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Original Article

The association between postdiagnosis smoking cessation and survival in advanced non-small cell lung cancer patients in Southern Taiwan: A retrospective cohort study

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Abstract

Objectives: Smoking is a major lung cancer risk factor. Studies show that smoking after lung cancer diagnosis is associated with an increased risk of developing other cancers and shorter survival. The purpose of this study was to examine the association between postdiagnosis smoking cessation and survival in patients with advanced non-small cell lung cancer (NSCLC). **Materials and Methods:** A retrospective cohort study was conducted. Data were collected between January 2014 and December 2019 in three hospitals in Southern Taiwan. Patient data were collected from the hospitals' databases, and the correlation between smoking status and patient survival was analyzed using Kaplan–Meier curves and Cox proportional hazards regression modeling. **Results:** A total of 681 patients with advanced NSCLC were included in this study. The numbers (percentage) of ex-smokers and current smokers were 334 (49%) and 347 (51%), respectively. More than half of the patients in this study continued to smoke postdiagnosis advanced NSCLC. Furthermore, ex-smokers had lower mortality risk, even though this was not statistically significant (P = 0.212). The results of this study suggest that older than 65 years, men, Eastern Cooperative Oncology Group performance score of 3 and higher, history of chronic disease, receive chemotherapy, and targeted therapy are correlated with and have predictive effects on advanced NSCLC survival. **Conclusion:** There is no significant difference between postdiagnosis smoking cessation and survival in patients with advanced NSCLC. The reason for this finding may be due to lower survival rates after diagnosis with advanced NSCLC, and the benefits of smoking cessation cannot be seen immediately.

Keywords: *Lung cancer, Smoking cessation, Survival*

Introduction

Lung cancer is the most frequently occurring malignant tumor in Taiwan, accounting for 19.2% of all cancer-related deaths [1]. One in five cancer-related deaths is due to lung cancer, indicating the detrimental effects of lung cancer on the health of the citizens of Taiwan.

Smoking is a major lung cancer risk factor [2], and 65%–80% of men diagnosed with lung cancer had a history of smoking. Among nonsmoking patients diagnosed with lung cancer, 60%–90% reported secondhand smoke exposure [3]. Exposure to cooking oil fumes, air pollution, asbestos, nickel, chromium, and other occupational hazards; radiation damage; genetic problems; and chronic obstructive pulmonary disease are also known to increase the risks of developing lung cancer [2,4]. Although 17% of women diagnosed with lung cancer have a history of smoking [5], exposure to secondhand smoke increases the risk of developing lung cancer by 20%–30% [6,7]. A study by Su *et al.* [8] found that lung cancer survival is correlated with gender, age, clinical stage, and pathological type.

Findings from both clinical and epidemiological studies have consistently identified an association between smoking and lung cancer development [2,5]. Studies performed in other countries have reported that 37%–57% of lung cancer patients continued to smoke after diagnosis [9,10]. In Taiwan, a 2019 study reported that 44% of lung cancer patients continued to smoke after diagnosis [11]. Perlík [12] reported that lung cancer patients who continued to smoke after diagnosis are

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associated with an increased risk of developing a second smoking-related primary malignancy and reduced survival. The study reported by Shenker *et al*. [13] noted an increased risk of neurological death among nonadenocarcinoma patients who continued to smoke after diagnosis. A Turkish study by Avci *et al*. [14] examining the smoking status of patients with lung cancer showed a two-fold increase in mortality risk among smokers compared with nonsmokers. Tabuchi *et al*. [15] found that Japanese patients with lung cancer who quit smoking had a 10% reduction in mortality risk compared with patients who continued smoking.

Past studies indicate a close association between smoking status and lung cancer prognosis. In a previous study of patients with non-small cell lung cancer (NSCLC), smoking cessation before diagnosis was associated with lower mortality following a lung cancer diagnosis [16]. However, most lung cancer patients continued to smoke after diagnosis, and many patients do not understand the benefits of postdiagnosis smoking cessation. Therefore, the objective of this study was to examine the association between postdiagnosis smoking cessation and survival in patients with advanced NSCLC in Southern Taiwan.

