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ORIGINAL ARTICLE

The clinicopathological and survival differences between never and ever smokers with non-small cell lung cancer

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Summary

Purpose: *Cigarette smoking was regarded as the most important carcinogenic factor of lung cancer, yet in recent years lung cancer in never-smokers is an increasingly prominent public health issue. The aim of this study was to assess the epidemiological and clinicopathological characteristics of never-smoker patients with non small cell lung cancer (NSCLC), focusing on clinical risk factors and survival.*

Methods: *We retrospectively analyzed 290 NSCLC patients who presented between 2006 and 2011. Differences in clinical features and survival between never- and ever-smoker patients were analyzed. Student's t-test and Mann-Whitney U-test were used to assess the significance of the variables between the groups. Survival curves were calculated using Kaplan-Meier method. Hazard ratio (HR) for death and its 95% confidence interval (CI) were calculated by Cox regression analysis.*

Results: *There were 243 (83.8%) ever-smokers and 47 (16.2%) never-smokers. In never-smokers females predominated (80.9%) as well as patients with adenocarcinomas (78.7%). At the time of analysis 143 (49.3%) patients had died. The 5-year overall survival (OS) rates were not significantly different between never- and ever-smokers (p=0.410) . The median OS of all patients was 26 months (95% CI: 16.8-35.2). The median OS was 23 months (95% CI: 11.8-34.2) for never-smokers and 30 months (95% CI: 19.7-40.3) for ever-smokers (p=0.410). Never-smokers tended to present with more advanced disease than ever-smokers (p<0.004) and also with more advanced age (p<0.001). The HR for death increased with poorer Eastern Cooperative Oncology Group (ECOG) performance status (PS) (ECOG 2-3), advanced stage (stage 3-4) and untreated patients. Slightly lower risk for death was registered in patients with adenocarcinoma vs those with squamous cell carcinoma (SCC).*

Conclusion: *Although no difference in survival was seen, definite epidemiologic differences do exist between never-smokers and ever-smokers patients with NSCLC. Future efforts should focus on the underlying biological differences, and on identifying potential non-tobacco related risk factors in order to improve treatment strategies for these two groups of NSCLC patients.*

Key words: *adenocarcinoma, never smoker, non-small cell lung cancer, survival*

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Cigarette smoking was regarded as the most important carcinogenic factor of lung cancer [2]. However, the disease is also observed in patients who are lifelong never-smokers. Worldwide, approximately 15-20% of men with lung cancer and 50% of women with lung cancer, are people who had never smoked [1]. Never-smokers have been estimated to constitute about 30-40% of all lung cancer patients [3].

Clinical observations suggest that the percentage of never-smokers among lung cancer patients may be on the increase; however, it is unclear whether this apparent trend represents an increase in the incidence of lung cancer among never-smokers or the increasing prevalence of never-smokers in the general population.

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The causes of lung cancer in individuals who have never smoked are unknown, but several factors such as secondhand smokes, radon exposure, cooking fumes, other toxins (asbestos, chromium, or arsenics), radiation therapy to the chest, other lung diseases (idiopathic pulmonary fibrosis), human papilloma virus, and differences in ability to repair DNA damages may increase the risk [4].

The aim of this study was to assess the epidemiological and clinicopathological characteristics of never-smoker patients with NSCLC, focusing on clinical risk factors and survival.

Methods

We retrospectively analyzed the medical records of 290 consecutive patients with pathologically proven NSCLC, referred to the Medical Oncology department of Baskent University Adana Hospital between 2006 and 2011.

All of them were considered eligible. Some patients were excluded because of missing or unrretrievable case notes.

Individual case records were reviewed and selected epidemiological characteristics (American Joint Committee on Cancer/AJCC stage, histologic subtypes, and ECOG PS) were recorded. NSCLC cases were further divided into 3 major histological subtypes: adenocarcinoma, SCC, and other types of NSCLC.

Disease stage was categorized into 3 groups: early disease (stage I-II), local-advanced disease (stage IIIa, IIIb) and advanced disease (stage IV). Smoking status was classified into two levels: never-smoker and ever-smoker. Patients with any history of smoking (current and former smokers) were classified as ever-smokers, whereas never-smokers were defined as those who had never smoked in the past. Data regarding passive exposure to environmental tobacco smoke were not consistently available in the medical records.

