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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI :10.21474/IJAR01/20054

DOI URL : <http://dx.doi.org/10.21474/IJAR01/20054>



RESEARCH ARTICLE

PRIMARY BRONCHOGENIC CANCER IN NON-SMOKERS: A CASE SERIES

R. Amiali¹, M. Karhate¹, L. Senhaji¹, M. Serraj¹, M. Elbiaze¹, B. Alami², M. Smahi³, MC. Benjelloun¹ and B. Amara¹

1. Department of Pneumology, University Hospital Center Hassan II, Fez, Morocco.
2. Department of Radiology, University Hospital Center Hassan II, Fez, Morocco.
3. Department of Thoracic surgery, University Hospital Center Hassan II, Fez, Morocco.

Manuscript Info

Manuscript History

Received: 13 October 2024

Final Accepted: 16 November 2024

Published: December 2024

Key words:-

Primary, Bronchopulmonary, Cancer, Non-Smokers

Abstract

Primary bronchopulmonary cancer (PBPC) in non-smokers, particularly among women, is on the rise. This study aims to characterize lung cancer in non-smokers in the Fès-Meknès region, where traditional wood-burning practices are common. A retrospective analysis of 561 bronchogenic cancer cases from 2020 to 2024 showed that 13.9% of patients were non-smokers, predominantly women, with nearly half from rural areas. Environmental exposure to wood smoke was noted in 42.3% of non-smokers. Adenocarcinoma was the most common histological type (74.35%), followed by squamous cell carcinoma. Most patients were diagnosed with metastatic disease and received palliative care. This highlights the need for multicenter studies to improve personalized management strategies and outcomes for patients with non-small cell lung cancer (NSCLC).

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Introduction:-

Globally, primary bronchopulmonary cancer (PBPC) remains the leading cause of cancer diagnoses in men and the second leading cause of cancer-related deaths in women. In addition to the role of smoking, several other factors are implicated, including genetic, environmental, and hormonal influences.... (1).

In non-smokers, adenocarcinoma is the predominant histological type of lung cancer. Despite advancements in treatment and management, lung cancer continues to be a significant public health concern. (2).

Objective: -

The aim of this article is to identify the risk factors for primary bronchopulmonary cancer in non-smoking patients, along with the epidemiological and histological characteristics, treatment methods, and survival outcomes in the Fez-Meknes region. This study covers a four-year period from 2020 to 2024.

Demographics of the Fez-Meknes Region

The Fez-Meknes region is located in the Middle Atlas Mountains and covers an area of 40,075 km². It comprises two prefectures, Fez and Meknes, as well as seven provinces: Taounate, Taza, Sefrou, El Hajeb, Boulemane, Moulay Yacoub, and Ifrane). (Figure 1)

Corresponding Author:-R. Amiali

Address:-Department of Pneumology, University Hospital Center Hassan II, Fez, Morocco.



Figure 1:- Prefectures and provinces of the Few-Meknes region (3).

The region's climate ranges from Mediterranean to continental in winter and hot in summer, particularly in the province of Boulemane. The climate in the highlands of the Rif and Pre-Rif is mild in summer, while in winter it is colder, with frequent and severe frosts. The population relies on traditional wood heating and the use of wood ovens... (3)

Materials and Methods:-

Study design

This is a four-year retrospective study conducted from July 1, 2020, to June 30, 2024, focusing on patients with primary bronchogenic cancer. Data were collected in the Pneumology Department of Hassan II University Hospital in Fez.

Study population

Inclusion criteria

- Patients included in the study were individuals aged 18 and older, of all genders, diagnosed with primary bronchopulmonary cancer. They were recruited from the Pneumology Department of Hassan II University Hospital in Fez over the four-year study period.
- All cases were reviewed in a multidisciplinary consultation meeting at the hospital..

Exclusion criteria

- All incomplete files.

Data collection

Data were collected from patients' computerized medical records. The analysis of clinical records focused on epidemiological data, including age, sex, and the date of symptom onset, as well as patients' medical history. Clinical, radiological, and histological data were also evaluated, along with the treatments received and the patient's evolution after a four-month follow-up period.

Statistical analysis

Data entry was conducted using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS Statistics, Armonk, NY, USA) at the epidemiology laboratory of the Faculty of Medicine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University.

Ethical considerations

All patients participating in the study provided informed consent, and data were collected anonymously. Confidentiality was maintained throughout the data collection and processing stages.

