LUNG CANCER AND GENDER DIFFERENCES

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For a long period of time lung cancer has been 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 1980s, mainly as a consequence of the huge spread of tobacco consumption during the past 60 years. It has been known, from US data, that the prevalence of smoking in American women peaked in 1965 at 33% and remained at that elevated level throughout the 1970s before beginning to slowly decrease in 1980. In 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, reflecting the earlier and more marked decline in the prevalence of tobacco use in men1. Nowadays more women die from lung cancer each year than from breast, ovarian, and uterine cancer, combined.

Lung cancer is the leading cause of cancer death for women in the United States and other countries, with more than 109,000 new cases and more than 72,000 estimated deaths in 20122. In European countries there are more than 79,000 new cases in female sex per year with more than 78,000 estimated deaths in 20123,4. Considering that this increase in women continues worldwide, the incidence of lung cancer is projected to be identical in both sexes over the next decade5.

Gender differences in terms of susceptibility to carcinogens and natural history of the disease have been reported and several case-control studies suggest that women are more vulnerable to tobacco carcinogens than men, even remaining this data controversial6,7. Freedman et al reported on a cohort of nearly 500,000 individuals, aged from 50 to 71 years, a significant increase in the rate of lung cancer for women who did not smoke, compared with male non-smokers, whereas no increased risk was described in current and former female smokers compared with matched males8. Histological subtypes also differ significantly according to gender, being adenocarcinoma in women the commonest histologic subtype. Although tobacco smoke remains the main risk factor for adenocarcinoma, approximately 20% of women with lung cancer are never smokers9. The rate of lung cancer in never smokers is higher in women than in men. When compared with them, women
are more likely to be younger at the time of diagnosis and to have a better survival at any stage and independently from the therapeutic approach\textsuperscript{10}.

Hormonal status is one of potential explanations for such difference. Estrogens may be involved in lung tumorigenesis through several mechanisms such as cell proliferation induced by ligand-estrogen receptor (ER) interaction and the cross-talk between estrogen receptors and other growth factor receptors (i.e. epidermal and insulin growth factor receptors). In addition, there is new evidence demonstrating progesterone receptor expression in NSCLC tumors. Combinations of estrogen and progesterone work synergistically in vitro to promote vascular endothelial growth factor secretion, increase tumor-associated angiogenesis, and increase putative tumor stem/progenitor cells\textsuperscript{11}. The role of hormonal receptor in lung cancer needs more elucidations, but, based on preclinical data, some investigators explored the implications of this pathway in the therapeutic scenario, as it has already been done in breast and prostatic cancer\textsuperscript{12}.

There are several biomolecular differences in lung cancer, that are hypothesized to be responsible for gender differences, such as a decreased DNA repair capacity in women, a higher susceptibility to tobacco carcinogens because of a different expression of metabolizing phase I/II enzymes, having all these mechanisms a possible role in the increased risk for lung cancer development in female sex\textsuperscript{10}.

Also with regard to the expression of specific gene alterations there are relevant differences in men and women. By far, the most widely recognized is the epidermal growth factor receptor mutation, that is found at a much higher frequency in adenocarcinomas, women, Asians and never smokers. K-ras mutations are primarily observed in smokers and historically associated with male sex, but there are also publications demonstrating an higher frequency in women of “non-classical” type of K-ras mutations. These data need further validations and it’s not still perfectly defined a clear role on prognosis and therapy. One of the new west genetic markers in non small cell lung cancer is the echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK): from phase I/II prospective trials and from retrospective evaluation it has been evidenced that this alteration occurs more frequently in young patients, light or never smokers and male subjects and granted impressive response rates when treated with Crizotinib which was approved by FDA in 2011. B-Raf (V600) is described respectively in 2\% of patients with lung adenocarcinoma in western countries, it is noted more frequently in women and has worse prognosis, but, since some successes have already been noted in melanoma where these mutation occurs, it would seem likely that similar results could be obtained with therapies targeting the same mutations in lung cancer.\textsuperscript{13,14}.
Gender-based variations in multiple regulating gene pathways as well as hormonal factors have been implicated in the epidemiological, clinical and molecular disparity between men and women in lung cancer. At the moment there are no gender-based approaches on diagnosis and treatment in lung cancer but an improvement in understanding genetic, metabolic, and hormonal factors could stimulate research towards further personalized sex-based investigations.

References

5. www.registri-tumori.it