Patient treatment status was divided in 2 categories: treated (surgery, chemotherapy, chemo-radiotherapy or only radiotherapy) and best supportive care.

OS for each patient was measured from the date of diagnosis to the date of death or the date the patient was last known to be alive for censored observation.

Statistics

Data analysis was performed using the SPSS for Windows 11.5 package program. Definite statistics were expressed as mean±standard deviation or median (min-max) for repeated nominal variables and as case number and percentage for categorical variables. Student's t-test was used to assess the significance of the difference between the means of variables. Mann-Whitney U-test was used to assess the significance of the difference between the medians of the variables in the groups. Pearson chi-square test, Fisher's exact chi-square test or odds radio test were used to assess categorical variables.

Univariate Cox proportional hazard regression analysis was used to assess whether all possible risk factors had statistically significant impact on OS. Multivariate Cox proportional hazard regression analysis was used to assess the most definite risk factors on OS. HR for each variable and 95% CI were calculated. A p-value of <0.05 was considered as statistically significant.

Results

A total of 330 NSCLC patients diagnosed between 2006 and 2011 were reviewed and 40 were excluded because of incomplete data, leaving 290 patients for analysis.

There were 243 (83.8%) ever-smokers and 47 (16.2%) never-smokers. Among the never-smokers females predominated (80.9%), as well as patients with adenocarcinomas (78.7%).

As expected, the majority of patients presented with advanced disease stage (III-IV). Interestingly, never-smokers tended to present with more advanced disease than ever-smokers (p<0.004) and also with more advanced age (p<0.001).

No significant differences were noticed between never- and ever-smokers in relation to ECOG PS and treatment. The demographic and clinical characteristics of the studied cases are listed in Table 1.

Supplementary analyses were carried out for the never-smoker group according to gender. Patients of both genders were similar with respect to age, histological types, ECOG PS, and stage (Table 2).

At the time of analyses, 143 (49.3%) patients had died. The 5-year OS rates were not significantly different between never- and ever-smokers (p=0.410; Figure 1). The median OS was 26 months (95% CI: 16.8-35.2). The median OS was 23 months (95% CI: 11.8-34.2) for never-smokers and 30 months (95% CI: 19.7-40.3) for ever-smokers (p=0.410).

Unadjusted HR for ever-smokers (HR 0.844; 95% CI 0.560-1.273) was not significantly different from never-smokers (p=0.418). The HR for death increased with poorer ECOG PS (ECOG 2-3), advanced stage (stage 3-4) and untreated patients. Slightly lower risk for death was registered for patients with adenocarcinoma vs those with SCC (p=0.019).

According to multivariate Cox regression analysis of factors associated with OS, stage 3 and 4 disease were the factors most related to

Table 1. Demographic and clinical characteristics of the study population according to their smoking status

Characteristics	*Never-smokers N=47 (16.2%) N (%)*	*Ever-smokers N=243 (83.8%) N (%)*	*p-value*
Gender			<0.001
Male	9 (19.1)	223 (91.8)	
Female	38 (80.9)	20 (8.2)	
Age, years, mean±SD	64.9±11.9	58.6±9.1	<0.001
Histologic subtype			<0.001
Adenocarcinoma	37 (78.7)	114 (46.9)	
Squamous cell	6 (12.8)	81 (33.3)	
Others	4 (8.5)	48 (19.8)	
ECOG PS			0.260
0	16 (34.0)	116 (47.7)	
1	23 (48.9)	104 (42.8)	
2	7 (14.9)	21 (8.6)	
3	1 (2.1)	2 (0.8)	
AJCC stage			0.004
1-2	6 (12.8)	50 (20.6)	
3	12 (25.5)	106 (43.6)	
4	29 (61.7)	87 (35.8)	
Treatment			0.064
Supportive/ no treatment	7 (14.9)	15 (6.2)	
Yes	40 (85.1)	228 (93.8)	
Follow-up time months, median (range)	16 (1-78)	20 (1-80)	0.744

ECOG PS: Eastern Cooperative Oncology Group performance status, AJCC: American Joint Committee on Cancer, SD: standard deviation

