Lung cancer in women. An overview with special focus in Spanish women

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Abstract:

Lung cancer incidence is decreasing worldwide among men but rising among women due to recent changes in smoking patterns in both sexes. In Europe, the smoking epidemic has evolved different rates and times, and policy responses to it, vary substantially between countries. Differences in smoking prevalence are much more evident among European women reflecting the heterogeneity in cancer incidence rates. Other factors rather than smoking and linked to sex may increase women's susceptibility to lung cancer, such as genetic predisposition, exposure to sex-hormones and molecular features, all of them linked to epidemiologic and clinical characteristics of lung cancer in women. However, biological bases of sex-specific differences are controversial and need further evaluation. This review focuses on the epidemiology and outcome concerning non-small cell lung cancer in women, with emphasis given to the Spanish population.

Key words: Lung cancer, women, epidemiology, outcome, Spain

Lung cancer burden worldwide in women: mortality and incidence

Lung cancer is the most common malignant disease worldwide [1]. By the year 2008 there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the major cause of cancer death, with 1.38 million deaths around the world (18.2% of the total). A large increase in lung cancer incidence is being observed since 1980, especially in developed countries, where it has been estimated that 31% of all lung cancer cases occurred [2].

In women, lung cancer incidence rates are generally lower than in men, and it has become the fourth most frequent cancer of women worldwide (513,000 cases, 8.5% of all cancers) and the second most common cause of death from cancer (427,000 deaths, 12.8% of the total). Incidence rates are higher in developed countries (19 per 100,000 women) than in less developed countries (10 per 100,000 women, such as Middle Africa where lung cancer is the 15th most frequent cancer) [2] (Table 1).

Lung cancer is a major cause of premature mortality; about 20% and 10% of all premature deaths are due to lung cancer in men and women, respectively [3]. Because of its fatality (the ratio of mortality to incidence is 0.86) and the lack of variability in survival in developed and developing countries, the highest and lowest mortality rates are estimated in the same regions [2] (Figure 1).

Table 1. Estimated mortality and incidence of lung cancer in females in some countries in 2008. Estimated number of cancer deaths/cancer cases and age-standardized rates (World standard population, ASR-W) x 100,000 females.

Countries	Mortality		Incidence	
	Number of deaths	ASR-W	Number of cases	ASR-W
USA	71,032	24.1	100,330	36.2
Denmark	1,790	30.0	1,974	34.6
Hungary	2,733	26.2	3,051	30.7
United Kingdom	15.349	20.8	17,974	25.8
Norway	853	18.3	1,122	24.7
Sweeden	1,750	16.3	1,589	16,4
Poland	5.643	15.5	6,513	18.6
Austria	1,241	13.6	1,392	16.9
Czech Republic	1,483	13.2	1,826	17.1
Germany	12,521	12.8	15,070	16.4

France	6,884	10.8	8,194	14.7
Italy	7,303	9.0	8,493	11.4
Spain	2,722	6.2	3,126	7.7
EU-27	**71,099**	**12,8**	**82,532**	**16.0**

Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 23/2/2013

Estimates of lung cancer incidence in women in 2012 (EU-27 and Spain)

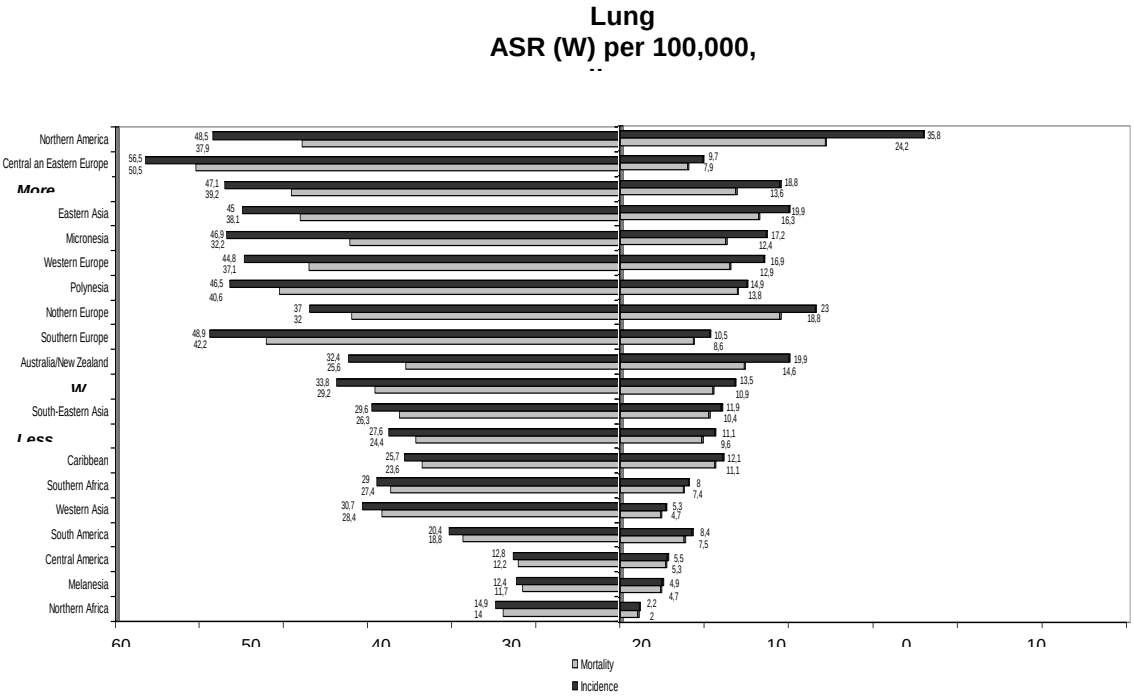
The International Agency for Research on Cancer (IARC) has published regularly over the last decades estimates of lung cancer incidence, mortality and prevalence worldwide (GLOBOCAN) and in the 27 member states in European Union as in 2007 (EU-27), as well as individually at the country level (EUCAN).

