



# Brazilian Women With Lung Cancer Have a Higher Overall Survival Than Their Male Equivalents: A Cohort Study

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## Abstract

**The epidemiologic, clinical, and histologic profile of women with lung cancer is better known in developing countries. This study was a cohort retrospective including 1283 patients with lung cancer from the Brazilian National Cancer Institute between 2006 and 2014. This study showed that the overall survival in women with lung cancer is higher than men.**

**Background:** Lung cancer is the principal cause of cancer-related deaths worldwide; however, there has been controversy as to whether there is a difference in survival rate according to gender in Brazil. The aim of the present study, therefore, was to compare the epidemiologic and clinical profile and the overall survival of patients with lung cancer according to gender. **Patients and Methods:** A retrospective cohort study was performed involving 1283 patients diagnosed with lung cancer between 2006 and 2014 at a single cancer center. Survival analysis was conducted using Kaplan-Meier statistics. A log-rank test was used to assess differences between survival curves, and Cox proportional hazards regression analysis was performed to quantitate the relationship between gender and overall survival. **Results:** Compared with men, women were more frequently younger ( $P < .001$ ), nonsmokers ( $P = .007$ ), diagnosed with adenocarcinoma ( $P < .001$ ), had early stage disease ( $P < .001$ ), received surgery or surgery in combination with chemotherapy ( $P < .001$ ), and had a better survival rate ( $P < .001$ ). The median overall survival rate was higher in women (14.2 vs. 10.5 months in men;  $P < .001$ ). Cox regression-adjusted analysis shows that women were 16% less likely to die than men (hazard ratio, 0.84; 95% confidence interval, 0.72-0.98;  $P = .03$ ). **Conclusions:** A higher overall survival rate was found in women with lung cancer as compared with men with lung cancer in Brazil.

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**Keywords:** Brazil, Gender, Histology, Lung cancer, Survival, Women

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## Introduction

Lung cancer is the most common type of cancer and the principal cause of cancer-related deaths worldwide. In 2018, over 2.1 million new cases were reported, with 18.86 million deaths globally.<sup>1</sup> Prognostic factors frequently reported in patients with lung cancer are stage, performance status, and appropriate treatment. Gender has also been shown to be related to differences in survival, because women with lung cancer have a better survival rate than their male equivalents.<sup>2-4</sup> However, many confounding factors associated with gender may influence survival.<sup>3</sup>

Women with lung cancer display important differences in the epidemiologic, clinical, and histologic profile. Women are generally younger, at a more advanced stage, possess epidermal growth factor receptor (EGFR) and anaplastic large-cell lymphoma kinase (ALK)

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**Table 1** Characteristics of the Patients With Lung Cancer According to Gender

