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REVIEW ARTICLE

A consensus statement on the gender perspective in lung cancer

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Abstract Lung cancer is the most common cancer globally and has the highest mortality. Although this disease is not associated with a particular gender, its incidence is rising among women, who are diagnosed at an increasingly younger age compared with men. One of the main reasons for this rise is women taking up smoking. However, many non-smoking women also develop this disease. Other risk factors implicated in the differential development of lung cancer in women are genetic predisposition, tumour histology and molecular profile. Proportionally more women than men with lung cancer have a mutation in the *EGFR* gene. This consensus statement reviews the available evidence about the epidemiological, biological, diagnostic, therapeutic, social and psychological aspects of lung cancer in women.

Keywords Smoking · Quality of life · EGFR · Gender · Lung cancer

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Introduction

Lung cancer is the most common cancer globally, and has the highest mortality [1]. However, whereas its mortality is falling in men, in women it is increasing exponentially [2, 3], probably as a consequence of recent changes in gender-specific smoking patterns [4]. The biological basis, natural history and prognosis of lung cancer in women are not the same as in men. However, the reasons behind these differences are not yet fully understood [5].

The Association for Lung Cancer Research in Women (ICAPEM) was set up in 2010, in response to the increasing incidence of this disease in women. Its aims are to promote knowledge, research, prevention and social awareness of this health issue. In order to perform a detailed analysis of the gender perspective in lung cancer, ICAPEM invited a number of experts in this disease to a meeting, the end result of which is the first consensus statement on this subject.

This document addresses the available evidence about the epidemiological, biological, psychological, diagnostic and therapeutic aspects of this disease. Social issues, smoking habits and patients' own views are also considered. This multidisciplinary discussion has shown that lung cancer certainly needs to be addressed and researched in more depth, to determine whether or not different approaches to this disease are required according to gender.

Lung cancer epidemiology and risk factors

According to World Health Organisation (WHO) estimates, the incidence of cancer in 2012 was 14.1 million new cases, with 8.2 million deaths worldwide [6]. Lung cancer was the most common, in terms of both the number of new cases (1.8 million; 12.9% of the total) and the mortality rate (1.6 million deaths; 19.4% of the total). Worldwide, lung cancer is still the most common disease in men (1.2 million; 16.7% of the total). Although its incidence in women is low, there are large geographical variations depending on the number of women who have taken up smoking. Even so, a progressive rise in the incidence of this disease is apparent in all regions [2]. This fact, combined with its high mortality, constitutes the so-called "lung cancer epidemic in women" [7].

In Spain, the estimated overall cancer incidence in 2012 was 215,534 new cases, of whom 128,550 (59.64%) were male and 86,984 (40.35%) female. Of all cancers, lung cancer has the second highest incidence rate in males (16.94%) and the fourth highest in females (5.67%; 4935 new cases) [8]. In terms of mortality, it is also responsible for the greatest number of cancer deaths (20.55%; 21,118 of the total): 27.41% in males (17,430 deaths) compared with 9.41% in females (3688 deaths) (Table 1). This high

Table 1 Incidence, mortality and prevalence by tumour type in Spain

	Incidence by tumour type (*n*)			Mortality by tumour type (*n*)			5-year prevalence (%)		
	Overall	Men	Women	Overall	Men	Women	Overall	Men	Women
1	Colon (32,240)	Prostate (27,853)	Breast (25,215)	Lung (2118)	Lung (17,430)	Breast (6075)	Breast (17.9)	Prostate (31.4)	Breast (40.8)
2	Prostate (27,853)	Lung (21,789)	Colorectal (12,979)	Colon (14,700)	Colon (8742)	Colon (5985)	Prostate (17.6)	Colorectal (16.4)	Colorectal (14.1)
3	Lung (26,715)	Colorectal (19,261)	Uterus (5121)	Breast (6075)	Prostate (5481)	Lung (3688)	Colorectal (15.4)	Bladder (12.2)	Uterus (7.6)
4	Breast (25,215)	Bladder (11,584)	Lung (4935)	Pancreas (5720)	Bladder (4102)	Pancreas (2717)	Bladder (8.1)	Lung (7.0)	Melanoma (4.1)
5	Bladder (13,789)	Stomach (4866)	Ovarian (3236)	Prostate (5481)	Stomach (3335)	Stomach (2054)	Lung (4.8)	Kidney (3.9)	Cervix (3.5)

mortality rate means that the 5-year prevalence of lung cancer is minimal (4.8% overall; 28,148 of the total), being slightly higher in males and only 2.1% in females.