According to latest EUCAN estimates derived for the year 2012, which were based on age-period-cohort modelling data derived from the IARC and WHO databases, lung cancer is the third most frequent cancer in women from the EU-27, with an estimated 98,188 new cases, an age-standardized rate (European standard population; Age-Standardized Rate (ASR) EASR-E) of 26.1 per 100,000 women, representing the 8.18% of the total cancer incidence in females. Denmark, Hungary and Netherlands were the European countries with the highest incidence rates in females, with an estimated ASR-E of 54.9, 46.5 and 44.5 per 100,000 women, respectively. The lowest incidence rates were reported in Russia, Belarus and Ukraine (9.8, 8.7 and 8.7 per 100,000 women, respectively) (Figure 2). Lung cancer is the fourth most common cancer among women in Spain, after cancer of the breast, colon and corpus uteri, with 4.935 lung cancer incident cases and an ASR-E of 15.7 per 100,000 women (5.6% of all cancers) [4,5].

Latest estimates over the period 1981-2006 and short-term projections up to 2012 for cancer incidence and mortality in Spain, derived from 13 Spanish population-based cancer registers data and by applying the Mortality-Incidence Analysis MODel (MIAMOD) method, show marked differences in lung cancer incidence and mortality rates between both sexes. In men, incidence and

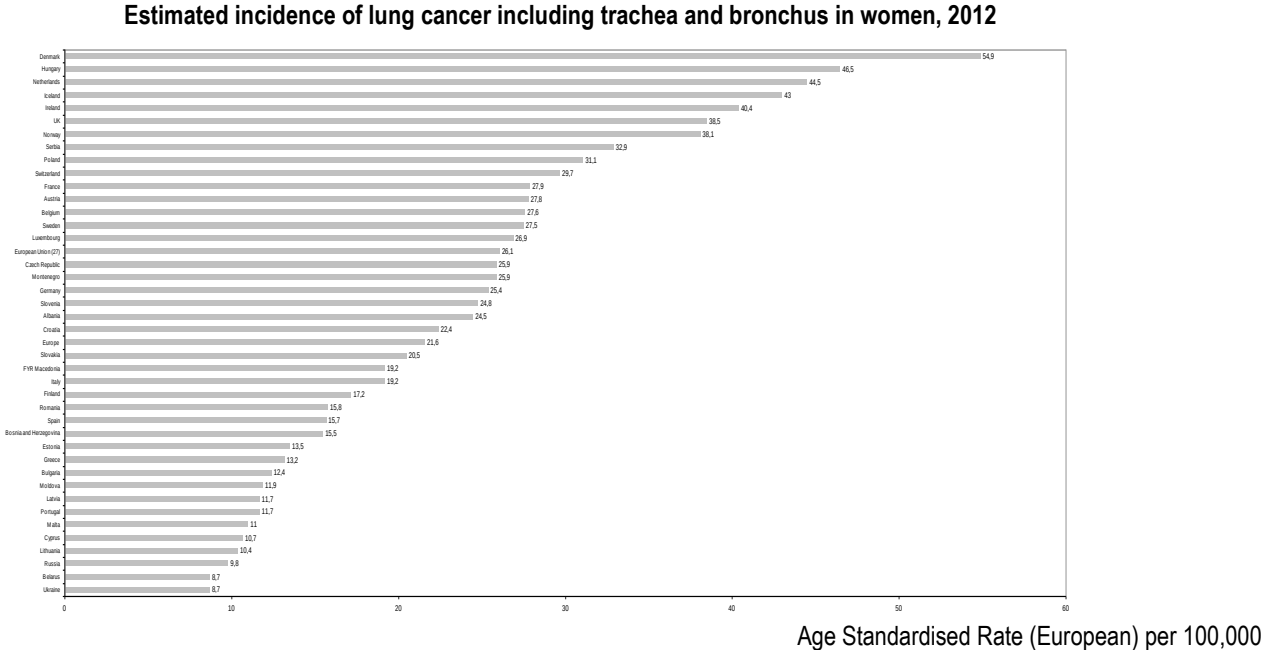
mortality reached a peak during the late 1990s and decreased afterwards. In women, however, both mortality and incidence were on the rise. This increase among Spanish women was of greater magnitude than that observed for other cancers, such as breast and colon cancer [6]. As a result, male-to-female ratio of age-standardized incidence rates was almost 7-fold in 2006 and 4-fold in 2012. According to this Spanish estimates, the number of lung cancer cases estimated in women in 2012 was 5,228, with an ASR-E of 17 per 100,000 women, compared with 3,498 cases in 2006, with an ASR-E of 12 per 100,000 women (Figure 3).

