Characteristics of non-small cell lung cancer: differences by sex and hormonal status in a Mexican population

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Abstract

Objective. To analyze the differences in the clinico-pathological and molecular characteristics of non-small cell lung cancer (NSCLC) as well as the clinical outcome of patients by sex and hormonal status. **Materials and methods.** We performed a retrospective study among 1 104 NSCLC patients. Clinic-pathologic data was recorded and survival outcomes were compared between male and female sex patients, and further by pre and postmenopausal status in females. **Results.** Women were significantly more likely to be non-smokers ($p<0.001$), had higher frequency of wood-smoke exposure ($p<0.001$), *EGFR*-sensitizing mutations ($p<0.001$), had better performance status ($p=0.020$) and had a better overall survival (OS) compared to men ($p=0.021$). Differences were found also by hormonal status, postmenopausal women had a longer OS compared to premenopausal women (31.1 vs. 19.4 months $p=0.046$). **Conclusion.** Our results support the differences in lung cancer presentation by sex and also by hormonal status.

Keywords: lung carcinoma, non-small-cell; men; women; postmenopausal; premenopausal

Resumen

Objetivo. Analizar las diferencias en las características clínico-patológicas, moleculares y en la evolución del cáncer de pulmón de células no pequeñas (CPCNP) por sexo y estadio hormonal. **Material y métodos.** Estudio retrospectivo (N=1 104) en pacientes con CPCNP. Se recabaron datos clínico-patológicos y desenlaces de sobrevida y se compararon entre hombres y mujeres, y entre mujeres pre y postmenopáusicas. **Resultados.** Las mujeres de este estudio tuvieron significativamente mayor probabilidad de ser no fumadoras ($p<0.001$), tener exposición a humo de leña ($p<0.001$), mutaciones en *EGFR* ($p<0.001$), mejor estado funcional ($p=0.020$), y una mejor sobrevida global (SG) en comparación con los hombres ($p=0.021$). Estas diferencias también se encontraron en cuestión al estatus hormonal, con las mujeres postmenopáusicas presentando una mayor sobrevida en comparación con las premenopáusicas (31.1 vs. 19.4 meses; $p=0.046$). **Conclusión.** Los presentes resultados apoyan las diferencias en la presentación del CPCNP de acuerdo con el sexo y estatus hormonal.

Palabras clave: cáncer de pulmón de células no pequeñas; hombres; mujeres; premenopausia; postmenopausia

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Lung cancer remains the leading cause of cancer-related deaths among males and has increased in women in the last decades.[1] Lung cancer in women has become an important health problem, surpassing mortality from breast cancer and being the first cause of cancer-related death in EEUU and in some countries from Europe.[1-5] Interestingly, a higher incidence among young women compared to men has been observed in the last decades in EEUU, however, this increase in incidence among women cannot be attributed solely to an increase in tobacco use, due to the fact that young women and men show a similar pattern in terms of smoking behavior, nonetheless the increased incidence of lung cancer in women is notorious.[6] Moreover, an increased incidence of lung cancer has also been reported in Latin American women, who present a lower smoking index compared to European and American women.[7,8] These data suggest that even though tobacco use remains an important risk factor for developing lung cancer, women face other risk factors, which also appear to play an important role in lung carcinogenesis. Furthermore, a higher percentage of women who develop lung cancer are never smokers compared to the low percentage of non-smoking men who present with this pathology (53 vs. 15%).[9,10] Other risk factors that might partially explain the increased incidence of lung cancer in women include: wood smoke exposure,[11] cooking oil fumes exposure[12] or second hand exposure to cigarette smoke,[13] however exposure to these risk factors does not fully explain the increased incidence of lung cancer in women. In the last years, it has been reported that estrogen and progesterone play an important role in lung cancer in women, mainly in the adenocarcinoma subtype, activating carcinogenic pathways.[14,15] Also, several studies have shown that hormone replacement therapy based on estrogen and progestin can increase lung cancer incidence and mortality.[16,17]