In Spain, the incidence of lung cancer in women is among the lowest in the world, although, since the early 1990s, it is one of the countries that has seen the greatest increase [9]. This is probably because tobacco use by Spanish women started late and peaked between 1960 and 1990, tending to stabilise from the year 2000 onwards [10]. During this period, the incidence of lung cancer in the female population rose by 4.2% each year [11]. Tobacco use is, thus, the most important risk factor for the development of lung cancer, being directly responsible for 80–90% of cases and indirectly responsible because of passive smoking [12]. In fact, women are the most vulnerable to tobacco carcinogens, which means they have a higher risk than men of developing lung cancer [13].

Other known risk factors are industrial pollution, occupational exposure (asbestos, arsenic, chromium, cadmium, polycyclic aromatic hydrocarbons), exposure to radon gas in dwellings and mines, and exposure to ionising radiation. Exposure to these factors varies greatly between individuals and populations, creating a geographical pattern that also differs according to gender. The areas with the highest mortality rates are the northern area of La Coruña and Lugo regions, some towns in Pontevedra, Orense, the Malaga coast, Girona, Asturias, the Canary Islands and Madrid. The higher lung cancer mortality rate in these areas might also be linked to exposure to environmental factors, such as radon and industrial pollution, and not just to smoking [14].

Although genetic influences on lung cancer are not yet clearly defined, the presence of a first-degree relative affected by lung cancer almost doubles the risk of developing the disease, and this risk is higher in female descendants [5]. Also, molecular mechanisms associated with lung cancer susceptibility have been detected in women. Female genotypes contain higher levels of reactive metabolites and DNA adducts than are found in the male population, which might explain why women are more susceptible to molecular aberrations caused by tobacco smoke [15]. Another matter of debate is whether oestrogen affects the risk of lung cancer. Information concerning the influence of hormone therapy on lung cancer risk is also controversial [16].

Biological aspects implicated

There is some evidence to suggest greater susceptibility to tobacco carcinogens in women than in men, irrespective of their smoking habits. Lung carcinomas that arise in women have significantly more tobacco-related mutations (G → T transversions in the *TP53* or *KRAS* genes), despite women being diagnosed at a younger age and smoking fewer packs a year than men [17–21]. An attractive hypothesis therefore postulates that targetable oncogenes should be highly prevalent in female lung cancers, because many of these oncogenes have classically been associated with light smoking.

Analysis of several recent studies from both the USA and Europe shows that female gender is, on the whole, more often associated with a genotype that permits personalised therapy, especially among primary adenocarcinomas of the lung [22–24]. A trend is apparent in these global studies for mutations in the epidermal growth factor receptor gene (*EGFR*), but less obviously for *ALK*, *ROS1* and *RETS* translocations or mutations in *HER2* [22–24]. This is partly because the systematic study of some of these genes is very recent, and not all studies include them or test for them by methods that are sufficiently sensitive and specific. Data from studies addressing a single gene are discussed below. To avoid the conclusions being biased by the greater presence of Asian patients in studies from the USA, we focus mainly on European studies.

In the case of *ALK* translocation, two Spanish articles reported finding this alteration in roughly 60–90% of women [25, 26]. Another French study, involving the screening of over 3,000 patients, documented a more than twofold relative risk for this molecular event in women [27]. Analysis of the literature on *ROS1* translocation is interesting. A multicentre study involving one of the largest series of patients with lung adenocarcinoma only documented 19 cases positive for this translocation, with no differences by gender [28]. These results are in contrast to the clear preponderance for women with *ROS1*-positive lung carcinoma in two other European studies, including a Spanish study in which the percentage was 80% [29, 30]. As regards *RET* translocation, this seems more common in males, and the smoking context is not so clear [31]. A review of *HER2* mutation data yields very similar results: between 62 and 69% of *HER2*-mutated lung carcinomas were detected in women [32, 33].

All this evidence points to the need for thorough molecular investigation of lung adenocarcinomas in women. Recently published genome data for these cancers further reinforces the idea that therapeutic targets in lung adenocarcinomas are almost always mutually exclusive [34], that is, for every negative predictive biomarker result obtained in these patients, the likelihood of finding a targeted treatment might increase.