Results:-

In this study, we analyzed data from 561 cases of bronchogenic carcinoma, which included 78 non-smokers and 483 smokers. Non-smokers accounted for 13.9% (78 out of 561 cases) of the sample, with a predominance of females (17 males and 61 females), yielding a male-to-female ratio of 0.28. In contrast, the smoker cohort exhibited a male predominance (10 females vs. 473 males), resulting in a male-to-female ratio of 47.3, demonstrating a statistically significant difference (Pearson chi-square p-value of 0.0001). The mean age of non-smoking patients was 62.32 ± 13.82 years, with a range from 30 to 91 years, compared to 63.39 ± 10.064 years for smokers ($P = 0.326$).

Among non-smokers, nearly half (38 patients, or 48.72%) were from rural backgrounds. Environmental exposure to wood smoke was identified in 33 patients, accounting for 42.3%, and one case exhibited clear asbestos exposure.

In non-smoking patients, the circumstances of diagnosis were predominantly characterized by cough accompanied by dyspnea in 36 patients (46.15%). Isolated cough was observed in 6 patients (7.69%), while hemoptysis was reported in 21 patients (26.92%). Dysphonia occurred in 3 patients (3.84%), and pleuritic chest pain was noted in 20 patients (25.64%). Additionally, extra-respiratory signs included neurological manifestations in 8 patients (10.26%), and 7 patients (8.97%) were asymptomatic with respect to respiratory symptoms.

Clinical examination of the thorax was abnormal in 42 patients (53.84% of the study population). Liquid effusion syndrome was found in 39 patients (50%), followed by condensation syndrome in 21 patients (26.92%), and superior vena cava syndrome in 4 patients (5.13%).

All patients underwent thoracic imaging, including extension work-up and biopsy with subsequent histopathological examination. The most prevalent histological type was adenocarcinoma, identified in 280 cases (49.91%), with 58 patients (74.35%) being non-smokers compared to 222 (45.96%) who were smokers. This was followed by squamous cell carcinoma, which accounted for 158 cases (28.16%), with 11 non-smokers (14.29%) versus 147 smokers (30.43%).

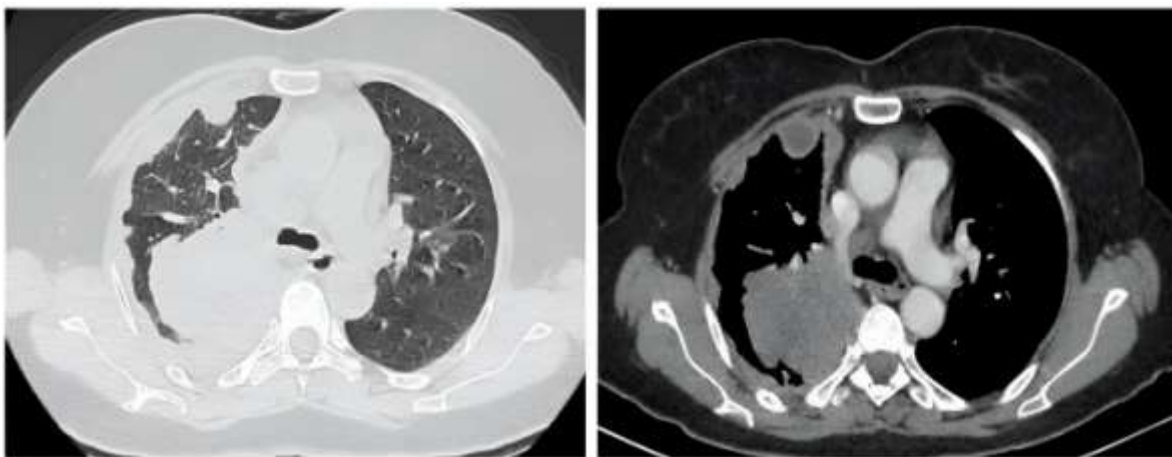


Figure 2 (AB):- Axial-slice CT scan, parenchymal and mediastinal window showing right upper lobar pulmonary lesional process, (green arrow).

