

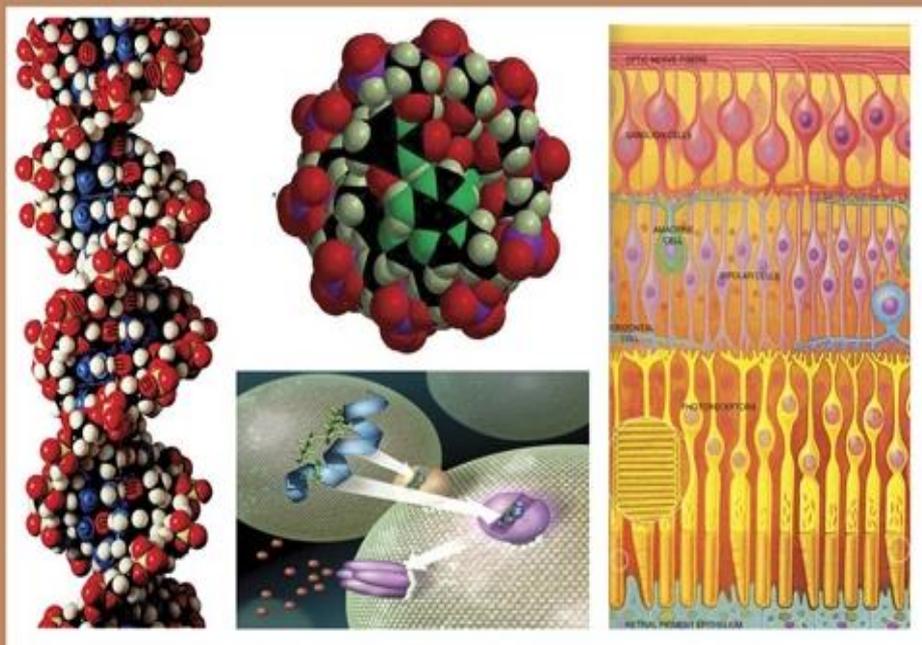


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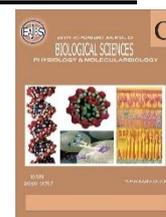
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## Primary Broncho-Pulmonary Cancer in Women: Epidemiological Study, Clinical-Pathological Study and Therapeutic Load.

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### ABSTRACT

**Introduction:** Primary bronchial cancer in women is a major public health problem; its incidence has increased steadily over the past 20 years.

**Objective:** The objective of this work was to analyze the epidemiological, clinical, therapeutic and prognostic characteristics of lung cancer in women in the region of Sidi Bel Abbès.

**Materials and methods:** A descriptive retrospective study of 50 women diagnosed with primary lung cancer collected in the oncology and radiotherapy department of anti cancer centre between January 2008 and May 2019.

**Results:** The average age of our patients was 64 years ( $\pm 15,063$ ). Respiratory symptoms were dominated by chest pain. The main risk factors were passive smoking (26% of cases), family history of cancer, hormonal factors, environmental factors, history of respiratory diseases.

The most common histological type was adenocarcinoma (74% of cases), stages III and IV accounted for 95% of cases. The main metastatic locations were bone and cervical (23.8%). Treatment management was based mainly on chemotherapy (50% of cases), of which 19% were palliative.

**Discussion:** Our results confirm that bronchial cancer in women is steadily increasing. Its risk factors are different from those of men. The dominant histological type in women was adenocarcinoma, which has a better prognosis, however, the diagnosis remains late, which explains the predominance of stages III and IV in women.

**Conclusion:** The female primary broncho-pulmonary cancer has anatomopathological, hormonal and genetic peculiarities that characterize it, which should encourage us to apprehend it differently from the therapeutic strategies better for women.

### INTRODUCTION

Globally, primary broncho-pulmonary cancer (PBC) is the number one cancer diagnosed in men and number three in women (Yoshida *et al.*, 2019).

