, as measured in pack-years, is associated with decreased survival after diagnosis of stage IIIB/IV NSCLC. However, the patients of that study received a wide variety of therapies, raising the possibility that the outcomes might have been the result of distinct therapeutic responses. Although we only assessed the prognostic value of smoking status at diagnosis, assessment of smoking status at a later point, that is, at the time of treatment, would also have been of interest to determine whether cessation at the time of diagnosis leads to improved survival.

TABLE 3. Hazard Ratios According to Quantitative Aspects of Smoking

	Ad			Non-Ad		
	HR	95% CI	p	HR	95% CI	p
Years after cessation	(n = 1731)			(n = 740)		
Current	1.492	1.271–1.750	<0.001	1.204	0.849–1.707	0.297
Exsmoker 1–4 yr	1.438	1.114–1.857	0.005	1.101	0.733–1.653	0.643
Exsmoker 5–9 yr	1.549	1.101–2.180	0.012	1.228	0.700–2.155	0.474
Exsmoker 10–14 yr	1.127	0.783–1.621	0.520	1.235	0.680–2.245	0.488
Exsmoker 15–19 yr	1.199	0.761–1.890	0.433	1.410	0.712–2.794	0.325
Exsmoker ≥20 yr	0.873	0.834–1.203	0.407	1.103	0.662–1.837	0.706
Trend p	<0.001			0.434		
Pack-yr	(n = 1665)			(n = 702)		
<10	1.267	0.899–1.785	0.176	1.196	0.535–2.672	0.662
10–19	1.118	0.801–1.561	0.513	0.963	0.512–1.812	0.908
20–29	1.346	1.048–1.729	0.020	1.368	0.887–2.109	0.157
30–39	1.345	1.071–1.689	0.011	0.954	0.624–1.458	0.827
40–49	1.370	1.096–1.712	0.006	1.128	0.763–1.669	0.546
50–59	1.483	1.164–1.890	0.001	1.238	0.828–1.851	0.298
≥60	1.595	1.312–1.939	<0.001	1.135	0.791–1.628	0.491
Trend p	<0.001			0.519		

[a] Nonsmokers were set as the reference category.
Ad, adenocarcinoma; HR, hazard ratio; CI, confidence interval.

In agreement with the findings of another study,[15] we also found that a large proportion of Ad patients were nonsmoking. The prognostic difference between Ad in never-smokers and smokers may suggest that both are different disease entities. Of note, tumor-mutational frequencies and spectra suggest differences between smokers and nonsmokers.[16,17] However, significant differences in the frequency of somatic mutations in oncogenes such as *EGFR* and *KRAS* have been observed between smoking and nonsmoking lung cancer patients.[11] *EGFR* mutations, clinical predictors of EGFR-TKI therapeutic benefits, are more frequently found in nonsmoking Ad patients.[11] In another study, *EGFR* mutations were identified in nonsmokers (51%), former smokers (19%), and current smokers (4%).[18] Moreover, the incidence of *EGFR* mutations decreased with increasing number of pack-years of cigarette smoking.[18] However, *KRAS* mutations, predicting poor survival and resistance to EGFR-TKI, are more frequently found in smoking Ad patients. Interestingly, *EGFR* and *KRAS* mutations are mutually exclusive.[11]

Currently, therapeutic options other than EGFR-TKIs (e.g., bevacizumab and pemetrexed) are available in Japan. Still, NSCLC subtypes have been showing variable response rates and adverse events.[2,4,19,20] Non-Sq histology, especially Ad, is currently the NSCLC subtype with broader and more efficacious treatment options. At the time of this study, however, the only approved therapeutic agent for NSCLC in Japan was gefitinib. Unfortunately, we did not investigate *EGFR* mutation status. However, genetic background could possibly predict response to gefitinib. Along with its retrospective nature, this was a limitation of our study. However, we found that the treatment choice was made on the basis of clinical background, and we were unable to conclude whether or not gefitinib contributed to better survival under unknown *EGFR* mutation status. Hence, we suggest that decision-making based on clinical information alone is inappropriate. Both the V15-32 study[21] and the Iressa Survival Evaluation in Lung Cancer (ISEL) study[22], support our observations. Furthermore, the IRESSA Pan-Asia Study (IPASS) study,[23] conducted under the hypothesis that EGFR-TKI would be effective in clinically selected patients, confirmed the strong predictive value of *EGFR* mutations for the response of Ad to gefitinib.

This retrospective study has a few other limitations as well. First, information on smoking was not obtained from the interview or the self-administered questionnaire. Smoking data can be inaccurate, particularly when collected retrospectively. Second, we did not collect data on the procedures for histological diagnosis. The basis for pathological diagnosis is important because cytological assessment alone may lead to underdiagnosis of specific histologic types.

In conclusion, this survey demonstrated that Ad histology is associated with better prognosis, and that smoking status has a prognostic impact only in patients with Ad.

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