WOMEN AND LUNG CANCER: LITERATURE ASSUMPTIONS AND NEWS FROM RECENT PUBLICATIONS

Tiziana Vavalà, *Silvia Novello

Oncology Department, University of Turin; Thoracic Oncology Unit, AOU San Luigi Gonzaga Hospital, Turin, Italy

**Correspondence to silvia.novello@unito.it*

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ABSTRACT

For a long period of time, lung cancer (LC) was considered as a malignancy affecting only males, but epidemiological data have shown a dramatic increase of the incidence of this disease among women, and the gender gap has been narrowing steadily since the 1980s, mainly as a consequence of the huge spread of tobacco consumption during the past 70 years. In 2013, the percentage of current cigarette smokers among adults aged 18 and over in the US was 19.9% for men and 15.2% for women (selected estimates based on data from the January-June 2013 National Health Interview Survey), reflecting the earlier and more marked decline in the prevalence of tobacco use in men. Nowadays, cigarette smoking accounts for >90% of LCs in men and 75-85% of LCs in women in the US and Europe, but 20% of women with LCs have never smoked. Many studies describe differences between males and females in the clinical presentation and biology of LC, suggesting that the disease should be considered a specific entity in women, where adenocarcinoma is the most common histological subtype, and prognosis and response to treatment appear to be different. In line with these findings, hormonal receptors have been isolated in LC tissues: the interaction of oestrogen receptors with growth-factor-receptor signalling is an emerging area of investigation and - considering the potential impact of hormonal factors - lung carcinogenesis appears distinctive in women. Despite these considerations, no 'gender driven' diagnostic or therapeutic approaches are available nowadays. Improving knowledge of LC in women will allow identification of specific genetic alterations or hormonal profiles which could be targeted by therapy in order to stimulate research progress towards personalised sex-based investigations.

Keywords: Women, gender, sex, lung cancer, cigarette smoking, never smokers, biological abnormalities, hormones, oestrogen receptors.

INTRODUCTION

At the beginning of the 20th century only a few hundred cases of lung cancer (LC) were diagnosed annually, but the largely progressive spread of tobacco consumption caused a dramatic increase of the incidence of this disease among men, and then later among female smokers, in Western countries.[1] Trends in LC incidence and mortality have reflected changing habits in cigarette smoking during the past years, but it has been known that women have a 1 in 16 lifetime risk of developing LC regardless of smoking status, and a higher percentage of LC in non-smoking women, as compared with non-smoking men, suggests that LC behaves differently in female patients.[2]

The purpose of this paper is to review recent scientific assumptions concerning LC in women, exploring more recent data about smoking susceptibility, as well as biological and hormonal features, in order to discuss the future implications of gender-related approaches and therapeutic options. To be eligible for this systematic review,

a publication had to fulfil the following criteria: to deal with LC, gender, and biological and hormonal aspects; to have been published as a full paper in English, Italian, or French language. Abstracts were also included. Studies were identified by an electronic search on Medline databank using the following keywords: "lung cancer", "lung adenocarcinoma", "lung squamous carcinoma", "NSCLC", "SCLC", "women", "sex", "gender", "never smokers", "cigarette smoking", "tobacco", "molecular issues", "biological abnormalities", "next-generation sequencing", "hormones", "oestrogen receptor", "progesterone receptor", "lung cancer risk", "antioestrogen", "EGFR", "K-Ras", and "ALK". The search ended in April 2014.

