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ORIGINAL ARTICLE

Lung cancer in never-smokers – what are the differences?

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ABSTRACT

Introduction: Characteristics of never-smokers with lung cancer are still not fully clarified. The aim of this study was to compare never-smokers and ever-smokers with non-small cell lung cancer (NSCLC) regarding patient and tumor characteristics.

Methods: All consecutive newly NSCLC patients with known smoking status diagnosed between 2011 and 2015 were included in this retrospective cohort study. Clinical, histological, and molecular characteristics were compared between ever-smokers and never-smokers.

Results: Of the 558 included patients, 125 (22.4%) were never-smokers. These patients were more likely to be female (74% vs. 7%, $p < .001$), older (67 vs. 66 years-old, $p = .019$), and have adenocarcinoma (93% vs. 65%, $p < .001$). Never-smokers took longer to seek medical care after the symptoms onset (3 vs. 2 months, $p < .001$), regardless of the symptoms, histological type, or gender (OR: 1.2 [1.4–2.0]). The metastatic pattern was different in never-smokers: pleural metastases were more frequent (OR: 2.1 [1.1–4.0]), regardless of the histological type and gender. Never-smokers had a higher prevalence of ALK translocations (26% vs. 4%, $p < .001$) and EGFR mutations (36% vs. 8%, $p < .001$). The type of EGFR mutation was also significantly different between groups.

Conclusions: Never-smokers with NSCLC present distinct demographic and clinical characteristics. The characteristics of tumor also differ between never-smokers and ever-smokers, which may suggest different carcinogenic pathways.

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Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Smoking is unquestionably the major risk factor of lung cancer in both genders [2]. The odds ratio (OR) of lung cancer for current-smokers vs. never-smokers was estimated at 23.9 (19.7–29) for men and 8.7 (7.4–10.3) for women [3,4]. However, the prevalence of lung cancer in never-smokers has been increasing overtime and, currently, 10–30% of all lung cancers arise in never-smokers [5]. Some authors argue that lung cancer in never-smokers is a distinct entity, but descriptive studies are still sparse [6,7]. Furthermore, most studies about lung cancer in never-smokers emerged from Asia and most only describe lung cancer in never-smokers without comparing them with a group of ever-smoking patients [6,8,9].

The aims of this study were to describe the characteristics of never-smoking patients with non-small cell lung cancer (NSCLC) and to compare them with the characteristics of ever-smokers.

Methods

Study design and data collection

This was a retrospective cohort study conducted in the Lung Cancer Unit of Centro Hospitalar Gaia/Espinho, in Portugal, between 2011 and 2015.

The source of data was the database of our Lung Cancer Unit. Each new diagnosis of lung cancer is inserted in this database using a standard form that includes, among other items, the patient's demographic data, smoking status, initial symptoms, time between symptoms onset and first medical appointment, lung cancer histology, lung cancer stage and mutational status of the tumor regarding epidermal growth factor receptor (EGFR) mutations, and anaplastic lymphoma receptor tyrosine kinase (ALK) translocation.

Smoking status was self-declared by each patient and recorded by their medical doctors, who being pulmonologists did it as part of their regular practice.

For histological analysis, all available pathologic samples were analyzed by physicians with extensive experience in the pathologic diagnosis of lung cancer. Histological types were classified according to the International Classification of Lung Tumors [10]. EGFR mutations were tested in patients with advanced non-squamous cell carcinoma or in patients with squamous cell carcinoma who were never-smokers or who smoked less than 15 pack years. In EGFR wild-type tumors, ALK translocation was tested by fluorescence *in situ* hybridization. EGFR mutations and ALK translocations were performed in an accredited laboratory subject to external quality control – the Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP).

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Inclusion criteria were being newly diagnosed with NSCLC and having a registry of the smoking status.

First, we described the characteristics of never-smoking patients and of their tumor. Afterward, we compared lung cancer patients regarding their smoking status.

Ethical approval was not necessary as only anonymized data were used.