It is the leading cause of cancer death in men and the second in women. The incidence and mortality of PBC continues to increase in women as these parameters stabilize or decrease in men (Fakhri, 2017). Primary bronchial cancer in women has many specificities resulting from environmental, genetic and hormonal factors, alongside the determining role of passive smoking (Menecier and Quoix, 2005). The diagnosis of CBP in women is often made at a late stage before non-specific respiratory signs. It is mainly based on imaging, bronchial fibroscopy with biopsy followed by a histological study to make the diagnosis and determine the histological type. Schematically, we distinguish: non-small cell bronchial cancers (CPNP) which represent more than (80%) of cases, and small cell bronchial cancers (CPPC) which represent about (15%) of cases.. The distribution of different histological types has also changed over the past decade, with an increase in adenocarcinoma and a decrease in squamous cell carcinoma (Bouhali, 2016). Therapeutic management is multidisciplinary, based on regional (surgery and radiotherapy) and systemic (chemotherapy and targeted therapy) treatments.

The aim of this work was to review the epidemiological, clinical, therapeutic and prognostic aspects of early bronchial cancers in women in the Sidi Bel Abbes region. It was carried out on 50 women diagnosed with primary broncho-pulmonary cancer between January 2008 and May 2019, at the Anti-Cancer Center of the Sidi Bel Abbés region.

#### **MATERIALS AND METHODS**

The objective of our descriptive retrospective study was to study the epidemiological, clinical and therapeutic aspects of broncho-pulmonary cancers that affect women in the oncology and radiotherapy department at the cancer centre of Sidi Bel Abbés, during the period between January 2008 and May 2019.

**Study Population: (n=50)** Our study included 50 female patients, aged between 36 and 93 years, with primary bronchial cancer diagnosed in the oncology and radiotherapy departments of the Sidi Bel Abbés cancer centre. The compilation of data on files allowed us to establish the inclusion and exclusion criteria:

**Criteria for Inclusion:** The cases included in our study are female patients, managed and treated for primary broncho-pulmonary cancer after histological confirmation.

**Exclusion Criteria:** We excluded from our study patients with a personal history of cancer regardless of location or suspected secondary tumour, male records and all incomplete records. There were no criteria regarding the age or stage of the disease.

**Statistical Study:** For this work, we consulted the hospital registry of oncology service and radiotherapy of the anti cancer centre. All data were collected retrospectively and manually extracted from each patient's medical record. The files were analyzed according to a predetermined form return. This sheet allowed the analysis of epidemiological, clinical and therapeutic data.

Statistical analysis of the data was performed using IBM SPSS Statistics version 25 and Microsoft Office Excel 2017. Qualitative and quantitative variables were expressed in percentage and frequency.

#### **RESULTS**

In our series, the average age was 64 years (15,063). Of the 50 patients studied in our series 69% were married, 12% were single 19% were widowed.

The study of occupational activity revealed a predominance of housewives with a frequency of 45 cases (90%), 5% of active women were housewives.

**Circumstances of Discovery and General Signs:**

The main respiratory symptom that motivated the consultation in our study

population was chest pain in 8 patients (or 16.7% of cases), followed by hemoptysis and dry cough in 7 patients (or 14.3% of cases) for each patient. Dyspnea, chronic bloody cough and left shoulder pain accounted for 11.9%, 7.9% and 2.4% respectively of the reasons for consultations (Table 1).

**Table 1: Distribution of patients according to circumstances of discovery**

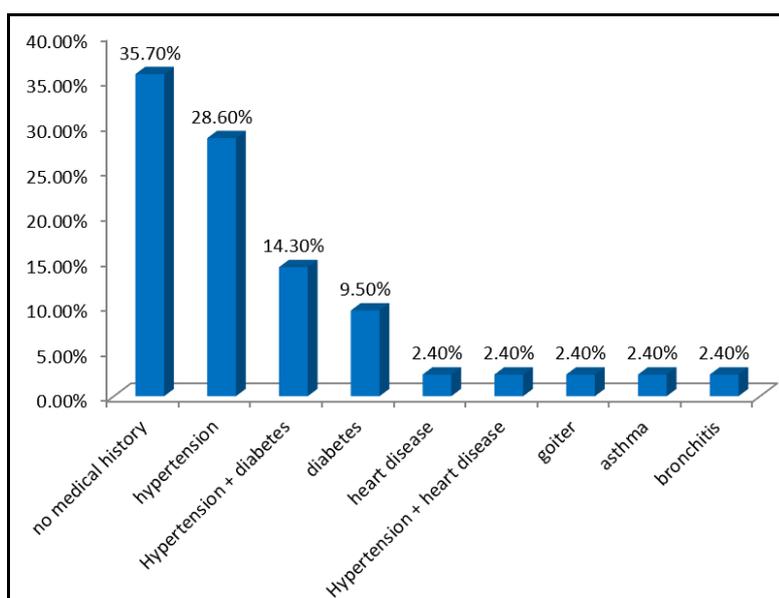
Symptoms	Percentage (%)
Chest pain	16,7
Dry cough	14,3
Hemoptysis	14,3
Productive cough	9,5
Dyspnea	9,5
Neurological disorders	9,5
Bloody cough	7,1
Chronic cough	7,1
Bone pain	7,1
Secondary pleurisy	2,4
Left shoulder pain	2,4

