Sex-Based Differences in Lung Cancer: Does It Matter?

Claudia Poleri, MD*

The analysis of incidence and mortality of any disease by sex is complex owing to the multiple causes that influence them. Particularly in lung cancer, differences have been observed by GLOBOCAN estimations for 2020 revealing there are sex differences according to continents. North America and Oceania have higher proportion of female lung cancer incidence as compared with males (35.7 versus 30.1 and 27.4 versus 21, respectively, age-standardized rate by world standard population) than in other continents wherein the proportion of women is less than half that of the men incidence. It can be considered that heterogeneity of data collection and records interfere with the precision, but these data suggest that there are true regional differences. Therefore, because the socioeconomic and cultural factors in men and women vary in the different regions, there are limitations to make recommendations for developing prevention, screening, and treatment strategies valid for all over the world.

Yu et al. conducted a large prospective investigation in Australia to determine potential predictor value of lung cancer survival disparity between men and women studying simultaneously tumor characteristics, treatment modalities, and sociodemographic, health, and lifestyle factors. Being a prospective study, they were able to consider sociodemographic and lifestyle factors that usually could not be measured. The study included marital status, private health insurance, remoteness of residence, education, neighborhood socioeconomic status, physical disability, country of birth, family history of lung cancer, height, tobacco smoking, passive smoking, physical activity, and alcohol consumption. They found that women with lung cancer as compared with men were younger at diagnosis, had fewer comorbidities, had a low level of education, and were more likely not a smoker and less likely to be exposed to passive smoking, to be diagnosed with having adenocarcinoma, and to receive surgery within 6 months after diagnosis. Similar differences led Ragavan and Patel to suggest that lung carcinoma is a different disease in men and women.

How to include these young women who smoke lightly or not in screening plans to be identified and provided with the appropriate treatment early? In 2013, U.S. Preventive Services Task Force lung screening guidelines, for example, developed sex disparity eligibility criteria that persist in the 2021 criteria, because they are based on age and smoking history. In a study of patients from an urban, community-based thoracic oncology practice at the University of Illinois Hospital & Health Sciences System, it was found that sensitivity in women was lower than in men (46.7% versus 64.6% [p = 0.003] by 2013 criteria and 56.8% versus 71.8% [p = 0.02] by 2021 criteria). Nevertheless, the 2012 Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial application criteria mitigated these disparities because it uses a greater number of predictors, uses continuous values for continuous variables, and considers nonlinear effects instead of categorical age–pack-years–quit-years. This indicates that it is possible to continue improving the eligibility criteria for lung cancer screening to reduce the sex gap.

Regarding sex difference in mortality, similar to incidence, it is also variable according to regions. Europe and Asia have the highest men mortality rates (34.9 and 27.8 age-standardized rate by world standard population, respectively), but women mortality rate is higher in North America (16.9 age-standardized rate by world standard population) than in other continents. Analysis of United States of America and Europe from the Centers for Disease Control and Prevention Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) and the WHO Mortality Databases since 2000 to 2017 reveals an overall decrease in the ratio of male-to-female mortality in all countries. The reduction of rates...
observed is associated to the decrease in male mortality in all countries except in Romania, Portugal, and Bulgaria and the increase in female mortality, except in United States of America and Ireland. Because this is an observational study, it is difficult to hypothesize about the factors that contributed to these changes.

In this direction, the study presented in this issue of the Journal of Thoracic Oncology from an Australian cohort provides valuable information. The risk of dying from lung cancer was significantly higher for men than for women. Differences in treatment related factors explained 50% of the sex survival differential, followed by lifestyle and tumor-related factors (28% and 26%, respectively). Women in other series also received surgical treatment more frequently than men, were younger, had fewer comorbidities, smoked little or never, had better perioperative outcome, and have a significantly better prognosis than men. The differences in tobacco consumption could explain the previous well health that lets good outcome after surgery, the greater frequency of adenocarcinoma, and the presence of genetic and molecular alterations that allow women to benefit from targeted treatments more frequently than the men. Nevertheless, these differences alone do not explain the higher survival in women.

Fan et al. compared the differences in tumor immune microenvironment between male and female with lung adenocarcinomas applying the Estimation of Stromal and Immune cells in MAInTumor using Expression data (ESTIMATE) algorithm. They identified that estimate immune and stromal scores of females were higher than those of male and were associated with better overall survival only in women. Furthermore, the study described higher density of memory B cells in the tumor microenvironment in female than in male adenocarcinomas. A recent review analyzes the differences in immunity by sex, pointing out that many aspects of functional activity of innate immune cells and downstream adaptive immune responses are potentially influenced by hormonal mediators, such as differentiation, maturation, and functions of dendritic cells, neutrophils, natural killer cells, macrophages, and B and T lymphocytes. These findings could provide a theoretical basis for explaining the different prognosis of female with lung adenocarcinoma, but more investigation is necessary.

The patients included in the study by Yu et al. did not receive targeted therapies or immunotherapy because they began their follow-up before utilization of these treatments. Review of cellular oncogenic alterations that make tumors susceptible to molecularly targeted drugs and the differences in frequency and response according to sex exceeds this text. But it needs to be stressed that mutation testing of patients with NSCLC is still suboptimal in some places of the world, regardless of sex.

The difference by sex in response to immunotherapy is not clear. In two meta-analyses, Conforti et al. observed better survival in men treated with mono-therapy based in anti–programmed cell death protein 1 and programmed death-ligand 1 drugs, but women presented a statistically significantly larger benefit with addition of chemotherapy. These observations could not be confirmed in a retrospective study, suggesting sex did not significantly influence outcomes in the reported cohorts of patients. But there are no conclusive data about gender differences in response to immune therapies.

Does it matter to analyze the differences by sex in lung cancer? It matters. It is necessary to implement screening programs (as mentioned previously) and build artificial intelligence diagnostic algorithms considering the role of sex and gender equity to ensure that innovative technologies do not induce disparities in clinical care. It is crucial to conduct education and health public programs that consider these differences, optimizing the use of available resources. It is essential to improve the accuracy of research design and clinical trials. In this way, each person in every region could receive the best prevention and medical care without discrimination.

CRediT Authorship Contribution

Claudia Poleri: Conceptualization, Writing - review & editing.

References