Figure 1: Estimated age-standardized (world standard population) incidence and mortality rates for lung cancer in 2008.



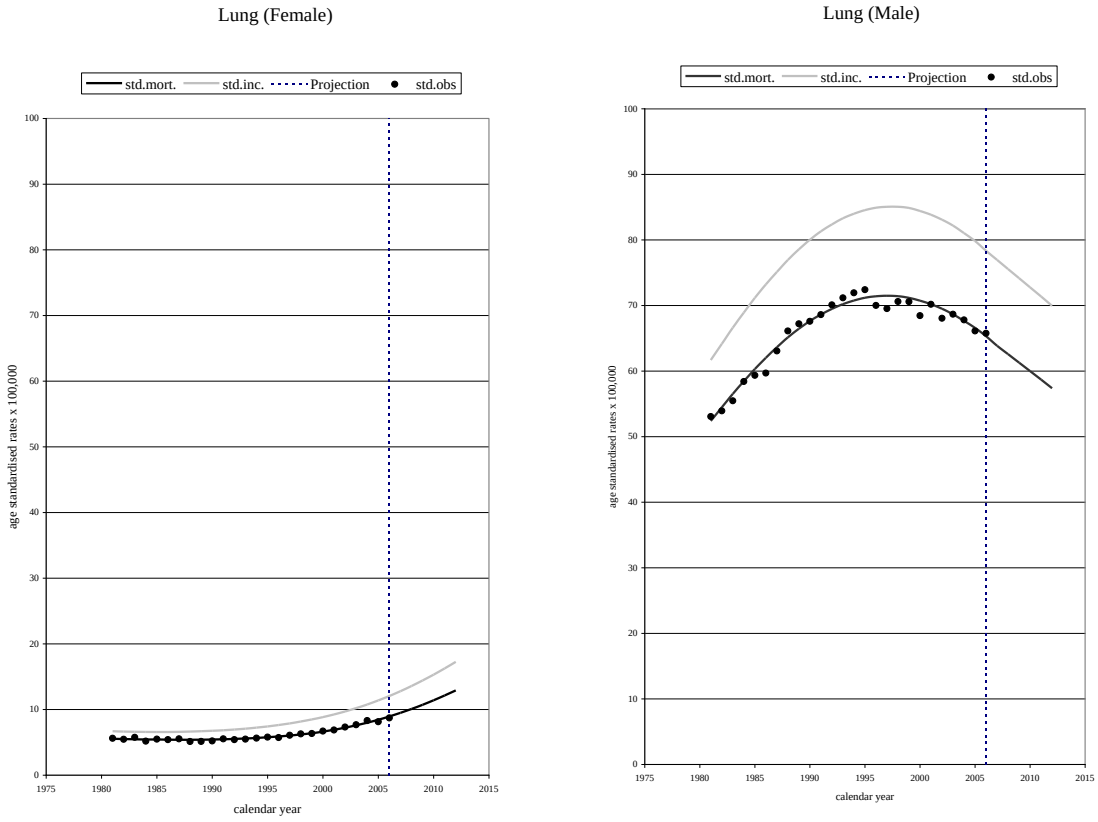
Source: Modified from GLOBOCAN 2008.

Figure 2: Estimated incidence of lung cancer in women in EU-27 in 2012, overall and by country (Age-standardized rates using European Standard population)



Source: Modified from EUCAN/IARC

Figure 3: Mortality and incidence estimates (black and grey continuous lines) 1981-2012 for lung cancer in Spain, compared to observed mortality data (dots). Men and women age-standardised rates (European standard population) per 100,000 inhabitants.



Source: Sánchez MJ, et al (Ann Oncol 2010)

Another study on lung cancer incidence and mortality trends in Spain, using similarly data from the Spanish population-based cancer registries, reported trend analysis of the lung cancer incidence rate, adjusted by age and Spanish population cancer registry. Results of this study showed that among men maximum incidence was reached in 1995-1999, with a rate of 76.5 per 100,000 men and rose by 2.7% per year until 1991, after which it began to decrease. By contrast, among women, the incidence rate increased progressively (3.20% per year) until 1989, and increased annually by 4.4% thereafter [7].