Definitions

A person was considered never-smoker if the person declared having smoked fewer than 100 cigarettes during their lifetime. Ever-smoker was defined as a person who declared having smoked at least 100 cigarettes during their lifetime.

Statistical analysis

Descriptive statistics of the variables of interest were expressed as absolute and relative frequencies or median and range.

Groups were compared by unpaired *t*-tests for continuous variables, chi-square test for categorical variables, and Mann Whitney *U*-test for nonparametric variables.

Logistic regression models were used to measure the influence of other variables, beside tobacco exposure, on ECOG performance status, histological type, and stage at diagnosis. The initial selection of independent variables was done based on evidence from previously published journal articles [11]. Then a logistic regression where all variables were considered simultaneously was performed.

All statistical analyses were carried out using the SPSS 22.0 package program (IBM Corp., Armonk, NY). The significance level was set at 0.05.

Results

Five hundred and sixty-six patients were newly diagnosed with NSCLC. Of those, 558 (99%) had smoking status information and were included in the analysis. Patients were mostly men ($n = 433$; 78%) and the median age was 66 (25–92) years old.

One hundred and twenty-five (22%) patients were never-smokers, and 433 (78%) were ever-smokers.

Never-smokers were predominantly women ($n = 93$, 74%) and median age was 67 (35–92) years old. Adenocarcinoma was the most frequent histological type ($n = 116$, 93%). ALK translocation and EGFR mutations were only found in patients with adenocarcinoma. EGFR mutations were found in 36 (36%) of 99 never-smokers with adenocarcinoma who were tested for these mutations. ALK translocation was identified in 11 (26%) of the 43 never-smokers with adenocarcinoma who were tested.

The comparison between never-smokers and ever-smokers is presented in Tables 1 and 2. Never-smokers with NSCLC were more frequently women (74% vs. 7%, $p < .001$) and older (median 67 years vs. 66 years, $p = .019$) compared to ever-smokers. The performance status at diagnosis was significantly worse in never-smokers. However, after adjustment for age, gender, histological type, and disease stage, this association no longer exists (Table 3).

The proportion of patients without symptoms at diagnosis was similar between the two groups (35% vs. 36%, $p = .820$). Among symptomatic patients, ever-smokers had more often

Table 1. Characteristics of patients with lung cancer, depending on their smoking status.

	Never-smokers, $n = 125$	Ever-smokers, $n = 433$	*p* Value
Gender [*n* (%)]			
Female	93 (74%)	32 (7%)	<.001
Male	32 (26%)	401 (93%)	
Age, years [median (range)]	67 (35–92)	66 (25–90)	.019
ECOG performance status [*n* (%)]			
0–1	88 (70%)	352 (83%)	.003
2–4	37 (30%)	74 (17%)	
Initial symptoms [*n* (%)]			
No symptoms	45 (36%)	149 (35%)	.820
Cough	27 (22%)	118 (28%)	.178
Dyspnea	24 (19%)	79 (19%)	.860
Hemoptysis	2 (2%)	58 (14%)	<.001
Chest pain	23 (18%)	77 (18%)	.925
Asthenia	22 (18%)	75 (18%)	.993
Loss of appetite	14 (11%)	73 (17%)	.112
Weight loss	23 (18%)	118 (28%)	.037
Time between onset of symptoms and medical appointment, months [median (range)]	3 (0.1–24)	2 (0.1–24)	<.001

Table 2. Characteristics of the tumor, depending on patient's smoking status.

