Epidemiological changes in the histological subtypes of 35,018 non-small-cell lung cancer cases in Brazil

Guilherme Costa a, Luiz Claudio Santos Thuler b,∗, Carlos Gil Ferreira b,c

a Department of Oncology, Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Pernambuco, Brazil
b Clinical Research Division, Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil
c National Clinical Cancer Research Network (RNPPC), Brazilian Ministry of Health, Brazil

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A B S T R A C T
Objectives: Regarding the fatality rates stemming from various existing forms of cancers worldwide, lung cancer (LC) is ranked as the main cause of death amongst those who suffer from cancer. Although the epidemiological, clinical, and histological profile of patients with this type of cancer is largely unknown, Brazil has made tremendous efforts to generate data for supporting healthcare policies concerning lung cancer. Taking these factors into account, this study aims to analyse the epidemiological, clinical, and histological profiles of patients with non-small-cell lung cancer (NSCLC) in Brazil.

Material and methods: For this study, a cross-sectional epidemiological study was conducted to nationally analyse patient’s data within the cancer hospital registries found in the National Cancer Institute (INCA) and the São Paulo Cancer Foundation (FOSP) between 2000 and 2011.

Results: A total of 35,018 patients diagnosed with NSCLC in Brazil between 2000 and 2011 were analysed. The analysis demonstrated the occurrence of an epidemiological shift, related to the most prevalent histological type of NSCLC in the study population from 2003. The shift resulted in a higher percentage of adenocarcinoma (43.3%) over squamous cell carcinoma (36.5%). Additionally, there was a significant increase in both the number of cases of LC in women and in the rates of patients diagnosed with metastatic disease.

Conclusion: The use of filtered cigarettes since the 60’s and the increase in the number of LC cases in women, were one of the causes for the switch in the histological profile of NSCLC in Brazil. Consequently, adenocarcinoma is now the predominant type of cancer detected. Late diagnosis is a hallmark sign.

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1. Introduction

When considering the main causes of death among cancer patients worldwide, lung cancer is the leading cause of cancer-related mortality: with an estimated 1.82 million individuals dying annually from this malignant neoplasm [1]. In the United States alone, it is estimated that approximately 221,200 patients were diagnosed with LC in 2015 [2]. In South America, the lowest incidence rates adjusted per age were recorded in Cuenca, Ecuador; constituting 2.2/100,000 for women and 5.0/100,000 for men. The highest incidence rate recorded within the South American context was in Antofagasta, Chile; constituting 19.4/100,000 for women and 55.9/100,000 for men [3]. In Brazil, LC is the second most common type of cancer in males; with 17,330 new estimated cases found in 2016. Moreover, lung cancer is the fourth most common type of cancer found in females; with 10,890 new cases reported within that same year. This form of cancer is responsible for the greatest number of deaths caused by cancer in the country; with 23,501 of them occurring in 2012 [3]. In terms of treatment, cancer treatment is provided free of cost throughout the whole country by the National Health System: the Sistema Único de Saúde (SUS); whilst, some 25% of the population have private health insurance, even if facilities throughout the country are distributed disproportionately.

Consequently, the high LC incidence rates worldwide, is due to tobacco use and its derivatives. A possible explanation for the changes in the number of lung cancer cases by histology could be correlated to changes in smoking habits, the use of filtered cigarettes, a reduction in the number of smokers, and gender differences. In Brazil, a reduction has been noted in the prevalence of smoking. Nevertheless, 16% of the Brazilian adult population

∗ Corresponding author at: Brazilian National Cancer Institute—INCA, Rua André Cavalcante, 37/2° andar—Centro, 20231-050—Rio de Janeiro—RJ—Brazil.
E-mail addresses: lsthuler@inca.gov.br, lsthuler@gmail.com (L.C.S. Thuler).

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continue to smoke, in spite of governmental agencies’ efforts, through policies to restrict cigarette advertisement and sales [2,4].

Respectively, LC has been divided into two main groups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC); with the latter being subdivided into adenocarcinoma (ACA), squamous cell carcinoma (SCC), and undifferentiated/large cell carcinoma (LCC). Changes in histological patterns in smokers and males from predominantly SCC to predominantly ACA, were reported in several countries [5,6,8,9–11]. The histological type plays a role in defining the appropriate type of systemic treatment that should be implemented with the largest therapeutic arsenal being available for ACA; mainly in terms of targeted chemotherapy [7].