Epidemiology

In the last decades, LC incidence rates worldwide have decreased or levelled-off among men, being instead dramatically risen among women by 600% in the last 50 years.[3] Particularly, in this population in the US, a significant increase in smoking habit started in 1973, reaching a plateau in the late 1990s - over a decade later than men - while LC mortality stabilised for the first time in 2003, two decades later than men, and has yet to decline.[4,5] The International Agency for Research on Cancer estimated 1.8 million new LC cases worldwide in 2012 (12.9% of the total). This disease is still the most common cancer in men (1.2 million, 8.74% of the total) and the third most frequent in women (583,000 cases, 4.16% of the total). It is the most common cause of death from cancer worldwide in men and the second cause in women with 1.59 million deaths, of which, 491,000 were female patients.[6] Nowadays in the US, LC is the leading cause of cancer death for this population, with >108,000 new estimated cases and >72,000 estimated deaths in 2014, while in European countries there are >79,000 new cases of LC in the female sex per year and 82,000 have been estimated in 2013[4,7-9] (Figures 1-4). Thus, compared to the historical data, recent publications confirm that the epidemiology of LC is still changing and that sex differences, in terms of incidence and mortality, are still present with increasing rates for women in many countries.

SMOKING HABITS

Currently, tobacco smoking accounts for >90% of LCs in men and 75-85% of LCs in women, in the US and Europe; it is the most well-established risk factor for this disease.[10-12] Several case–control studies have found a higher relative risk among women when compared with men for the same level of smoking exposure.[13-16] In contrast, other cohort studies have not shown higher smoking-related risks, evidencing that the incidence of LC among female smokers was approximately the same as that in male smokers, after standardising for the amount smoked.[17,18] To address this issue, two recent publications evaluated analogous populations (European subjects, similar gender distribution) using different metrics. De Matteis et al.[19] evaluated the interaction between female sex and tobacco smoking in association with LC risk within 2,100 cases and 2,120 controls. LC odds ratios (OR) for pack-years were higher in men than in women, with a negative female sex-smoking interaction (p=0.0009). The association within former and current smokers was also explored and no major difference was seen. In the analyses for the main LC histological types, OR for pack-years among adenocarcinoma cases were higher in men than in women, with a negative female sex-smoking interaction (p=0.005), while, in the analyses restricted to former and current smokers, there was no evidence of interaction (p=0.76 and p=0.47, respectively).[19] Papadopoulos et al.[20] evaluated 2,276 male/650 female cases and 2,780 male/775 female controls, estimating lifetime smoking exposure by the comprehensive smoking index (CSI), which combines the duration, intensity, and time since cessation of smoking habits. They found that the LC risk was similar among men and women, but evidenced that women had a 2-fold greater risk associated with a 1-unit increase in CSI than men of developing either small cell carcinoma (OR=15.9, 95% CI 7.6-33.3 and 6.6, and 95% CI 5.1-8.5, respectively; p<0.05) or squamous cell carcinoma (OR=13.1, 95% CI 6.3-27.3 and 6.1, and 95% CI 5.0-7.3, respectively; p<0.05), while the association was similar between men and women for adenocarcinoma.[20]

Active cigarette smoking is the most important risk factor for LC, but it is only one of a well-characterised set of established risk factors that include: smoking types of tobacco other than cigarettes (e.g. cigars, pipes), passive smoking, occupational exposure to lung carcinogens such as radon, asbestos, arsenic, radiation, outdoor, and indoor air pollution (e.g. coal-fuelled stoves and cooking fumes), family history, and infections.[21,22] Biological explanations have also been proposed to demonstrate sex differences in LC susceptibility:

oestrogen receptors (ERs) are present in both normal and neoplastic lung tissues and could accelerate the metabolism of smoke-related carcinogens in a dose-dependent way, as suggested by higher levels of polycyclic aromatic hydrocarbon–DNA adducts in female smokers compared with males, or inherited, gender-related polymorphisms could affect activating and detoxifying enzymes.[12,23-25]

