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Lung Cancer in Women with a Family History of Cancer: The Spanish Female-specific Database WORLD07

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Abstract. *Background: The WORLD07 project is a female-specific database to prospectively analyze the characteristics of Spanish women with lung cancer. Patients and Methods: We analyzed and compared lung cancer features in women with and without a family history of cancer/lung cancer. Results: Two thousand and sixty women were included: 876 had a family history of cancer (lung cancer, 34%) and 886 did not, with no significant differences between groups, except for smoking status (p=0.036). We found statistically significant correlations between epidermal growth factor receptor (EGFR) mutation and smoking status in patients with a family history of cancer (r=−0.211; p<0.001) and lung cancer (r=−0.176; p<0.001). Longer median overall survival was observed in women with a family history of cancer and lung cancer. Conclusion: Among Spanish women with lung cancer, a greater proportion were current smokers in those with a family history of cancer/lung cancer. There was a significant correlation between the presence of EGFR mutation and smoking.*

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Key Words: Cancer, lung cancer risk, Spanish women, family history, WORLD07 database, smoking, epidermal growth factor receptor, menopausal status.

Globally, lung cancer still remains the leading cause of cancer death in Europe (1), with contrasting trends in mortality rates between sexes (2-5). Differences in lung cancer between women and men exist due to factors such as pathophysiology, histology, etiology, risk factors, prognosis and treatment outcomes, indicating that the disease in women is biologically different from that in men (6-11). A retrospective study conducted by the Spanish Lung Cancer Group revealed significant differences in the pathophysiological characteristics

of lung cancer between female and male patients with advanced non-small cell lung cancer (NSCLC), and better outcomes for women compared to men (12).

Despite several studies having noted a decreasing trend in death rates from lung cancer in men, in women, lung cancer death rates continues to increase (3, 13-15). In fact, lung cancer was predicted to account for the highest cancer mortality rate among women in the European Union in 2015 (3). In Spanish women, the increases in lung cancer incidence and mortality have been greater than for other types of cancer, including of the colon and breast (14).

Lung cancer is frequently cited as an example of a malignancy almost exclusively attributable to environmental exposure (16). The role of family history of cancer as a potential risk factor has been the subject of numerous studies (17-22). Findings from the literature have suggested that a family history of lung cancer is a predictor of an increased risk of developing the disease (17, 20, 21), especially in those aged less than 50 years (19). Likewise, in never-smokers, the risk of lung cancer has been shown to be increased among those with familial aggregation of lung cancer (23, 24). Additionally, patients with lung cancer with a first-degree relative with lung cancer have been shown to have a worse outcome than those without a family history (25).

All the above prompted the Association for Research Lung Cancer in Women (ICAPEM group) to conduct a female-specific database to prospectively analyze the characteristics of Spanish women with lung cancer in order to gain a better understanding of lung cancer in this group of patients. This is the WORLD07 project. The aim of this study was to characterize and compare the clinical, histological, and molecular features of Spanish women diagnosed with lung cancer with and without a family history of cancer or lung cancer participating in the WORLD07 project.

Patients and Methods

Design and study population. The WORLD07 project was a prospective, multicenter, female-specific epidemiologicaI study conducted in 38 Oncology-based centers across Spain, in accordance with the Declaration of Helsinki including all amendments. The study was approved by the Institutional Review Board at each hospital participating in the study, and all patients provided their written informed consent to the use of their data prior to inclusion.

All consecutive adult (aged ≥18 years) women with a pathological diagnosis of lung cancer, regardless of whether they were receiving treatment for the disease, were eligible for the study.

Following routine clinical practice, patient data were prospectively gathered from both medical records and interviews conducted by trained interviewers, using a standardized questionnaire that was prepared by the ICAPEM Board. Patient data were recorded in an electronic database. The security and confidentiality of the data in the database was guaranteed.

Data collected included age, body mass index, educational level, family history of cancer (first- and second-degree relatives) and patient's previous history of cancer, race, Eastern Cooperative Oncology Group (ECOG) performance status, number of children, menopausal status (premenopausal or postmenopausal), previous hormone replacement therapy (HRT), smoking status, other lung cancer risk factors, histology, disease stage, epidermal growth factor receptor (*EGFR*) mutational status or other molecular markers tested, age of menarche, type and duration of HRT, oral contraceptive use, lung cancer history and treatment, and survival data.