Materials and methods

Participants and data collection

Study design and sample

In this retrospective cohort study, we recruited patients diagnosed with advanced NSCLC at three hospitals in Southern Taiwan. Patients' medical records were collected from the hospitals' databases and the Taiwan Cancer Registry. Data were collected retrospectively from patients who had been diagnosed with advanced NSCLC between January 2014 and December 2019. The data of patients who causes of death into noncancer were excluded from this study. This study was conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee in Kaohsiung Medical University Hospital approved this study (IRB-E (I) -20200360). Patient consent was waived by the IRB, because the data were obtained from routinely collected information and personal information had been de-identified.

Data collection and variables

After being exported from the databases, data were first sorted, and patients with incomplete data or unknown smoking status were excluded. The following data were included in the analysis: gender, age, medical diagnosis, histology, cancer stage (Stage IIIB–IV), history of chronic disease (i.e., diabetes mellitus, chronic pulmonary disease, cardiovascular disease, stroke, renal disease, and liver disease), treatment type (i.e., radiation therapy, chemotherapy, and targeted therapy), survival status, if the patient died and the time from diagnosis to death, smoking status (on the basis of smoking status of patients at the time of diagnosis, patients were classified into quit smoking and currently smoking. Those who had smoking cessation >1 month after diagnosis were defined as quit smoking. Those who had smoking cessation <1 month or who still smoked after diagnosis were defined as currently smoking), and Eastern Cooperative Oncology Group (ECOG) performance status.

Data processing and statistical methods

Collected data were encoded and edited using Microsoft Excel, and identification numbers of patients were encrypted. Statistical analyses were performed through SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical analyses were used to describe demographic characteristics, histology, history of chronic disease, treatment type, survival/death rates, and smoking status, and results are presented as the percentage, mean, and standard deviation. A patient's death was regarded as an event in the survival analysis model, and the survival time (in days) was measured as the time from diagnosis to death. For patients who survived, the last recorded follow-up date was used in the survival analysis. First, survival analysis was performed using the Kaplan–Meier curves, and the log-rank test was applied to examine the differences in this survival rate among ex-smokers and current smokers. All variables were subjected to Cox proportional hazards regression modeling with corrections for confounding factors to identify predictive factors associated with survival and prognosis.

Results

Patient demographics and disease characteristics

This study recruited 681 patients diagnosed with advanced NSCLC between 2014 and 2019, including 334 (49%) ex-smokers and 347 (51%) current smokers. Slightly more patients were older than 65 years (n = 378, 55.5%) than those younger than 65 years (n = 303, 44.5%). Much more male (n = 640, 94%) than female (n = 41, 6.0%) were enrolled. Adenocarcinoma was the most common histology, accounting for 62.8% of all identified cancer types. Over half (62.3%) of the patients had an ECOG score of 1. Fifty-one percent of the patients had received chemotherapy. More than 70% (specifically, 73.7%) of patients did not receive radiation therapy. Over half (67.8%) of the patients did not receive targeted therapy. Almost 70% of patients had a history of chronic disease [Table 1].

Correlations between survival status and demographic characteristics

Ex-smokers' mean survival was 15.4 months, whereas postdiagnosis smokers had the shorter mean survival at 14.9 months. The log-rank (Mantel–Cox) test result was not significant difference (P = 0.373) in survival across these two smoking statuses [Figure 1].

All variables were subjected to Cox proportional hazards regression modeling to identify predictive factors. The analysis revealed that gender, age, ECOG, chronic disease, radiation therapy, chemotherapy, and targeted therapy correlated with and were predictive for cancer survival. Furthermore, ex-smokers had lower mortality risk, even though this was not statistically significant (P = 0.212).

Based on the adjusted multivariable analysis, which included gender, age, ECOG performance status, chronic disease, radiation therapy, chemotherapy, and targeted therapy [Table 2], patients 65 years and older had 1.24-fold higher mortality risk than those younger than 65 years (95% confidence interval [CI]: 1.03–1.48, P = 0.023). Male had a

