

Never smokers with lung cancer in Morocco: epidemiology and gender differences

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Article Info

Article history:

Received Sep 9, 2021

Revised Jan 1, 2022

Accepted Jan 29, 2022

Keywords:

Adenocarcinoma

Lung cancer

Never smokers

Tuberculosis

ABSTRACT

Even through smoking is a definite risk factor for lung cancer, it is possible for people who have never smoked to suffer lung cancer. This research aimed to describe the epidemiology of lung cancer in never smokers in Morocco. Also, an assessment of differences between men and women never smokers was performed. The researchers analyzed retrospectively all patients diagnosed with lung cancer between 2014 and 2017. The results showed that of 606 patients, 157 (25.9%) were never smokers. Of these, 79 patients (50.32%) were women. Women were more likely to be younger ($p=0.034$), had adenocarcinoma ($p=0.046$), and being in advanced stage of the disease ($p=0.032$). Men were more exposed to professional carcinogens ($p<0.001$). Tuberculosis was the most frequent previous lung disease in never smokers, but no difference was noted between men and women. Performance status and comorbidities did not vary by gender. Never smokers in Morocco represent a significant proportion of lung cancer. Evident epidemiologic differences are found between men and women never smokers, notably, age, histological type and risk factor exposure.

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1. INTRODUCTION

Lung cancer is the second most diagnosed cancer globally, with approximately 2.2 million cases in 2020. In terms of mortality, lung cancer ranks first, with 1.8 million death recorded in 2020 [1]. In Morocco, according to the Cancer Registry, lung cancer is the most frequent cancer in men and the eighth in women [2], resulting in a serious social and economic burden.

Although lung cancer is strongly related to smoking [3], it has been shown that 10-25% of lung cancer cases are detected in non-smokers [4]. Also, among never smokers, lung cancer is the seventh cause of cancer mortality worldwide [5]. Interestingly, an American study has shown that lung cancer in never smokers is increasing [6]. Possible causes of lung cancer in never smokers included previous lung diseases, secondary exposure to cigarette smoke, radon, and cool indoor use [4], [7], [8].

Several studies have concluded that the characteristics of lung cancer in never smokers are different from those in smokers [9], [10]. These differences are mainly manifested in the histology distribution (increased adenocarcinoma in never smokers) and in response to specific therapies (especially epidermal growth factor receptor inhibitors) [9], [10]. Other studies have found differences even among never smokers between men and women. Indeed, women are more affected and have a higher proportion of adenocarcinoma than men [4], [9]. Regarding the mortality rate, the existing data are contradictory. Some authors have reported differences in mortality between the two sexes [11], while others have found that the mortality rate is the same for women as for men [12].

Despite these results, a recent Spanish study has concluded that the epidemiology of lung cancer in never smokers is not well-developed [13]. This study aimed to describe the epidemiology of lung cancer in never smokers in Morocco. Also, an assessment of differences between men and women never smokers was performed.

2. RESEARCH METHOD

This retrospective study was conducted at Ibn Sina University Hospital Center in Rabat (Capital of Morocco). Patients diagnosed with lung cancer between 2014 and 2017 were included. Patients' files were reviewed to collect the data for this study. Patients for which a patient file was not available or patients with metastatic lung cancer of another organ were excluded. Epidemiological data required for this study were: i) socio-demographic characteristics: age, sex, and occupations; ii) Patient history: presence or not of comorbidities and exposure to risk factors; iii) clinical characteristics: presence or not of respiratory symptoms at presentation, presence or not of other non-respiratory symptoms at presentation (fever, weight loss, anorexia), and performance status; iv) tumor characteristics: diagnostic method, histological subtypes, tumors stage, and metastatic sites.

Comorbidities included one or more of the following diseases: hypertension, heart disease, and diabetes. Exposure to risk factor included previous lung disease, exposure to occupational carcinogens, personal history of cancer, and family history of cancer. Occupational exposure to carcinogenesis was studied concerning the patients' occupation.

Respiratory symptoms at presentation included one or more of the following symptoms: cough, dyspnea, hemoptysis, and chest pain. Performance status was measured using the Eastern Cooperative Oncology Group Performance Scale (ECOG PS), which is a commonly used method of evaluating the functional status of patients with cancer. EGO uses a 5-point score [14]:

0: Fully active, able to carry on all pre-disease performance without restriction.

1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4: Completely disable. Cannot carry out any self-care. Totally confined to bed or chair.

5: Dead.

The stages of the tumor were reported according to the 8th edition of the tumor, node, metastasis (TNM) staging international system [15]. Metastatic sites of lung cancer may include the liver, bone, brain, opposite lung, pleura, lymph node. Statistical analysis was performed using Jamovi version 2.0.0. Differences between males and females never smokers were analyzed using Chi-square and Student's t-test. Differences were considered statistically significant for p-values <0.05.