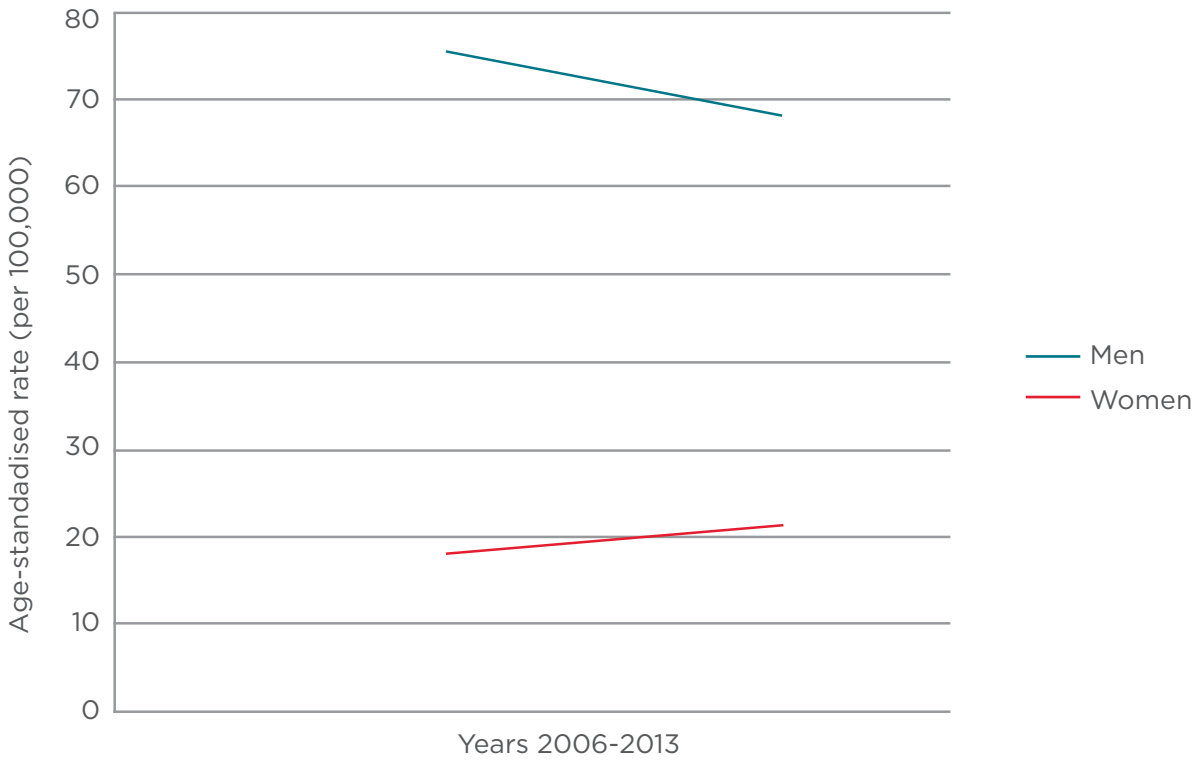

Figure 1: Lung cancer incidence trends by sex in Europe during 2006-2013.