	Never-smokers, $n = 125$	Ever-smokers, $n = 433$	*p* Value
Histology [*n* (%)]			
Adenocarcinoma	116 (93%)	281 (65%)	<.001
Squamous cell carcinoma	6 (5%)	110 (25%)	
Other	3 (2%)	42 (10%)	
EGFR mutations [*n*/*N* tested (%)]	36/101 (36%)	24/294 (8%)	<.001
Deletions in exon 19	22 (61%)	6 (25%)	.047
Substitutions in exon 18	1 (3%)	2 (8%)	
Substitutions in exon 20	3 (8%)	4 (17%)	
Substitutions in exon 21	10 (28%)	12 (50%)	
ALK translocations [*n*/*N* tested (%)]	11/43 (26%)	4/108 (4%)	<.001
Stage at diagnosis [*n* (%)]			
IA to IIIB	47 (38%)	223 (52%)	.006
IV	78 (62%)	210 (49%)	
Location of metastasis [*n*/total *N* (%)]			
Pleura	36/78 (46%)	53/210 (25%)	<.001
Contralateral lung nodules	29/78 (37%)	73/210 (35%)	.703
Brain	12/78 (15%)	37/210 (18%)	.654
Bone	26/78 (33%)	80/210 (38%)	.456
Liver	10/78 (13%)	30/210 (14%)	.749
Adrenals	7/78 (9%)	48/210 (23%)	.008
Kidney	2 (3%)	6 (3%)	.893
Skin	2 (3%)	6 (3%)	.893

EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma receptor tyrosine kinase.

Table 3. Univariate analysis and multiple logistic regression model to identify factors associated to a poorer ECOG performance status (ECOG 2–4 vs. 0–1).

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Advanced staged	3.0 (1.9–4.7)	<.001	3.0 (1.9–4.9)	<.001
Age	1.1 (1.1–1.2)	<.001	1.1 (1.1–1.2)	<.001
Adenocarcinoma	0.82 (0.53–1.3)	.366	0.54 (0.33–0.90)	.018
Never-smokers	1.8 (1.2–2.9)	.003	1.8 (0.28–1.1)	.098
Female	1.3 (0.82–2.1)	.257	1.1 (0.54–2.2)	.791

OR: odds ratio; CI: confidence interval.

hemoptysis (14% vs. 2%, $p < .001$) and weight loss (28% vs. 18%, $p = .037$) as initial symptoms. However, after adjusting for histological type and gender, this association no longer exists. Time between the onset of symptoms and the first medical appointment was 1 month longer for never-smokers (median 3 vs. 2 months, $p < .001$). This difference is still significant after adjusting for symptoms, such as hemoptysis, gender, and age (OR: 1.2 [1.4–2.0]).

Histologically, adenocarcinoma was the most common type of NSCLC in both groups. However, the OR associated with the presence of adenocarcinoma (vs. all other histological types) in never-smokers was 6.9 [3.4–14] relative to ever-smokers. After adjusting for age and gender, this association was still significant (OR 4.1 [0.11–0.56]) (Table 4).

Never-smokers were more likely to present a metastatic stage at diagnosis (62% vs. 49%, $p = .006$). However, this difference regarding smoking status was not significant after adjusting for gender, age, histological type, and time between symptoms and medical appointment (Table 5).

Of patients with metastatic disease, pleural metastases were more frequent in never-smokers (46% vs. 25%, $p < .001$) even after adjusting for histological type and gender (OR: 2.1 [1.1–4.0]). Adrenal metastases were more frequent in ever-smokers (9% vs. 23%, $p = .008$) but with no significant association after adjusting for histological type.

Among patients with adenocarcinoma, never-smokers had a higher prevalence of ALK translocations (26% vs. 4%, $p < .001$) and of EGFR mutations (36% vs. 10%, $p < .001$). In never-smokers, deletions in exon 19 were the most common EGFR mutation (63%), while in ever-smokers substitutions in exon 21 were the most frequent (50%).

Discussion

Never-smokers with lung cancer are an understudied subset of patients [12]. In our study, we found a prevalence of 22% never-smokers among patients newly diagnosed with NSCLC. Our results do not differ from the reported rate ranging from 10% to 30% in European or American studies [5]. This should increase our interest about this subset of patients. In the search for causes and biological mechanisms of lung cancer in never-smokers, understanding the histopathological and clinical features may reveal important clues.