Additionally, lung cancer presentation, behavior and response to treatment seem to differ between women and men. For instance, the median age for lung cancer diagnosis in women is lower compared to men. Women with lung cancer more often have no history of smoking and the predominant subtype is adenocarcinoma, frequently associated with mutations in epidermal growth factor receptor gene (EGFR). In addition, women show better response to chemotherapy and longer overall survival, regardless of the clinical stage at diagnosis, compared to men.[18,19] Recently, it has been observed that non-small cell lung cancer (NSCLC) tumors are more immunogenic in men and consequently male patients respond better to immunotherapy compared to women.[20] All these differences in lung cancer by sex suggest a role of sexual hormones in lung cancer; however, differences by hormonal status in women (premenopausal/postmenopausal) have been poorly studied. Nevertheless, when characteristics of premenopausal women have been analyzed, they show that these patients are diagnosed in advanced stages, with less differentiated tumors, distant metastases and worse prognosis compared to postmenopausal women. This information suggests that lung cancer is not only influenced by sex, but also by hormonal status.[21,22]

Several studies have focused on reporting the differences by sex and despite this information, these differences are poorly understood, and the results of studies are contradictory. The controversy in these studies might be due to the inherent characteristics of the population analyzed, differences in the main risk factors, mutational tumor profile, genetic characteristics of patients and hormonal status. With a better understanding about the role of sexual hormones in lung cancer, it is important to investigate differences by hormonal status in Latin America population.[23]

Nowadays, it is recognized that sex and sexual hormones influence lung cancer. Due to the impact that these differences have in future treatment strategies, it is important to comprehensively characterize them. In this study, we sought to investigate the differences in clinical features and survival of NSCLC patients by sex and hormonal status, in a Mexican population.

Materials and methods

Patient selection

We retrospectively reviewed demographic, clinical, molecular and pathological data of 1 104 NSCLC who attended at the National Cancer Institute of Mexico (Incan) between May 2008 through March 2017. All included patients had a histologically confirmed diagnosis of NSCLC and molecular genotype available in their clinical file (EGFR and Kirsten rat sarcoma virus oncogene [KRAS] mutation status). Information including sex, age, and menopausal status at diagnosis was collected. Menopause was defined according to the international menopause guideline[24] as the permanent cessation of menses for 12 or more months in the absence of chemotherapy. Patients who had undergone oophorectomy were excluded from this study. According to standardized guidelines for smoking measurement,[25] we defined any patient who smoked 100 or more cigarettes in his or her lifetime and those who currently smokes, as a smoker. A person was defined as a non-smoker if he or she had either never smoked at all, or had never been a daily smoker and had smoked less than 100 cigarettes in his or her lifetime.

Smoking index was obtained by multiplying the number of cigarettes smoked per day by the number of years the patient reported that he/she had smoked [(# cigarettes per day)(years smoking)/20) and reported as pack-year]. Self-reported wood-smoke exposure while cooking was recorded and the wood smoke exposure index was calculated by multiplying the number of daily hours exposed by the number of years' exposure.[11]

Outcome measurement

Clinical baseline characteristics included age, sex, hormonal status (premenopausal/postmenopausal), weight, histologic tumor type, disease stage, smoking status, wood-smoke exposure, exposure to asbestos, ECOG performance status, metastatic sites, and mutation profile for EGFR and KRAS. Overall survival (OS) was defined as the time from histological diagnosis until death or last follow-up.

Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means with standard deviations, while categorical variables were summarized as frequencies and percentages. The chi^2 or Fisher's exact tests were used to assess the significance among categorical variables. The primary endpoint was OS, defined as the time from histological diagnosis until death or last follow-up. Median OS was estimated using the Kaplan-Meier's method, whereas the log-rank test was used for making comparisons among subgroups. A multivariate Cox regression model was used to adjust for potential confounders and hazard ratios (HR) were calculated along with their corresponding 95%CI as a measure of association. Statistical significance was determined as $p \leq 0.05$ using a two-tailed test. SPSS software version 21 (SPSS Inc., Chicago, IL) was used for all statistical analysis.