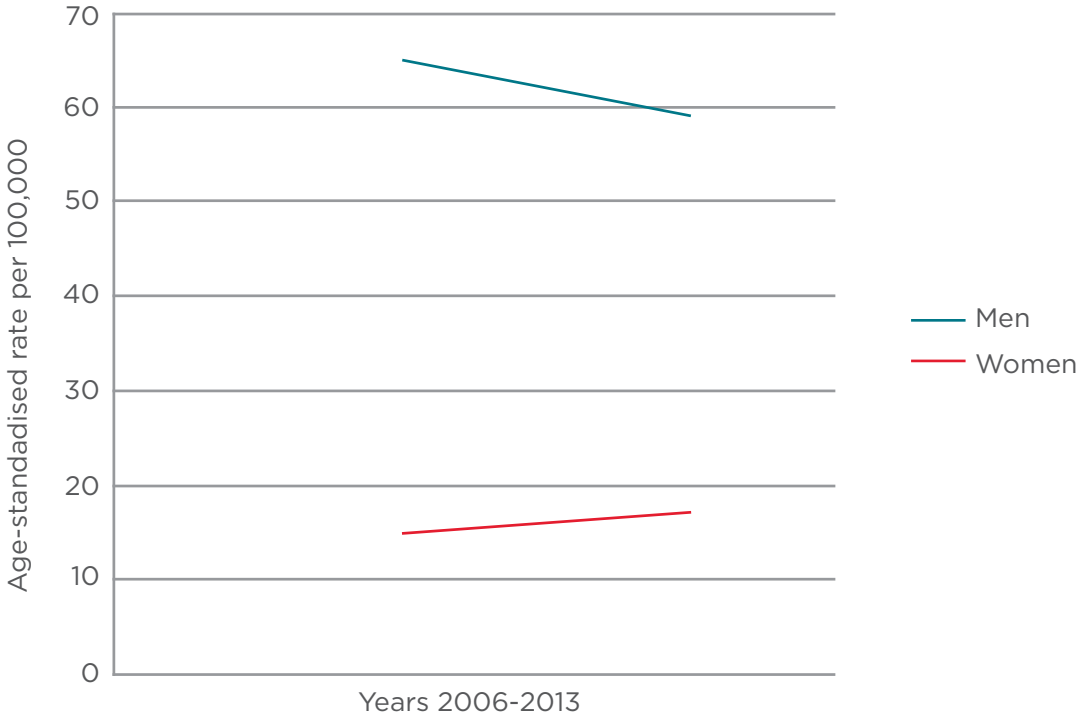

Figure 2: Lung cancer mortality trends by sex in Europe during 2006-2013.

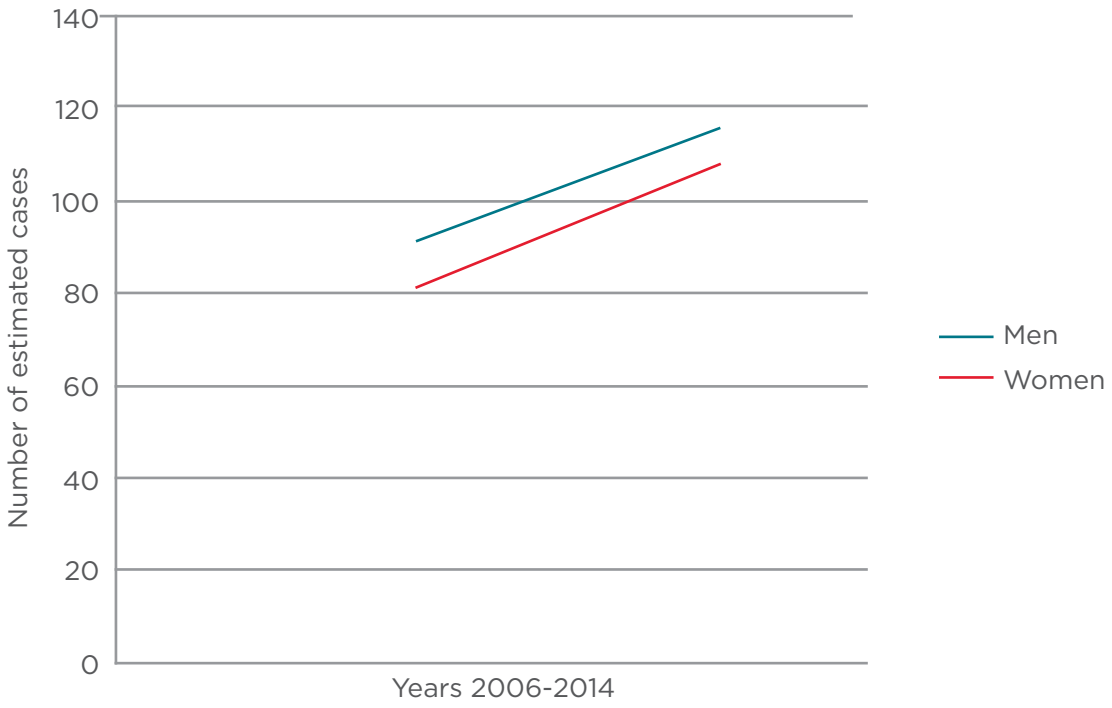

Figure 3: Lung cancer incidence trends by sex in US during 2006-2014.