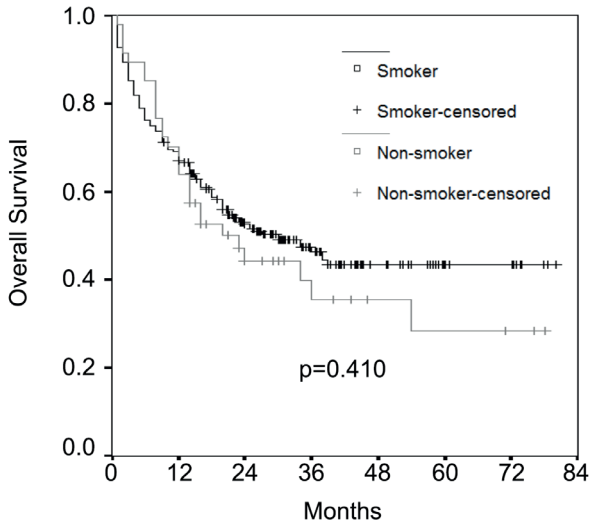

Figure 1. Kaplan-Meier overall survival for NSCLC patients according to smoking status.

Table 2. Characteristics of never-smokers according to sex

Characteristics	*Males N=9 (19.1%) N (%)*	*Females N=38 (80.9%) N (%)*	*p-value*
Age, years, mean±SD	64.9±13.8	64.9±11.6	0.996
Histologic subtype			0.305
Adenocarcinoma	7 (77.8)	30 (78.9)	
Squamous cell	2 (22.2)	4 (10.5)	
Others	-	4 (10.5)	
ECOG PS			0.255
0	3 (33.3)	13 (34.2)	
1	6 (66.7)	17 (44.7)	
2	-	7 (18.4)	
3	-	1 (2.6)	
AJCC stage			0,471
1-2	2 (22.2)	4 (10.5)	
3	3 (33.3)	9 (23.7)	
4	4 (44.4)	25 (65.8)	
Follow-up time, months, median (range)	14 (8-78)	16 (1-76)	0.567

For abbreviations see footnote of Table 1

mortality. Furthermore, this analysis demonstrated that mortality was 2.382-fold higher in stage 3 (p=0.009) and 5.474-fold higher in stage 4 (p<0.001) as compared to stages 1-2. Mortality was 3.588-fold higher in ECOG PS 2-3 patients (p<0.001) as compared to ECOG PS 0-1, while it was 2.368-fold higher in the non-treatment group as compared to treatment group (p<0.001). Table 3 presents the univariate and multivariate Cox regression results of factors considered to be associated with OS in all NSCLC cases.

Discussion

There are major geographic differences, particularly in Asia, where 60-80% of women with NSCLC are never-smokers [5]. In our population, similar to the Asian populations, never-smokers constituted 16.2% of the NSCLC patients, with 19.1% being males and 80.9% females.

Adenocarcinoma is more common in never-smokers, while SCC and small cell lung cancer are seen with a higher incidence in heavy smokers [5,6]. Although adenocarcinoma is most commonly found in women (79.8%), never-smoking men also showed a higher proportion of adenocarcinoma (77.8%) in our study, suggesting that a factor unrelated to sex is responsible for the predomi-

Table 3. Univariate and multivariate Cox regression analyses of factors considered to be associated with overall survival in all non small cell lung cancer patients

Variables	*Univariate analysis*		*Multivariate analysis*	
	HR (95%CI)*	*p-value*	*HR** (95%CI)*	*p-value*
Gender				
Male	1.000	-	1.000	-
Female	1.164 (0.791-1.711)	0.441	0.997 (0.537-1.850)	0.992
Age (mean)	1.015 (0.999-1.031)	0.061	1.009 (0.992-1.026)	0.298
Histologic subtype				
Adenocarcinoma	1.000	-	1.000	-
Squamous cell	0.621 (0.417-0.926)	0.019	0.756 (0.498-1.147)	0.189
Others	1.209 (0.811-1.802)	0.351	1.117 (0.729-1.711)	0.611
Smoking status				
Never	1.000	-	1.000	-
Ever	0.844 (0.560-1.273)	0.418	1.654 (0.835-3.276)	0.149
ECOG				
0-1	1.000	-	1.000	-
2-3	6.585 (4.311-10.057)	<0.001	3.588 (2.206-5.834)	<0.001
AJCC Stage				
1-2	1.000	-	1.000	-
3	2.594 (1.355-4.968)	0.004	2.382 (1.239-4.579)	0.009
4	7.509 (3.988-14.139)	<0.001	5.474 (2.821-10.624)	<0.001
Treatment				
Yes	1.000	-	1.000	-
Supportive/no- treatment	4.228 (2.643-6.764)	<0.001	2.368 (1.392-4.026)	<0.001