Lung cancer mortality in European women: trends and predictions

Several studies have reported lung cancer mortality statisitcs using data from the World Health Organization (WHO) database and considering the EU-27 as a whole [8,9,10], as well as for a number of separate countries [8,10,11]. According to these studies, lung cancer mortality in men has been declining since the late 1980s in most European countries. In the EU as a whole, mortality rates decreased from 53.3 per 100,000 men in the late 1980s to 44.0 per 100,000 men (17% fall) in the early 2000s [8]. In the EU-27 countries, it has been predicted that it will decrease to 37.2 per 100,000 men (15% fall) in 2013 [9].

An upward trend in lung cancer mortality among European women is observed, with an approximate 50% increase since the mid 1960s to the early 2000s in 36 European countries [11]. In the EU as a whole, lung cancer mortality in women increased from 9.0 to 11.4 per 100,000 women (+27%) at all ages and from 13.9 to 18.5 per 100,000 women (+33%) at middle ages (35-64 years) between the late 1980s and the early 2000s [8]. An additional rising trend in mortality has been predicted for 2013 in the EU-27, reaching a rate of 13.9 per 100,000 women and increasing by 7% since 2009 [9].

Analyses of mortality trends in 33 European countries between 1970 and 2009, have revealed that the increase in female lung cancer mortality is observed up to recent calendar years in most European countries, with the exception of Belarus, Malta, Russia and Ukraine, where relatively low rates are estimated,

and the UK, Iceland or Ireland, where high rates were reached in the mid/late 1990s and dropped down thereafter. In the EU, female lung cancer mortality rates rose over the last decade from 11.3 to 12.7/100,000 (+2.3% per year) at all ages and from 18.6 to 21.5/100,000 (+3.0% per year) in middle-aged women. Recent trends in young women (age 20-44) were more favourable in many European countries over the last calendar years with a 13% fall from 1.6 to 1.4/100,000 women, except in Belgium, Bulgaria, Denmark, Ireland, Malta, Portugal, Slovenia, and Northern Ireland. In Spanish women aged 35-64 years an increase in lung cancer mortality during 1990-2008 was seen, with an estimated annual percent change of 6.1%. A decline was observed only in women aged 20-44 years and in most recent years (2002-2008) although this was not statistically significant [10].

Table 3. Gender based differences in age, histology and smoking status in NSCLC

			% F	Age at Diagnosis		Histology in Female (%)			% NonSmokers	
	Year	N		M	F	ADC	SCLC	SCC	M	F
Ferguson[37]	1990	772	38	60	57	45	20.4	23.5	6	16
Zang[35]	1996	1889	41	NR	NR	46	17	20	8.2	12.8
De Perrot[38]*	2000	1,037	19	61	62	54	--	31	2	27
Minami[40]*	2000	1,242	27	64	62	86	--	9.5	8.6	87
Radzikowska[45]	2002	20,561	14	62	60	21.6	26.6	32.5	2.4	18.8
Visbal[41]	2004	4,618	41	68	66	59.5	NR	22	7.6	19.1
Fu[39]	2005	228,572	36	66	66	45	23	21	NR	NR
Hsu[36]	2009	695	45	65	59	81	14.3	4.8	22.9	93.6
Sagerup[42]	2011	40,118	35	NR	NR	31	20	15	NR	NR
Parent[47]	2011	1,290	15	68	67	53	20	13	5	83
Salmeron[46]	2012	10,990	10	67	67	47.3	8.1	12.9	NR	NR
WORLD07[48]	2012	1,371**	100	--	62	68	12.2	11.3	--	39.3

F: Female; M: Male; ADC: adenocarcinoma, SCC: Squamous cell, SCLC: small-cell lung cancer; F-Non-S: Female non smokers; NR: not reported; **surgical series; ** preliminary results*

The increase in women lung cancer mortality in most European countries over the last few years, particularly at middle ages, likely reflect a cohort effect due to an increased smoking initiation in generations born in the 1950s, who were

young adults in the 1970s and whose increasing smoking prevalence were also observed. However, the female lung cancer epidemic is still expanding in countries of western and southern Europe, particularly in France, Portugal and Spain, where smoking in women was uncommon before the 1970s and has been appreciably increasing up to the late 1990s, to level off only over the last decade [10].

By 2015, a further increase in female lung cancer mortality in the EU is predicted with 85,204 lung cancer deaths and reaching an overall rate of 14 per 100,000 women. In Spain the number of lung cancer deaths in women is projected to reach 7.1 deaths per 100,000 women by 2015, which is still the lowest rate when compared to all other European countries (France: 12.8 per 100,000 women, Germany: 14.8 per 100,000 women, Hungary: 28.5 per 100,000 women, UK: 21.9 per 100.000 women) [10].

Notwithstanding the persisting unfavourable trends in most European countries, lung cancer mortality in European women remains lower than in the USA, where lung cancer is the second most common cancer (110,110 new cases, 14% of all new cancer cases among women) and the first cause of cancer death among women (72,220 deaths, 26% of all cancer deaths) [12]. Lung cancer has indeed become the first cause of cancer death in women in several countries of Northern and Eastern Europe, including Denmark, Hungary, the Netherlands, Poland, Sweden and the UK [4]. However, if the rising mortality trend continues by 2015, deaths from lung cancer in women could overtake those from breast cancer, turning to the current leading cause of cancer death among European women [9].