Characteristic	Male (A) N (%)	Female (B) N (%)	Comparison Between Groups	P Value <sup>a</sup>
No. patients	776 (60.5)	507 (39.5)		
Mean age, y	63.90 ± 9.4	60.92 ± 9.3	A>B	<.001 <sup>a</sup>
Age group, y				<.001 <sup>a</sup>
<50	54 (7.0)	71 (14.0)	A<B	
50-69	500 (64.4)	335 (66.1)	A = B	
>70	222 (28.6)	101 (19.9)	A>B	
Smoking				<.001 <sup>a</sup>
Never smoker	32 (4.1)	100 (19.7)	A<B	
Smoker/former smoker	724 (93.3)	393(77.5)	A>B	
Missing	20 (2.6)	14 (2.8)		
Histology				<.001 <sup>a</sup>
Adenocarcinoma	309 (39.8)	277 (54.6)	A<B	
Squamous cell carcinoma	352 (45.4)	144 (28.4)	A>B	
Large cell	19 (2.4)	11 (2.2)	A = B	
Small-cell lung cancer	96 (12.4)	75 (14.8)	A = B	
Stage				<.001 <sup>a</sup>
Early (I or II)	114 (16.6)	106 (23.8)	A<B	
Local (III)	327 (47.7)	155 (34.8)	A > B	
Advanced (IV)	245 (35.7)	185 (41.5)	A = B	
Performance status				.509
0-1	554 (71.4)	363 (71.6)	A = B	
>2	208 (26.8)	137 (27.0)	A = B	
Missing	14 (1.8)	7 (1.4)		
Schooling, y				.113
Until 7	383 (49.4)	263 (51.9)	A=B	
>8	378 (48.7)	224 (44.2)	A=B	
Missing	15 (1.9)	20 (3.9)		
Marital status				.040 <sup>a</sup>
Marriage	691 (90.4)	426 (87.1)	A = B	
Others	73 (9.6)	63 (12.9)	A = B	
Missing	12 (1.5)	18 (3.6)		
Race				.064
White	532 (69.0)	319 (64.7)	A = B	
Others	239 (31.0)	174 (35.3)	A = B	
Missing				
Treatment				<.001 <sup>a</sup>
Surgery	62 (8.0)	62 (12.2)	A<B	
Chemotherapy	225 (29.0)	159 (31.4)	A = B	
Radiotherapy	186 (24.0)	93 (18.3)	A>B	
Surgery/chemo	56 (7.2)	59 (11.6)	A<B	
Chemo/radiotherapy	247 (31.8)	134 (26.4)	A>B	
Death				<.001 <sup>a</sup>
Yes	647 (83.4)	364 (71.8)	A>B	
No	129 (16.6)	143 (28.2)	A<B	

<sup>a</sup>χ<sup>2</sup> test.

mutations, have adenocarcinoma as the main histologic profile, and are nonsmokers as compared with men. Furthermore, men have the highest incidence, prevalence, and mortality rates for this type of

cancer. Recently, however, an important increase in the incidence and mortality rates of lung cancer has been reported in women in several countries,<sup>5-8</sup> including Brazil.<sup>9</sup>

This difference in the behavior of lung cancer in men and women has been attributed to different patterns of tobacco consumption, the principal factor associated with lung cancer<sup>6,10</sup>; however, smoking alone cannot fully explain the incidence, mortality, and survival differences according to gender. Genetic predisposition, hormonal factors, environmental situations, life expectancy, and viral infections and their associations can contribute to such differences between men and women with lung cancer.<sup>4,11-13</sup>

Two recent studies compared overall survival data according to gender in patients with non-small-cell lung cancer in Brazil,<sup>14,15</sup> with conflicting results; thus, this issue needs further exploration. The objective of the present study was to compare the epidemiologic and clinical profile and the overall survival of patients with lung cancer according to gender in a single cancer center in Brazil.

## Patients and Methods

### Study Design

A cohort study was performed in patients who were diagnosed with lung cancer between 2006 and 2014 and treated exclusively at the Brazilian National Cancer Institute (INCA). INCA is a reference institution for treatment of cancer in Brazil, and patients were mostly residents from different cities of the state of Rio de Janeiro. Hospital care is provided free of charge within the Brazil's Unified Public Health System as the vast majority of patients were not insured. The histologic subtypes included in the present study,

according to the International Classification of Diseases for Oncology 3rd Edition, were: squamous cell carcinoma (codes 8050-8076), adenocarcinoma (8140-8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8560, 8570-8572), large cell carcinoma (8012-8031, 8310), and small-cell lung cancer (8041, 8045).