According to our series of studies, the general condition of patients was marked by weight loss in 28.6% of patients, while 21.4% of cases represented no symptoms.

Association of asthenia with weight loss and anorexia was reported in 9 patients (19% each) for each sign.

**Medical-Surgical History:**

In our series, 62% of patients had a personal medical history, with high blood pressure coming first (or 28.6% of cases), followed by association of diabetes with high blood pressure in 6 patients (or 14.3% of cases) and diabetes in 3rd place with 9.5% of cases. Only one case of asthma and bronchitis was noted (Fig.1).



**Fig. 1: Distribution of patients according to medical history**

Only 13% of patients had a surgical history, including colectomy in 4 patients (9.5%), and cataract in 3 patients (7.1% of cases). In addition, 2 patients underwent a thyroidectomy and 2 others a

vasectomy. Hemorrhoidectomy, hysterectomy and ovarian, pulmonary and hepatic cyst were performed in 3 patients (Fig. 2).

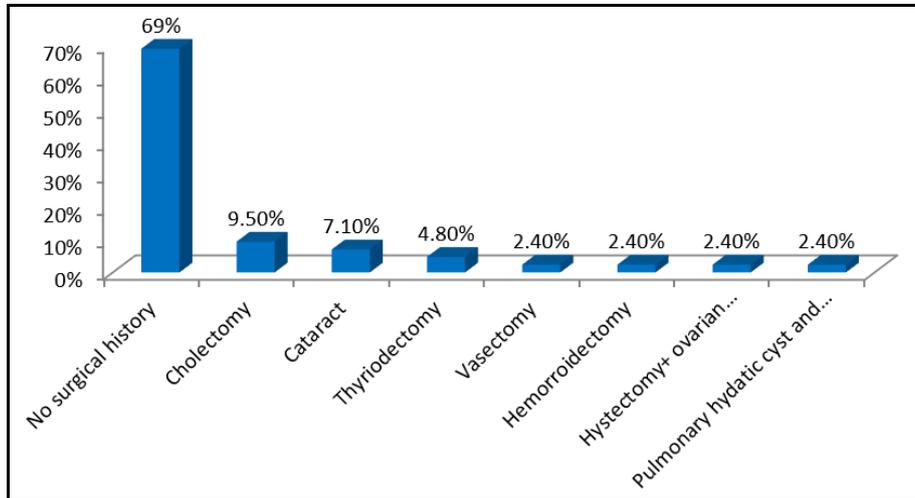


Fig. 2: Distribution of patients by surgical history

**Family History:**

The vast majority of cases had no family history (73.8% of cases), the family history of bronchial cancer was found in 3 patients (4.8% of cases). A family history of leukemia was noted in 6 patients (about

12% of cases), followed by a family history of breast cancer in 3 patients (7% of cases). The association of a history of lung cancer and leukemia was found in only one patient (Fig. 3).

