Lung Cancer in Never-Smokers: Epidemiological, Clinical, and Survival Patterns based on Gender

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Câncer de Pulmão em Indivíduos não Fumantes: Padrões Epidemiológicos, Clínicos e de Sobrevida baseados no Gênero

Cáncer de Pulmón en Individuos no Fumadores: Patrones Epidemiológicos, Clínicos y de Supervivencia basados en el Género

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Abstract

Introduction: Tobacco smoke is the leading risk factor for the development of lung cancer (LC). However, several countries have recently reported increases in LC in never-smokers. **Objective:** The study aimed to verify epidemiological and survival characteristics in never-smoker LC patients. **Method:** The study was based on a historical cohort of never-smokers with LC diagnosed from 2000 to 2009. Overall survival was compared using log-rank test, and Cox regression analysis was used to identify independent prognostic factors. **Results:** A total of 254 never-smoker LC patients were studied (median age 65.5 years; 66.5% women). The most common histological type was adenocarcinoma (65.7% in women and 60.0% in men), and the majority of the patients had advanced stages (III-IV) (79.6% in women and 92.8% in men). 9.9% of the patients were treated with surgery (13.1% of women and 3.6% of men). The overall survival rates at one, three, and five years were 37.2%, 14.2%, and 9.5%, respectively. Median overall survival was 8.3 months. Women showed better survival than men (9.6 vs. 6.9 months; p=0.023). Non-surgical treatment (p<0.001), performance status 2-4 (p=0.038), and stages III and IV (p<0.001) were associated with worse overall survival. **Conclusions:** The majority of LC cases in never-smokers were advanced-stage adenocarcinoma, submitted to non-surgical treatment. Women showed better survival than men. Based on the low overall survival, the data emphasize the importance of early diagnosis of LC in never-smoker patients.

Key words: Tobacco Smoke Pollution; Lung Neoplasm; Survival; Prognosis.

Resumo

Introdução: O tabagismo é o fator de risco predominante para o desenvolvimento do câncer de pulmão (CP). Contudo, um aumento recente de CP em não fumantes é proeminente em alguns países. **Objetivo:** O objetivo deste estudo foi verificar as características epidemiológicas e de sobrevida em não fumantes com CP. **Método:** Coorte histórica de não fumantes com CP diagnosticados de 2000 a 2009. A sobrevivência global foi comparada usando o teste Log-rank e a análise de regressão de Cox foi usada para identificar fatores prognósticos independentes. **Resultados:** Um total de 254 pacientes com LC não fumantes foram estudados (mediana de idade: 65,5 anos, 66,5% de mulheres). O tipo histológico mais comum foi o adenocarcinoma (65,7% nas mulheres e 60,0% nos homens) e a maioria tinha estadiamento avançado (III-IV) (79,6% nas mulheres e 92,8% nos homens). Um total de 9,9% dos pacientes foi tratado com cirurgia (13,1% em mulheres e 3,6% em homens). As taxas de sobrevida global de 1, 3 e 5 anos foram, respectivamente: 37,2%, 14,2% e 9,5%. A sobrevida global mediana foi de 8,3 meses. As mulheres tiveram melhor sobrevida do que os homens (9,6 vs. 6,9 meses, p=0,023). O tratamento não cirúrgico (p<0,001), o *performance status* 2-4 (p=0,038) e os estádios III-IV (p<0,001) foram associados com uma sobrevida global pior. **Conclusão:** Encontrou-se uma maior ocorrência de adenocarcinoma, estadiamento avançado e tratamento não cirúrgico. As mulheres tiveram uma sobrevida maior do que os homens. Em razão da baixa sobrevida global, esses dados reforçam a importância do diagnóstico precoce do CP em não fumantes.

Palavras-chave: Poluição por Fumaça de Tabaco; Neoplasias Pulmonares; Sobrevivência (Saúde Pública); Prognóstico.

Resumen

Introducción: El tabaquismo es el factor de riesgo predominante para el de cáncer de pulmón (CP). Sin embargo, un aumento reciente de CP en no fumadores es prominente en algunos países. **Objetivo:** El objetivo de este estudio fue verificar las características epidemiológicas y de sobrevida en no fumadores con CP. **Método:** Cohorte histórica de no fumadores con CP diagnosticados de 2000-2009. La supervivencia global fue comparada usando análisis de log-rank y la regresión de Cox para identificar factores pronósticos independientes. **Resultados:** Una muestra totalizando 254 pacientes no fumadores con CP fue estudiada (mediana de edad: 65,5 años, 66,5% de mujeres). El tipo histológico más común correspondió a adenocarcinoma (65,7% en las mujeres y el 60,0% en los hombres) y la mayoría en estadio avanzado (III-IV) (79,6% en las mujeres y el 92,8% en los hombres). Un total de 9,9% de pacientes fueron tratados con cirugía (13,1% en mujeres y 3,6% en hombres). Las tasas de supervivencia global de 1, 3 y 5 años fueron, respectivamente, el 37,2%, el 14,2% y el 9,5%. La supervivencia mediana global correspondió a 8,3 meses. Fue observada una mejor sobrevida en mujeres que em hombres (9,6 frente a 6,9 meses, p=0,023). El tratamiento no quirúrgico (p <0,001), el estado de equilibrio del estado 2-4 (p=0,038) y los estadios III-IV (p <0,001) se encontraron asociados con una peor sobrevida global. **Conclusiones:** Se encontró una mayor ocurrencia de adenocarcinoma, estadificación avanzada y tratamiento no quirúrgico. Las mujeres mostraron una sobrevida mejor que los hombres. En función de la baja sobrevida global, estos datos refuerzan la importancia del diagnóstico precoz del CP en no fumadores.