Smoking prevalence. Is there a different women's perception of smoking?

Cigarette smoking is the major risk for lung cancer in men and women and reflects lung cancer incidence two or three decades later [11]. Studies that have attempted to quantity the risk of lung cancer in women associated with tobacco smoking have been unable to accurately quantify it. In a multicenter case-control study among French women and within the ICARE study, smoking

cigarettes at some time was associated with a 8-fold increase in lung cancer risk [13]. It has also been reported that nearly 270,000 new cancer diagnoses per year can be attributed to cigarette smoking in eight European countries (Italy, Spain, United Kingdom, the Netherlands, Greece, Germany, Sweden and Denmark), e.g. 80% of lung cancers are caused by tobacco [14].

A four-stage model of cigarette consumption and subsequent mortality among men and women has been developed. In stage IV there is a decrease in male and female smoking prevalence rates, with also declining death rates, such as in Western Europe. Stage III includes Eastern and Southern Europe, defined by the fact that smoking rates in women had just started to increase with few resultant deaths and the male prevalence beginning to decline [15]. This model reflects that in Europe, tobacco consumption has evolved different rates and times. In the EU, most countries presented very high smoking rates among men (50% or more) between the 1960s and 1970s, while tobacco consumption took a downturn in 1980s and 1990s. Smoking rates have decreased since 2000, with the largest decline observed in Northern European countries (Denmark, The Netherlands, Norway and Iceland) followed by Spain, Finland and the UK, and an overall higher decline among men than women [16].

The Eurobarometer 385 showed that as of March 2012, 28% of the EU population smoked (32% male and 24% female). Smoking was more common in Southern and Eastern Europe (except Portugal with 23% of smokers), with the highest proportions observed in Greece (40%), Bulgaria (36%), Latvia (36%) and Spain (33%), and fewest smokers were reported in Sweden (13%). The proportion of former smokers rose with the age, and 21% of European citizens were former-smokers (26% male and 17% female). Of note, the proportion of never smokers in EU was 51% [17]. Moreover, the heterogeneity in smoking prevalence is much evident among European women due to different time period in which women initiated their smoking habit (uncommon before the 1970s in Southern countries) and different proportion of former-smokers among women (usually lower than male) reflecting the important heterogeneity in the quality and possibility to compare data between countries [18] (Table 2). In Spain, the peak in smoking among men was reached in the 1950-59-birth cohort, but smoking among women was rare until 1960. Female

smoking prevalence rates increased progressively among subsequent cohorts until 1980. The age distribution of smoking prevalence in women in 1990 mimics that observed in men 40 years earlier [19].

Smoking cessation is associated with a reduction in the risk of all histologic types of lung cancer particularly among women [20]. In the EU-27, those countries with more developed tobacco control policies were strongly, but not statistically, associated with a lower population prevalence of smokers [21]. Moreover, in a cross-sectional study of 18 European countries, countries with more developed tobacco control policies had a higher level of smoking cessation than those with less developed tobacco polices [22]. However, almost 25% of smokers from 3 European countries (Germany, France and United Kingdom) believed that some cigarette brands are less harmful than others, indicating a misperception about the tobacco's risk over the smoking population. This misperception has male gender predominance but nearly 22% of women also had this feeling [23].

Nonetheless, progress towards greater tobacco control across Europe is not homogeneous and smoking prevalence among women remains disproportionately high in some countries. Understanding women's perception of smoking may help to identify ways to reduce its prevalence and prevent uptake of smoking. For instance, a telephone survey of 5,000 women from France, Ireland, Italy, the Czech Republic, and Sweden showed that current smokers tend to minimise the health risks of cigarette smoking, as they were more likely to have lower knowledge and belief scores about smoking and cancer, and also about lung cancer risk reduction after smoking cessation. Women with above-the-median income seemed to have higher knowledge and belief scores about smoking and cancer than those with a median income, though there were no appreciable differences by education status [24]. Moreover, women who had quitted smoking believed that implementing smoke-free laws would prompt smoking cessation as compared with women who still smoked [25].

The knowledge about tobacco and lung cancer risk in Spanish population is high as reflected a telephone survey of 1,000 Spanish adults, which was

conducted in 2011: 58% participants named lung cancer as the first disease related to smoking, and nine out 10 knew the relationship between tobacco and lung cancer and believed that more than 50% of smokers would develop lung cancer [26]. However, the proportion of Spanish daily smokers at age 15 years and more is still high (27.9% in men and 20.2% in women), and even higher between ages 25 and 54 years [27]. Furthermore, in Spain, about one out of 7 death occurring annually in individuals aged over 35 years is attributable to smoking (one out of 4 in men and one out of 29 in women) [28].