Social and psychological aspects

There are differences in the way tobacco use affects males and females. One of the most important is weight gain; in general, women worry more than men about gaining

weight and tobacco can help them control it. Also, women gain more weight than men when they stop smoking. Women also smoke to protect themselves or manage negative feelings, whereas men tend to smoke to enhance pleasurable sensations. Lastly, some women smoke to switch off from the demands of running a household.

How adjustment to cancer is influenced by gender is not clearly defined. Gender differences are evident in the physical impact of cancer, quality of life, coping styles and partners' adjustment to the disease. In general, it seems it may be easier for women to adjust favourably to cancer than for men because they have larger social support systems [35].

Lung cancer in smokers tends to be associated with feelings of guilt and shame. It is experienced as a self-inflicted disease because of its link to smoking, and it leads to social isolation [36, 37]. Also, lung cancer patients have more feelings of guilt, shame, anxiety and depression than patients with other types of cancer [38].

Despite lung cancer now being the leading cause of cancer death in women worldwide, little information is available for evaluating female patients' quality of life. Most female patients experience severe disruption to their psychological and social wellbeing. Also, they see the disease as a complex challenge to be faced. Women with lung cancer have been reported to experience more mood disorders than men [39]. However, results are contradictory on this issue. Increased rates of depression in women with lung cancer have been found when compared to men, only when performance status (PS) is good, but gender difference is reduced for poor PS patients because of increased depression rates for men [40]. Women with lung cancer have higher levels of anxiety and concerns following diagnosis [41].

Quality of life data in women with lung cancer, however, yield better scores than in men at all stages of the disease [42]. Nevertheless, women are subject to a number of limitations that affect their quality of life more than men, such as difficulty performing domestic chores, caring for children, or other demands associated with their role. This is especially apparent in young women with recurrent disease or low socio-economic status [43]. Another important piece of information to bear in mind is that long-term lung cancer survivors suffer significant symptoms for a long time after the end of treatment, and these have an adverse impact on their quality of life [44].

Family is essential for maintaining and improving cancer patients' quality of life [45]. Although a diagnosis of cancer has a significant impact on the family's quality of life, the impact of lung cancer on family quality of life is variable and unrelated to the patient's quality of life or physical condition [46]. If a relative has health problems, his or her quality of life will be reduced, and he or she will also be less able to care for a cancer patient, and may experience more stress than the cancer survivor [47, 48].

Little information is available about the needs of female lung cancer patients and their relatives, and the resources they use. To learn more about this, ICAPEM set up the CIRCULOS study in 2015, focusing on women with lung cancer and their family environment in the Autonomous Region of Galicia (Spain). One thing seen in the study is a demand for greater emotional and social support, not just by patients, but also by families and carers, to be able to care for patients better. The overall study results will be published shortly.

Diagnosis and gender differences

At the time of lung cancer diagnosis, there are differences in some characteristics between men and women, notably age, tumour histology, smoking habits and mutations in the *EGFR* gene.

It seems that women with lung cancer are younger than men at the time of diagnosis. In the WORLD07 study, which recorded characteristics from 2,060 women diagnosed with lung cancer, the median age of women diagnosed with this cancer was 61 years [49]. In this same study, median age was 59 years for patients with a wild-type *EGFR* gene and 66 years for *EGFR*-mutated patients.

The distribution of histological types differs somewhat between men and women. In women, the most common histological subtype is adenocarcinoma. In the WORLD07 study, 86% of patients were diagnosed with NSCLC and 14% had small-cell carcinoma. Among patients diagnosed with non-small-cell carcinoma, 75% had adenocarcinoma, 11% squamous cell carcinoma, and 7% large-cell carcinoma [49].

Although the increased incidence of female lung cancer is clearly related to women taking up smoking, a substantial percentage of women with lung cancer are non-smokers. In the WORLD07 study, 39% of women diagnosed with lung cancer included in the database were non-smokers [49].