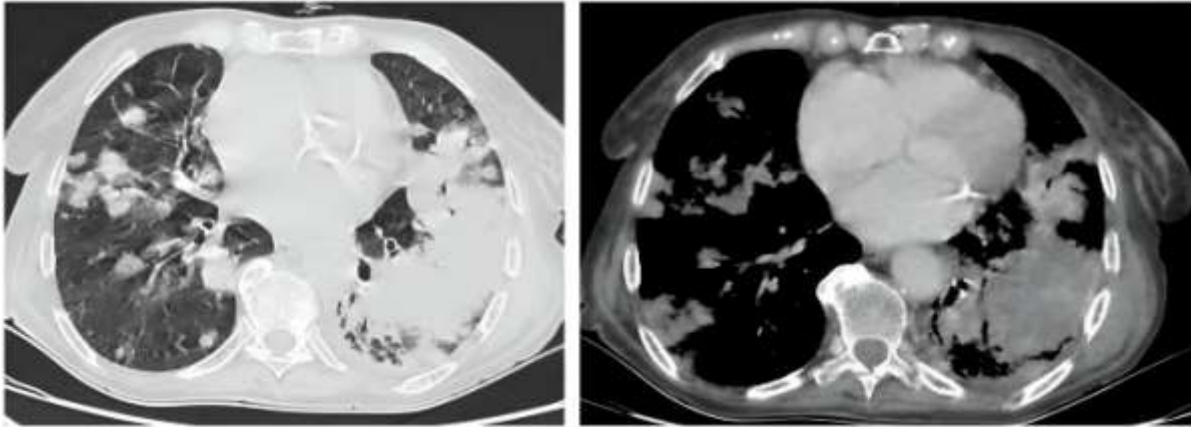


Figure 3 (AB):- CT scan in axial sections, parenchymal and mediastinal window showing left lower lobar pulmonary lesion with multiple bilateral confluent intra-parenchymal nodules (blue arrow).

Out of the total, 470 patients (83.78%) were diagnosed with metastatic disease: 31 non-smokers (39.74%) compared to 357 smokers (77.64%). Conversely, the absence of metastases was more commonly observed in non-smokers, with 47 patients (60.26%) compared to 113 smokers (23.4%). The data indicated that smokers were more likely to develop metastases ($P = 0.004$).

Mutational profiling was requested in all our patients, and was positive in 15 cases (19.23%), negative in 5 (6.41%) and not requested in 61 (78.21%).

In non-smoking patients, treatment options included surgery for 3 patients, radio-chemotherapy for 12 patients, and chemotherapy for 53 cases. Complete remission was achieved in 2 patients, while partial remission occurred in 9 patients (11.53% of cases). Radiological stability was maintained in 6 patients (7% of cases), whereas disease progression was observed in 20 patients (25.64%). Additionally, there were 22 deaths (28.20%) and 19 patients who were lost to follow-up.

Median survival was 3.260 years. Overall survival was lower in the non-smoking group (median overall survival: 3.222 years; 95% CI: 2.829 - 3.615) than in the smoking group (median overall survival: 3.260 years; 95% CI: 3.086- 3.434).