Results

Characteristics for the entire population of NSCLC patients

Out of 1 104 patient records reviewed for this study, 582 (52.7%) were men and 522 (47.3%) women. The median age was 60.6 years (±12.9). According to risk factors, 55.7% were ever smokers, while 38.5% of the patients had history of wood smoke exposure, and 10.5% had exposure to asbestos; 72.9 % of all patients have an ECOG $\leq$1. Most patients had adenocarcinoma histology (84.3%) and 98.9% presented with advanced or metastatic disease (stages IIIB or IV) at diagnosis. Nearly thirty percent of patients (29.6%) had EGFR mutations and 10.2% had KRAS alterations (table I).

Table I
CLINIC-PATHOLOGICAL CHARACTERISTICS OF PATIENTS TREATED AT THE NATIONAL CANCER INSTITUTE (INCAN) IN MEXICO CITY FROM 2008-2017 (N=1 104)

| | All patients % (n/N) | Sex | | p-Value |
		Female (n=522) % (n/N)	Male (n=582) % (n/N)	
Age (years)				
Mean (+SD)	60.6 (12.9)	59.8 (13.4)	61.2 (12.5)	0.068
BMI (Kg/m2)				
Mean (+SD)	24.8 (4.6)	25.1 (4.9)	24.6 (4.2)	0.036
BMI groups				
Normal (<25 kg/m2)	55.2 (609/1 104)	51.6 (269/522)	58.5 (340/582)	
Overweight (25 - 29.9 kg/m2)	32.4 (358/1 104)	32.4 (169/522)	32.4 (189/582)	
Obese (30+ kg/m2)	12.4 (137/1 104)	16.0 (84/522)	9.1 (53/582)	0.003
Tobacco exposure				
Absent	44.3 (489/1 104)	68.0 (355/522)	23.0 (134/582)	
Present	55.7 (615/1 104)	32.0 (167/522)	77.0 (448/582)	<0.001
Tobacco index				
Mean (+SD)	34.4 (167.9)	17.7 (21.8)	40.4 (195.3)	0.133

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Wood-smoke exposure				
Absent	61.5 (679/1 104)	50.0 (261/522)	71.8 (418/582)	
Present	38.5 (425/1 104)	50.0 (261/522)	28.2 (164/582)	<0.001
Exposure to asbestos				
Absent	89.5 (988/1 104)	90.8 (474/522)	88.3 (514/582)	
Present	10.5 (116/1 104)	9.2 (48/522)	11.7 (68/582)	0.178
Tumor histologic type				
Adenocarcinoma	84.3 (931/582)	88.9 (464/522)	80.2 (467/582)	
Squamous	15.7(173/1 104)	11.1 (58/522)	19.8 (115/582)	<0.001
Disease stage				
II - IIIA	1.1 (12/1 104)	1.2 (6/522)	1.1 (6/582)	
IIIB - IV	98.9 (1 092/1 104)	98.8 (516/522)	98.9 (576/582)	0.866
ECOG performance status				
0-1	72.9 (805/1 104)	76.2 (398/522)	69.9 (407/582)	
>2	27.1 (299/1 104)	23.8 (124/522)	30.1 (175/582)	0.020
*Brain metastases at diagnosis**				
Absent	53.6 (535/999)	54.7 (262/479)	52.5 (273/520)	
Present	46.4 (464/999)	45.3 (217/479)	47.5 (247/520)	0.487
*Lymphatic nodes metastases at diagnosis**				
Absent	81.8 (817/999)	79.1 (379/479)	84.2 (438/520)	
Present	18.2 (182/999)	20.9 (100/479)	15.8 (82/520)	0.037
*Adrenal glands metastases at diagnosis**				
Absent	95.5 (954/999)	96.0 (460/479)	95.0 (494/520)	
Present	4.5 (45/999)	4.0 (19/479)	5.0 (26/520)	0.431
EGFR mutation status‡				
WT EGFR	70.4 (286/406)	61.2 (134/219)	81.3 (152/187)	
EGFR sensitizing mutation	29.6 (120/406)	38.8 (85/219)	18.7 (35/187)	<0.001
KRAS mutation status‡				
KRAS (-)	89.8 (256/285)	89.8 (132/147)	89.9 (124/138)	
KRAS (+)	10.2 (20/285)	10.2 (15/147)	10.1 (14/138)	0.987

SD: standard deviation, BMI: body mass index, ECOG: eastern cooperative oncology group, WT: wild-type, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma virus oncogene.
*Estimation over 999 patients with stage IV disease and known metastases at diagnosis.
‡ Estimations over the number of patients tested for each molecular status.