Mutations in the *EGFR* gene are seen in 10–16% of lung cancer patients in the Caucasian population. *EGFR* mutations are more common in adenocarcinoma histology, non-smokers, Asian population and women [50]. In a study examining the molecular profile of lung cancer patients in France, 11% of patients had a mutated *EGFR* gene, but when women were analysed, the percentage of patients with an *EGFR* mutation rose to 21% [23]. In a meta-analysis looking at patients with *EGFR* mutations treated with first-line EGFR inhibitors, female gender and not smoking were predictors of a better outcome [51]. In a study by the Spanish Lung Cancer Group (SLCG), longer

progression-free survival was also seen in women with *EGFR* mutations treated with erlotinib compared with men [52].

Treatment and gender perspective

In numerous large studies, women with lung cancer were diagnosed at younger ages than men, and women, compared with their male counterparts, were more likely to be lifetime nonsmokers, smoked fewer years and consumed fewer cigarettes per day, suggesting different tobacco susceptibility [5]. All of these lung cancer clinicopathological characteristics in women should be borne in mind when implementing lung cancer screening programmes and women should be screened younger and with a lower pack/year cut-off point. Also, 25% of lung cancers occur in never-smokers: lung cancer in never-smokers is the seventh cause of cancer-related death worldwide with a truncated age-adjusted incidence higher among women compared with men [5]. However, based on National Lung Cancer Screening Trial cohort, currently, never-smokers should not be screened [53].

Surgery

The surveillance, epidemiology, and end results programme (SEER) database currently shows that 16% of NSCLC are diagnosed at localised stage [54], where surgery remains the standard treatment for fit patients and platinum-based adjuvant chemotherapy is recommended for stage II-IIIA patients. Nowadays, it is unclear whether less invasive surgical procedures in early stages may be optimal. Two randomised phase III trials (CALGB 140503 and JCOG0802) are trying to validate sub-lobar resection as a surgical procedure in stage IA lung cancer patients compared with lobectomy (ClinTrials.gov NCT00499330) [55].

It is not known whether gender has any influence in surgical procedure and in post-surgical complications. A prospective Spanish trial investigated clinical characteristics and post-surgical complications according to gender in a cohort of 3,307 resected NSCLC patients [56]. Similar to previous clinical series, women ($n = 741$, 22.4% of the total cohort) were diagnosed younger than men (62 years vs. 66 years; $p < 0.05$); adenocarcinoma was more common in females than males (70.4 vs. 46.2; $p < 0.001$); the proportions of never-smokers were higher among females (35% vs. 5.3%; $p < 0.001$); and among smoking patients, women smoked fewer packs/year than men (36.6 vs. 52.9; $p < 0.001$). This lower smoking history among women corresponds with their lower comorbidities reported in this study ($p < 0.05$). All these factors rather than gender might justify the significantly lower number of pneumonectomy interventions, post-surgical complications and mortality among women compared with men.

Chemotherapy

Approximately 60% of NSCLC are diagnosed with advanced disease [54]. Platinum-based doublet chemotherapy is the standard first-line treatment for non-selected patients with advanced NSCLC who have a good PS. A French study reported that gender is a prognostic factor. One-year survival is 41.9% for women and 38.8% for men [57]. Moreover, in locally advanced and metastatic stages, women live longer than men especially with platinum-base schedules [58, 59]. However, no survival differences according to gender occurred with new agents such as pemetrexed and bevacizumab [60, 61]. 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 [5]. Therefore, gender should be the first thing to bear in mind for personalised treatment among lung cancer patients.

Targeted therapies

Personalised treatment based on the recognition of oncogenic driver mutations has changed the treatment paradigm of lung cancer patients, especially among the adenocarcinoma subtype. Approximately 50% of advanced NSCLC have a genetic alteration but only 20–25% of them are actionable oncogenic driver mutations [23].

To date, nine randomised phase III trials have established EGFR tyrosine kinase inhibitors (TKI) as standard first-line treatment in *EGFR* mutant NSCLC [62]. A recent meta-analysis has reported lack of association between the type of *EGFR* mutation and gender ($p = 0.81$). EGFR TKI treatment demonstrated a 27% greater benefit in women than in men in terms of progression-free survival compared with chemotherapy ($p = 0.02$). The predictive effect of gender was independent of smoking status and *EGFR* mutation type [63].

EML4-ALK rearrangements occurred in ~5% of NSCLC patients, and it is more frequent in never/light smokers, adenocarcinoma subtype and young patients. Compared with female NSCLC patients, the odds ratio of carrying *ALK* rearrangements was reduced by 28% in males, especially among Asian patients [64]. However, opposite results have been reported among European populations [65]. In randomised phase III trials with crizotinib, higher numbers of females have been included with a trend toward differences in the efficacy of crizotinib according to gender-subgroup analysis [66, 67].