3. RESULTS AND DISCUSSION

A total of 606 patients were included in this study. There were 289 (47.70%) current smokers, 160 (26.40%) former smokers, and 157 (25.90%) never smokers. In never smokers, 79 (50.32%) were women and 78 (49.68%) were men. The mean age at diagnosis in the general population of never smokers was 57.7 (± 11.5) years. Women had a significantly lower mean age at diagnosis than men (56.00 versus 59.5) ($p=0.034$).

Almost two-thirds (65.6%) of patients were presented with at least one respiratory symptom. Cough, followed by dyspnea, chest pain, and weight loss were the most frequent symptoms in both sexes. In women, cough ($p=0.005$), dyspnea ($p<0.001$), weight loss ($p<0.001$), and asthenia (0.003) were more frequent than in men. Sociodemographic and clinical characteristics by gender are summarized in Table 1.

Exposure to studied risk factors is shown in Table 2. More than half (59.23%) of patients have already suffered from at least one previous non-malignant lung disease. Tuberculosis was the most frequent lung disease among never smokers, followed by chronic obstructive pulmonary disease (COPD), and pneumonia, with respectively, 40.13%, 23.56%, and 19.74%. There was no significant difference between women and men in terms of previous lung diseases.

Regarding exposure to environmental carcinogens that can be seen in Table 2, 8.86 % of women reported exposure to cool smoke, and 57.14% of men exercised occupations with a high risk of lung cancer. Of these men, 50% worked in masonry/construction, 30.55% in agriculture, and 19.45% in transportation. There was a significant difference between men and women in exposure to environmental carcinogens, with

higher exposure in men ($p < 0.001$). Eight patients had previous cancer and five of them were treated by radiation therapy. A history of familial cancer was noted in four cases.

Table 1. Characteristics of the never smokers by gender

Characteristics	Entire group		Male		Female		p
	N	%	N	%	N	%	
Age at diagnosis (n=157)							
Mean (SD)	57.7	(±11.5)	59.5	(±10.1)	56.00	(±12.5)	0.034
Comorbidities (n=157)							
Yes	37	23.56	16	10.19	21	13.37	0.370
No	120	83.92	62	39.49	58	36.94	
Respiratory symptoms at presentation (n=157)							<0.001
Yes	103	65.5	38	24.20	65	41.40	
No	54	34.39	40	25.48	14	8.92	
Symptoms (n=157)							
Cough	55	35.03	19	12.10	36	22.93	0.005
Dyspnea	49	31.21	14	8.92	35	22.29	<0.001
Weight loss	28	17.83	6	3.82	22	14.01	<0.001
Chest pain	37	23.56	15	9.55	22	14.01	0.203
Hemoptysis	18	11.46	7	4.46	11	7.01	0.330
Asthenia	19	9.55	6	3.82	13	8.28	0.003
EGOC PS (n=127)							0.527
0-1	77	60.63	28	22.05	49	38.58	
2-4	50	39.37	24	18.90	26	20.47	

SD: Standard deviation; EGOC: Eastern cooperative oncology group performance status

Table 2. Exposure to studied risk factors in never-smoker patients by gender

Risk factors	Entire group		Male		Female		p
	N	%	N	%	N	%	
Previous lung disease (n=157)	93	59.23	45	28.66	48	30.5	0.696
Tuberculosis	63	40.13	34	21.66	29	18.47	0.379
COPD	37	23.56	16	10.19	21	13.37	0.283
Pneumonia	31	19.74	14	8.92	17	10.83	0.099
Exposure to professional and domestic carcinogens (n=142)	43	27.39	36	22.93	07	4.46	<0.001

COPD: Chronic obstructive pulmonary disease

Adenocarcinoma was the most frequent histological type in never smokers, followed by far by squamous cell carcinoma. In terms of histological type, there was a substantial difference between men and women: 35.67% of women had adenocarcinoma versus 28.66% of men, and 7.64% of women had squamous cell carcinoma versus 11.47% of men ($p = 0.046$). Also, a significant difference was observed between the two sexes in terms of diagnostic method ($p = 0.001$). Men were more likely diagnosed by CT-guided biopsy and women by pleural biopsy as shown in Table 3.

Table 3. Tumor characteristics of never smokers by gender

Characteristics	Entire group		Male		Female		p
	N	%	N	%	N	%	
Diagnostic method (n=157)							0.001
CT ¹ -guided biopsy	55	35.03	37	23.56	18	11.46	
Bronchoscopy	41	26.11	22	14.01	19	12.10	
Pleural biopsy	26	16.56	06	3.82	20	12.74	
Transparietal biopsy	19	12.10	10	6.37	09	5.73	
Others	16	10.19	07	4.46	09	5.73	
Histological type (n=157)							0.046
Adenocarcinoma	101	64.33	45	28.66	56	35.67	
Squamous cell carcinoma	30	19.11	18	11.47	12	7.64	
Others	26	16.56	14	8.92	12	7.64	
Stage (n=117)							0.032
I-II	15	12.82	08	6.84	07	5.98	
III	26	22.22	12	10.25	14	11.96	
IV	76	64.96	30	25.64	46	39.32	
Metastatic sites (n=102)							
Opposite lung	43	42.15	21	20.59	22	21.57	0.897
Pleura	33	32.35	08	7.84	25	24.51	0.001
Bone	15	14.70	09	8.82	06	5.88	0.068
Lymph node	11	10.78	06	5.88	05	4.90	0.253

Majority of never smoker patients (87.18%) were detected at an advanced stage. More women than men were diagnosed at a late stage of the disease ($p=0.032$). The most prevalent metastatic sites observed in this study were opposite lung (42.15%), pleura (32.35%), bone (14.70%), and lymph node (10.78%). The highest metastasis place for women was pleura (24.51%) while for men was the opposite lung (20.59%).