Our findings demonstrated several clinical differences among patients with NSCLC patients regarding their smoking status. First, never-smokers with NSCLC were mainly women and ever-smokers mainly men. Previous studies showed similar results, but this association is still not well understood [7,13]. Some authors defend that this could reflect the fact that most never-smokers in general population are women instead of indicating an increased risk of lung cancer among never-smoking women [8]. However, in our study, the prevalence of women among never-smokers with NSCLC (74%) was higher than the prevalence of women among never-smokers in general population, described in a recent national report (67.5%) [14]. Although this national report used the same criteria to define never-smokers, they did not report age-adjusted results, which makes comparisons difficult. Due to this limitation, we cannot exclude or conclude if the high prevalence of women among never-smokers with NSCLC may also be associated with genetic, hormonal, or other characteristics of women that may increase their susceptibility to lung cancer [7,15]. Furthermore, women can be more exposed to other risk factors beside tobacco, such as cooking oil fumes or radon, which was not possible to investigate in our study [6,7]. Further studies are needed to answer this question.

Another important difference between never-smokers and ever-smokers was the different histological type distribution. Adenocarcinoma was over-represented among never-smokers, compared to other histological types. This is consistent with previous studies and in our study the odds ratio for adenocarcinoma among never-smokers was even higher than reported by Sun et al. and Clément-Duchêne et al. [7,11]. Regarding tumor mutations, EGFR mutations and ALK translocation were significantly more frequent in never-smokers with adenocarcinoma, as described in previous studies [16,17]. A potential targetable molecular alteration was identified in 62% of never-smoking patients. This result was similar to that of a recent French study that found these genetic alterations in 55.7% of never-smokers with lung cancer [6]. However, the frequency of each genetic alteration was different from our study. The French group found EGFR mutations in more patients compared to our cohort (43% vs. 36%) and less ALK translocations (13% vs. 26%). These differences can be explained by a bias in the selection of patients tested for

Table 4. Univariate analysis and multiple logistic regression model to identify factors associated to an histological type of adenocarcinoma (vs. All other histological types).

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Never-smokers	6.9 (3.4–14)	<.001	4.1 (1.8–9.5)	.001
Female	6.2 (3.1–12)	<.001	2.6 (1.2–5.8)	.019
Age	0.99 (0.97–1.0)	.198	0.99 (0.97–1.0)	.152

OR: odds ratio; CI: confidence interval.

Table 5. Univariate analysis and multiple logistic regression model to identify factors associated to an advanced stage of disease (Stage IV vs. Stage IA–IIIB).

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Time between symptoms onset and edical appointment (months)	1.1 (1.1–1.2)	.001	1.1 (1.1–1.2)	.001
Adenocarcinoma	1.7 (1.2–2.5)	.005	1.7 (1.2–2.6)	.007
Never-smoker	1.8 (1.2–2.7)	.006	1.4 (0.78–2.5)	.255
Age	0.99 (0.98–1.0)	.607	1.0 (0.98–1.0)	.927
Female	1.55 (1.1–2.3)	.034	1.0 (0.55–1.7)	.903

OR: odds ratio; CI: confidence interval.

these mutations; as in both studies, not all patients were tested for these mutations. Furthermore, our study found that the types of EGFR mutations in never-smokers diverge from those found in ever-smokers, which may suggest different carcinogenic pathways. Interesting, deletions in exon 19 were the most frequent EGFR alteration in never-smokers and substitutions in exon 21 were the most frequent EGFR mutation in ever-smokers. Although both mutations are typically sensitive to EGFR tyrosine kinase inhibitors (TKI), several studies showed that deletions in exon 19 are associated to an improved time to progression and a longer overall survival of patients treated with EGFR-TKI [18,19]. Together, these data suggest that never-smokers with EGFR mutations and treated with EGFR-TKI are more likely to have a better outcome.

Less is known about others characteristics of lung cancer in never-smokers, namely, age, performance status, symptoms, and stage of disease [11].