Palabras clave: Contaminación por Humo de Tabaco; Neoplasias Pulmonares; Supervivencia (Salud Pública); Pronóstico.

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INTRODUCTION

Lung cancer (LC) is the most commonly diagnosed cancer (11.6% of all cancer cases) and the leading cause of cancer death (18.4% of all cancer deaths) worldwide[1]. Globocan 2018 estimates that there will be 2.1 million new cases of LC worldwide in 2018, followed closely in incidence by female breast cancer (2.09 million), colorectal cancer (1.85 million), and prostate cancer (1.27 million). The number of predicted deaths from LC in 2018 is 1.8 million, accounting for nearly one out of five cancer deaths. [(1)] In men, LC is the most commonly diagnosed cancer and the leading cause of cancer death, followed in incidence by prostate and colorectal cancer, and by liver and stomach cancer in terms of mortality. In women, lung cancer is the leading cause of cancer death in 28 countries[1].

In the United States, LC causes as many deaths as the four next most deadly cancers combined (breast, prostate, colon, and pancreas)[2]. The five-year relative survival rate for LC in the United States in 2003-2009 was 17.5%[3].

According to estimates for Brazil, in 2019 there will be 18,740 new LC cases in men and 12,530 in women. In Brazil, LC is the leading cause of cancer death in men and the second leading cause in women[3]. The estimated number of new LC cases in Brazil corresponds to a risk of 18.16 new cases/100,000 men and 11.81 new cases/100,000 women[3]. LC incidence rates are a reflection of a country's tobacco consumption. Estimated median five-year survival for LC was 14% in males and 18% in females[4]. A Brazilian national household survey showed that the proportion of current consumers of tobacco products ranged from 13.4% in the North of the country to 16.1% in the South[5]. Lung cancer incidence in Brazil has increased in recent years and mortality remains high, similar to the rest of the world[3].

Many causes of LC have been identified, including active cigarette smoking, exposure to second-hand cigarette smoke, pipe and cigar smoking, occupational exposure to agents such as asbestos, nickel, chromium, and arsenic, exposure to radiation, including radon gas, and exposure to indoor and outdoor air pollution[6]. Despite the identification of this constellation of well-established causal risk factors, the global lung cancer epidemic is mainly caused by a single factor: cigarette smoking[7]. The attributable risk of smoking as a causative agent of lung cancer exceeds 90.0% in Brazil[8,9]. LC prevalence in never-smokers is increasing, according to several authors[10-15]. Global estimates indicate that about 300,000 annual LC deaths are not due to tobacco use[10]. Even though this estimate represents a minority of the LC burden, its incidence in never-smokers ranges from 4.8 to 20.8 per 100,000 in individuals aged 40 to 79 years[16]. Although a genetic risk remains to be discovered in LC, identification of genes involved in the cause of the disease could further elucidate the underlying mechanisms and eventually lead to additional prevention strategies and targeted treatments[17]. Family history of lung cancer is associated with a 1.5 to 4-fold increased risk of lung cancer after adjustment for clustering of smoking in families[17]. Large, collaborative genome-wide association studies have identified three separate loci associated with lung cancer (5p15, 6p21, and 15q25) and that include genes regulating nicotinic acetylcholine receptors and telomerase production[6].

To date, there have been few published studies focusing on clinical, epidemiological, and survival patterns exclusively in never-smoker LC patients, especially in Brazil. The main objective of this study was thus to verify the clinical, epidemiological, laboratory, and survival characteristics in a sample of Brazilian never-smoker LC patients referred to a tertiary hospital for general oncology.

METHOD

Study design

The study protocol was approved by the Institutional Review Board of the Brazilian National Cancer Institute José Alencar Gomes da Silva (INCA), and informed consent was waived because it was a retrospective review. The study was conducted at a tertiary referral center for general oncology in Rio de Janeiro State, Brazil, that is accessible to patients from all socioeconomic strata (although most of the patients are from lower social classes). A retrospective analysis of a prospective LC database was performed for patients with LC diagnosed from January 1, 2000, to December 31, 2009. All tumors were confirmed by histopathology, corresponding to events recorded under ICD-10 Chapter C-34 to C-39 on Malignant Neoplasms in the Brazilian Unified National Health System (SUS).