Smoking status was defined according to the Centers for Disease Control and Prevention tobacco glossary (26) as current smoker (an adult who has smoked 100 cigarettes in their lifetime and who currently smokes cigarettes), former smoker (an adult who smoked at least 100 cigarettes in their lifetime but who had quit smoking at the time of the interview) and never smoker (an adult who has never smoked, or who has smoked fewer than 100 cigarettes in their lifetime). Information on passive smoking was also recorded, defined as the breathing in of cigarette smoke from people who are smoking nearby.

Statistical analysis. Descriptive analyses were used to analyze the clinical, histological and molecular characteristics of patients. Overall survival (OS) was defined as the date from pathological diagnosis of lung cancer to death or last recorded follow-up, and was calculated using the Kaplan–Meier method to construct survival plots and the log-rank test was used to analyze differences in survival. A bivariate analysis of variables associated with family history (yes/no) as the dependent variable was conducted. Variables with statistical significance or with $p<0.25$ in the bivariate model were analyzed in a multivariate logistic regression model. Odds ratios (OR) and 95% confidence interval (CI) were calculated for the independent predictive factors. Possible correlations between age, stage, histology, *EGFR* status (wild-type or mutant), and smoking or menopausal status were investigated using the Pearson correlation coefficient. Tumor biopsy samples were tested for *EGFR* mutations (exons 18, 19, 20, and 21) using polymerase chain reaction. Significance level was set at $p<0.05$ and all statistical analyses were carried out with the Statistical Package for the Social Sciences (version 13.0; SPSS Inc., Chicago, IL, USA).

Results

Patients. From October 2007 to December 2012, a total of 2,072 women with lung cancer were recruited and followed-up until December 2013. Of these, 12 women were non-eligible, hence the study population comprised of 2,060 patients.

A total of 876 (42.5%) women reported having a family history of cancer, among these, over half had a first-degree relative with cancer. The most common malignancies in a family member were lung (34.7%), colon (25.0%) and cervical (17.6%) cancer. There were no significant differences in family history between patients with small-cell lung cancer (SCLC) and those with NSCLC (Table I).

Patient characteristics and demographics according to whether had a family history of cancer or not are shown in Table II. We found a significant difference in the proportion

Table I. *Characteristics of patients' family history of cancer.*

Characteristic	SCLC (n=285)	NSCLC (n=1,775)	Total (N=2,060)
Family history of cancer			
Yes	124 (43.5)	752 (42.4)	876 (42.5)
No	132 (46.3)	754 (42.5)	886 (43.0)
Missing/unknown	29 (10.2)	269 (15.1)	298 (14.5)
Relationship			
First-degree	66 (53.2)	401 (53.3)	467 (53.3)
Second-degree	16 (12.9)	123 (16.4)	139 (15.9)
First and second degree	36 (29.0	192 (25.5)	228 (26.0)
Missing/unknown	6 (4.8)	36 (4.8)	42 (4.8)
Type of cancer			
Lung	43 (34.7)	261 (34.7)	304 (34.7)
Colon	32 (25.8)	187 (24.9)	219 (25.0)
Breast	6 (4.8)	31 (4.1)	37 (4.2)
Cervical	26 (21.0)	128 (17.0)	154 (17.6)
Ovarian	2 (1.6)	11 (1.5)	13 (1.5)
Head and neck	15 (12.1)	65 (8.6)	80 (9.1)
Gastrointestinal	20 (16.1)	97 (12.9)	117 (13.4)
Endometrial	3 (2.4)	14 (1.9)	17 (1.9)
Liver	9 (7.3)	56 (7.4)	65 (7.4)
Leukemia	3 (2.4)	34 (4.5)	37 (4.2)
Pancreatic	8 (6.5)	37 (4.9)	45 (5.1)
Prostate	6 (4.8)	71 (9.4)	77 (8.8)
Kidney	4 (3.2)	21 (2.8)	25 (2.9)
CNS	6 (4.8)	24 (3.2)	30 (3.4)
Uterine	7 (5.6)	18 (2.4)	25 (2.9)
Bladder	7 (5.6)	29 (3.9)	36 (4.1)
Other	19 (15.3)	105 (14.0)	124 (14.2)

Data are number of patients and percentage (%). CNS, Central nervous system; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

of patients with smoking history between both groups (p=0.036). Overall, in patients without a family history of cancer, there was a higher proportion of never smokers (43.0%) and a lower proportion of current smokers (40.5%) than in patients with a family history of cancer (36.4% and 47.2%, respectively). Most patients in both groups were postmenopausal (79.6% and 81.9% for patients without and with a family history of cancer, respectively) and had not received previous HRT (73.7% and 76.9%, respectively).