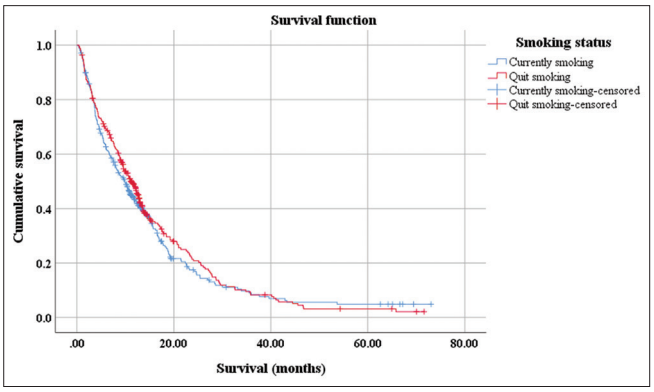

Figure 1: Kaplan–Meier curves analysis of smoking status and survival

Table 1: Demographic and disease characteristics of the patients

Variable	Currently smoking (*n*=347), *n* (%)	Quit smoking (*n*=334), *n* (%)	Total (*n*=681), *n* (%)
Age (years)			
<65	187 (53.9)	116 (34.7)	303 (44.5)
≥65	160 (46.1)	218 (65.3)	378 (55.5)
Gender			
Female	259 (7.2)	16 (4.8)	41 (6.0)
Male	322 (92.8)	318 (95.2)	640 (94.0)
Histology			
Large cell/NSCLC	43 (12.4)	28 (8.4)	71 (10.5)
SqCC	93 (26.8)	89 (26.6)	182 (26.7)
Adenocarcinoma	211 (60.8)	217 (65.0)	428 (62.8)
ECOG			
0	6 (1.7)	6 (1.8)	12 (1.8)
1	232 (66.9)	192 (57.5)	424 (62.3)
2	94 (27.1)	109 (32.6)	203 (29.8)
≥3	15 (4.3)	27 (8.1)	42 (6.2)
Chronic disease			
No	94 (27.1)	92 (27.5)	186 (27.3)
Yes	253 (72.9)	242 (72.5)	495 (72.7)
Radiation therapy			
No	247 (71.2)	255 (76.3)	502 (73.7)
Yes	100 (28.8)	79 (23.7)	179 (26.3)
Chemotherapy			
No	161 (46.4)	173 (51.8)	334 (49.0)
Yes	186 (53.6)	161 (48.2)	347 (51.0)
Targeted therapy			
No	251 (72.3)	211 (63.2)	462 (67.8)
Yes	96 (27.7)	123 (36.8)	219 (32.2)

NSCLC: Non-small cell lung cancer, SqCC: Squamous cell carcinoma, ECOG: Eastern cooperative oncology group

1.51-fold higher mortality risk than female (95% CI 1.01-2.24, P = 0.044). Patients with an ECOG performance status score of 3 or higher had a 3.63-fold higher mortality risk than those with an ECOG performance status score of 0 (95% CI: 1.64–7.99, P = 0.001). Patients with chronic disease had a 0.78-fold lower mortality risk than patients without chronic disease (95% CI: 0.64–0.95, P = 0.013). Patients with chemotherapy had a 0.75-fold lower mortality risk than patients who did not receive chemotherapy (95% CI: 0.59–0.96, P = 0.023). Patients with target therapy had a 0.51-fold lower mortality risk than patients who did not receive targeted therapy (95% CI: 0.41–0.63, $P \leq 0.001$).

Discussion

In the present study, we found that patients 65 years and older had higher mortality risk than those younger than 65 years. This finding is consistent with previous studies, in which age is associated with survival. The percentage of male patients with advanced NSCLC in this study was higher than that of female patients, regardless of whether they continued to smoke or had quit smoking. In other words, genetic and environmental factors are thought to contribute to the high incidence of lung cancer among Asian female never-smokers [17,18].

More than half of the patients in this study continued to smoke postdiagnosis advanced NSCLC. Ex-smokers had lower mortality risk, even though this was not statistically significant. However, Sheikh *et al.*'s [19] study found that smoking cessation after diagnosis improved overall and progression-free survival in early-stage lung cancer. It is inferred that this study collected data on advanced NSCLC patients. The inability to see the benefits of smoking cessation might be due to the lower survival rates after diagnosis with advanced NSCLC or because past exposure to carcinogens has a long-term effect.

Recent review identified different mechanisms that may contribute to the negative impact of continued smoking on lung cancer survival [20]. These include carcinogens in tobacco smoke, which may lead to an increase in the rate of tumor growth, reduce the effectiveness of drug therapy, and enhance tumor recurrence and other comorbidities. Another study found that post-diagnosis smoking increases treatment complications and reduces quality of life, as well as reducing the efficacy and tolerance toward systemic treatment [21]. Therefore, we recommend that smoking cessation be incorporated into the cancer treatment process. Additionally, case managers should regularly monitor patients' progress in quitting smoking and offer the necessary support to ensure successful cessation.