Collection of patient data

Eligibility requirements included pathologically proven LC with negative history of current tobacco use, age >18 years, absence of other concurrent cancer treatment, medical charts with recorded epidemiological characteristics, treatment provided, and no previous or other concomitant malignant disease except basal cell carcinoma. Never-smokers were defined as patients that had smoked <100 cigarettes in their lifetime and were not current smokers. Patients had their medical charts reviewed for demographic data, disease stage, histology, and treatment. The study variables were: gender, age,

race, histology (non-small cell lung cancer [NSCLC] subtypes), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-4), disease extent (advanced versus non-advanced), distant metastases (negative versus positive), treatment regimen, number of chemotherapy (CT) cycles, and dose of thoracic radiotherapy (RT).

Clinical PS was evaluated according to the ECOG scale[18]. Histological diagnosis was performed according to previous guidelines for NSCLC[15-20]. Staging was defined according to the 7th edition of tumor-node-metastasis (TNM)[21]. Tumor staging was based on physical examination, chest radiography, fiberoptic bronchoscopy with biopsy and cytologic examination, computed tomography of the chest and brain, abdominal ultrasound or computed tomography, radionuclide bone scan, positron emission tomography-computed tomography scans, and other tests as needed and recorded in the patient charts. Advanced disease was defined as stages IIIa, IIIb, and IV; non-advanced disease included stages Ia, Ib, IIa, and IIb. Treatment status was stratified in two categories: a) surgical treatment and non-surgical treatment (including best supportive therapy). Medical charts were also evaluated for pre-treatment laboratory parameters: hemoglobin, white blood cell count, platelet count, urea, creatinine, sodium, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, albumin, calcium, lactate dehydrogenase, and glucose.

In addition, waiting times (recorded in months) were defined as follows: a) specialist's delay as time between first visit to specialist in our institution and LC diagnosis and b) treatment delay as time between LC diagnosis and initial treatment.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0; SPSS; Chicago, IL). Data were expressed as medians and inter-quartile ranges to summarize continuous data. Categorical variables were reported as percentages of the population. Comparisons between groups were performed using the chi-square test for dichotomous variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U-test for non-normally distributed continuous variables. The study's endpoint was overall survival, measured as the time from date of diagnosis to date of death or last contact. Survival rates were estimated using the Kaplan-Meier method and compared between groups by the log-rank test. Crude hazard ratios (HR) with 95% confidence intervals (CI) were calculated by univariate Cox regression. Additional multivariate analysis was performed, adjusting for known prognostic factors and potential confounders that were significant in the univariate analysis ($p<0.10$). Correlation was evaluated using the Spearman rank correlation coefficient (r_s). Two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Demographic characteristics

From January 1, 2000, to December 31, 2009, 279 consecutive never-smoker LC patients were enrolled in a single institution. Of these, 20 were excluded due to incomplete demographic and/or survival data, and five were excluded due to small cell lung cancer diagnosis. Thus, 254 NSCLC subjects were studied (median age: 65.5 years; 66.5% women). For diagnosis, the most widely used diagnostic method was transthoracic needle aspiration or biopsy in 91 subjects (35.8%), followed by flexible fiberoptic bronchoscopy in 72 (28.3%), thoracentesis with or without closed pleural biopsy in 27 (10.6%), exploratory thoracotomy in 26 (10.2%), peripheral lymph node biopsy in 15 (5.9%), mediastinoscopy in five (2.0%), and other diagnostic tests in 18 patients (7.2%). As shown in Table 1, median age was higher in female patients compared to males (p=0.040). The majority of patients had advanced-stage disease (III-IV) at diagnosis: 79.6% in women and 92.8% in men; p=0.005. A total of 148 cases (58.2%) were classified as metastatic disease (stage IV). Family history of cancer was positive in 36.8% (44.2% in women and 23.8% in men; p=0.001). Women showed lower laboratory test results for hemoglobin ($p<0.001$), urea (p=0.003), creatinine (p=0.001), alanine aminotransferase (p=0.004), and lactate dehydrogenase (p=0.027). Inversely, albumin and sodium levels were higher in women than in men (p=0.004 and p=0.026, respectively).

Treatment

As shown in Table 2, of the entire patient sample, 9.9% were treated with surgery (13.1% of women and 3.6% of men; p=0.015). The most common form of treatment was chemotherapy alone, offered to 35.0% of patients. A total of 221 patients (87.0%) were treated, and 33 patients (13.0%) were followed with palliative care. Of the treated patients, 25 received surgical treatment, 127 received chemotherapy, and 111 received RT. For patients that received chemotherapy (83 women and 44 men), the most frequent regimens were platinum-based (88.6%). Of all the patients that received chemotherapy, 32 received two cycles, 21 patients received three cycles, 64 patients received four cycles, and 10 patients received six cycles. One hundred and eleven patients received chest

Table 1. Demographic and laboratory characteristics of a sample of never-smoker lung cancer patients in Brazil