There were no statistically significant differences between the groups of patients with previous history of lung cancer and those without (Table II).

Regression analyses. Logistic regression analysis showed a positive correlation between smoking status (current smoker, former smoker, and never-smoker) and family history of cancer (yes/no), indicating that smoking was associated with an increase in the 'risk' of having a family history of lung cancer (OR=1.31; 95% CI=1.086-1.585; p=0.005). We found that the power of classification, specificity, and sensitivity were 53.4%, 59.2%, and 47.5%, respectively.

Subgroup correlations. In patients with a family history of cancer, *EGFR* mutation was significantly associated with smoking (r=–0.211; p<0.001). A similar result was obtained for smoking status between current smokers *versus* never smokers or former smokers (r=–0.292; p<0.001). There was no correlation between *EGFR* mutation and menopausal status (r=0.078; p=0.111).

In patients with a family history of lung cancer, we found a significant association between *EGFR* mutation and smoking (r=–0.176; p<0.001). There was no correlation between *EGFR* mutation and menopausal status (r=0.070; p=0.117).

Survival. Median OS for the total population was 24.0 (95% CI=22.1-26.0) months. Median OS was 23.0 (95% CI=20.7-25.3) months in patients without a family history of cancer *versus* 25.3 (95% CI=21.9-28.8) months in patients with a family history of cancer (log-rank p=0.029) (Figure 1A). We found a median OS of 24.9 (95% CI=20.8-29.0) months in patients without a family history of lung cancer *versus* 29.9 (95% CI=21.7-38.0) months in patients with a family history of lung cancer (log-rank p=0.191) (Figure 1B).

Discussion

To the best of our knowledge, this is the first study addressing the impact of a family history of cancer or lung cancer on a large population of women with lung cancer in Spain.

In our analysis of the WORLD07 study, we found that nearly 43% of patients had a family history of cancer, with a first-degree relative being the most frequently affected family member category in just over half of the patients. Although we did not record significant differences between patients with SCLC and those with NSCLC, our findings suggest that patients' characteristics were similar for those with a family history of cancer and those without, except for smoking status. Among those women without a family history of cancer, it was found that there was a higher proportion of patients who had never been smokers than those who were current smokers, whereas among patients with a family history of cancer, we found a lower proportion of patients who had never smoked in comparison to those who were current smokers. Although there is a lack of information regarding this correlation, the clinic-based case–control study conducted by Lin *et al*. with Chinese never-smoker patients, showed that familial aggregation of cancer or lung cancer in non-smoker patients had been shown to increase their risk of lung cancer (24).

In our series, regression analyses revealed weak correlations (albeit statistically significant) between the presence of the *EGFR* mutation and smoking habit in patients with both a family history of cancer and lung

Table II. *Patient characteristics and demographics according to family history of cancer and lung cancer.*