However, there is still a considerable lack of highly detailed epidemiological data on LC in developing countries. In Brazil, measures within the Ministry of Health, led by the Brazilian Network for Clinical Cancer Research, were taken to generate data to support healthcare policies regarding LC [12]. Within this context, the objective of the present study was to characterise the epidemiological, clinical, and histological profile of patients with NSCLC in Brazil between 2000 and 2011.

2. Materials and methods

A cross-sectional retrospective study was conducted on LC patients using data from the cancer hospital registries (CHR) found in the National Cancer Institute (INCA) and the São Paulo Cancer Foundation (FOSP) between 2000 and 2011, encompassing a total of 258 hospitals in the 25 states of Brazil and the Federal District (Brasília). In conjunction, these registries cover about 90% of the Brazilian public health system; where they have been progressively implemented through the entire country overtime. However, it is still difficult to estimate exactly how complete the case ascertainment is. By using histologic codes from the International Classification of Diseases for Oncology (ICD-O-3) [13], the following primary incident cancers of the bronchus and lung (ICD 162.0–162.9) were considered for the present analysis: ACA (8140, 8250, 8251, 8252, 8253, 8254, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550), SCC (8050, 8070, 8071, 8072, 8073, 8074, 8075), Undifferentiated/LCC (8012, 8020, 8021, 8022, 8031, 8032) and small cell carcinomas (8002, 8041, 8042, 8043, 8044, 8045). From a total of 58954 cases of lung cancer registered in the period, 7512 carcinoma not otherwise specified (NOS), 5385 small cell carcinomas (8002, 8041, 8042, 8043, 8044, 8045), and 11039 cases with other histology types were excluded from this study. The percentage of carcinomas NOS remained practically unchanged throughout the period (12.9% in 2000 to 11.3% in 2012). All cases included in the study were microscopically verified.

In this study, we analysed the following variables: age groups (18–49 years, 50–69 years or ≥70 years), sex (male versus female), smoking (never smokers versus smokers/former smokers), schooling (0–7 years versus ≥8 years of schooling), and place of residence (considering the differences across the North, Northeast, Midwest, Southeast, and the Southern regions of Brazil), year of diagnosis (2000–2011), TNM staging according to the 5th (from 2000 to 2005) and 6th (from 2006 to 2011) editions (early disease – stages IA, IB, IIA and IIB; locally advanced disease – stages IIIA and IIIB; or metastatic disease – stage IV), the first line of treatment implemented (surgery, radiotherapy, chemotherapy or best support care), response to the first treatment, and death by the end of the initial treatment (death or survival).

The therapeutic response at the end of the first course of treatment was classified as either an inadequate response (progressive disease or death) or an adequate response (partial remission, stable disease, or complete response).

SPSS (Statistical Package for the Social Sciences) software, version 21.0, was used for the data analysis. A descriptive analysis was performed using central tendency and dispersion measures for the continuous variables and to determine the frequency distribution of the categorical variables. The chi-square test was used to compare the frequency of the categorical variables. The coefficient of determination was calculated to identify annual variations. Differences were considered to be statistically significant when the p-values were <0.05.
3. Results

The study included 35018 patients with NSCLC, who were treated in 258 medical institutions. The number of cases per year, ranged between 1301 and 3989 (median = 2924). Almost a third of the cases (29.1%) were of unspecified part of bronchus or lung (n = 10,204), ranging from 21.8% in 2007 to 45.9% in 2011. The average age of the patients was 62.9 years (SD 11.0 years; range 18–103 years). Most of the individuals included in the study were male (male/female ratio of 2 to 1). The majority of the patients lived in the South or Southeast of the country (83.9%); were smokers/former smokers (77.9%); were classified as having an advanced stage of lung cancer or metastatic disease (54.9%); and underwent chemotherapy (31.3%) as the main method of oncological treatment (Table 1).

The most common histological type of NSCLC found was ACA (50.0%), followed by SCC (42.1%). Still, a change was found in the distribution of the subtypes of NSCLC, with ACA taking over SCC as the most common histological type from 2003. Indeed, the ACA case proportions continues to rise in comparison with SCC; which is actually decreasing. There was a slight reduction in the number of cases of undifferentiated large-cell carcinoma during the same period (Fig. 1A). In the male population, there was a progressive reduction in the prevalence of NSCLC cancer between 2000 and 2011, with a slight but persistent increase in the number of cases of ACA compared with SCC detected from 2008 (Fig. 1B). In the female population, there was a progressive increase in the prevalence of NSCLC during the period of the study; however, there was no change in the histological pattern, with ACA remaining the most prevalent histological type and increasing steadily throughout the study period (Fig. 1C). Contrary to the case of smokers/former smokers, a similar distribution of ACA and SCC was observed in recent years (Fig. 1D).