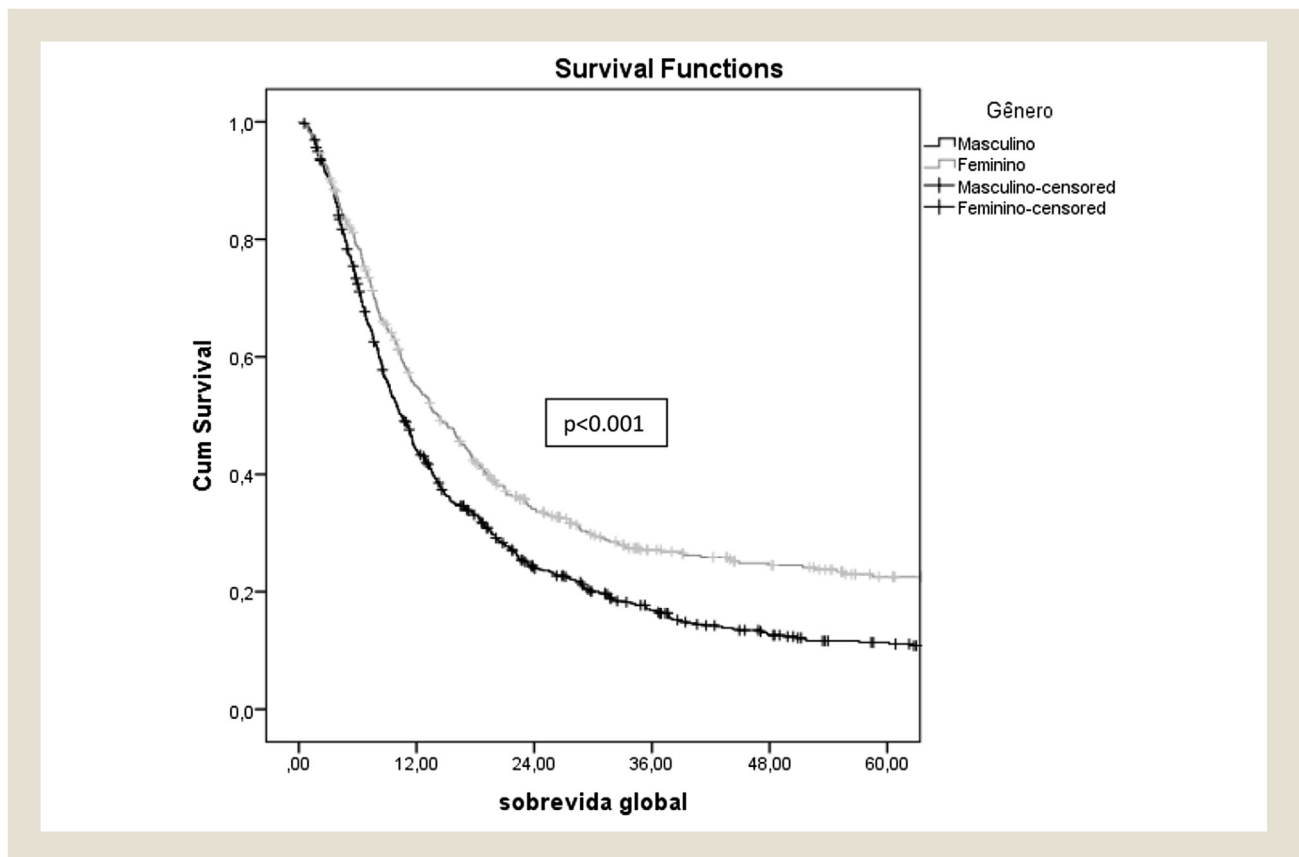
Clinical and sociodemographic data were extracted from medical records. The variables investigated were: age, age group (<50, ≥ 50 but < 70, and ≥ 70 years), smoking status (categorized as never smoked vs. smokers/former smokers), histology, clinical stage (early stage I and II, local III, and advanced IV), Eastern Cooperative Oncology Group performance status, education level (years of formal education: ≤ 8 and > 8), marital status, race (ethnicity), modality of treatment (surgery, chemotherapy, radiotherapy, surgery combined with chemotherapy, and chemotherapy combined with radiotherapy), and survival. Gender was the variable of most interest.

### Statistical Analysis

A descriptive analysis of the variables was compiled using the median ± standard deviation for continuous variables and percentage for categorical variables. The  $\chi^2$  test was used to identify differences between groups.