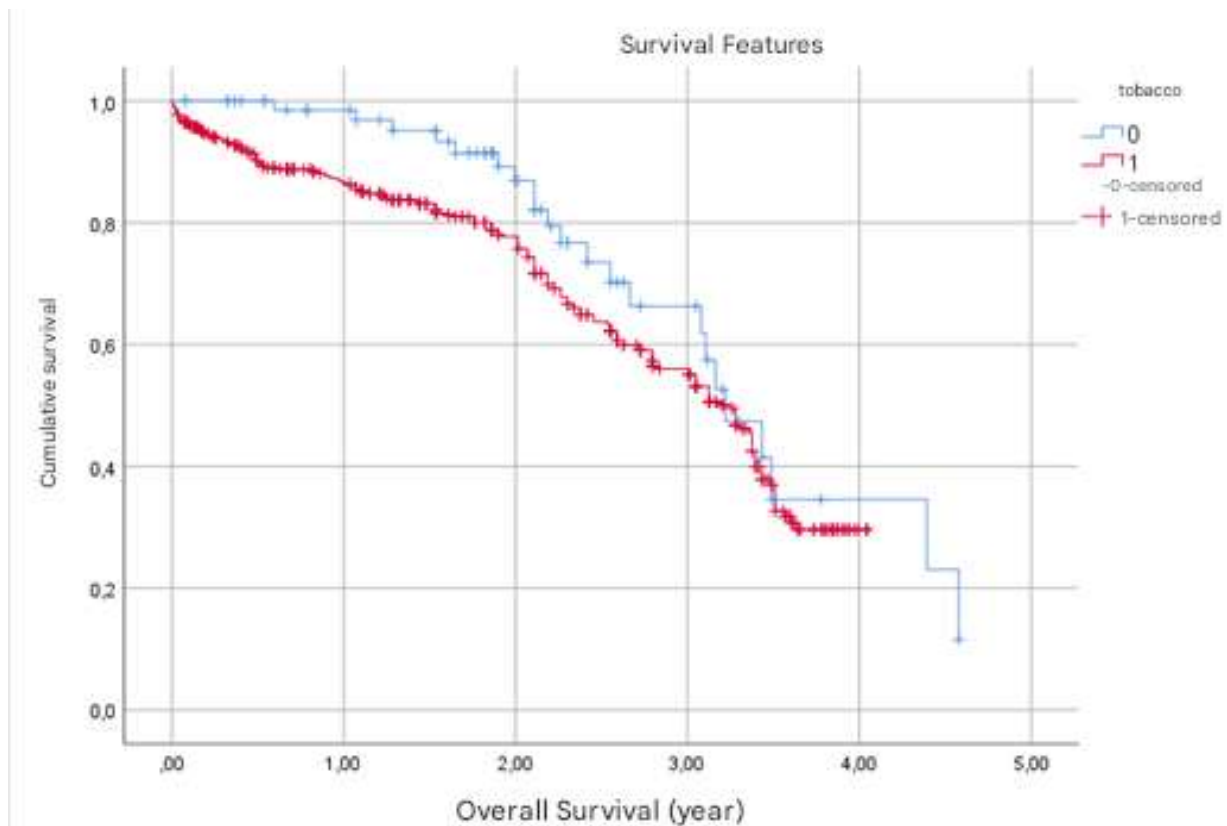


Figure 5:- Survival according to smoking status in lung cancer patients, in blue: survival in non-smokers and in red: survival in smokers.

Summary tables

Table 1:- General characteristics of lung cancer in our patients (n=561 patients: 78 non-smokers and 483 smokers).

Non-Smokers	Smokers	P
Sex	Male	Female
(N (%))	17 (21.79)	61 (78.21)
Average Age	62.44 ± 9.672	63.39 ± 10.064
Median Age	63	64
Age by Group		
< 50 years (N (%))	16 (20.51)	37 (7.66)
50 - 59 years (N (%))	13 (16.67)	98 (20.29)
60 - 69 years (N (%))	24 (30.77)	240 (49.69)
>= 70 years (N (%))	25 (32.05)	108 (22.36)
Origin		
Rural (N (%))	40 (51.28)	238 (49.28)
Urban	38 (48.72)	245 (50.73)
Smoking Status		
No (N (%))	71 (91.03)	
Active (N (%))		483 (100)
Passive (N (%))	7 (8.97)	
Exposure to Wood Smoke		
No (N (%))	45 (57.69)	289 (59.83)
Yes (N (%))	33 (42.30)	194 (40.17)
Histological Types		
Small Cell Carcinoma (N (%))	9 (11.53)	39 (8.07)

Adenocarcinoma (N (%))	58 (74.35)	222 (45.96)
Squamous Cell Carcinoma (N (%))	11 (14.29)	147 (30.43)
Other* (N (%))		75 (15.53)
Stages		
Localized (N (%))	31 (39.74)	113 (23.39)
Diffuse (N (%))	47 (60.26)	357 (73.91)

Table 2:- Therapeutic Modalities and progression of lung cancer in non-smokers.

Therapeutic Modalities	(N (%))
Surgery	3 (3.85)
Chemotherapy	63 (80.77)
Chemoradiotherapy	12 (15.38)
Evolution	
Complete Remission	2 (3.28)
Partial Remission	9 (11.54)
Radiological Stability	6 (7.69)
Progression	20 (25.64)
Death	22 (28.20)
Lost to Follow-Up	19 (24.36)

Discussion:-

Lung cancer is the leading cause of cancer-related mortality worldwide, affecting both men and women with a higher mortality rate. In 2022, it was responsible for 2.5 million new cases, accounting for 1 in 8 cancer diagnoses globally (12.4% of all cancers), followed by breast cancer in women, which represented 11.6% of cases.

In Morocco, approximately 2,918 new cases of lung cancer were recorded in Casablanca between 2018 and 2021, representing 13.2% of all incident cases. A predominance of males was observed, with lung cancer accounting for 25.8% of all male cancers compared to 3.3% of all female cancers. The crude incidence rates were 27.5 per 100,000 among men and 4.5 per 100,000 among women. Smoking remains the primary risk factor for lung cancer, contributing to approximately 100,000 deaths annually in the United States.