The onset and development of cigarette smoking occurs primarily during adolescence and the number of young people who smoke is increasing [29]. Eurobarometer 385 reported that 29% of young (15-24 years) European's are smokers [17]. The 2011 ESPAD database with more than 100,000 students from 37 European countries (Spain is not included) reported 28% of smokers among the adolescent population (students born in 1995) in both sexes, with a higher proportion in Czech Republic, Bulgaria, Finland and Italy. Of note is that, 7% of the students said that they had smoked daily at the age of 13 or younger [30].

Among Spanish young people aged 15-24 years, there were 21.7% smokers (22.5% men and 21.0% women) [27]. However, the smoking prevalence in Spanish girls aged 15 to 17 years old is higher than in boys, and girls are heavier smokers and are more frequently becoming daily smokers than boys [31].

Prevention of smoking initiation through effective policy initiatives targeted to adolescents is therefore a priority. A multilevel cross-national study at individual level in 29 European countries with more than 50,000 adolescents aimed at investigating the cost-effective tobacco control policies, showed that gender differences exist in how policy influences young people's smoking behaviour. It was concluded that the current policies (prices, bans an advertisements, legality of vending machines) are not sufficient for girls [32]. Cost-effective tobacco control policies should therefore be different according to gender.

Lung Cancer in women: Histology and presentation

All histological types of lung cancer are significantly associated with cigarette smoking. The association was stronger with squamous-cell carcinoma and small-cell lung cancer than with adenocarcinoma (ADC) [33]. However, the incidence rates for the various histological subtypes have changed over time turning to ADC as the most common histologic subtype in both genders [34]. This ADC histologic predominance has also been reported in different clinical database (Table 3) [35,36,37,38,39,40,41,42]. Low tar cigarettes and implementation of filters allow for deeper inhalation of tobacco smoke and facilitate the development of ADC by delivering carcinogens to the more peripheral area of the lung and filtered cigarettes were the ones marketed to women [43].

Risk of lung cancer development increases with age [44]. However, in numerous large studies women were diagnosed with lung cancer at younger ages than men (Table 3). Women also accounted for a higher proportion of patients younger than 50 years of age at lung cancer diagnosis compared to men [39,42]. Furthemore, women compared with their male counterparts, were more likely to be lifetime nonsmokers, smoked fewer years and consumed fewer cigarettes per day [45].

These epidemiologic features have been confirmed in Spain [46,47]. The prospective and multi-centre epidemiologic WORLD07 Spanish female-lung cancer database has recently been closed with 2101 patients included. Preliminary results including 1371 female patients have shown that the median age at lung cancer diagnosis was 61.9 years. Approximately 60% of patients were current/former smokers. ADC was the most common histological type (68%) followed by SCLC (12.2%) and SQC (11.3%). More than 40% of patients had a familiar history of cancer (32.7% lung cancer) and 12.1% had a previous cancer (38% breast cancer) [48] (Table 3).

Lung cancer risk in women: Different susceptibility?

Over the time, the relative risk of lung cancer in female smokers compared to male smokers has increased, hypothesising that women would be at increased susceptibility for lung cancer [35,49]. Recently, among heavy smokers (≥ 20 cigarettes per day), women carried a higher risk for lung cancer than men (OR 19.10, 95% CI 16.98-21.49 *vs.* 12.81, 95% CI 11.52-14.24, respectively) [50].

Different tobacco metabolism pathways could explain this gender-susceptibility difference. Tobacco carcinogens are absorbed rapidly and metabolized, involving members of the cytochrome P450 system. This process includes a *phase I* enzymes which activate carcinogens, and a *phase II* enzymes which produce a detoxifying conjugation reaction. Maintenance of an appropriate balance between the *phase I* and *II* enzymes is required to ensure optimal cellular protection. However, female smokers have a significantly *phase I* enzymes overexpression compared with male smokers probably induced by estrogens [51]. Also, inherited genetic polymorphisms affecting genes encoding tobacco carcinogen-metabolizing enzymes are related to increased tobacco-damage. The *phase II*-null genotype is greatest in female smokers. A recent meta-analysis suggested an association between lung cancer and *phase I* enzym polymorphysms, with an increased risk in women [52]. Women with both *phase I* and *phase II* enzym mutations had higher lung cancer risk than men independent of age and smoking history [53]. Furthermore, carcinogens present in tobacco smoke, may also exert their biologic effects through the formation of DNA adducts. Female smokers had higher levels of DNA adducts than males, probably due to estrogens induction and have lower capacity than men for DNA repairing [54]. Another mechanism that may be involved in the increased susceptibility is the overexpression of the X-linked gastrin-releasing peptide receptor (GRPR), more frequently expressed in female smokers at a lower mean pack-year exposure than male smokers, and its expression is linked to risk of lung cancer. GRPR expression also appears to be increased by exposure to estrogen [55].

However, epidemiologic evidence about gender susceptibility is controversial, and prospective cohorts did not support a higher female susceptibility to tobacco-related lung cancer [56,57].