There were many elderly patients in this study, and the older adults are more likely to have chronic diseases. The study found that patients with a history of chronic diseases have a lower risk of death than those without a history of chronic diseases. It is unclear why this is the case. The reason for this finding may be that patients with a history of chronic diseases often follow up on their disease status in the hospital, including imaging examinations and blood tests, and pay more attention to their health. Thus, it would be of interest to determine this issue. In addition, patients who received chemotherapy and targeted therapy had a lower risk of death than those who did not receive treatment. This result is expected and also shows that patients who are suitable for treatment in clinical practice should be encouraged to receive treatment according to the treatment guidelines.

According to the recommended treatment standards established by the American National Comprehensive Cancer Network [22], cancer patients should undergo ECOG

Table 2: Univariate analysis of correlations between survival status and demographic characteristics (*n*=681)

Variable	Univariate analysis				Multivariate analysis			
	β	*P*	HR	95% CI	β	*P*	HR	95% CI
Age (years)								
<65 (reference)								
≥65	0.26	0.007	1.30	1.07–1.57	0.21	0.023	1.24	1.03–1.48
Gender								
Female (reference)								
Male	0.40	0.050	1.49	1.00–2.22	0.41	0.044	1.51	1.01–2.24
Smoking status								
Currently smoking (reference)								
Quit smoking	−0.11	0.212	0.89	0.74–1.06				
Histology								
Large cell/NSCLC (reference)								
SqCC	−0.11	0.500	0.89	0.63–1.24				
Adenocarcinoma	−0.08	0.609	0.91	0.66–1.26				
ECOG								
0 (reference)								
1	0.30	0.403	1.35	0.66–2.74	0.33	0.357	1.39	0.68–2.82
2	0.64	0.082	1.90	0.92–3.93	0.65	0.075	1.93	0.93–3.99
≥3	1.27	0.002	3.56	1.61–7.85	1.28	0.001	3.63	1.64–7.99
Chronic disease								
No (reference)								
Yes	−0.24	0.014	0.78	0.63–0.95	−0.25	0.013	0.78	0.64–0.95
Radiation therapy								
No (reference)								
Yes	0.10	0.346	1.10	0.89–1.37				
Chemotherapy								
No (reference)								
Yes	−0.30	0.018	0.73	0.57–0.94	−0.28	0.023	0.75	0.59–0.96
Targeted therapy								
No (reference)								
Yes	−0.67	<0.001	0.51	0.41–0.64	−0.68	<0.001	0.51	0.41–0.63

HR: Hazard ratio, CI: Confidence interval, NSCLC: Non-small cell lung cancer, SqCC: Squamous cell carcinoma, ECOG: Eastern cooperative oncology group

assessments prior to treatment to obtain a comprehensive understanding of their health status and capacity to tolerate treatment. ECOG performance status scores serve as the basis for determining whether or not patients are capable of withstanding the adverse events associated with treatment. The treatment is generally recommended for patients with ECOG scores of 0–2. In this study, the number of patients with ECOG scores of 0–2 was higher than those with scores of 3 or higher (93.2% vs. 6.8%). Patients with higher ECOG scores had shorter survival and higher mortality risk, which agrees with the findings reported by Yu *et al*. [23], who found that NSCLC patients with ECOG scores of 3 or 4 had significantly shorter survival and higher mortality risk.

Limitations and recommendations

Our study has limitations. First, the data used for this study were sourced from the databases of three hospitals in Southern Taiwan, which may not be representative of the status of patients with NSCLC treated at different hospital types nationwide, limiting the generalizability of our findings. We recommend expanding the scope of analysis using the National Health Insurance database for future studies. Second, the data for our sample were obtained from the hospitals' cancer registries, which lacked clinical data regarding the patients' history of exposure to other potential risk factors, including secondhand smoke, cooking oil fumes, asbestos, and the duration and intensity of smoking. This shortcoming in data acquisition may have led to biases in our findings. Finally, although we adjusted for some confounding factors in the multivariate analysis, there might be other unmeasured confounders that could influence the association between smoking status and survival. More future research is needed to confirm these findings.

Conclusions

Because almost half of advanced NSCLC patients continued to smoke postdiagnosis, it is important to understand the continued risks of continuing to smoke after diagnosis. This study finds no difference in mortality risk between ex-smokers and continued smokers.

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Data availability statement

The data that support the findings of this study are available from KMUHRD in Taiwan, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of KMUHRD.

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Conflicts of interest

There are no conflicts of interest.

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