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Gender differences in lung cancer

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Lung cancer (LC) is the leading cause of cancer-related death both in men and women and represents a major healthcare burden in both sexes[1]. However, epidemiology, risk factors, clinicopathological and molecular features and outcomes are different between males and females.

Epidemiology

The epidemiological data have shown an increase of LC incidence among women (in the US from 25 per 100,000 in 1975 to 52 per 100,000 in 2006), whereas the incidence decreased among men (from 90 per 100,000 in 1975 to 70 per 100,000 in 2006). This is mainly due to the very large growth in tobacco consumption over the past 60 years: the prevalence of smoking in American women peaked in 1965 at 33% and remained elevated throughout the 70s before beginning to slowly decrease in 1980. By contrast, more than half of American men smoked before 1965, but the prevalence dramatically decreased during the subsequent 20 years. Currently, 18% of American women smoke compared with 23% of men[2].

More men are diagnosed with LC each year, but more women live with the disease (age-adjusted death rate in 2014 in the US 51.7 per 100,000 in men, 34.7 per 100,000 in women)[3].

The Italian epidemiological data reflect the US trend (LC incidence rate in women 24 per 100,000 in 2003, 32 per 100,000 in 2012; whereas in men 120 per 100,000 in 2003, 101 per 100,000 in 2012; LC mortality rate in women 20 per 100,000 in 2003, and 24 per 100,000 in 2012, in men 108 per 100,000 in 2003, but 90 per 100,000 in 2012)[4].

Risk factors

Cigarette smoking is estimated to cause about 85% of LC in the US. Women tend to smoke low tar content cigarettes and cigarettes with different filters and flavours[5,6]. Some case-control and cohort studies suggest that smoking causes a significantly larger increase in the relative risk of developing LC in women than in men, guessing that women are more susceptible to tobacco smoke carcinogens than men[7,8]; on the contrary, results from different cohort studies generally find similar incidence and mortality rates between women and men with comparable smoking histories[9].

About 15% of LC patients are never-smokers, most of them are female patients (53% of LC in females develops in never-smokers and 15% in males)[10-12]. LC incidence in never-smoking women may be attributable to exposure to environmental tobacco smoke, residential radon, cooking oil vapours, indoor coal and wood burning[13].

Moreover, hormonal factors are also hypothesized to play an important role in LC carcinogenesis[14]. Estrogens promote carcinogenesis, activating carcinogens such as polycyclic aromatic hydrocarbons (PAH). Smoking women have an increased expression of the cytochrome P450, family 1, member A1 (CYP1A1) gene in the lung compared with smoking men; this enzyme is probably induced by estrogens, with a following increased level of DNA adducts and a decreased ability to detoxify tobacco carcinogens. On the other hand, estrogens promote directly the formation of DNA adducts, after metabolic activation to catechol estrogens[15,16]. The progesterone receptor (PR) and estrogen receptor alpha and beta (ERα, ERβ) are expressed in both extra nuclear and nuclear sites in non-small cell lung cancer (NSCLC)[17]. A retrospective study has shown that estrogen therapy may increase the risk of developing lung adenocarcinoma (ADC), indeed lower age at diagnosis and poorer survival have been observed in women who received estrogens as a part of a hormonal replacement therapy regimen[18].

Clinico-pathological features

Women are more likely to receive a diagnosis at an earlier age[19].

Among NSCLC, which represents 85% of LC histologies, ADC is currently the most common subtype both in men and women, but women present with proportionally more ADCs and fewer squamous cell carcinomas (SCCs) than men, and with a lower histological grade[19–21]. Smoking habits can explain the difference in histological distribution, but other genetic and hormonal factors are likely to contribute.

Molecular druggable alterations show different frequencies between sexes. About 15% of NSCLC harbours EGFR mutations; these are found at a much higher frequency in women, non-SCC histologies, Asians, and never smokers[22,23]. ALK translocations are found in 3 to 7% of NSCLC and are more common among patients with a never or light smoking history, non-SCC histologies, a younger age, and in tumours wild-type for EGFR, but in the case of gender conflicting findings have been reported[24-26].

Treatment and outcomes

Multiple studies have shown better overall survival rates in women with early stage LC after surgical resection, both in NSCLC and small cell lung cancer (SCLC)[27-32]. A meta-analysis of 39 publications, which included more than 32,000 women and 54,000 men, reported that survival of women was significantly better than the survival of men[33]. Also in locally advanced and advanced disease, women experienced significantly longer survival than men independently from stage and treatment, smoking habit, or age at diagnosis[34].

Sex may be regarded not only as a prognostic factor, but as a predictive factor as well: an improved benefit from chemotherapy has been observed for women with SCLC compared to men[35-37]. However, in advanced NSCLC this issue is controversial[38,39]. Women have been reported to experience greater toxicity from certain chemotherapeutic drugs[38], but the choice of chemotherapy is currently not influenced by the patient's sex. Furthermore, no predictive value of sex has yet been demonstrated for EGFR tyrosine kinase inhibitors[40-42] and ALK-targeted treatment[43].

As regards immunotherapy, the analysis of overall survival carried out across patient subgroups in the pivotal studies of nivolumab and pembrolizumab did not show a significant difference in the hazard ratio between women and men[44,45]. Carcinogens in tobacco smoke are responsible for much of the mutagenesis in NSCLC[46] and smoking-related lung cancers have 10 times as many somatic mutations as those from never-smokers[47]. Fingerprint mutation due to tobacco exposure is a cytosine to adenine transversion, which is predominantly found in smokers[48]. In patients with NSCLC treated with the anti-PD-1 antibody pembrolizumab, higher nonsynonymous mutation burden in tumours was associated with improved objective response, durable clinical benefit, and progression-free survival; efficacy also correlated with the molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations; each factor was also associated with mutation burden[49].

Pooled prospective data on more than 1300 NSCLC inoperable patients treated with radiotherapy (RT) included in Radiation Therapy Oncology Group (RTOG) nonoperative trials showed that women treated with RT had a better overall survival[50].

As far as anti-estrogen therapy in LC is concerned, a retrospective study conducted on a population of breast cancer survivors showed that anti-estrogen treatment may reduce the incidence of a second cancer in the lung when compared with non-users[51]. Moreover, a randomized phase II trial of erlotinib alone or combined with the anti-estrogen fulvestrant in previously treated advanced NSCLC found that the combination strategy was well tolerated and had significantly greater clinical benefit among wild-type EGFR patients[52].

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