Although smoking is the major risk factor for lung cancer, smoking habits are insufficient to explain gender-differences in lung cancer because about 25% of lung cancers occur in never smokers: lung cancer in never smokers is the 7th cause of cancer-related death worldwide if considered as an independent entity. In Europe, lung cancer in never smokers is the 17th cause of cancer mortality (9th for women) [58], and 21% of lung cancers are diagnosed in women who are never-smokers compared with 2% in non-smoking men [59,56]. However, other analysis observed a lack of gender difference in the incidence when the rates were standardized to all ages (40 years and above), albeit with some variation by age [60]. In contrast, data from six large cohorts showed that the truncated age-adjusted incidence to have non-smoking-associated lung cancer was higher among women compared with men [61]. Then, it is no clear whether this higher incidence in females is due to inherent susceptibility or to a greater contribution of risk factors other than smoking or this simply represents the fact that twice as many women as men are never smokers and this difference increases with age [62].

The effect of circulating estrogens is the most clinically relevant biological difference between NSCLC in both genders. Estrogen stimulation causes proliferation in NSCLC cell lines through the estrogen receptor (ER-alfa and ER-beta). ERs are expressed in both normal lung tissue and lung tumors in both sexes. However, patterns of of hormonal-receptor expression according to gender and smoking status or its prognostic factor remains undefined [63]. Several epidemiological studies have examined the effect of hormone-related variables (menarche and menopause) [64,65,66], and exogenous steroid hormones (hormonal replacement therapy) [65,67,68] in the etiology of lung cancer in women, but the findings have not been consistent, mostly driven by the confounding effect of some variables (smoking status and hormone therapy type) not accounted for in most studies. Furthermore, some studies have suggested a different risk of mortality according to endocrine therapy type [69,70]. With regard to oral contraceptive use, most observational studies found

no association with lung cancer risk. However, two studies have reported a decreased risk, but no trend with duration of use was detected. On the contrary, in other study, prolonged use of oral contaceptives was associated with a slightly increased risk [65]. In women with a history of breast cancer, there was a marked decrease in lung cancer mortality among those with prolonged antiestrogen treatment, but not a significant difference in lung cancer incidence [71].

A pooled analysis that included 24 case-control studies, demonstrated that individuals with a first-degree relative with lung cancer had 1.51-fold increased risk of lung cancer, after adjustment for smoking and other potential confounders, with no statistically significant differences by gender [72].

Incidence of HPV in lung cancer depends on geographical location and it was of 17% in Europe and 24.5% worldwide. All lung cancer subtypes were affected [73]. More work remains to determine the possible modyfing effect of gender and smoking history on this potential risk factor.

A meta-analysis revealed that pre-existing diabetes might increase the risk of lung cancer, (Relative risk: 1.11) especially among females (the mechanism behind this phenomenon is not fully understood) even after controlling for age and smoking history [74].

Sex differences in driver mutations

Those patients with an identified mutated oncogene and treated with a targeted agent, live longer than those patients who do not receive targeted therapy [75]. These mutations can have different predominance according to the gender.

The Epidermal Growth Factor Receptor (EGFR) mutation is present in approximately 16% of Caucasian patients diagnosed with metastatic lung adenocarcinoma. These mutations were more frequent in women and in never smokers. Male sex was a negative prognostic factor for PFS and OS in the multivariable analysis in EGFR mutant patients who received treatment with an EGFR tyrosine-kinase inhibitor (TKI) [76]. Also, a recent meta-analysis reported

that female gender significantly predicted a higher response rates to EGFR TKI [77]. However, in 159 *EGFR* mutant NSCLC and treated with EGFR TKI, multivariable analysis indicated that gender was not an independent prognostic factor for survival [78]. Nearly 90% of lung-cancer-specific EGFR mutations comprise a L858R and deletion mutants in exon 19. In Asiatic patients, deletions in exon 19 were more common in male gender while exon 21 deletions were more associated with female gender [79].

Interactions between ER and EGFR pathways have been suggested. EGFR protein expression is down-regulated in response to estrogens and is up-regulated in response to anti-estrogens, underlying the possibility of treating those women with drugs that target both factors [80]. In a pilot-study with 21 post-menopausal women, the combination of antiestrogen-therapy plus EGFR TKI, demonstrated disease activity and a subset analysis revealed that a higher ER-beta expression was related with a better OS [81].

In a retrospective study, HER2 mutation occurred in 65 (1.7%) of 3800 patients with lung adenocarcinoma, mainly female and never smokers [82]. In other study, HER2 mutation represented 6% of cases but it was not gender-related [83].

KRAS mutations have been found in 20-30% of NSCLC and most commonly occur in adenocarcinoma. However, the molecular epidemiology and prognosis of KRAS mutations remains unclear. A genotype of 3,026 lung adenocarcinomas for EGFR and KRAS mutations showed that, KRAS mutation did not differed according to gender, although there was a higher incidence among former or current smokers. KRAS G12C, the most common G > T transversion mutation in smokers was more frequent in women who were also younger than men with the same mutation and had smoked less [84].