In our study, never-smokers with lung cancer were slightly older than ever-smokers. However, this difference of 1 year of age is not necessarily clinically significant. Most studies also showed that never-smokers are older at diagnosis, but others reported that never-smokers were younger and Wakelee et al. found no differences regarding age [5,7,13,20]. Several factors can explain such discrepancies across studies, including differences in smoking history and family history of cancer; nevertheless, these findings remain unclear.

Discussions related to differences in disease stage at diagnosis regarding smoking status have also been reported [5,7,11,21]. Once more, there are discrepancies between published studies, but most of these studies did not present adjusted results [11]. Our study found that smoking status was not independently associated to the stage of disease at diagnosis. In turn, time between symptoms and medical appointment as well as adenocarcinoma histology was associated to a more advanced stage of lung cancer at diagnosis. In fact, in our study, never-smokers took 1 month longer to seek medical care after the onset of symptoms, regardless the symptoms, such as hemoptysis, gender, and age. As lung cancer is considered a tobacco-related disease, the level of awareness of this disease among never-smokers may be lower. Moreover, some symptoms associated with lung cancer, such as hemoptysis and weight loss are significantly less frequent in never-smokers. However, these differences seem to be associated to the histological type of the tumor and not directly related to the smoking habits. It is still unclear whether there is any impact on outcomes caused by delays in diagnosing and treating lung cancer. Interestingly, several recent studies have shown that delays in lung cancer diagnosis and treatment are not associated to a poorer outcome [22,23].

About one-third of our patients were asymptomatic at diagnosis, independently of their smoking status. There are few published data about incidental lung cancer, but a study from South Korea reported that 6.5% of patients with lung cancer were asymptomatic and that this condition was more frequent in never-smokers [24]. Different levels of awareness and of access to health care may justify the differences in relation to our study.

Finally, never-smokers with metastatic lung cancer had more pleural metastases than ever-smokers, regardless of the histological type or gender, whereas in other organs these differences were not observed. Although in our study, there were a limited number of patients with metastatic disease, these results suggest a potential association of smoking status and the pattern of metastasis.

Our study presents some limitations which need to be discussed. First, the proportion of never-smokers is low, which can compromise the results. Nevertheless, this is a limitation of most of the studies on lung cancer in never-smokers and even then, our percentage of never-smokers is slightly higher than in most of other studies. Other limitation is the absence of data about other risk factors for lung cancer, such as second-hand smoke exposure or other environmental exposures, family history of cancer, menopausal hormone replacement therapy, and diet [7,15]. However, the retrospective design of the study did not allow a correct investigation of these factors.

The major strength of our study was the analysis of multiple clinical, histological, and molecular characteristics of NSCLC in never-smokers, which enable a comprehensive evaluation of this distinct entity. One of the major findings was that doctors addressing a never-smoker with lung cancer should keep in mind that at least two-thirds of them may have a targetable mutation and could be treated with targeted therapies.

Further prospective studies are needed to validate our findings, to clarify risk factors for lung cancer in never-smokers and to explore the carcinogenic pathways involved, in order to optimize the approach of NSCLC in never-smokers. For example, in recent years, recommendations were proposed for screening and early diagnosis of lung cancer in ever-smokers [25]. The recommendations are not so clear for never-smokers. Further studies could help to understand how to improve early diagnosis of lung cancer in never-smokers. Moreover, with improved understanding of the molecular biology of lung cancer in never-smokers, it is likely that this population will be treated very differently than ever-smokers with lung cancer. Finally, although the focus of this study was the never-smokers, smoking is implicated in most cases of lung cancers and, as such, smoking cessation efforts should be taken worldwide.

Disclosure statement

Dr Barroso reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, Lda, personal fees from Eli Lilly and Company, personal fees from Pierre Fabre Portugal, personal fees from Roche Farmacêutica Química, Lda, personal fees from Merck and personal fees from Bristol-Myers Squibb, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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