When current and former smokers were analysed separately from the never-smokers, there was a greater prevalence of males in all histological subtypes. Yet, in the case of never-smokers, there was a greater prevalence of women with ACA (Table 2). In compari-
son to the male counterparts, there was a significant increase in the frequency of NSCLC in women throughout the study period (from 28.2% to 37.4%; chi-square for trend p < 0.001) (Fig. 2).

Regarding disease staging, there was a 20.5 lack of patient data, due to incomplete records; thus, requiring the analysis to be conducted using data from 27,823 patients. Stages III and IV accounted for 85.2% of the valid cases (39.0% and 46.3%, respectively). When the metastatic disease occurrence was analysed annually, a significant increase was found over the study period, resulting in a relative percent change of 17% (Fig. 3).

Analysis of the first line of treatment indicated that chemotherapy was the main type of treatment implemented (56.3%), followed by surgery (18.8%), alone or associated with another form of therapy. In 11.4% of the cases, no treatment was given. Analysis of deaths at the end of the first line treatment, indicated that 27.3% of the patients had died.

4. Discussion

Analysis of 35018 cases of NSCLC treated at oncology centers throughout Brazil between 2000 and 2011, showed changes in the epidemiology of the disease insofar as concerning its histological profile, with ACA becoming the most common histological type starting in 2003. In addition, a persistent increase was found in the percentage of cases occurring in women during the study period and an increase in the percentage of cases diagnosed at advanced stages of the disease.

In retrospect, this change in histology patterns in which ACA rather than SCC became the most common histological type of LC, had already been reported in recent decades in Europe [8], the US [5], France [8], Tunisia [10], Canada [6], and Japan [11]. This worldwide trend towards a change in the histological pattern of the disease, has been attributed to the composition of cigarettes and the use of filters; particularly since the 1960s [14]. Cigarette filters only block the larger particles of tar; hence, allowing the smaller particles to pass through the filter. Furthermore, smokers adapt themselves by smoking more intensively, taking deeper puffs to achieve a greater absorption of nicotine, thus favouring the penetration and deposit of carcinogens in the peripheral lung; a more common site of ACA. Additionally, the chemical composition of cigarettes with a lower tar and nicotine content contains a greater concentration of nitrosamines; an important carcinogens for peripheral lung tumours rather than the polycyclic aromatic hydrocarbons that cause SCC [15,16]. In the case of former smokers who stopped smoking for more than 10 years and developed NSCLC, ACA was the most common histological type [17]. This has been related to a greater exposure to carcinogens, due to deeper inhalation and less excretion in the peripheral lung. Also, ACA is the most common histological type in never-smokers [18].

Recent increases in the number of cases of lung ACA can also be reflected by the development of technological advances and the implementation of a new classification system for the histological LC subtypes [19,20]. The incorporation of immunohistochemical techniques such as TTF-1 as a marker of ACA and p63 and p40 for SCCs has contributed towards the reduction of the rates of undifferentiated or unclassified tumours in clinical practice and in clinical studies [19–21]. Moreover, advances in DNA sequencing techniques have allowed ACA subclassification and have led to progress in individualised or personalised cancer treatment and the development of new therapeutic options [20].

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Table 2

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Sex</th>
<th>Adenocarcinoma n (%)</th>
<th>Squamous cell carcinoma n (%)</th>
<th>Undifferentiated / large cell carcinoma n (%)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Never-smoker</td>
<td>Male</td>
<td>698 (40.7)</td>
<td>533 (60.3)</td>
<td>89 (56.7)</td>
<td>0.001</td>
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<tr>
<td></td>
<td>Female</td>
<td>1019 (59.3)</td>
<td>351 (39.7)</td>
<td>68 (43.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1717 (100)</td>
<td>884 (100)</td>
<td>157 (100)</td>
<td></td>
</tr>
<tr>
<td>Smoker/former smoker</td>
<td>Male</td>
<td>3343 (67.5)</td>
<td>4239 (77.8)</td>
<td>606 (73.0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1607 (32.5)</td>
<td>1213 (22.2)</td>
<td>224 (27.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4950 (100)</td>
<td>5452 (100)</td>
<td>830 (100)</td>
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<tr>
<td>Total</td>
<td>Male</td>
<td>4041 (60.6)</td>
<td>4772 (75.3)</td>
<td>695 (70.4)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2626 (39.4)</td>
<td>1564 (24.7)</td>
<td>292 (29.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>6667 (100)</td>
<td>6336 (100)</td>
<td>987 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Gender distribution of patients with non-small-cell lung cancer per year of diagnosis. Brazil, 2000–2011.
In terms of LC, smoking is the main cause of this disease; because a direct correlation can be drawn between the number of cigarettes smoked and the amount of time in which an individual smokes over a lifetime. In recent decades, smoking has decreased progressively in populations worldwide and also in Brazil [24,18]. However, we can find that LC has always been more prevalent in males. Consequently, the current male/female ratio is steadily decreasing because the smoking epidemic that first involved predominantly men later also reached women, with a persistent increase in the number of cases of LC in women, most of whom began smoking after the introduction of filters and low-tar, low-nicotine cigarettes [21–23]. Concerning women, ACA is the most common histological type; both in smokers and in non-smokers [18,22]. Recently, three large population-based studies; two in the United States [20,21] and one involving eleven countries situated in three different continents [23], reported a persistent increase in the number of cases of LC in women, an increase in the number of cases of ACA in both sexes, and an increase in SCC in women alone. Those authors emphasised the need to introduce new, broader-reaching policies and therapy aimed at preventing smoking within the general population [23] and in LC patients as an integral part of their treatment [24,25].