Characteristics of NSCLC patients according to sex

The relative frequency of obese patients was substantially higher in women (16%) than in men (9%), p=0.003, likewise, female patients showed a higher body mass index (BMI) in comparison with their male counterparts (24.6 vs. 25.1; p=0.036). In addition, women had higher frequencies of wood-smoke exposure (50 vs. 28.2%; p=<0.001), EGFR-sensitizing mutations (38.8 vs. 18.7%; p=<0.001) and better ECOG performance status (≤1) (76.2 vs. 69.9%; p=0.020). By contrast, men showed higher frequencies of tobacco smoking exposure compared to women (70 vs. 32%; p=<0.001). We did not find differences among men and women in terms of age, histology, disease stage or KRAS mutation status. Table I shows the clinicpathological characteristics by sex.

Factors associated with the overall survival of patients

The median OS for the entire cohort was 21.6 months. The univariate analysis showed that the factors associated with OS were: sex, weight, smoking history, ECOG performance status, liver metastases and alterations in KRAS. The OS was prolonged in women compared to men (27.6 vs. 18.4 months, respectively [*p*=0.021]) (figure 1). Similarly, overweight patients had better results in terms of OS compared with normal weight or obesity (28.4 vs. 17.4 vs. 22.4 months, respectively; *p*=0.045). Patients with tobacco exposure had a shorter OS compared to never smoker patients (18.1 vs. 28.2 months; *p*=0.002).

On the other hand, patients with an ECOG <2 (23.5 vs. 14.5 months; *p*=0.006), absence of liver metastases, and wild type KRAS (38.9 vs. 15.7 months; *p*<0.001) had better OS. The multivariate analysis showed that ECOG performance status (HR: 0.4, 95%CI (0.2–0.7); *p*=0.001) and KRAS mutation (HR: 2.1, 95%CI (1.1–3.8); *p*=0.017) were independently associated with OS (table II).

Characteristics of women with NSCLC by hormonal status

Among 522 female patients with NSCLC analyzed, 120 were premenopausal (23%) and 402 postmenopausal (77%). Table III shows the characteristics the female sex

Table II

Univariate and multivariate analysis of the OS of patients treated at the National Cancer Institute (Incan) in Mexico City from 2008-2017 (N=1 104)

	Univariate analysis		Multivariate analysis	
	Median (95%CI)	p-Value	HR (95%CI)	p-Value
Overall	21.6 (17.8-25.4)			
Sex				
Female	27.6 (21.4-33.8)			
Male	18.4 (15.5-21.3)	0.021	0.9 (0.5 - 1.4)	0.582
BMI groups				
Normal (<25 Kg/m2)	17.4 (13.9-20.9)			
Overweight (25 - 29.9)	28.4 (21.0-35.8)			
Obese (30+ Kg/m2)	22.4 (9.4-35.4)	0.045	0.9 (0.7 - 1.4)	0.880
Tobacco exposure				
Absent	28.2 (19.1-37.3)			
Present	18.1 (15.1-21.1)	0.002		
Wood-smoke exposure				
Absent	19.2 (15.7-22.8)			
Present	27.4 (21.3-33.5)	0.221		
Exposure to asbestos				
Absent	23.5 (19.5-23.4)			
Present	16.8 (13.7-19.9)	0.165	1.0 (0.4 - 2.4)	0.955
Disease stage				
II-IIIA	8.5 (6.9-10.2)			
IIIB-IV	21.5 (18.2-24.7)	0.220		
ECOG performance status				
0 - 1	23.5 (19.2-27.7)			
>2	14.5 (10.5-18.5)	0.006	0.4 (0.2 - 0.7)	0.001
Liver metastases at diagnosis				
Absent	20.8 (17.1 - 24.5)			
Present	13.6 (8.9 - 18.3)	0.043	1.6 (0.8 - 3.3)	0.188