In this study, we describe the epidemiological profile of lung cancer among never smokers in Morocco. The significant proportion of never smokers in our series (25.90%) allowed a comparison between men and women. Studies around the world have reported heterogeneous proportions of never smokers among patients with lung cancer, ranging from about 10% in males in the western countries to nearly 40% in Asian females [16], [17]. A study performed in Senegal found a proportion of 33.3% of never smokers [18]. Another Brazilian study showed that 19.65% of lung cancer cases were never smokers [19]. Despite this heterogeneity of proportion, several studies have shown that lung cancer in non-smokers is increasing. A cohort study reported an increased incidence of lung cancer in never smokers in the Swedish patients from 1.5 to 5.4/100,000 of the population [20]. Similarly, an American population-based study registers found a significant increase of lung cancer proportion in never smokers from 8% to 14.9% between 1990-1995 and 2011-2013 [6].

Many studies have concluded that lung cancer differs according to smoking status, notably concerning the histological type. Adenocarcinoma is more frequent in never smokers [10]. When comparing the two sexes among never smokers, Toh *et al.* found no significant differences between men and women, apart from the histological types [9]. Santoro *et al.* showed that the two sexes were similar even for the histological type [19]. In our research, men and women were similar in terms of comorbidities and performance status, which is concordant with these studies; however, different regarding age at diagnosis, histological subtype, and disease stage.

Age at diagnosis of never smokers, in our study, was relatively younger compared with other research [19]–[22]. Several studies have shown that never smokers comparing to smokers were diagnosed at an early age [9], [18], [21]. Some authors explained this by the susceptibility of non-smokers to environmental pollutants, especially passive smoking [17]. Many risk factors have been reported for the development of lung cancer in never smokers [8]. In our series, a significant proportion of patients had a previous non-malignant lung disease, such as tuberculosis, chronic obstructive pulmonary disease (COPD), and pneumonia. These pathologies are associated with a higher risk of lung cancer even in non-smokers [7]. COPD and tuberculosis are important sources of inflammation in lung tissue [23], [24]. These inflammatory processes play a central role in lung carcinogenesis, and could therefore be a major source of increased lung cancer risk [25]. We were unable to obtain information on secondary exposure to tobacco, which is a limitation of our study. However, information on the patients' occupations allowed us to study occupational exposure to carcinogens. A not negligible fraction of our male patients was practicing an occupation that presents a high risk of lung cancer. Also, exposure to domestic fuel smoke was noted in female patients. Studies have shown that the risk of lung cancer increases among farmers, construction workers, professional drivers, and people exposed to domestic fuel smoke [8], [26]–[28]. In addition to previous pulmonary disease and professional exposure to carcinogens, it has been reported that treatment by radiation therapy increases the risk to develop a second pulmonary cancer [29].

Our results found that adenocarcinoma is the most common histological subtype among never smokers. This finding is in line with the literature. Many studies found that adenocarcinoma were more frequent in never smokers [9], [10], [19], [30], [31]. Interestingly, studies have shown that molecular features of adenocarcinoma in never smokers are distinct from those in smokers [5], [30]. This implies differences between smokers and never smokers even in terms of response to treatment and survival [10], [19], [32]. Women in our series had significantly more adenocarcinoma than men. Many studies have reported the same result [9]. Patel *et al.* reported that women, especially those who do not smoke, are two to four times more likely to develop adenocarcinoma than men [33].

The majority of our patients were diagnosed at stage IV. This supports the findings of previous studies, which have shown a late stage of diagnosis associated with never smokers [9], [19], [31]. Also, we found a higher proportion of women never smokers were in the late stage compared to men never smokers. This can be explained on the one hand by a late presentation of the patients. On the other hand, by a delayed diagnosis by the doctor, since lung cancer in never smokers and, especially, in women is not known by patients and doctors to be frequent.

4. CONCLUSION

A significant number of patients with lung cancer in Morocco were never smokers. Evident epidemiologic differences were found between men and women never smokers. Women were younger, had more adenocarcinoma, and were more diagnosed at late stages. While men were more exposed to occupational carcinogens. Also, a considerable proportion of never smokers, men and women, had

tuberculosis. These finding may help to prevent lung cancer in never smokers in Morocco. A public health policy based on early detection and medical surveillance, especially for patients with tuberculosis and people exposed to carcinogens in their occupational environment, should be implemented. It is important to decrease the incidence of lung cancer among never smokers in Morocco.




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
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