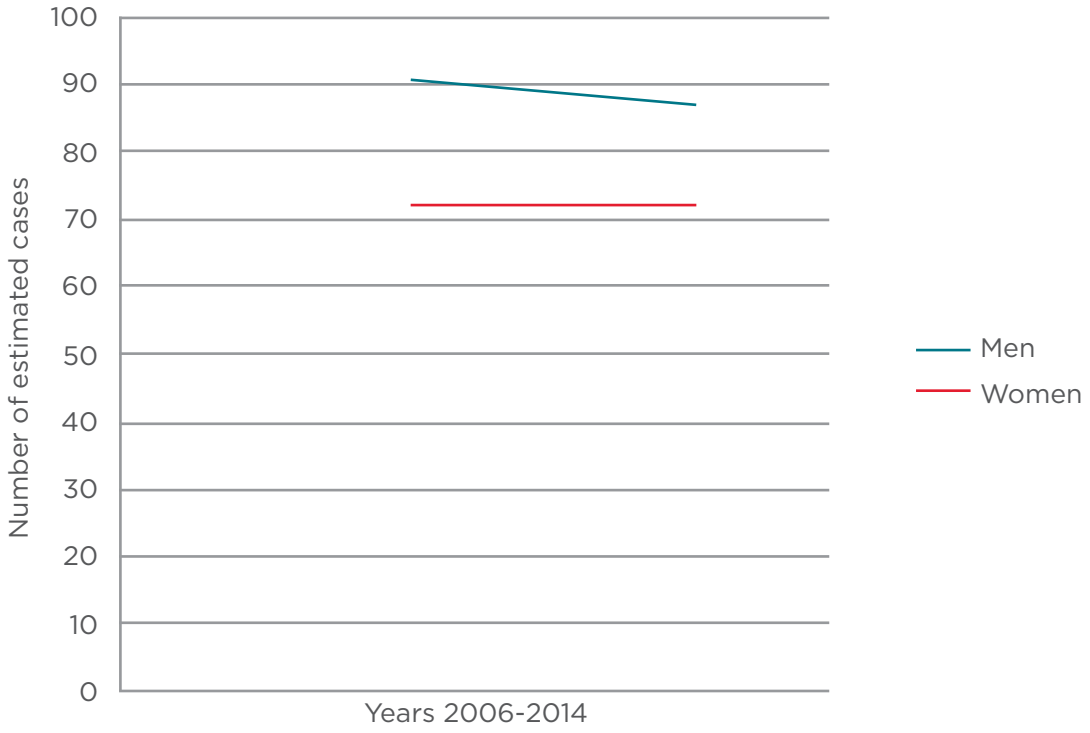

Figure 4: Lung cancer mortality trends by sex in US during 2006-2014.

Chlebowski et al.[26] examined oestrogen plus progestin (E+P) association with LC incidence and outcome in >30,000 postmenopausal women, and evidenced that in non-users of E+P, LC incidence, deaths from LC, and deaths after LC were significantly and substantially greater in current smokers versus never smokers ($p<0.0001$ for all comparisons) and, in current smokers, the same variables were significantly and substantially greater in E+P users versus non-users ($p=0.0021$, 0.0005, and 0.0002, respectively), nearly doubling a smoker's already high risk of death from LC and

after LC. Thus, compared to the historical data, recent publications confirm the prominent role of smoking habit as a risk factor of LC, even in female population, but no conclusions are yet available regarding the potential difference in susceptibility to the carcinogenic effects of cigarette smoke on women's lungs when compared with their male counterparts.