Variables	n	Total (n=254)	Men (n=85)	Women (n=169)	P value
Demographics					
Age (years)	254	65.5 (54.0-74.0)	62.0 (50.0-73.5)	67.0 (57.0-74.0)	0.040
Race (%)					
White	193	76.1	86.1	71.4	0.044
Non-white	61	23.9	13.9	28.6	
Histology (%)					
Adenocarcinoma	162	63.8	60.0	65.7	0.606
Squamous cell carcinoma	33	13.0	17.6	10.7	
Non-typed NSCLC	31	12.2	14.1	11.2	
Carcinoid tumor	15	5.9	4.7	6.5	
Large cell carcinoma	8	3.1	2.4	3.5	
Carcinoma not otherwise specified	5	2.0	1.2	2.4	
Stage (%)					
I-II	41	16.0	7.2	20.4	0.005
III-IV	213	84.0	92.8	79.6	
PS (%)					
0-1	180	70.9	67.5	72.6	0.256
2-4	74	29.1	32.5	27.4	
Family history of cancer (%)					
Negative	146	63.2	76.2	55.8	0.001
Positive	85	36.8	23.8	44.2	
Blood tests					
Hemoglobin (g/dL)	233	12.9 (11.7-13.8)	13.8 (13.1-14.2)	12.9 (11.4-13.6)	<0.001
WBC count (x 10^3/mm^3)	231	8.7 (6.5-11.8)	11.0 (8.1-14.2)	7.7 (5.7-9.9)	0.056
Platelet count (x 10^3/mm^3)	231	294.0 (241.0-368.5)	289.0 (238.0-376.0)	298.0 (247.0-373.5)	0.976
Urea (mg/dL)	226	30.0 (25.0-38.0)	33.0 (25.2-39.0)	29.0 (23.7-37.0)	0.003
Creatinine (mg/dL)	231	0.8 (0.7-1.0)	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.001
Sodium (mEq/L)	221	140.0 (138.0-142.0)	139.0 (137.0-141.7)	141.0 (139.0-143.0)	0.026
AST (U/L)	167	20.0 (16.0-28.0)	22.5 (17.2-28.7)	19.0 (15.7-22.5)	0.056
ALT (U/L)	165	19.0 (14.0-31.0)	22.0 (13.0-40.0)	14.0 (12.0-20.2)	0.004
Bilirubin (mg/dL)	119	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.897
Alkaline phosphatase (U/L)	183	156.5 (96.2-269.0)	176.0 (104.0-337.0)	146.0 (92.5-265.0)	0.087
GGT (U/L)	160	37.0 (23.0-77.0)	42.5 (26.7-117.5)	33.5 (20.0-46.7)	0.061
Albumin (g/dL)	157	4.1 (3.7-4.4)	4.0 (3.7-4.1)	4.1 (3.8-4.4)	0.004
Calcium (mg/dL)	176	9.4 (9.1-9.8)	9.4 (9.1-9.9)	9.6 (9.0-10.0)	0.892
LDH (U/L)	168	386.0 (329.5-496.0)	414.0 (350.0-598.2)	344.0 (302.7-444.7)	0.027
Glucose (mg/dL)	227	100.5 (92.2-112.0)	101.0 (89.0-117.2)	99.5 (92.0-107.2)	0.468

NSCLC: Non-small cell lung cancer; PS: Performance status; WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; LDH: Lactate dehydrogenase.
Continuous variables are presented as median (inter-quartile range) and categorical variables are presented as percentages.

RT with a median radiation dose of 30.0 Gy (range: 6-66 Gy). Median radiation dose did not differ by gender: men received 30.0 Gy (range: 8-66 Gy) and women received 45.0 Gy (range: 6-65 Gy); p=0.265.

Survival

The authors also investigated whether blood tests dichotomized by the median were relevant predictors of survival. Patients with white blood cell count [x 10^3/mm^3] <8.7 (vs. ≥8.7), platelet count [x 10^3/mm^3] <294.0 (vs. ≥294.0), sodium [mEq/L] ≥140 (vs. <140), gamma-glutamyl transpeptidase [U/L] <37.0 (vs. ≥37.0), and albumin (g/dL) ≥4.1 [vs. <4.1] showed higher overall survival (in months). However, when these variables were analyzed by multiple regression, this difference was not significant (data not shown).

As shown in Table 3, women and men showed similar overall survival rates at one, three, and five years, but with a trend toward better survival in women, mainly at three and five years (p=0.058 and p=0.072; respectively).