*Crude hazard ratio, ** Adjusted hazard ratio, HR: hazard ratio, ECOG PS: Eastern Cooperative Oncology Group performance status, AJCC: American Joint Committee on Cancer

nance of adenocarcinomas in the never-smoking population.

One of the most apparent differences between NSCLC in never-smokers vs ever-smokers is in the expression and mutations of the epidermal growth factor receptor (EGFR). Mutations in the EGFR gene are more common in lung cancer of never-smokers compared to smokers [7-11]. Several studies in patients with the most common activating mutations in the EGFR gene (predominantly deletions in exon 19 and the L858R mutation on exon 21) report that the frequency of mutations, especially exon 19 and 21 mutations, is much higher in never-smokers than in ever-smokers, in both men and women [12,13].

K-RAS mutations are thought to be more common in lung cancer patients who are ever-smokers [11,14]. Although K-RAS mutations are historically considered to represent a tumorigenic pathway in smokers, their prevalence has been reported to be similar in smokers and non-smokers. Despite being still controversial, molecular differences between groups may be responsible for distinct clinical responses to treatment.

Although it has been postulated that NSCLC occurs at a younger age in never-smokers [15,16], this has not been validated in some recent cohort analyses in Western populations [17]. According to our findings, age at diagnosis in never-smoker NSCLC patients differed between older adults (mean age 64.9 years) compared to ever-smokers (mean age 58.6 years). This difference may be explained by the hypothesis that either never-smokers exposed to passive smoke could have a lower amount of carcinogen compared to smokers and should develop lung cancer later or indoor air pollutants, such as cooking fumes, play a role in lung carcinogenesis in developing countries such as Turkey.

It is an interesting and significant observation that the majority of never-smoker patients presented with the disease at later stages (61.7% stage 4), whereas, only 35% of ever-smoker patients presented at stage 4. This may either be

due to late presentation on the part of the patients or late diagnosis on the part of the physicians, as lung cancer in never-smokers is clearly less common and not at the top of a diagnostic list. Thus, the public and clinicians should be aware that lung cancer is not purely a disease of the smokers.

Our main finding was that no significant differences exist between never-smokers and ever-smokers (p=0.410). Some observational studies have demonstrated that never-smokers had better 5-year OS rates than ever-smokers [18-22]. In an analysis of 12,000 patients from California, smokers had a shorter survival compared to never-smokers [18]. However, this has not been true in all studies [23-25]. Similarly, in another study of patients with lung adenocarcinoma comparing 132 never-smokers with 522 current-smokers, it was found that the 5-year OS was significantly different on multivariate analysis [19]. In contrast, in another study of 254 patients with NSCLC the 5-year OS was not significantly different in never-smokers compared to smokers (27 vs 31%, respectively)[23]. In our study, OS was shorter in never-smokers as compared to smokers. A possible explanation could be that never-smokers were admitted to the hospital in advanced disease stages and older age, and because EGFR determination was not performed in all centers during 2006-2011, erlotinib usage was limited.

The limitations of our retrospective study are related to the inadequate information about passive smoking, cooking fume exposure, as well as molecular analysis of the tumors.

In conclusion, we demonstrated that the vast majority of never-smoker NSCLC patients were female, exhibited adenocarcinoma as the predominant histologic type and showed a higher proportion of advanced disease. There was not statistically significant difference in the 5-year OS between never- and ever-smoker patients. Among NSCLC patients, ECOG PS (ECOG 2-3), advanced stage (stage 3-4) and untreated patients were associated with the poorest prognosis.

Future efforts should focus on the underlying biological differences, and on identifying potential non-tobacco related risk factors in order to improve treatment strategies for these two groups of NSCLC patients.

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