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EGFR mutation status				
WT EGFR	27.9 (16.5 - 39.2)			
EGFR sensitizing mutation	38.0 (28.9 - 47.1)	0.215		
KRAS mutation status				
KRAS (-)	38.9 (30.4 - 47.4)			
KRAS (+)	15.7 (12.3 - 19.2)	<0.001	2.1 (1.1 - 3.8)	0.017

CI: confidence interval, HR: hazard ratio, BMI: body mass index, ECOG: eastern cooperative oncology group, EGFR: epidermal growth factor receptor, WT: wild-type, KRAS: Kirsten rat sarcoma virus oncogene

population according to hormonal status. The relative frequency of wood-smoke exposure was substantially higher in postmenopausal than premenopausal women (52.5 vs. 41.7%, *p*=0.037). Likewise, postmenopausal patients showed a higher wood-smoke exposure index (113.2 vs. 50.6; *p*=0.006) and tobacco smoking index (19.8 vs. 10.2; *p*=0.017) compared to premenopausal women. By contrast, premenopausal women showed higher frequencies of exposure to asbestos in comparison to postmenopausal patients (16.7 vs. 7.0%; *p*=0.001). We did not find differences among women according to their hormonal status in terms of BMI, tobacco exposure, histology, disease stage, ECOG performance status, sites of metastases (brain, lung, liver, bone, lymphatic nodes, and adrenal glands) nor by EGFR or KRAS mutation status (table III).

Factors associated with overall survival among women NSCLC patients

Median OS for women was 27.6 months; in the univariate analysis the factors associated with a better OS were hormonal status (postmenopausal vs. premenopausal) (31.1 vs. 19.4 months; *p*=0.046) (figure 2), tobacco exposure (never vs. ever) (32.1 vs. 18.5 months; *p*=0.037), ECOG performance status (<2 vs. 2+) (27.9 vs. 18.5 months; *p*=0.022), adrenal glands metastases (no vs. yes) (27.6 vs. 10.7; *p*=0.023) and KRAS mutation status (absent vs. present) (37.6 vs. 15.8 months; *p*=0.007). In the multivariate analysis, the independently associated factors with OS were tobacco exposure (HR: 1.4, 95%CI (1.0 – 1.9); *p*=0.031), ECOG performance status (HR: 01.7, 95%CI (1.2-2.4); *p*=0.005) and KRAS mutation status (HR: 2.1, 95%CI (1.1-4.0); *p*=0.022) (supplementary table I).[26]
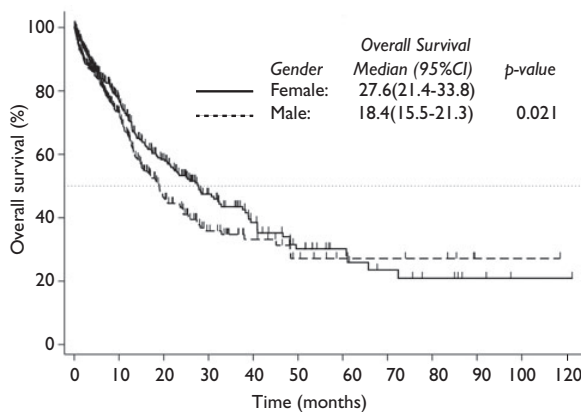

Figura 1. Overall survival in months according to gender, in Mexican population with non-small cell lung cancer. 2008-2017
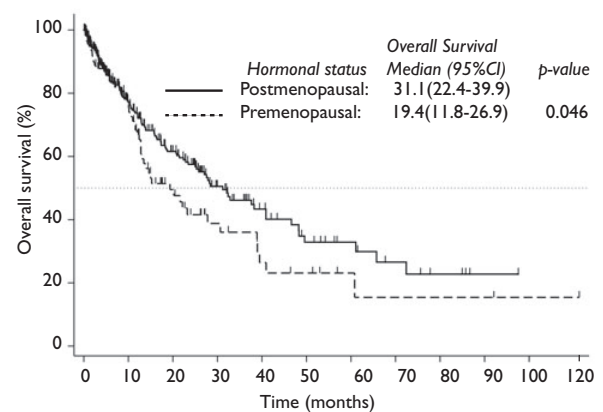