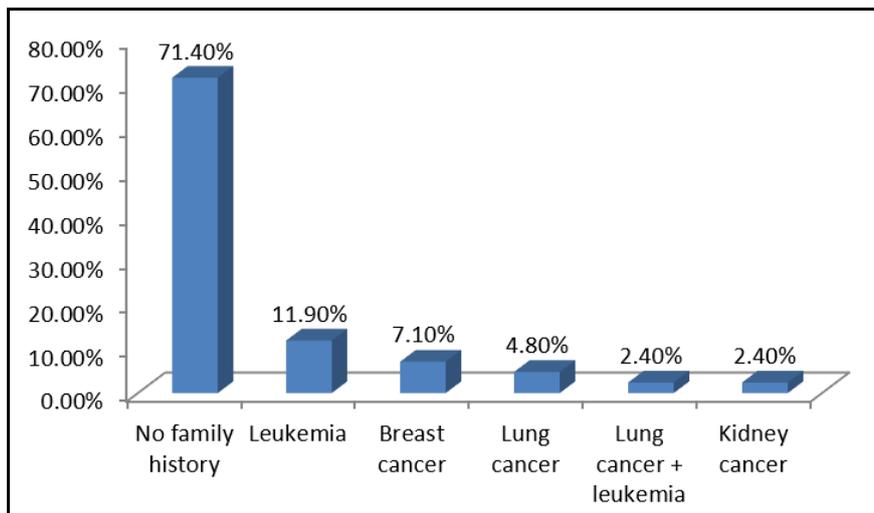


Fig. 3: Distribution of patients according to family history

**Risk Factors:**

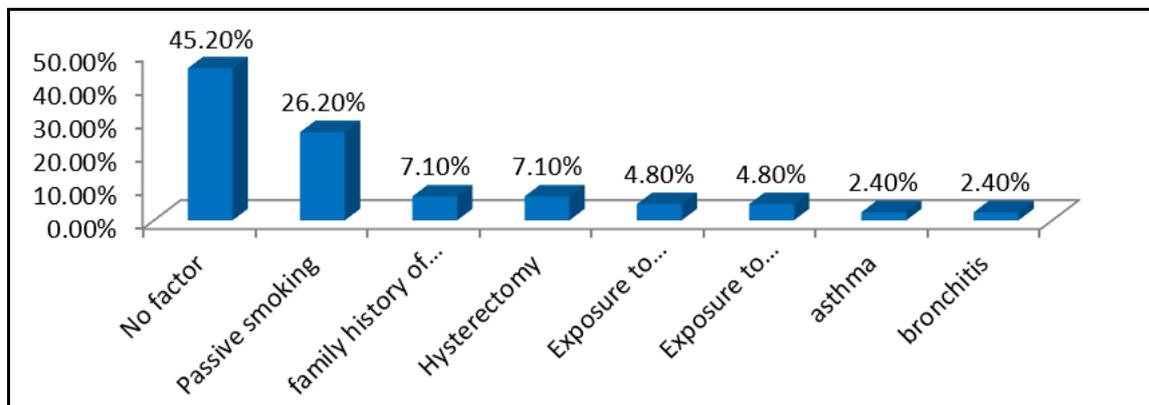
According to our series of studies, 22 patients (45% of cases) had no mention of risk factors. The dominant factor was passive smoking intoxication, found in 13

patients (26.2% of cases), followed by a family history of pulmonary neoplasia found in 3 patients (about 7%). Environmental exposure to wood smoke (chimney) was noted in 2 women in our

study. Hormonal factors including hysterectomy were noted in 3 patients (7%).

Occupational exposures were also marked by the use of detergents in 2

housewives of our population. Finally, the respiratory history of bronchitis and treated asthma was reported in only one patient each (Fig. 4).



**Fig. 4:** Distribution of patients by risk factors.

#### Location:

The tumour was bilateral lung localization in 45% of cases, right lung localization in 45% of cases, and left lung in 17% of cases.

#### Histological type:

Adenocarcinoma was the most frequently diagnosed histological subtype, found in 74% of cases, followed by squamous cell carcinoma in 12 patients (24% of cases). Finally, large cell carcinoma was found in only one patient.