All patients were followed from diagnosis of LC for a minimum of 24 months or until the occurrence of death, the last contact (in the case of patients lost to follow-up), or the end of the study period

Figure 1 Overall Survival of the Patients with Lung Cancer by Gender



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**Table 2** Survival of the Patients With Lung Cancer

Variable	Total, N	Deaths, N	Deaths, %	Median	95% CI		Log Rank P
Smoking							<b>0.007<sup>b</sup></b>
Yes	449	350	78.0	12.4	10.995	13.843	
No	132	92	69.7	17.7	12.965	22.452	
Ex-smoker	668	538	80.5	10.9	10.02	11.861	
Gender							<b>&lt;0.001<sup>b</sup></b>
Male	776	647	83.4	10.4	9.558	11.337	
Female	507	364	71.8	14.1	12.019	16.302	
Age, y							0.103
<60	545	425	78.0	12.5	11.178	13.988	
≥60	738	586	79.4	11.1	10.003	12.206	
Histology							<b>&lt;0.001<sup>b</sup></b>
Adenocarcinoma	526	432	82.1	10.8	9.818	11.931	
Non adenocarcinoma	586	431	73.5	14.1	11.447	16.61	
Performance status							<b>&lt;0.001<sup>b</sup></b>
0-1	917	674	73.5	15.4	13.818	17.065	
≥2	345	321	93.0	6.5	5.814	7.327	
Race							0.216
White	851	666	78.3	11.6	10.48	12.715	
Others	413	330	79.9	11.6	10.052	13.078	
Marital status							0.929
Married	1117	883	79.1	11.4	10.45	12.351	
Others	136	110	80.9	12.9	10.22	15.538	
Alcohol consumption							0.352
Yes	681	548	80.5	11.5	10.304	12.825	
No	443	336	75.8	11.6	10.141	13.186	
Schooling							<b>0.031<sup>b</sup></b>
≤8 years	646	535	82.8	11.5	10.133	12.865	
>8 years	602	449	74.6	11.6	10.299	12.896	
Stage							
Early (I e II)	220	92	41.8	105.7	<sup>a</sup>	<sup>a</sup>	<b>&lt;0.001<sup>b</sup></b>
Locally advanced (III)	482	402	83.4	11.4	10.041	12.76	
Advanced (IV)	430	383	89.1	8.1	7.455	8.841	
Treatment							
Surgery + chemotherapy	239	97	40.6	105.7	<sup>a</sup>	<sup>a</sup>	<b>&lt;0.001<sup>b</sup></b>
Chemo + radiotherapy	1044	914	87.5	9.4	8.788	1.071	

<sup>a</sup>Not available.

<sup>b</sup>Log-rank test.

(December 31, 2016). The patients were followed-up clinically as well as radiologically according to institutional protocol for a median of 19.6 months. A Kaplan-Meier survival analysis was performed, in addition to the log-rank test, to identify whether the differences between the curves were statistically significant. A Cox multiple regression model using the forward stepwise method was performed, with the aim of estimating the independent factors associated with lung cancer death that could act as confounding or effect-modifying factors in the relationship between gender and survival rate. Variables with a *P*-value < .20 in the univariate

analysis, in addition to clinically significant variables, were selected for the multiple regression model.

All statistical tests were 2-tailed. Analyses were performed with SPSS (Statistical Package for the Social Sciences for Windows, São Paulo, Brazil), version 21.0.

### Ethics

This research was approved by the Research Ethics Committee of the INCA (protocol CAAE: 11556513.2.0000.5274, number 233 245/2013 on March 11, 2013).

## Results

The analysis included 1283 lung cancer cases reported between 2006 and 2014.

Patients were more likely to be men (60.5%), and the mean age of the patients was  $62.72 \pm 9.5$  years, with men being older ( $63.9 \pm 10.80$  years) than women ( $60.92 \pm 11.69$  years) ( $P < .001$ ). In both genders, individuals in the 50- to 69-year-old age group predominated; nevertheless, there was a higher percentage of women in the  $< 50$ -year-old age group, whereas the highest percentage of men was in the  $\geq 70$ -year age group (Table 1).