Figura 2. Overall survival in months according to hormonal status in Mexican woman with non-small cell lung cancer. 2008-2017

Table III

Baseline characteristics of women patients treated at the National Cancer Institute (Incan) in Mexico City from 2008-2017 (N=522)

	Hormonal status		
	Premenopausal (n=120) % (n/N)	Postmenopausal (n=402) % (n/N)	p-Value
Age (Years)			
Mean (+SD)	41.8 (7.3)	65.2 (9.6)	<0.001
BMI (Kg/m2)			
Mean (+SD)	25.4 (5.2)	25.1 (4.8)	0.556
BMI groups			
Normal (<25 kg/m^2)	51.7 (62/120)	66.9 (207/402)	
Overweight (25-29.9 kg/m^2)	34.5 (41/120)	42.0 (128/402)	
Obese (30+ kg/m^2)	13.8 (17/120)	20.9 (67/402)	0.717
Tobacco exposure			
Absent	70.0 (84/120)	67.4 (271/402)	
Present	30.0 (36/120)	32.6 (131/402)	0.594
Tobacco index	10.2 (18.7)	19.8 (22.2)	0.017
Wood-smoke exposure			
Absent	58.3 (70/120)	47.5 (191/402)	
Present	41.7 (50/120)	52.5 (211/402)	0.037
Wood-smoke expossure index	50.6 (70.3)	113.2 (154.7)	0.006
Exposure to asbestos			
Absent	83.3 (100/120)	93.0 (374/402)	
Present	16.7 (20/120)	7.0 (28/402)	0.001
Tumor histologic type			
Adenocarcinoma	90.0 (108/120)	88.6 (356/402)	
Squamous	10.0 (12/120)	11.4 (46/402)	0.659
Disease stage			
II - IIIA	0.8 (1/120)	1.3 (5/402)	
IIIB - IV	99.2 (119/120)	98.7 (397/402)	1.000
ECOG performance status			
0-1	78.3 (94/120)	75.6 (304/402)	
>2	21.7 (26/120)	24.4 (98/402)	0.534
Brain metastases at diagnosis*			
Absent	53.5 (61/114)	55.1 (201/365)	
Present	46.5 (53/114)	44.9 (164/365)	0.770
Lung & pleural metastases at diagnosis*			
Absent	55.3 (63/114)	61.9 (226/365)	
Present	44.7 (51/114)	38.1 (139/365)	0.205
Liver metastases at diagnosis*			
Absent	92.1 (105/114)	92.3 (337/365)	
Present	7.9 (9/114)	7.7 (28/365)	0.938

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Bone metastases at diagnosis *			
Absent	74.6 (85/114)	71.8 (262/365)	
Present	25.4 (29/114)	28.2 (103/365)	0.562
Lymphatic nodes metastases at diagnosis *			
Absent	74.6 (85/114)	80.5 (294/365)	
Present	25.4 (29/114)	19.5 (71/365)	0.170
Adrenal glands metastases at diagnosis *			
Absent	95.6 (109/114)	96.2 (351/114)	
Present	4.4 (5/114)	3.8 (14/365)	0.793
EGFR mutation status ‡			
WT EGFR	65.3 (32/49)	60.0 (102/170)	
EGFR sensitizing mutation	34.7 (17/49)	40.0 (68/170)	0.502
KRAS mutation status ‡			
KRAS (-)	86.2 (25/29)	90.7 (107/118)	
KRAS (+)	13.8 (4/29)	9.3 (11/118)	0.476

SD: standard deviation, ECOG: eastern oncology group, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma virus oncogene.
*Estimation over 479 patients with stage IV disease and known metastases at diagnosis.
‡ Estimations over the number of patients tested for each molecular status