#### Stade:

In our series, 64% of cancer cases were stage IV, 31% were stage III, stage I and stage II represented only one case

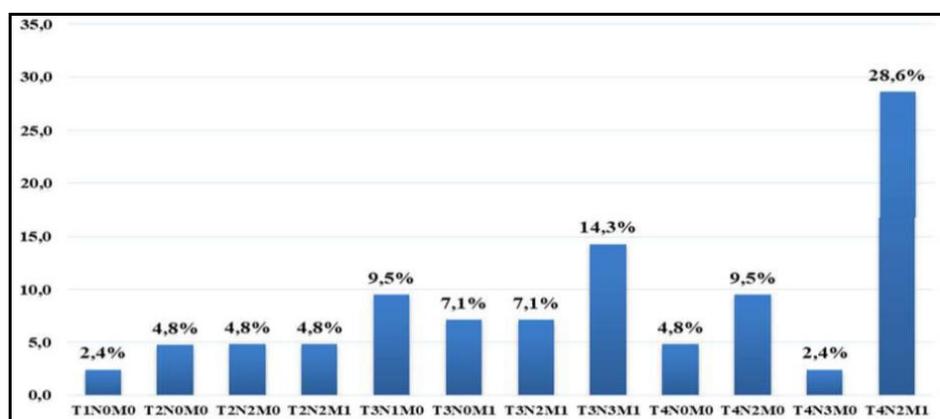
each.

#### TNM Classification:

The anatomopathological classification (TNM) of our series, showed that among the 50 patients, 64.3% of cases in our population had stage IV tumors including:

We noted a predominance of T4N2M1 with 28.6% of cases, followed by 14.3% of patients with T3N3M1. In addition, 9.5% of cases were in the T4N2M0 and T3N1M0 stages.

The least represented stages are: T2N0M0 (4.8% of cases) and T1N0M0 (2.4% of cases) (Fig. 5).



**Fig. 5:** Distribution of patients by TNM classification.

**Metastases:**

The presence of metastases, at the time of diagnosis, was found in 39 patients or 78.6% of cases, including 30 cases with several secondary locations.

Bone metastases were the most common metastases (23.8% of cases), followed by brain localization in 19% of patients, and hepatic in 14.3% of cases.

We also noted 3 cases (about 7%) of liver and bone metastatic association and a single case of brain and bone association. Finally, the primary metastasis occupied the last place with 5 cases, including 1 case of mediastinal and pleural ganglion metastasis respectively and 3 cases for supraclavicular ganglion localization (Table 2).

**Table 2:** Distribution of patients by the site of metastases.

The site of metastases	Frequencies (%)
Bone metastases	23,8%
Metastases Cerebral	19%
Hepatic metastases	14,3%
Hepatic + bone metastases	7,1%
Metastases supraclavicular lymph node	7,1%
Cerebral + Bone metastasis	2,4%
Pleural metastases	2,4%
Metastases mediastinal lymph node	2,4%

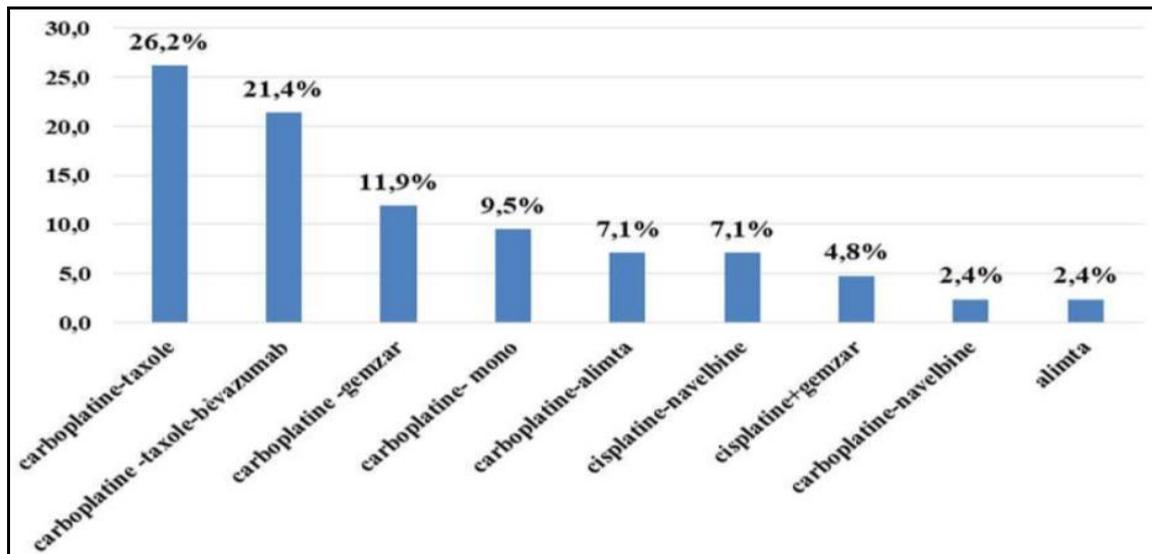
**Treatment:**

Of the 50 patients in our study population, 25 had received only chemotherapy (50%), followed by 9 patients (18%) who received a combination of palliative treatment and chemotherapy. In addition, 16.7% of the patients in our series had received all three treatments: chemotherapy, radiotherapy and palliative treatment.