NEVER SMOKERS AND MOLECULAR ABNORMALITIES

Tobacco smoking is the main cause of LC, but it also occurs in people who have never smoked, ranking as the seventh most common cause of cancer death worldwide.[25] LC in never smokers is more frequently observed in women: in the US and Europe, approximately 20% of women with LCs have never smoked and this trend is further accentuated in Asian populations where 60-80% of women with LC, in contrast to 10-15% of men with LC, have never smoked.[5,27] Passive smoking is the most widely studied and confirmed risk factor of LC among non-smokers. Furthermore, in this cohort of patients, a higher rate of gene mutations involving epidermal growth factor receptor (EGFR) or echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4–ALK) translocations has also been evidenced. Mazières et al.,[28] in an evaluation of 140 women with adenocarcinoma (63 were never smokers), evidenced EGFR mutation more frequently and mutated K-Ras less frequently in women who had never smoked; more precisely, 50.8% of never smokers displayed the mutation compared with 10.4% of former or current smokers ($p<0.001$). In contrast, K-Ras mutation was more frequent in smokers (33.8%) compared with never smokers (9.5%; $p=0.001$). It also described a higher percentage of ER alpha expression ($p=0.03$; and $p=0.008$ with two different antibodies) in women who never smoked when compared with smokers.[28]

No definitive data are currently available about the EML4-ALK translocation or *ROS1* gene regarding a possible difference between men and women. From prospective trials and from retrospective evaluation, EML4-ALK has been evidenced to occur more frequently in young patients, light or never smokers, and male subjects, while *ROS1* seems to occur slightly more often in the young female population.[29,30] On the contrary, mutations in *HER2* gene are identified in approximately 2% of non-small-cell lung cancer (NSCLC) and in a recent publication, Mazierès et al.,[28] who retrospectively collected clinicopathologic characteristics, patient outcomes, and treatments of 65 NSCLC, diagnosed with a *HER2* in-frame insertion in exon 20, evidencing a higher proportion of women (45 women versus 20 men).[31] Finally B-Raf (V600) is described in 2% of patients with lung adenocarcinoma in Western countries; it seems to be slightly more frequent in women and represents a negative prognostic factor.[32]

At a molecular level, the Tumor Sequencing Project revealed that smokers suffer mutations at rates 5 to 10-times higher than never smokers; as a consequence, the smaller number of mutations among never smoker patients suggested the opportunity to easily isolate driver mutations.[33] In this regard, Kim JH et al.[34] conducted a genome-wide association study of non-smoking Korean women with LC to identify the effect of genetic polymorphisms on LC risk. They analysed 440,794 genotype data of 285 cases and 1,455 controls, and evidenced that 19 single nucleotide polymorphisms (SNPs) were associated with LC development ($p<0.001$); however, only rs10187911 on 2p16.3 was significantly associated with LC development ($p=0.025$). The effect of this SNP was found to be consistent only in adenocarcinoma patients (1.36 and <0.001 in the additive model, 1.49 and <0.001 in the dominant model, and 1.54 and <0.001 in the recessive model). This is a novel genetic locus in the 2p16.3 region, associated with susceptibility of adenocarcinoma in Korean never smoking females.[34] Further replication studies in larger populations are needed to confirm this hypothesis, considering that Kim SC et al.,[35] performing a high-throughput, multidimensional sequencing study of primary lung adenocarcinoma tumours (EGFR, KRAS, and EML4-ALK negative) in six Korean female never smoker patients, found that none of the mutations or fusion genes were present in more than one patient.[35] This evaluation suggests that, at the present time, for the large proportion of NSCLC cases, negative for the established 'driver' mutations, it is difficult to predict the function of a given mutation (i.e. gain in oncogenic activity or a loss of tumour suppressor activity, or neither) unless an extensive characterisation of the gene activity is performed *in vitro* and *in vivo*, the first step to propose potential target pathways for establishing effective and personalised therapies.

Thus, compared to the historical data, recent publications confirm LC in never smokers as a

different disease per se; this remains to be clarified in the role of sex in this context, even if some interesting preclinical data are already available showing specific molecular features.