Table 2. Patient characteristics according to treatment modality

Treatment offered	Total (n=254)	Men (n=85)	Women (n=169)
Surgical	25 (9.9)	3 (3.6)	22 (13.1)
Surgery alone	16 (6.3)	2 (2.4)	14 (8.3)
Surgery plus CT	5 (2.0)	-	5 (3.0)
Surgery plus RT	2 (0.8)	-	2 (1.2)
Surgery plus CTRT	2 (0.8)	1 (1.2)	1 (0.6)
Non-surgical	229 (90.1)	82 (96.4)	147 (86.9)
CT alone	89 (35.0)	37 (43.5)	52 (30.8)
RT alone	76 (29.9)	19 (22.4)	57 (33.7)
CTRT	31 (12.2)	6 (7.1)	25 (14.8)
Supportive care	33 (13.0)	20 (23.4)	13 (7.6)

CT: chemotherapy; RT: radiotherapy; CTRT: chemoradiotherapy. Data presented as n (%).

Overall survival rates at one, three, and five years were 37.2%, 14.2%, and 9.5%, respectively. Median overall survival was 8.3 months. Women showed better median survival than men (9.6 vs. 6.9 months; p=0.023). Figure 1 shows the Kaplan-Meier curves for overall survival for all patients classified according to PS, histology, stage, and treatment offered. The difference found was statistically significant in all situations: p<0.001 (for PS, stage, and treatment offered) and p=0.017 (for histology).

As shown in Table 4, in the univariate analysis, PS, stage, and treatment offered were important predictors of survival with p <0.001, p=0.035, and p<0.001, respectively. Multivariate analysis was performed with these three variables plus the variable race (white vs. non-white). Treatment modality, PS, and stage were independent predictors of survival in never-smokers with NSCLC. Adjusted HR for non-surgical treatment (vs. surgical) was 9.009 (95% CI: 3.289-24.390), PS 2-4 (vs. 0-1) was 2.016 (95% CI: 1.440-2.816), and stage III-IV (vs. I-II) was 1.801 (95% CI: 1.031-3.144).

In our sample, median delay from the first appointment with a specialist to initial treatment was 1.48 months. Median delay from first visit to specialist to diagnosis was 0.56 months and did not differ between men and women (0.56 and 0.53 months, respectively; p=0.451). Median delay from LC diagnosis to initial treatment was 0.66 months. Likewise, there was no difference in treatment delay according to gender (0.26 months for men and 0.90 months for women; p=0.589). Median overall survival (in months) was positively correlated with time from the initial appointment to diagnosis (r_s=0.193; p=0.002), with time from diagnosis to initial treatment (r_s=0.180; p=0.008), and with time from initial appointment to initial treatment (r_s=0.407; p<0.001).

DISCUSSION

The overall survival rates at one, three, and five years were 37.2%, 14.2%, and 9.5%, respectively. The study's

Table 3. Differences in survival related to gender

Outcome	Total (n=254)	Men (n=85)	Women (n=169)	P value
Survival (%)				
1-year (%)	37.2	30.6	40.5	0.132
3-year (%)	14.2	8.2	17.3	0.058
5-year (%)	9.5	4.7	11.9	0.072
Survival in months				
Overall	8.3 (3.9-19.1)	6.9 (2.6-16.0)	9.6 (4.7-20.9)	0.023
Treatment modality¶				
Surgical	80.9 (46.3-97.3)	97.0 (84.3-109.7)	67.3 (32.6-94.1)	0.320
Non-surgical	7.7 (3.5-15.1)	6.5 (2.6-13.6)	8.3 (4.2-15.9)	
PS*				
0-1	9.9 (5.3-25.7)	8.0 (5.5-20.7)	11.9 (5.2-30.4)	0.076
2-4	5.0 (1.7-9.5)	2.3 (0.7-5.4)	6.8 (3.6-10.2)	
Stage#				
I-II	57.3 (9.7-85.6)	38.0 (8.1-88.6)	57.8 (10.2-86.8)	0.798
III-IV	7.5 (3.6-14.9)	6.2 (2.0-13.8)	8.2 (4.4-15.7)	
Histology§				
Adenocarcinoma	8.3 (3.9-19.1)	7.0 (2.7-16.9)	9.7 (4.6-19.2)	0.066
Non-adenocarcinoma	7.9 (4.1-19.1)	6.4 (1.4-15.7)	9.4 (5.0-41.9)	

PS: Performance status.
¶Surgical treatment showed better survival than non-surgical treatment in all patients and in both genders (all with p<0.001).
*PS 0-1 showed better survival than PS 2-4 in all patients (p<0.001), in men (p=0.011), and in women (p=0.001).
#Stages I-II showed better survival than stages III-IV in all patients, in men, and in women (all with p<0.001).
§Adenocarcinoma histology showed better survival than non-adenocarcinoma histology in all patients (p=0.017) and in women (p=0.012).
Survival in months is expressed as median (inter-quartile range).