BRAF mutations have been described in 2-4% of lung cancers, especially adenocarcinoma without ethnicity,

smoking pattern or gender predominance [68, 69]. These clinicopathological characteristics have been also reported in a European cohort [70]. The V600E mutation accounts for 50% of cases, more frequent in women, and it is a negative prognostic factor [69]. In a phase II trial, the BRAF inhibitor dabrafenib in combination with the MEK1 inhibitor trametinib showed a response rate of 63%. In this trial, a high number of females were included, but outcome according to gender is not reported [68].

ROS1 rearrangements have been detected in 1.5% of patients, usually young (~50 years), never-smokers and patients with adenocarcinoma subtype, and female predominance. Crizotinib showed marked antitumor activity in this subgroup of lung cancer patients. In the European cohort, a higher number of females had *ROS1* rearrangements than males [71].

In a retrospective study, *HER2* mutations occurred in 65 (1.7%) of 3800 patients with lung adenocarcinoma, mainly female and never-smokers [33]. In another study, *HER2* mutations represented 6% of cases but were not gender-related [32]. In a retrospective European cohort, *HER2* mutations were more common in females (62.4%) and HER2-targeted agents demonstrated their potential activity in these patients [33].

RET rearrangements occur in 1–2% of NSCLC patients, mainly in never-smokers and men [31]. Oncogenic *MET* mutations in exon 14 occur in 4% of lung adenocarcinomas, especially in women of older age (~75 years). This mutation confers clinical sensitivity to MET inhibitors such as crizotinib and cabozantinib [72].

Nowadays, the limited number of patients included in some of these databases does not allow conclusions to be drawn about gender predominance in some of these molecular alterations or whether smoking pattern might be a confounding factor in the interaction between gender and the molecular profile. Moreover, it is important to evaluate whether the toxicity profile of these TKIs are different according to gender.

Immunotherapy

Immunotherapy is a second-line option in advanced NSCLC. PD-L1 expression has been reported as a putative predictive marker and its expression is higher in tumours in women than in men [73]. However, there is no a clear relationship between gender and immunotherapy efficacy, which could be influenced by smoking pattern [74].

Cancer therapy toxicity and fertility

It is known that the side effects of treatments, and responses to them, can differ between men and women. For example, chemotherapy treatments can produce higher rates of vomiting and haematological toxicity in women than in men. Conversely, males have a higher incidence of lower gastrointestinal tract toxicity, related to lower expression and activity of glutathione S-transferase in the gut [75].

Table 2 Chemotherapy agents according to their potential to cause infertility

Risk type	Drugs
High	Cyclophosphamide
	Melphalan
	Busulphan
	Nitrogen mustard
	Chlorambucil
	Procarbazine
Intermediate	Cisplatin
	Doxorubicin
	Paclitaxel
Low	Fluorouracil
	Vincristine
	Bleomycin
	Dactinomycin

In the last few years, various sociological factors have led to a delay in the age at which women embark on motherhood. Because cancer is increasingly diagnosed at a younger age (an estimated 2% of lung cancer cases occur in women under 40 years old) the wish to start a family is jeopardised, as the cancer treatments indicated may compromise fertility [76, 77]. To date, specific clinical guidelines on fertility are only available for breast cancer and lymphomas. A young woman diagnosed with cancer must always be informed about the long-term repercussions treatment may have on fertility.

Chemotherapy may affect ovarian reserve to differing degrees depending on the type of drug (Table 2) [78]. Radiotherapy also entails a risk to fertility, depending on the dose and the area to which it is administered. The risk is higher when the abdomen, pelvis or central nervous system (hypothalamic-pituitary axis) is irradiated.

Therefore, when cancer is diagnosed in women of childbearing age, it is important to offer them comprehensive information about their life expectancy and the risks and benefits of indicated treatments, taking account of whether the patient has already completed her family (Fig. 1) [79, 80].

Conclusions

The significant increase in smoking in the female population has produced a dramatic rise in lung cancer incidence and mortality.