HORMONAL FEATURES

Hormonal status is one of the most cited potential explanations for differences in LC between men and women. There are several lines of biological evidence that suggests oestrogen acts as a promoter for LC.[36-38] Experimental data are still conflicting due to the presence of two ER isoforms (α and β) and the expression of ER β isoforms (mainly ER β1), the range of antibodies used, and the absence of a validated threshold or score. In fact, Wu et al.[39] observed an overexpression of ER β in lung tumours significantly more frequently in female patients (53.8%) than in males.[39] In contrast, Schwartz et al.[40] found that ER β was preferentially expressed in men, while Rouquette et al.[41] described ER β overexpressed in the majority of patients, regardless of gender (Table 1).[40,41] For the same reasons the impact of reproductive and hormonal factors on the aetiology of LC in women is still unclear, even if it is hardly debated.

Table 1: Hormones and lung cancer (selected studies).

References	Methodology	n	Principal Findings
Rodriguez-Lara et al.[51]	IHC	90	ER β and *CXCL12/CXCR4* expression in lung adenocarcinoma depends on sex and hormonal status.
Verma et al.[52]	IHC	169	Co-expression of ER β and aromatase in NSCLCs of Japanese males may result in tumour progression.
Rouquette et al.[41]	IHC	100	Positive link between EGFR expression and expression of ER α and ER β, both men and women.
Abe et al.[53]	IHC	105	ER expression associated with aromatase expression in NSCLC.
Raso et al.[54]	IHC	317	ER expression associated with EGFR mutations in NSCLC.
Wu et al.[39]; Schwarz et al.[40] Skov et al.[55]	IHC	278/301 104	ER expression associated with better clinical outcome in NSCLC.
Niikawa et al.[56]	IHC	59	Aromatase expression was associated with intratumoural estradiol concentrations in NSCLC.
Hershberger et al.[57,58] Jarzynka et al.[59]	*in vitro* (NSCLC cell lines)		ER demonstrated tumour promoting features in the absence of ER.
Hammoud et al.[60]; Jarzynka et al.[59]	*in vivo* (mouse)		Estradiol stimulated the growth of lung carcinoma xenografts.
Mah et al.[61]	IHC	442	Lower levels of aromatase predicted a better survival in females >65.
Márquez-Garbán et al.[62]; Weinberg et al.[63]	*in vitro* *in vivo*		Aromatase inhibitor suppressed the lung tumour growth.
Issa et al.[64]	Southern blot	46	Lung cancer patients with a history of smoking had a significantly lower incidence of ER promoter methylation than non-smokers.

IHC: immunohistochemistry; ER: oestrogen receptor; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor.
Modified and updated from Verma et al.[50]

Endogenous Hormones

A meta-analysis by Zhang et al.[42] evaluated 25 articles in order to estimate the impact of menstrual and reproductive factors on LC risk. Older age at menarche in North American women and a longer length of menstrual cycle were associated with a significant decreased risk of LC (rate risk [RR]= 0.83; 95% CI: 0.73-0.94 and RR=0.72; 95% CI: 0.57-0.90, respectively). Particularly, shorter length of menstrual cycle indicated an overall increase in the period of unopposed oestrogen exposure; younger age at menarche implied more menstrual cycles over the lifetime and hence longer periods of oestrogen exposure in total. Women who undergo shorter length of menstrual cycle and younger age at menarche may have an increased risk of LC, possibly due to more cumulative exposure to endogenous oestrogen, which may be involved in the aetiology of this disease.[42]

Pesatori et al.[43] examined 407/499 female cases/controls and observed a reduced risk of LC among women with a later age at first live birth (≥31 years: OR=0.57, 95% CI=0.31-1.06, p-trend=0.05), later age at menopause (≥51 years: OR=0.49, 95% CI=0.31-0.79, p-trend=0.003), and longer reproductive periods (≥41 years: OR=0.44, 95% CI=0.25-0.79, p-trend=0.01).[43] Finally, Gallagher et al.[44] evaluated a cohort of 267,400 female textile workers in Shanghai, enrolled in a trial of breast self-examination where information on reproductive history, demographical factors, and cigarette smoking were collected at enrolment. The cohort was followed until July 2000 for incidence of LC and 824 cases were identified. Nulliparous women were at increased risk compared to parous women (HR=1.33, 95% CI 1.00-1.77). Women who had gone through menopause at baseline were at an increased risk compared to women of the same age who were still menstruating. Risk was higher in women with a surgical menopause (HR=1.64, 95% CI 0.96-2.79) than in those with a natural menopause (HR=1.35, 95% CI 0.84-2.18), and risk was highest in those postmenopausal women with a hysterectomy and bilateral oophorectomy at baseline (HR=1.39, 95% CI 0.96-2.00), although the risk estimates were not statistically significant.[44]