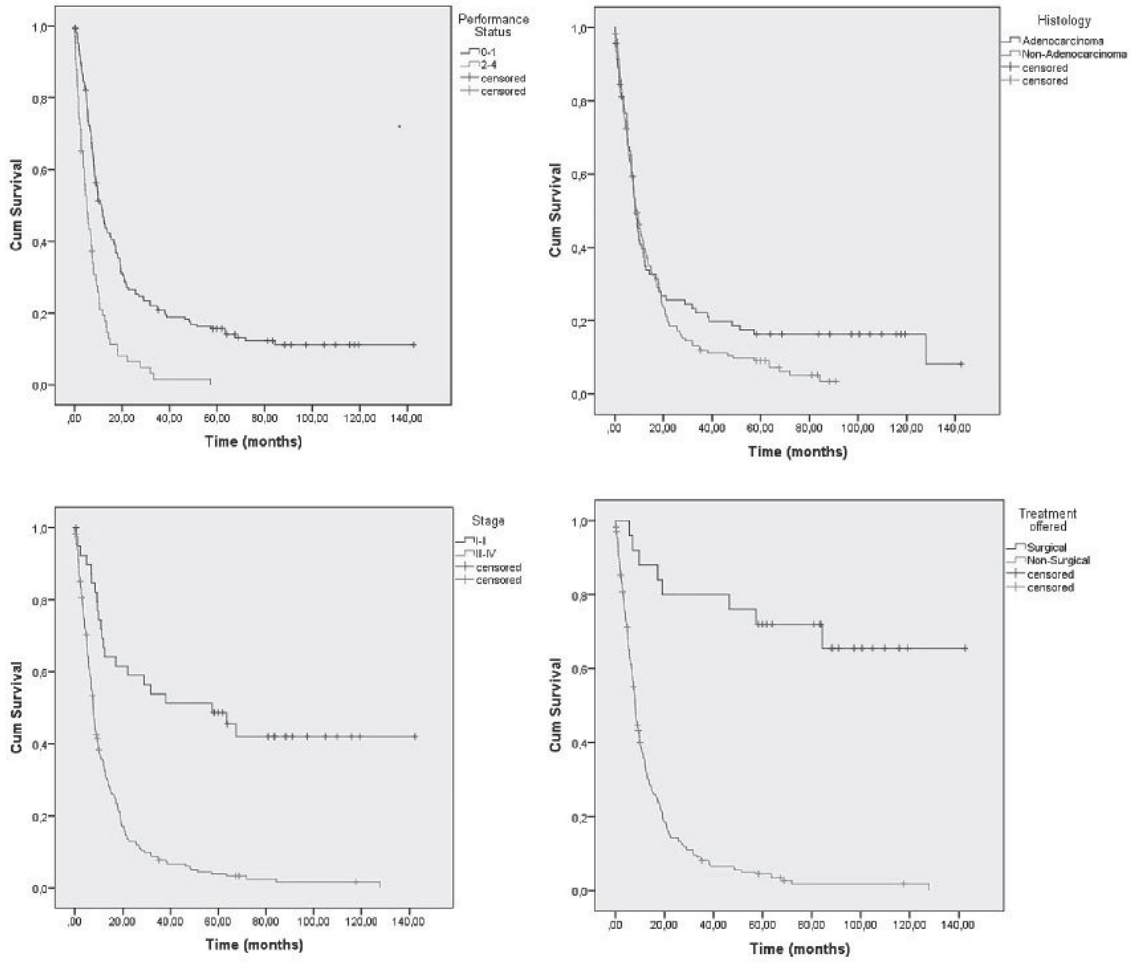

Figure 1. Kaplan-Meier curves for overall survival in never-smoker lung cancer patients (n=254) classified according to performance status, histology, stage, and treatment modality. The differences were statistically significant in all situations: p<0.001 (for performance status, stage and treatment modality) and p=0.017 (for histology).

main finding was that in a sample of never-smokers with NSCLC, median survival was better in women than in men. Overall, the cases involved higher proportions of women, adenocarcinomas, and advanced-stage disease, leading to a small proportion of patients who underwent surgery. The findings are consistent with previous studies showing that LC cases in non-smokers show a clear predominance of women with adenocarcinoma[11,12,14,16,22]. In addition, five-year overall survival was 9.5%, which is lower than in LC patients in the United States (17.5%)[2]. A previous study[22] reported better survival in never-smokers compared to current smokers with adenocarcinoma, with a five-year survival rate of 23% for never-smokers compared to 16% for current smokers (p=0.004). In general, never-smoker LC patients have better survival compared to LC patients with a positive smoking history (current and former smokers)[14,22]. Thus, our hypothetic overall survival (including patients with positive and negative smoking history) would be even lower. Unfortunately, our study did not compare never-smoker patients to patients who were current or former smokers. One explanation for the poor survival rates even in this never-smoker patient sample could be the high proportion of patients with advanced-stage disease.