	Family history of cancer		Family history of lung cancer	
	No (n=886)	Yes (n=876)	No (n=572)	Yes (n=304)
Median age (range), years	62.1 (49.9-74.3)	61.1 (49.5-72.7)	61.2 (49.9-72.8)	60.7 (49.2-72.2)
p-value	0.063		0.489	
Smoking history				
Never smoker	381 (43.0)	319 (36.4)	218 (38.1)	101 (33.2)
Former smoker	139 (15.7)	137 (15.6)	98 (17.1)	39 (12.8)
Current smoker	359 (40.5)	413 (47.2)	252 (44.1)	161 (53.0)
Missing/unknown	7 (0.8)	7 (0.8)	4 (0.7)	3 (1.0)
p-value	0.036		0.066	
Histology				
SCLC	132 (14.9)	124 (14.2)	81 (14.2)	43 (14.1)
NSCLC	754 (85.1)	752 (85.8)	491 (85.8)	261 (85.9)
Adenocarcinoma	548 (72.7)	532 (70.7)	352 (71.7)	180 (69.0)
Bronchioloalveolar cancer	31 (4.1)	32 (4.3)	17 (3.5)	15 (5.7)
Squamous cell carcinoma	79 (10.5)	89 (11.8)	55 (11.2)	34 (13.0)
Large cell carcinoma	43 (5.7)	51 (6.8)	35 (7.1)	16 (6.1)
Other	27 (3.6)	31 (4.1)	22 (4.5)	9 (3.5)
Missing/unknown	26 (3.4)	17 (2.3)	10 (2.0)	7 (2.7)
p-value	0.685		0.512	
NSCLC: TNM classification at diagnosis				
I	89 (11.8)	91 (12.1)	65 (13.2)	26 (10.0)
II	36 (4.8)	41 (5.5)	29 (5.9)	12 (4.6)
IIIA	67 (8.9)	82 (10.9)	57 (11.6)	25 (9.6)
IIIB resectable	26 (3.4)	23 (3.0)	11 (2.2)	12 (4.6)
IIIB unresectable	66 (8.8)	85 (11.3)	56 (11.4)	29 (11.1)
IV	458 (60.7)	420 (55.9)	268 (54.6)	152 (58.2)
Missing/unknown	12 (1.6)	10 (1.3)	5 (1.0)	5 (1.9)
p-value	0.446		0.343	
SCLC stage				
Limited	61 (46.2)	58 (46.8)	36 (44.4)	22 (51.2)
Extensive	67 (50.8)	65 (52.4)	44 (54.3)	21 (48.8)
Missing/unknown	4 (3.0)	1 (0.8)	1 (1.2)	0
p-value	1.000		0.428	
EGFR status				
Number of patients tested	410	420	276	144
Mutated	139 (33.9)	142 (33.8)	91 (33.0)	51 (35.4)
Wild-type	271 (66.1)	278 (66.2)	185 (67.0)	93 (64.6)
p-value	1.000		0.664	
Menopausal status				
Premenopausal	129 (14.5)	123 (14.0)	75 (13.1)	48 (15.8)
Postmenopausal	705 (79.6)	717 (81.9)	474 (82.9)	243 (79.9)
Missing/unknown	52 (5.9)	36 (4.1)	23 (4.0)	13 (4.3)
p-value	0.241	0.605		
Previous HRT				
Yes	49 (5.5)	70 (8.0)	46 (8.0)	24 (7.9)
No	653 (73.7)	674 (76.9)	445 (77.8)	229 (75.3)
Missing/unknown	184 (20.8)	132 (15.1)	81 (14.2)	51 (16.8)
p-value	0.002		0.631	

Data are number of patients (%), unless otherwise indicated. *EGFR*, epidermal growth factor receptor gene; HRT, hormone replacement therapy; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.

cancer, whereas no correlation between *EGFR* mutation and menopausal status was achieved, irrespective of the type of familial aggregation of cancer. However, our results are not concordant with previous literature. Studies including both sexes have shown a link between a family history of lung cancer and *EGFR* mutation in patients with NSCLC (27) and in patients with NSCLC who have never smoked (27-29). Smoking status is related to family history due to social