NSCLC among EGFR (+) women by hormonal status

Among 522 female patients, only 219 patients were tested for EGFR mutation status, among them only 85 (38.8%) patients harbored an EGFR mutation (17 [20%] were premenopausal and 68 [80%] were postmenopausal women). We did not find any differences between premenopausal and postmenopausal EGFR-mutated women in terms of BMI, tobacco, wood-smoke and, asbestos exposure, histology, disease stage, ECOG performance status, sites of metastases (brain, lung, liver, bone, lymphatic nodes, and adrenal glands) nor by KRAS mutation status (supplementary table II).[26]

Factors associated with the overall survival among EGFR- mutated women

Median OS for women harboring EGFR mutations was 32.4 months; in the univariate analysis the factors associated with a better OS included a good ECOG performance status (<2 vs. 2+) (38.9 vs. 12.9 months; *p*=0.012) and absence of adrenal glands metastases (no vs. yes) (32.4 vs. 8.3; *p*=0.009). We did not find differences in OS when evaluating by hormonal status, age, BMI, tobacco exposure, wood-smoke exposure, exposure to asbestos, disease stage, sites of metastases (brain, lung, liver, bone, lymphatic nodes, and adrenal

glands) nor by KRAS mutation status. None of the previously mentioned characteristics were independently associated with OS in the multivariate analysis (supplementary table III).[26]

NSCLC among wt-EGFR women by hormonal status

Among 522 female patients, only 219 were tested for EGFR mutation status; among them, 134 had wt-EGFR (32 [23.9%] premenopausal and 102 [76.1%] postmenopausal). Premenopausal wt-EGFR women were more likely to have a history of exposure to asbestos (25% vs. 3%; *p*<0.001). We did not find differences among premenopausal and postmenopausal wt-EGFR women by the other analyzed variables (supplementary table IV).[26]

Factors associated with the overall survival among wt-EGFR women with NSCLC

Median OS for women without an EGFR mutation was 32.1 months. In the univariate analysis the factors associated with OS were liver metastases (no vs. yes) (27.9 vs. 18.7 months; *p*=0.044) and *KRAS* mutation status (absent vs. present) (37.6 vs. 15.8 months; *p*=0.002). We did not find any significant differences in OS for the

other analyzed factors. None of the characteristics were independently associated with OS in the multivariate analysis (supplementary table V).[26]

Discussion

Lung cancer presentation, behavior and response to treatment depend on several factors including grading and staging of the disease, molecular and histological tumor features, and recently it have been proposed that sex and hormonal status are also associated with tumor behavior and survival of NSCLC patients, however, this information is still controversial. We reported differences in lung cancer presentation and OS according to the sex and hormonal status in a Mexican population of NSCLC.

We observed that women presented higher frequencies of wood-smoke exposure, EGFR sensitizing mutations, better ECOG performance, had a higher frequency of obesity and, as a result, higher BMI compared to men who instead exhibited a higher smoking index compared to women. OS was also higher in women compared to men, as well as in patients who were overweight, never smokers, had a good ECOG performance status, a wt-KRAS molecular status and were free of liver metastases.

In Mexico, as in other Latin-American countries, smoking habit does not appear to be the main risk factor for the development of lung cancer in women, since a higher percentage of women with NSCLC are never smokers. Previously it had been reported that wood-smoke exposure was an important risk factor to develop lung cancer in non-smoking Mexican women,[27,28] we observed that this factor remains relevant in the etiology of lung cancer in women to this day. In addition EGFR-mutations have also been associated with patients who are never smokers and women,[29] which was also confirmed by our results. Nowadays patients with lung adenocarcinomas that exhibit EGFR sensitizing mutation are treated with targeted therapy based on Tyrosine Kinase Inhibitors (TKIs) which produce a high response rate as a first-line treatment.[30] Moreover, obesity and high BMI were recently correlated with a reduced risk of death from lung cancer[31] consistent with the data reported in the present study. The characteristics exhibited by women with lung cancer in our population, such as lower smoking index, higher frequency of EGFR sensitizing mutations, better ECOG performance status and higher frequency of obesity as well as high BMI, could explain the better OS we observe in women compared to men.