Exogenous Hormones

It is important to underline that endogenous and exogenous sex hormones could play different roles in lung tumourigenesis.[45] In a Women's Health Initiative randomised, placebo-controlled clinical trial it has been evidenced that more women died from LC in the combined hormone therapy group than in the placebo group (HR 1.71, 1.16–2.52, p=0.01).[26] Based on these data, Bouchardy et al.[46] argued that the use of anti-oestrogens should be associated with decreased LC mortality risk. The authors compared LC incidence and mortality among 6,655 women diagnosed with breast cancer between 1980 and 2003, treated with and without anti-oestrogen therapy; 46% (3,061) of them received anti-oestrogens and 0.6% (40) developed LC. Standardised incidence rates for LC were not significantly decreased among breast cancer patients treated with and without anti-oestrogens (0.63, 95% CI, 0.33-1.10; and 1.12, 95% CI, 0.74-1.62, respectively) while standardised mortality ratios decreased among women with anti-oestrogens (0.13, 95% CI, 0.02-0.47, p<0.001) but not for women without anti-oestrogens (0.76, 95% CI, 0.43-1.23).[46]

The same concept has been applied by Lother SA et al.[47] who performed a retrospective population-based study identifying all women diagnosed with NSCLC in 2000-2007 and suggesting that anti-oestrogen use may influence survival in NSCLC female patients. They evaluated 2,320 women (of which 156 had received anti-oestrogens) to compare survival among anti-oestrogen users and nonusers. Exposure to anti-oestrogens was associated with a significantly decreased mortality in those exposed both before and after the diagnosis of NSCLC (adjusted HR: 0.42, p=0.0006). This association remained consistent across age and stage groups. Anti-oestrogen use before and after the diagnosis of NSCLC was also associated with decreased mortality.[47]

Oestrogens still represent a potential key player in the biology and outcomes of NSCLC and, consequently, a possible therapeutic approach. Garon et al.[48] evidenced, in NSCLC cell lines, that sensitivity to fulvestrant (Faslodex®) correlates with greater baseline ER α gene expression, and tumour xenografts regress significantly when both ER and EGFR pathways are inhibited.[48] Furthermore, Siegfried et al.[49] confirmed that the combination of vandetanib (Caprelsa®) (a multi-target inhibitor) with fulvestrant maximally inhibits cell growth when compared to single agents (p<0.0001), decreases tumour xenograft volume by 64%, compared to 51% for vandetanib (p<0.05) and 23% for fulvestrant (p<0.005) alone, and finally, produces a significant increase in apoptotic cells when compared to single agents.[49] Thus, compared

to the historical data, recent publications confirm the hormonal status as one of the major causes for sex differences in LC. Even without the possibility to make any final statements, women who continue to produce oestrogens seem to have a lower LC risk, and anti-oestrogens were shown to have a potential therapeutic implication, from preclinical and clinical experiences.

CONCLUSIONS

A better understanding of the genetic, metabolic, and hormonal factors in women still represents a research priority. Further and larger investigations with biomarkers of oestrogen and molecular classification of LC will help for a more comprehensive view of LC development in women. In the era of targeted drugs, variations in response to EGFR inhibitors and antiangiogenesis drugs between men and women are intriguing but insufficient to allow the gender of the patient guide the choice of therapy, and larger oncogenic platforms associated to dedicated protocols should represent an answer to the question.

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