Multivariate analyses showed that treatment modality, performance status, and tumor stage were independent predictors of survival in lung cancer patients with negative smoking history. Previous Brazilian studies have found similar results, generally with low overall survival and a high proportion of patients with advanced-stage disease and thus a low proportion of patients treated, especially with surgery[22-23]. Likewise, early diagnosis, treatment provided, and higher Karnofsky PS scores were also favorable independent predictors of survival[22]. A retrospective study[24] of LC patients diagnosed from 1995 to 2002 was done with 352 patients (74.4% men). The most common stages were IIIB and IV (45% and 21.5%, respectively). Of the total sample, 73.4% underwent

Table 4. Univariate and multivariate analyses of prognostic factors for overall survival in non-smoker lung cancer patients

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Gender				
Women	1			
Men	1.267 (0.900-1.782)	0.174		
Age				
<50	1			
≥50	1.300 (0.863-1.959)	0.209		
Race				
White	1		1	
Non-white	1.417 (0.964-2.082)	0.076	1.272 (0.895-1.808)	0.179
PS				
0-1	1		1	
2-4	2.092 (1.453-3.003)	<0.001	2.016 (1.440-2.816)	0.038
Family history				
Negative	1			
Positive	1.032 (0.740-1.441)	0.851		
Histology				
Adenocarcinoma	1			
Non-adenocarcinoma	1.239 (0.878-1.748)	0.221		
Stage				
I-II	1		1	
III-IV	1.838 (1.042-3.236)	0.035	1.801 (1.031-3.144)	<0.001
Treatment modality				
Surgical	1		1	
Non-surgical	9.009 (3.067-26.315)	<0.001	9.009 (3.289-24.390)	<0.001

HR: Hazard ratio; 95% CI: 95% confidence interval; PS: Performance status

treatment. Cumulative survival rates were low: 6.5% at three years and 3.5% at five years. Another retrospective study[25] evaluated 240 LC patients (64% men): only 131 patients (54.6%) were treated. Concerning staging, 34.4% were stage IV and 20.6% stage IIIB. Five-year survival was 65% for patients in stage I, compared to 25% for the remaining stages.

The etiology of lung cancer in never-smokers is interesting and remains unclear. Its occurrence obviously suggests the existence of risk factors other than active smoking: secondhand smoke, occupational exposures, preexisting lung diseases, diet, estrogen, human papillomavirus, and family history[22,24]. The causal relationship between environmental tobacco smoke and LC has been well established, but the increasing rate of NSCLC in individuals that have never smoked is inconsistent with the decrease in smoking rates in developed countries[26]. Never-smokers with LC may be genetically susceptible to carcinogen(s) or may be hereditarily predisposed to LC.[27] Previous studies support family history as an important risk factor for development of LC in never-smokers[27-30]. Our study showed a considerably higher percentage of women than men with a positive family history of LC.

Evidence suggests that smoking exposure from involuntary inhaling of smoke is a poor prognostic factor in NSCLC patients[28]. Since the majority of never-smokers with NSCLC are women with histological diagnosis of adenocarcinoma, the influence of both gender and histological types on survival may be attributable to smoking status. In addition, more female patients and more adenocarcinoma patients are likely to be in the group that has never smoked[12,29].

Another recent implication related to treatment is the good response to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors such as gefitinib and erlotinib, largely limited to never-smokers[27]. These mutations are more frequent in women (particularly of Asian ethnicity), adenocarcinoma, and especially never-smokers[27,28]. Interestingly, the frequency of EGFR mutations has been shown to be inversely proportional to exposure to environmental tobacco smoke in never-smokers[27]. Such findings suggest that EGFR-mutant tumors, which are closely linked to LC in never-smokers, occur by some mechanism other than the carcinogenic process induced by tobacco smoke[27-30].

Our study showed no gender differences in waiting times for appointments with specialists or for receiving

treatment. A previous study[25] showed that median delay between the first specialist appointment and final diagnosis was similar in men and women. The authors found a median delay of 41 days from the first specialist appointment to treatment [25]. The main factor related to shorter delay was more advanced disease, because these patients tend to receive treatment faster due to the severity of their signs and symptoms[30].

There were some limitations to the study. In the retrospective analysis, the results may have been biased by patient selection (selection bias), data collection (information bias), or confounding. Potential selection bias was controlled using appropriate definition of the eligible population. A standard protocol was used (approved by the institutional review board) in order to limit information bias. Moreover, confounding was neutralized in the analysis by the multivariate logistic model, including all variables with $p<0.10$. We thus conclude that internal validity was not systematically compromised. Another limitation to the study was the lack of information on comorbidities, tumor markers, environmental tobacco smoke, or molecular analyses of tumors.

In conclusion, we believe that the study demonstrated that lung cancer patients that have never smoked constitute a specific group with prominent demographic and survival characteristics. Based on the low overall survival, the results emphasize the importance of early diagnosis of LC in never-smokers. Further studies are needed, especially with a prospective design, to produce better knowledge of these patients' characteristics.

CONTRIBUTIONS

All the authors contributed to the study's conception and design, data analysis and interpretation, writing of the article, or critical revision of important intellectual content. RLMD performed the statistical analysis and interpreted the results. MMZ prepared the first draft of the paper. RLMD and ASM were responsible for acquisition of the clinical data, had full access to all the data, and were responsible for the data's integrity and accuracy of the data analysis. All the authors read and approved the final manuscript.