Analysis by hormonal status showed that postmenopausal women exhibited a higher wood smoke exposure and wood smoke exposure index as well as

tobacco-smoking index compared to premenopausal women, who exhibited higher asbestos exposure. No differences were observed in tobacco exposure, BMI, histology, disease stage, ECOG performance status, sites of metastases and mutation in KRAS and EGFR by hormonal status. Nonetheless an interesting finding was the fact that postmenopausal women presented a better OS compared to their premenopausal counterparts. Older postmenopausal women survived a median of 31.1 months while younger premenopausal women survived only 19.4 months. The lower OS observed in premenopausal women could be explained by the differences in estrogen levels between premenopausal and postmenopausal women and the influence of this hormone in lung carcinogenesis.

Previous studies which have considered hormonal status among women with lung cancer have reported that premenopausal women presented with more advanced stage-disease at the time of diagnosis, less differentiated tumors, distant metastases and had a worse prognosis [21,22] compared to postmenopausal women and men. Although our results did not show significant differences in disease stage, ECOG performance status and metastatic site by hormonal status, premenopausal women exhibited a statistically significant lower OS compared to postmenopausal. In Mexico as in other countries, lung cancer continues to be diagnosed at advanced stages both in women and men; it is likely that this delay in diagnosis and therefore treatment, as well as other problems concerning hospital admission, as well as the low percentage of premenopausal women analyzed in this study could conceal the probable differences in lung cancer metastases and stage at diagnosis by hormonal status. However, our study supports that there are differences in lung cancer behavior, presentation and prognosis not only by sex but also by hormonal status, which can be explained by the response of lung cancer to steroid sexual hormones.[14,32,33] Recently lung cancer is being considered as a hormone-dependent cancer, since NSCLC tissues and cell lines exhibited strong estrogen (ER) and aromatase enzyme expression;[14,32] the estrogen pathway has been related to carcinogenic pathway activation and lung cancer progression.[34,35] Probably the lower circulating estradiol levels present in postmenopausal women compared to premenopausal, explain the differences in terms of OS, however it is important to conduct a prospective study where hormonal biochemical characteristics (e.g. circulating estrogen level, exogenous estrogen intake, expression of estrogen receptor and aromatase in tumor) can be evaluated.

On the other hand, hormonal status does not appear to influence EGFR mutational profile, since no differences were observed between premenopausal and

postmenopausal women or by BMI, tobacco exposure, wood-smoke exposure, exposure to asbestos, histology, disease stage, ECOG performance status, sites of metastases and KRAS mutation status. Also no difference was observed in terms of the OS among EGFR-mutated women. Recently a functional relationship and a crosstalk between the estrogen and EGFR pathways in lung adenocarcinoma have been observed.[36,37] NSCLC cells stimulated with estradiol resulted in EGFR pathway activation and EGFR activation also increased the expression and activity of the aromatase enzyme in NSCLC cells.[14,38] Although premenopausal women usually exhibit higher circulating estrogen level compared to postmenopausal women and men, it is probably that the level of estrogen in tumor microenvironment as well as the ER tumor expression are important factors to consider in terms of stimulating EGFR expression as previously reported.[38,39] Accordingly, it is important to conduct a prospective study to evaluate the hormonal characteristics of each patient as well as hormone tumor status (aromatase and ER tumor expression, levels of estrogen in tumor microenvironment, etc.), in relation to EGRF expression, activity and mutation profile.

Finally, this study supports the differences by sex and also by hormonal status in lung cancer presentation and sustains the relevance that sexual hormones have in the course and prognosis of lung cancer, since women exhibited higher OS compared to men and premenopausal women showed a significantly lower OS compared to postmenopausal women. Due to the differences that lung cancer exhibited by sex and hormonal status it is important to consider not only women and men as it has previously been done, but also premenopausal and postmenopausal women in futures studies. Moreover the identification of hormonal markers in tumors from patients with lung adenocarcinoma would be relevant in order to design new treatment schemes based on anti-hormone therapy as has been recently proposed.[40-42]

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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