Finally, palliative treatment alone and an association of chemotherapy and radiotherapy were indicated in 3 patients (7%) for each patient.

The vast majority of patients (93%) had undergone chemotherapy based on cures, the most often used are carboplatin

or more rarely cisplatin, always alone or in combination with other medications, among which: Carboplatin was associated with taxol administered to 13 patients (or 26.2% of patients), followed by the combination of three drugs carboplatin, taxol and bevacizumab which benefited 10 patients (21% of cases). For 6 patients (11.9%), the protocol followed was carboplatin-gemza. Carboplatin-mono was administered to 5 patients (9.5% of cases). Carboplatin-alimta cures, the combination of cisplatin with navelbine and cisplatin with gemza and carboplatin-navelbine and alimta were administered to only 3 cases (Fig. 6).



**Fig. 6:** Distribution of patients according to the treatment administered.

## DISCUSSION

Primary broncho-pulmonary cancer has become a real public health problem in women, especially over the past 20 years (Yoshida *et al.*, 2019).

The World Health Organization has reported an alarming incidence in women, with millions of new cases in 2018 (WHO, 2018), requiring specific attention to primary pulmonary cancer in women.

In our descriptive retrospective study, 50 patients were recruited between January 2008 and May 2019 at the Sidi Bel Abbès cancer centre. We were mainly confronted with the recurrence of incomplete information including information about active smoking and gynecologic-obstetric history.

We found an increase in the incidence of female primary bronchial cancer between 2008 and 2018, which can be explained by the evolution of female smoking among others (Kazerouni *et al.*, 2004). On the other hand, some assumptions suggest that women are more sensitive to the effect of smoking (active or passive) “genetic theory”, and are more often exposed to other carcinogens “environmental theory”, such as those found in detergents and household products. Female hormones, particularly estrogen, may also play a role in the carcinogenesis of “hormonal theory” lung

cancer (Bunel and Mazières, 2014).

The age of diagnosis is usually lower in women than in men (Mennecier and Quoix, 2005), findings also from two US studies (Minami, 2000; Visbal *et al.*, 2004) and a European study (Radzikowska, *et al.*, 2002).

In our study, the average age was 64 years ( $\pm 15,063$  years), with extremes ranging from 36 to 93 years. The most affected age groups were those aged 50-59 and those over 70, which is consistent with the results of the French KBP survey, conducted between 2000 and 2010, which found that the average age of patients was around 64 (Blanchon and Grivaux, 2013). Two other North American studies (Ferguson, 2000) also noted that the average age of patients diagnosed with primary bronchial cancer was 63.5 years.

Most of the patients in our study were housewives (90% of the cases), married in 69% of the cases. Two patients in our series were housekeepers. Studies have shown that regular use of certain detergents may be harmful to the lungs, the American Journal of Respiratory and Critical Care Medicine (Svanes *et al.*, 2018). For example, a recent Norwegian study that followed 6,000 people for nearly 20 years found that housewives had lung function similar to that of women who smoked the equivalent of 20

cigarettes per day over 10 to 20 years (Strand *et al.*, 2018). On the other hand, two other patients in the study were exposed to wood fire (chimney). According to Delgado, exposure to wood smoke may be a risk factor for bronchial cancer (Delgado *et al.*, 2005). In Asia, a link between the risk of bronchial cancer and the number of years of use of Kang (charcoal baking oven) has also been reported (Soll-Johanning *et al.*, 1998).