Lung cancer among non-smokers is the seventh leading cause of cancer-related death in both men and women globally. The commonly accepted definition of a "non-smoker" is an individual who has smoked fewer than 100 cigarettes in their lifetime.

The demographic characteristics of lung cancer differ significantly in the non-smoking population; the majority of cases are found in women and tend to present at a younger age. Our analysis revealed a significant correlation between female sex and lung cancer incidence among non-smokers, with the prevalence of lung cancer in this group at 14% (85.91% in women compared to 3.47% in men). This finding suggests that genetic and/or environmental factors, aside from tobacco smoke exposure, may contribute to the development of lung cancer in non-smokers.

Risk Factors

Environmental Exposures

Several environmental exposures are associated with an increased risk of developing lung cancer, influenced by factors such as residential location, occupation, cooking or heating methods, and exposure to secondhand smoke. Women are particularly at heightened risk due to their roles in food preparation. In our cohort, environmental exposure to wood smoke was identified in 33 patients, accounting for 42.3%.

Radon

Areas with high background levels of radon are associated with an increased risk of developing lung cancer.

Suspended Particles

Outdoor suspended particles present a carcinogenic risk to humans, which partially explains the global incidence of lung cancer.

Genetic Susceptibility

Genetic predisposition to lung cancer has been extensively studied, revealing multiple genetic loci and single nucleotide polymorphisms associated with an increased risk. Notably, non-smoking lung cancer patients with somatic mutations in the EGFR gene are more likely to have a family history of lung cancer compared to those with wild-type EGFR tumors.

Other Factors

The consumption of meat and alcohol, along with a low intake of fruits and vegetables, has been suggested as potential risk factors for lung cancer. Additionally, there are well-established links between lung cancer and other pulmonary diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis.

Histology

Adenocarcinoma is predominantly the most common histological type among non-smokers, whereas smoking-related lung cancers are more frequently observed in smokers. Adenocarcinomas typically occur more often in women and individuals of Asian descent. In our study, adenocarcinoma represented 74.35% of cases ($P < 0.001$), aligning with findings in the existing literature. In contrast, squamous cell lung cancer is more commonly central and prevalent among smokers, developing near the epithelial airways and resulting in early symptoms.

Therefore, testing for EGFR gene mutations is systematically recommended for non-smoking patients. However, our results indicate that molecular analysis for EGFR mutations was conducted in only 12% of the patients. This low rate of molecular testing may be attributed to the high cost of these tests, along with the fact that most patients in Eastern Morocco lack the financial means to afford them.

Treatment

Non-smokers with lung cancer do not seem to respond more favorably to standard treatment or exhibit a better prognosis compared to smokers. It is essential to prioritize the development of new treatments for lung cancer patients. Additionally, it is equally important to enhance our understanding of the sequencing of currently available treatments—such as targeted therapies, immunotherapy, and chemotherapy—to mitigate or delay tumor resistance.

Radiation therapy plays a crucial role in the management of advanced lung cancer. While palliative radiation therapy is commonly employed in stage IV non-small cell lung cancer and is effective in controlling symptoms and enhancing survival, significant advancements have been made in systemic therapies. Despite the increasing use of palliative radiation therapy, it has been underrepresented in prior clinical trials. Further studies are needed to evaluate the timing, dosage, and fractionation of radiation therapy in relation to modern systemic therapies, whether administered before, during, or after treatment.

Prognosis

The survival rate for lung cancer remains low, with most reports indicating survival rates below 16%. In our series, there were 22 deaths, representing 28.20% of the cohort. The median survival was 3.26 years, which was lower in the non-smoker group at 3.22 years. This low survival rate is primarily attributed to the late detection of cancer, as most patients are diagnosed when the disease is already at a locally invasive or metastatic stage.

Limitations of the Study

Due to its retrospective nature:

- We encountered missing or incomplete data.
- There were difficulties in establishing causal associations.
- Additionally, the relatively small number of patients may also be a limitation, with approximately 24.36% of cases lost to follow-up.

These limitations must be taken into account when interpreting the results and extrapolating conclusions.

Conclusion:-

Lung cancers in non-smokers (LCNS) predominantly affect women and are primarily classified as adenocarcinomas. The attributable risk from tobacco is significantly lower in women, indicating the involvement of other etiological

factors. This highlights the need for analytical studies, ideally conducted in a multicentric format, to develop more personalized management strategies and enhance the prognosis for patients with LCNS.

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