The last version of Cancer Incidence in Five Continents (CISC) included 6 Brazilian cancer Population Based Cancer Registries (PBCR): Aracaju, Belo Horizonte, Cuiabá, Fortaleza, Goiânia and São Paulo. According to this publication, from 2003 to 2007, 12278 new lung cancers cases were diagnosed in these 6 cities [26]. Although data from the present study comes from CHR, in order to compare them with the incidence data from CISC, we performed a sub-analysis of the cases from these 6 cities (Supplementary Table 1). Of 35018 cases included in the present study, 5548 (15.8%) were recorded by these CHR. The percentage of cases in males were very similar in both data bases (64.3% in CISC versus 61.7% in CHR). Moreover, the distribution of cases according to the histological type, has shown that SCC was predominant in both registries; being 3 times more frequent in men than in women (4.8 versus 1.5 and 74.7% versus 25.3%, respectively in CISC and the CHR). In contrast, the presence of ACA was 1.9 and 1.4 times more frequent in men than in women, respectively in CISC and the CHR.

The analysis of LC highlights important differences between males and females. Women are more likely than men to develop cancer, even after controlling for smoking in the analysis [22,27]. Women are more likely than men to survive LC at all stages of the disease. Indeed, being a male is a negative prognostic factor for patients with advanced or metastatic stages of the disease [22]. DNA repair capacities was found to be lower in female lung cancer patients [27]. They are also at a greater risk of developing secondary tumours to primary cancer of the lungs, head and neck, oesophagus, kidneys, and bladder compared to men [27]. Variations in the CYP1A1 and GSTM1 genotypes; enzymes associated with the metabolism of carcinogens from cigarettes, are more common in women [22]. In addition, the TP53, HER-2 and KRAS mutations, which are associated with tobacco use, are more common in women, as is the EGFR mutation in non-smokers [22,27]. Therefore, smoking prevention and targeted molecular therapy may have different outcomes in women than in men. Alternative hypothesis for these trends could include second-hand smoking in spouses of smokers and regional or occupational exposure, as well as air pollution.

In the period analysed, a progressive increase occurred in the percentage of cases of advanced stages of LC. A population-based study conducted in the United States between 1998 and 2006 with more than 877,000 cases of LC also reported an increase in the percentage of cases of advanced stages of the disease; which increased from 35.5% to 38.8% over the study period. The increase was attributed to the development and implementation of new staging techniques [28] and to an increase in the number of institutions offering cancer treatment. Similarly, in Brazil, the Project Expande, from the Ministry of Health joined the National Cancer Institute – INCA, has been creating 24 new Oncology institutions since 2000 to increase treatment and diagnosis centers in Brazil [4]. However, the absence of an effective routine LC screening program [29] and the difficulties encountered by the population in accessing healthcare services proves that diagnosing the disease during advanced stages continues to persist.

The majority of the patients diagnosed with LC worldwide reside in developing countries such as Brazil [1]. Important technological advances in imaging, radiotherapy, minimally invasive surgery, less toxic chemotherapy and molecular analysis have been incorporated as a routine, with a significant increase in cancer treatment costs; both in public and private healthcare sectors. Biomarkers are being validated and new molecular tests are incorporated with the objective of improving and defining optimal therapy in a personalised manner, and these advances are already available for patients with lung ACA. This may represent the future for other histological subtypes such as SCC. Therefore, in addition to clinical epidemiological data, future molecular epidemiological data on LC
Conflict of interest

The authors declare no conflict of interest regarding this subject.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.lungcan.2016.04.019.

References