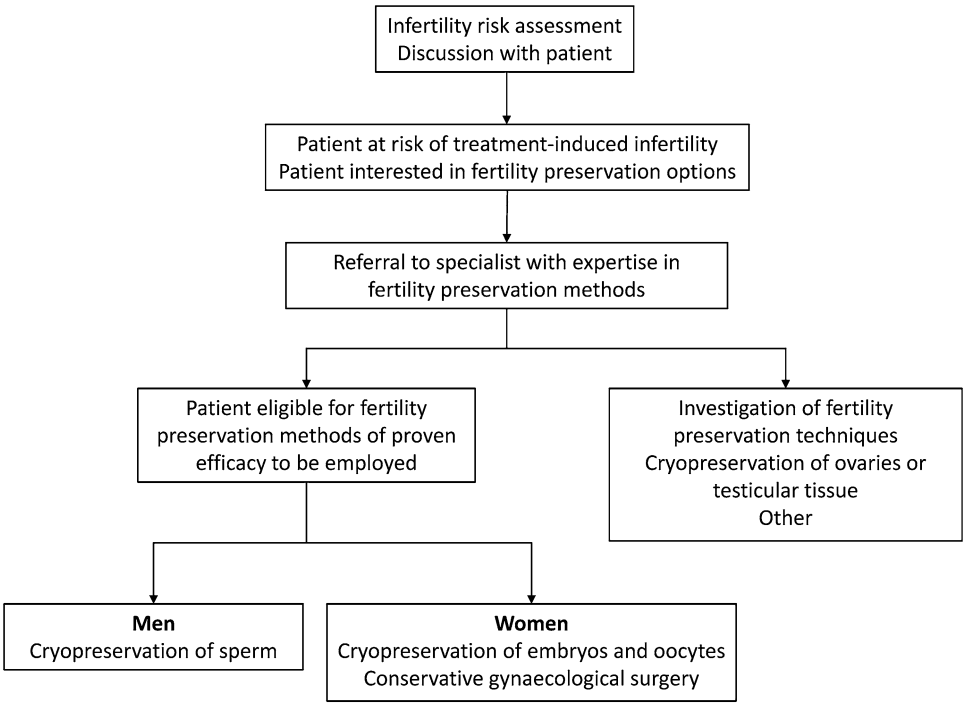

Fig. 1 Fertility preservation assessment and procedural algorithm in women with lung cancer

Table 3 Summary of the authors' conclusions

1. The increased prevalence of female smokers has resulted in a dramatic rise in the lung cancer mortality rate among women, the leading cause of cancer death worldwide
2. Little information is about evaluating quality of life and emotional impact on women with lung cancer and their carers/relatives: there is a need to develop support programmes
3. Some clinical and pathological characteristics of lung cancer seem to differ between men and women, including the percentages of adenocarcinoma subtype, non-smokers and *EGFR* mutation
4. Multiple lines of evidence support detailed molecular investigation of lung adenocarcinoma in women
5. Over 30% of women diagnosed with lung cancer are non-smokers
6. It is not clear whether women are more susceptible to carcinogens, as there are contradictory results concerning this issue
7. Smoking history and the limited number of patients in some clinical databases could be confounding factors for different prognosis by gender
8. Lesser smoking history rather than gender might justify the better outcome of lung cancer surgery in women
9. Chemotherapy treatments can cause greater toxicity in women than in men, especially haematological toxicity and nausea, probably due to gender differences in pharmacokinetics
10. Differences in toxicity do not result in worse outcomes, because women tend to have better efficacy results
11. There is a worldwide call to action for cancer patients of reproductive age to be informed of the repercussions of cancer treatments on fertility
12. Studies designed specifically for women are a high priority, to provide greater understanding of the biology and course of lung cancer, and to develop support programmes to improve its treatment

Various lines of evidence suggest that this disease behaves differently in women, with a higher percentage of adenocarcinoma or *EGFR* mutations, and no history of smoking in 30% of cases. There has also been speculation about greater female susceptibility to possible carcinogens implicated in the development of this cancer, or greater toxicity experienced with chemotherapy. Moreover, the potential impact on quality of life, fertility or emotional repercussions for female patients and their families is unknown.

For all these reasons, studies designed specifically for women are a high priority, to provide greater understanding of the biology and course of lung cancer, and to develop support programmes to improve treatment (Table 3).

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Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflict of interest that may inappropriately influence this work.

Ethical statement The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent statement Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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