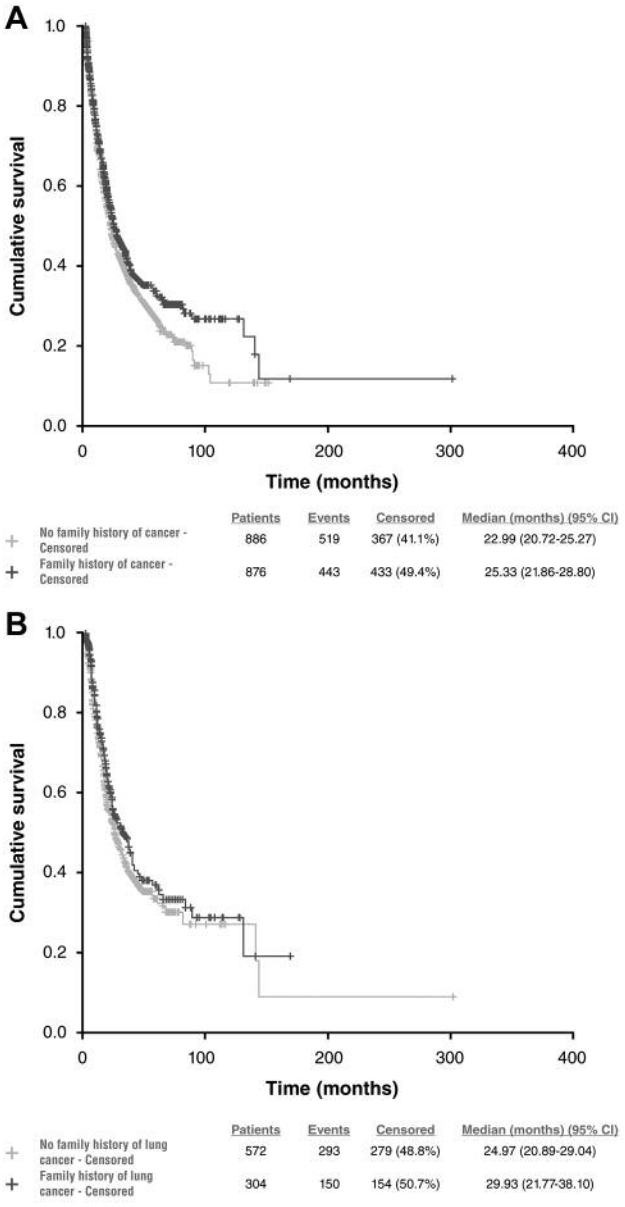

Figure 1. *Kaplan–Meier survival plots for overall survival stratified according to family history of cancer (A) and lung cancer (B).*

reasons and tumors harboring *EGFR* mutations (28). Possible reasons for the different results found in our series are that fewer than half of the eligible patients had been tested for *EGFR* status, and there was a high incidence of passive smokers (nearly 15%). Besides the different geographical locations, genetics and environmental or lifestyle factors, there are possible etiological factors for lung cancer in never-smokers that could partly explain our results (30). An important point regarding our results in women with lung cancer and a family history of cancer who were current smokers is that cancer risk is heavily influenced by extrinsic factors, in addition to the accumulation of endogenous mutations by intrinsic processes (31).

It would have been interesting to know the smoking history of those families with a past history of cancer or lung cancer, in order to investigate the possible links with passive exposure to tobacco smoke or the inducement to smoke in the WORLD07 population. Nonetheless, this analysis could still be addressed in the future.

Overall, when comparing the median OS of patients, we found that those without a family history of cancer or lung cancer presented a slightly shorter OS than those with a family history, although these differences only achieved statistical significance among those patients with and without a family history of cancer. Li *et al*. reported that patients with NSCLC and a family history of lung cancer had improved survival compared to patients without such history, but only at early stages of the disease (32). However, no difference was found between patients with or without a family history of cancer. In contrast, Ganti *et al*. reported that median survival in patients with a family history of lung cancer was lower than in patients without a family history (52 *vs*. 58 months) (25). It is not clear why in the WORLD07 population the OS was longer in patients with a family history of cancer or lung cancer, and there are insufficient data in the literature to draw any definite conclusions. A possible explanation could be that there are many biological subtypes of lung cancer in women associated with family history that are linked to genetic differences but also lifestyle/environmental factors (33, 34).

Some limitations to this study need to be highlighted when interpreting the results. Firstly, the actual study comprised a female cohort of patients with lung cancer. Therefore including a male cohort would have added important information by allowing comparisons between the sexes, revealing conclusions of differences between both sexes. Secondly, the poor specificity and sensitivity found in the regression analyses mean that it is difficult to reach any firm conclusions. Thirdly, despite the fact that this was a prospective epidemiological study, there was a high rate of missing or unknown data, which could have affected the results for some of the outcomes.

Despite all these limitations, our study does have strengths. These comprise the prospective design, the high number of patients included from all regions in Spain, and the inclusion of a large amount of epidemiological, clinical, molecular, and therapeutic data used to investigate potential differences between women with a family history of cancer *versus* those without. It would have been very interesting to know the clinical characteristics of other populations of women with lung cancer and a family history of cancer in order to compare our data.

In conclusion, this analysis shows that in Spanish women with lung cancer, there were a greater proportion of current smokers in those with a family history of cancer or lung cancer in comparison to those without. There was a significant correlation between the presence of *EGFR* mutation and smoking habit. In addition, OS was longer in patients who had a family history of cancer or lung cancer than that found for the overall population.

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