Clinical signs suggestive of the diagnosis of our series were marked by respiratory signs, such as chest pain (or 16.7% of cases), hemoptysis and cough (19% of cases). General signs such as weight loss (28.6% of cases) and asthenia were also very common. The remaining patients were asymptomatic (21.4% of cases), which is consistent with several European and American epidemiological studies, which reported that women were more likely to be asymptomatic at the time of diagnosis (Perrot *et al.*, 2000).

In a study based on the Missouri Cancer Registry (USA) (Brownson and Alavanja, 2000). Lung history was associated with an increased risk of bronchial cancer in women. In our series, 4.8% of patients had a personal history of breathing (asthma and bronchitis).

The first notion of the genetic determinism of bronchial cancer comes from the observation of family cancers. Indeed, many studies on non-smoking populations (to avoid smoking bias) have shown a high risk between primary bronchial cancer and family history (Schwartz 1996; Yoshida *et al.* 2019).

In our series, the family history of bronchial cancer was found in 4 patients (7.1% of cases). These results are similar to another Moroccan study (7% of cases) (Fakhri, 2017). In the course of our research, 4 patients were hysterectomized (7.1% of cases), and female hormonal physiology, including estrogen, plays a role as a promoter of primary BP cancer (Bunel and Mazières, 2014). Several

retrospective studies show that reproductive hormones are risk factors for bronchial cancer, particularly for women with fewer than 3 pregnancies, short menstrual cycles, or/and early menopause (Zatloukal *et al.*, 2003; Giaccone *et al.*, 2005). A Canadian study found that hysterectomy increases the risk of developing lung cancer (Slatore *et al.*, 2010).

As early as 1981, studies have shown that exposure to passive smoking may be a risk factor (Takeshi, 1981; Trichopoulos *et al.*, 1983). In 1986, studies by the National Research Council and Surgeon General reported a 30% risk of developing bronchial cancer in non-smoking women exposed to passive smoking (Horing *et al.*, 1986).

In our series, exposure to passive smoking was noted in 26% of cases, including 2 women who were exposed to it for more than 20 years in their homes. A meta-analysis of 37 studies on passive domestic smoking, or 4626 cases of bronchial cancer, also showed a relative risk of 24% with an 11% increase per 10 years additional exposure (Steenland *et al.*; 2001).

The distribution of different histological types of primary bronchial cancer in women has changed markedly in recent years, with an increasing incidence of adenocarcinoma at the expense of a decline in squamous cell carcinoma (Cadelis, 2013). This data fits perfectly with our results since adenocarcinoma was the first histological type in our series, with 74% of all primary broncho-pulmonary cancers. The results of Chabani and Schwartz also showed a predominance of adenocarcinoma with 53% and 41.66% respectively (Chabani, 2014; Schwartz, 1996). Squamous cell carcinoma occupies the 2nd place of broncho-pulmonary cancers in our series, they represent 24% of cases. Adenocarcinomas are the dominant histological type in women and non-smokers, while squamous cell cancers are more common in men and smokers

(Dodds *et al.*, 1986).

Broncho-pulmonary cancer in women is usually detected late, in stages III and IV most often, unlike men, for whom diagnosis is usually made during stages II and III (Mennecier and Quoix, 2005). This is consistent with our findings, where Stages III and IV represented most of the cases. This is explained by the fact that this type of cancer is more symptomatic in men because of their smoking.

In our study, bone metastases were most frequently found, liver metastases occupied the 2nd place, followed by brain metastases. Our results are not consistent with the literature, or it is often brain metastases that are the most common (Alaoui, 2011).

Among patients in our population, 50% of patients had received chemotherapy alone or associated with radiotherapy or palliative treatment, as well as radiation chemotherapy combined with palliative treatment (or 16.7% of cases). This is consistent with several studies that have shown that the female sex is a factor of good prognosis for men, with women responding better to combined treatments, such as chemotherapy alone or combination radiation and chemotherapy (Hespanhol *et al.*, 1995; Fukuoka *et al.*, 1991). Most studies confirm a better response to women's treatment the stage of the disease, the type of treatment, or histology (Thomas *et al.*, 2005).