In women, the frequencies of smokers/former smokers and nonsmokers were 77.5% and 19.7%, respectively. By histology, adenocarcinoma was more common in women than in men, whereas squamous cell carcinoma predominated among the men ( $P < .001$ ). There were no differences in the amount of cases of large cell carcinoma or small-cell lung cancer between the 2 groups. With respect to staging, early stage was more common in women, and locally advanced stage predominated in men ( $P < .001$ ). The 2 groups were similar regarding education level, race, marital status, and performance status. Surgery and surgery in combination with chemotherapy were more common in women, whereas radiotherapy and combination radiotherapy were more common in men ( $P < .001$ ). Men were more likely to die than women ( $P < .001$ ) (Table 1).

The median survival time was 10.5 months (95% confidence interval [CI], 9.55-11.34 months) for men and 14.2 months (95% CI, 12.02-16.30 months) for women, and this difference was statistically significant ( $P < .001$ ) (Figure 1). Estimates of overall survival time of lung cancer are presented in Table 2. The Kaplan-Meier analysis shows better survival in women ( $P < .001$ ).

The Cox regression analysis shows that there was an independent association between gender and survival time following lung cancer diagnosis. Following adjustment for smoking status, histology, performance status, treatment, and stage, women were 16% less likely to die than men (hazard ratio [HR], 0.84; 95% CI, 0.72-0.98;  $P = .03$ ) (Table 3).

## Discussion

The results of the present study show that women were predominantly younger, nonsmokers, with early stage disease, and received surgery or surgery in conjunction with chemotherapy more often; therefore, women had a better survival rate than men.

Many authors have previously shown that women with lung cancer have a better survival rate than their male equivalents.<sup>2-4,16-18</sup> Habitually, women are younger and nonsmokers, with an adenocarcinoma histologic profile and a better response to different treatment modalities<sup>4,11,19-21</sup>; however, it remains unclear why women have a better survival rate. Genetic predisposition, hormonal factors, environmental situations, life expectancy, and viral infections and their associations can contribute to the difference between men and women with lung cancer.<sup>4,11-13</sup> Women have an increased risk of developing lung cancer as a result of smoking, because they have decreased DNA repair capacity, increased smoking-related p53 mutations, differential expression of the X-linked gastrin-releasing peptide receptor, and increased amounts of CYP1A1 in response to smoking.<sup>19</sup> Different target gene mutations,

ALK, EGFR, and K-RAS, have been identified most frequently in women.<sup>11,19</sup> Hormonal factors intrinsic to women and hormonal therapy have been reported to be associated with a better prognosis or survival in patients with lung cancer.<sup>4,13,19</sup> Human papilloma virus is often recognized as a leading cause of cervical cancer, and a review has shown an increased incidence of human papilloma virus in lung tumors.<sup>4</sup> Taken together, these data suggest that lung cancer in women would have a different natural history.<sup>16</sup>

Two Brazilian population studies have determined that the most frequent histologic subtype of lung cancer is adenocarcinoma in both genders<sup>5</sup>; however, there has been an increase in incidence and mortality rates, especially in women.<sup>9</sup> Women with adenocarcinoma have a better response to, and survival following, treatment with novel target drugs<sup>22</sup> or platinum-based chemotherapy.<sup>23</sup> Women are most frequently nonsmokers. Nonsmokers who have more ALK or EGFR mutations also have a better survival rate, because they have a better response to novel target drugs.<sup>22,24</sup>

Survival rates in patients with lung cancer consistently decrease as staging increases.<sup>25</sup> Patients with advanced stage lung cancer have worse survival rates than those with early stage. In the present study, male patients had a higher frequency of locally advanced and advanced stage lung cancer, and women were more often treated with curative intention by surgery or surgery in conjunction with chemotherapy. However, Cox regression analysis adjusted for staging, treatment, and other important factors determined that the risk of death was higher in men than in women ( $P = .030$ ) in the present study. A recent Brazilian retrospective cohort study evaluating the role of age and gender in prognosis showed no difference in survival between the genders.<sup>15</sup> Another Brazilian study evaluating survival rates and risk factors in patients with lung cancer treated in private health care showed that survival rates were higher in female patients, who had a better performance status, no weight loss, and no history of smoking in all cases. When data in only the palliative treatment group were evaluated, survival rates were higher in patients without weight loss or history of smoking and with an adenocarcinoma histologic profile. Age, gender, staging, and performance status were not identified as prognostic factors<sup>14</sup>; however, these 2 Brazilian studies did not perform multivariate analysis adjusted for potential confounders. In general, most patients seek