CONFLICT OF INTEREST

Mauro Musa Zamboni declares a potential conflict of interest as the Educational Coordinator of INCA. Alessandra de Sá Earp Siqueira declares a potential conflict of interest as Associate Editor of the Brazilian Journal of Oncology. The other authors have no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. National Cancer Institute. SEER Cancer Statistics Review, 1975-2010 [Internet]. Bethesda, MD: The Association; c1975-2010 [cited in: 2018 Jul 27]. National Cancer Institute; [about 2 screens]. Available from: http://seer.cancer.gov/csr/1975_2010/
3. Instituto Nacional de Câncer Jose Alencar Gomes da Silva. Estimativa 2018: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2018.
4. Reis RS, Scaf AJM. Cancer survival in Brazil: estimate through the mortality to incidence ratio. J Public Health Epidemiol. 2018;10(8):295-02.
5. Instituto Brasileiro de Geografia e Estatística. Ministério da Saúde. Pesquisa Nacional de Saúde - PNS 2013: percepção do estado de saúde, estilos de vida e doenças crônicas. IBGE; 2014.
6. International Agency for Research on Cancer. World Cancer Report 2014. Lyon: WHO; 2014. p. 521.
7. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer diagnosis and management of lung cancer, 3rd Ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e1S-e29S.
8. Zamboni M. Epidemiologia do câncer do pulmão. J Pneumologia. 2002;28(1):41-7.
9. Malta DC, Abreu DMX, Moura L, Lana GC, Azevedo G, França E. Tendência das taxas de mortalidade de câncer de pulmão corrigidas no Brasil e regiões. Rev Saúde Pública. 2016;50:33.
10. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers: a different disease. Nat Rev Cancer. 2007;7(10):778-90.
11. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. J Clin Oncol. 2006;24(15):2245-51.
12. Yano T, Miura N, Takenaka T, Haro A, Okazaki H, Ohba T, et al. Never-smoking non-small cell lung cancer as a separate entity: clinicopathologic features and survival. Cancer. 2008;113(5):1012-8.
13. Boffetta P, Jarvholm B, Brennan P, Nyrén O. Incidence of lung cancer in a large cohort of non-smoking men from Sweden. Int J Cancer. 2001;94(4):591-3.
14. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, et al. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive

analysis of 26,957 patients with NSCLC. J Thorac Oncol. 2010;5(5):620-30.

15. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, et al. Gender, histology, and time of diagnosis are important factors for prognosis. Analysis of 1499 never-smokers with advanced non-small cell lung cancer in Japan. J Thorac Oncol. 2010;5(7):1011-7.
16. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, Clarke CA, et al. Lung cancer incidence in never smokers. J Clin Oncol. 2007;25(5):472-8.
17. Schwartz AG, Bailey-Wilson JE, Amos CI. Genetic susceptibility to lung cancer. In: Pass H, Ball D, Scagliotti G, editors. IASLC Thoracic Oncology. 2nd Ed. Philadelphia, PA: Elsevier; 2018. p. 46-51.
18. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996;32A(7):1135-41.
19. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC editors. Pathology and genetics: tumours of the lung, pleura, thymus and heart. Lyon: IARC; 2004.
20. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.
21. Rami-Porta R, Ball D, Crowley J, Giroux DJ, Jett J, Travis WD, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2007;2(7):593-602.
22. Santoro IL, Ramos RP, Franceschini J, Jamnik S, Fernandes ALG. Non-small cell lung cancer in never smokers: a clinical entity to be identified. Clinics. 2011;66(11):1873-7.
23. Westphal FL, de Lima LC, Andrade EO, Netto JCL, da Silva AS, de Carvalho BCN. Characteristics of patients with lung cancer in the city of Manaus, Brazil. J Bras Pneumol. 2009;35(2):157-63.
24. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers versus current smokers with primary adenocarcinoma of the lung. Chest. 2004;126(2):347-51.
25. Salomaa ER, Sällinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. Chest. 2005;128(4):2282-8.
26. Novaes FT, Cataneo DC, Ruiz Jr. RL, Defaveri J, Michelin OC, Cataneo AJM. Lung cancer: histology, staging, treatment and survival. J Bras Pneumol. 2008;34(8):595-600.
27. Sun Y, Ren Y, Fang Z, Li C, Fang R, Gao B, Han X, et al. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. J Clin Oncol. 2010;28(30):4616-20.
28. Duarte RL, Luiz RR, Paschoal ME. The cigarette burden (measured by the number of pack-years smoked) negatively impacts the response rate to platinum-based chemotherapy in lung cancer patients. Lung Cancer. 2008;61(2),244-54.
29. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361(10):958-67.
30. Lee YJ, Cho BC, Jee SH, Moon JW, Kim SK, Chang J, et al. Impact of environmental tobacco smoke on the incidence of mutations in epidermal growth factor receptor gene in never-smoker patients with non-small-cell lung cancer. J Clin Oncol. 2010;28(3):487-92.

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