BRAF mutations occurred in 36 (4.9%) of 739 patients with lung adenocarcinoma. Approximately half of BRAF mutations are non-V600E that was more frequent in smokers with no significant differences according to gender. The V600E BRAF mutations were significantly more prevalent in females, in never-smokers and was a negative prognostic factor compared with

patients without V600E mutation [85]. However, in other study, 18 out of 697 (3%) screened lung adenocarcinomas harbored BRAF mutation. BRAF mutant patients were current/former smokers with a female predominance [86]. In other retrospective clinical data, 36 (4%) of 883 tumors screened harboured BRAF mutation predominantly adenocarcinoma and smokers (29/36), but none of other baseline characteristics (age, gender and race) were significantly associated with *BRAF* mutation. Again, V600E *BRAF* mutation was suggested as a negative prognostic factor [87].

EML4-ALK rearrangements occurred in 5% of NSCLC patients, and it was more frequent in never/light smokers, adenocarcinoma subtype and young patients. Initially, this translocation was described more likely in men, but in the phase III trial in ALK positive patients, the proportion male/female was 43%/57% with no differences in the efficacy of crizotinib according gender-subgroup analysis [88].

ROS1 rearrangement has been detected in 1.7% of patients, usually young (median–age 49.8 years) and never-smokers patients with adenocarcinoma subtype with a certain female predominance (61% female vs. 39% male) [89].

Estimated RET rearrangements prevalence is 1%-2%. RET-positive tumors are more commonly found in never smokers and adenocarcinoma histology subtype. In resected NSCLC, RET positive tumors had roughly equal sex distribution [89].

It should be pointed out that this gender predominance in some driver mutations could be attribute to women are the highest proportion of lung cancer in never-smokers, and not to clear gender predominance. Also, there is no clear evidence supporting a statistically significant efficacy difference with these new drugs according gender-subgroup analysis.

Lung cancer outcome in women

EUROCARE-4 analysis including 1.6 million patients (40% women) reported that there was a survival difference by gender of 2.4% for lung cancer patients, suggesting a different exposure to risk factors among women and that sex

hormone patterns may have a role in women's survival [90]. However, in the WORLD 07 database, the menstrual status did not influence on survival (pre-menopausal women vs. post-menopausal women: 24.2 months and 27.5 months, respectively) [91].

Multiple large population-based studies have identified a superior response to NSCLC treatment in women compared with men regardless of stage, age, therapeutic modality, or histology [92,39].

The European Thoracic Oncology Platform Lungscape Project, collected clinical data from 20 European countries (36.2% women) with resected stage IB-IIIA NSCLC, and reported a higher statistically significant survival benefit in female [93].

The evidence of survival benefit in women with advanced disease is very consistent. However, women experienced more gastrointestinal and neuropathy treatment toxicity. It is postulated that decreased DNA repair capacity in women might be responsible for the increased response rate and toxicity with platinum agents [94]. This survival benefit among women even appears with new drugs such as bevacizumab (only in young-aged women) [95]. However, these studies are limited by the inability to control for all factors known to influence the outcome, such as comorbidities and smoking history. An analysis that covered eight Spanish regions 5-year relative survival for lung cancer was 10.2% (not different from other European countries, 9.7%) with a survival sex-related differences (lower among men) [96].

A pooled retrospective analysis of four Spanish trials with 1191 advanced-NSCLC patients (14.9% women), women had a longer survival than men in multivariable analysis [97].

The improved survival of women with lung cancer could be explained by differences in histology, smoking history, and different driver mutation pattern among women.

Regarding histology as prognostic factor, a pooled analysis with 2349 patients (34% women), only women with adenocarcinoma subtype had a longer survival

[98]. By contrast, a recent meta-analysis, reported significantly better survival for women regardless of stage, smoking status and histology [99]. In a recent study, never-smokers patients with advanced lung tumor lived 50% longer than smokers after adjusting for age, performance status, and sex [100]. Women are the highest proportion of lung cancer in never-smokers, with a higher proportion of druggable driver mutations. However, in a recent study, there were no statistically significant differences in survival between never-smokers and smokers within each genotype after adjusting for sex and age [101].

In spite of this survival advantage, the lung cancer treatment has not yet a different approach according to gender.

Conclusions

The epidemic of lung cancer among women is not over yet, especially in Southern Europe. If the rising mortality trend continues, by 2015 in the EU, deaths from lung cancer in women could overtake those from breast cancer. Changes in smoking patterns among the female population may therefore explain this increase. Implemention of aggressive tobacco control policies according to gender to reduce this fast growing epidemic is urgently needed. Other factors, rather than smoking, could also explain differences between both sexes. However, several aspects accounting for this increased lung cancer risk in women remain controversial. Future studies on lung cancer epidemiology and therapy considering women as target population and sex as a stratification factor are warranted.

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