**Table 3** Cox Regression Analysis for Risk of Death in Women With Lung Cancer

Women Patients	HR	95% CI	P Value
Univariate analysis			
Yes	0.73	0.64-0.83	<.001
No	1.0		
Adjusted analysis <sup>a</sup>			
Yes	0.84	0.72-0.98	.030
No	1.0		

Abbreviations: CI = Confidence interval; HR = hazard ratio

<sup>a</sup>Adjusted by smoking, histology, performance status, treatment, and stage.

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care when they notice signs and symptoms suspicious of lung cancer. The INCA, which is the auxiliary body of the Ministry of Health in the development and coordination of actions for prevention and control of cancer in the country, does not recommend screening for lung cancer.

Women with cancer have higher survival as compared with their male equivalents. Studies in the United States,<sup>26</sup> Canada,<sup>27</sup> and Europe<sup>28</sup> have shown better survival in women than in men according to data of different types of cancer. One study determined a better advantage in women than in men in 13 of the 18 cancer studies, with a 13% lower risk of death.<sup>27</sup> When adjusted for staging, another study showed that female patients have a lower risk of mortality than men in all cancer types combined, especially lung, stomach, and head and neck cancers.<sup>28</sup> Many factors have been postulated to explain this issue; male patients with cancer have more comorbidities than women at the time of cancer diagnosis<sup>26</sup>; compared with men, female patients engage earlier and more frequently in health assistance, for instance, screening programs<sup>26,27</sup>; and differences in incidence by subsite or/and histology for individual cancers can also explain survival differences between genders.<sup>27</sup>

In the healthy population in developed countries, women outlive men by an average of 7 years.<sup>29,30</sup> In Brazil, life expectancy is also higher in women; having been calculated to be approximately 79 years in women, and approximately 72 years in men in 2016.<sup>31</sup> Many factors could explain this phenomenon; the male population has higher mortality by external causes, especially in the younger adult period; men have more behaviors such as smoking and drinking alcohol; mortality in the female population is decreased during the fertile period; women often and earlier in disease visit the doctor's office or other health assistance such as screening.<sup>31</sup> Moreover, biological processes regulated by sex steroids, androgens, and estrogens could affect aging and lifespan. Women can have more malleability in dietary restriction situations and altered activity of nutrient-sensing pathways in favor of a better life expectancy.<sup>29</sup>

There are certain limitations associated with the present study. First, the data source was from a retrospective cohort in a single public cancer center. Second, overall survival was used as an outcome rather than cancer-specific survival, because the cause of death derived from the registry in the hospital records may be misclassified. Finally, it was not possible to evaluate comorbidities, health-related quality of life, or biological markers that are important predictors of survival. Conversely, the strengths of our study include the large population size and the long period of follow-up.

We conclude that women with lung cancer had higher overall survival than their male equivalents in a single cancer center, even after the analysis was adjusted for smoking status, age, histology, performance status, body mass index, education level, treatment, and stage.

## Clinical Practice Points

- The difference in the behavior of lung cancer in men and women has been attributed to different patterns of tobacco consumption, the principal factor associated with lung cancer. However, there

has been controversy as to whether there is a difference in survival rate according to gender in Brazil.

- This study showed that the overall survival in women with lung cancer is higher than men.
- Women with lung cancer were diagnosed younger, with adenocarcinoma histology, at early stage, and received more surgery or surgery with other treatment modalities than men.
- This information can help oncologists to choose the best decision to treat based on gender; moreover, it can help government to define special health care for women to prevent smoking, to quit smoking, and to treat women patients with lung cancer whose benefits could be better.

## Disclosure

The authors have stated that they have no conflicts of interest.

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