In a large U.S. epidemiological study of more than 30,000 patients, sex female emerges as an independent variable of good prognosis (Radzikowska *et al.*, 2002; Ramalingam *et al.*, 2016). These results are contradictory to those of Fukuoka and Lassen in terms of response no significant differences between the two sexes (Fukuoka *et al.*, 2003; Lassen, 1999). During our study period, only 16 patients died. Survival in women, therefore, appears to be superior to men with a good prognosis at any stage of

discovery (Radzikowska *et al.*, 2002; Ramalingam *et al.*, 2005).

#### **Conclusion:**

Female lung cancer is the second leading cause of cancer death worldwide after breast cancer. The increase in its incidence can be attributed to several factors such as exposure to passive smoking, and the existence of other specific occupational, environmental and genetic risk factors. Our results showed that the average age was 64 years, the dominant respiratory symptom was chest pain, and the main risk factor was passive smoking (26% of cases). The most common histological type was adenocarcinoma, with late stages accounting for 95% of cases whose metastasis was localized at the bone and cervical level and for therapeutic management was based primarily on chemotherapy. The presence of epidemiological contributors, as well as certain female characteristics represented by hormonal, genetic, molecular variations and possibly, increased susceptibility to tobacco carcinogens, make lung cancer in women a separate entity.

Therapeutic advances in the field of surgery, radiotherapy techniques and new systemic treatments have improved the prognosis of broncho-pulmonary cancers and have a relatively long-lasting response, to explore new avenues of research with the hope of proposing specific treatments in women, one of the most advanced avenues of research is that of hormonal treatments especially associated with tyrosine kinase inhibitors. The best current strategy remains the prevention of women from passive smoking through the establishment of a tobacco control policy.

Our work on lung cancer in women has allowed us to focus on the extent of this pathology, which until now has been little known by the population, but which continues to grow gradually.

**Conflict of Interest:** The authors have no conflicts of interest.

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## ARABIC SUMMARY

سرطان الشريان الرئوي الأولي لدى النساء: دراسة وبائية سريرية - مرضية والإدارة العلاجية

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يشكل سرطان الرئة لدى النساء مشكلة صحية عامة رئيسية ، وقد ازداد معدل الإصابة به باطراد على مدى السنوات 20 الماضية. والهدف من هذا العمل هو تحليل الخصائص الوبائية والعلاجية لسرطان الرئة لدى النساء في منطقة سيدي بلعباس. دراسة وصفية عن 50 امرأة تم تشخيصهن بسرطان الرئة الأولي تم جمعها في قسم الأورام والعلاج الإشعاعي في مركز سيدي بلعباس لمكافحة السرطان بين كانون الثاني/يناير 2008 وأيار/مايو 2019. **النتائج:** وجدت دراستنا أن متوسط عمر مرضانا كان 64 سنة. (±15,063) الأعراض التنفسية سيطر عليها ألم في الصدر. وكانت عوامل الخطر الرئيسية هي التدخين السلبي (26% من الحالات) ، والتاريخ العائلي للسرطان ، والعوامل الهرمونية ، والعوامل البيئية ، وتاريخ أمراض الجهاز التنفسي. وكان النوع الأكثر شيوعاً الأدينوكارسينوم (74% من الحالات) ، حيث شكلت المرحلتان الثالثة والرابعة 95% من الحالات. وكانت المواقع الرئيسية للانتشار العظام وعق الرحم (23.8%). كانت إدارة العلاج تعتمد في الأساس على العلاج الكيميائي (50% من الحالات) ، والتي كانت 19% منها مسكنة. **المناقشة:** تؤكد نتائجنا أن سرطان القصبات الهوائية في النساء يتزايد باطراد. وعوامل خطورتها تختلف عن عوامل مخاطر الرجال. وكان النوع المهيمن في النساء هو الورم الحليمي ، الذي لديه تشخيص أفضل ، ومع ذلك لا يزال التشخيص متأخراً ، مما يفسر هيمنة المرحلتين الثالثة والرابعة في النساء. **الخاتمة هنا:** إن سرطان الرئة لدى الإناث يتمتع بخصائص تشريحية وهرمونية وجينية تميزه ، وهو ما لا بد وأن يشجعنا على إلقاء القبض عليه بشكل مختلف عن الاستراتيجيات العلاجية الأفضل للمرأة. الكلمات الرئيسية: السرطان ، القرنية ، البدائية ، الأنثى ، سيدي بيل أبوتس