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Differences in the survival rate between premenopausal and postmenopausal women with lung cancer: US SEER database

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Abstract

In the United State, lung cancer remains the leading cause of cancer death in both men and women. Several reports have suggested a role for estrogens in the development and/or progression of lung cancer, especially in women. Data from the national SEER registry between the years of 1990-2011 was analyzed, women between the ages 31-50 years old were chosen as representative of the premenopausal group (*n*=1595) and 51-70-year-old women represented the postmenopausal group (*n*=7075) as defined by the American College of Obstetricians and Gynecologists. For comparison, men were divided into two categories: younger men (*n*=2233) aged 31- 50 years and older men (*n*=10908) aged 51-70 years. Survival rates were analyzed by Kaplan-Meier method and compared by Z-test through SEER*Stat software version 7.0.9. The adenocarcinoma had a significant difference between premenopausal and postmenopausal groups (62% *vs*. 51%) respectively. Furthermore, the survival rate in premenopausal inferior to postmenopausal women in both SCC and BAC *P*<0.05. Premenopausal women more commonly underwent curative surgery, 42%, and 19% of postmenopausal women treated palliative. Additionally, for every stage of disease, 55% of postmenopausal women have radiotherapy. The results suggest varying estrogen effects between the histology sub-types of NSCLC and support clinical strategies need to block the ER pathway for the treatment of NSCLC.

Keywords: NSCLC, SEER, Estrogens, Premenopause, Postmenopause, Survival rate

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Introduction

In the United State, lung cancer remains the leading cause of cancer death in both men and women. Several reports have suggested a role for estrogens in the development and/or progression of lung cancer, especially in women. Lung cancer (LC) remains the leading cause of cancer-related deaths worldwide. NSCLC is the predominant type, accounting for approximately 85% of all newly diagnosed cases, with adenocarcinoma being the most common subtype of NSCLC. Although LC was an important health problem predominantly among men, in the past three decades LC incidence rates have declined about twice as fast in

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men as compared to women. Similarly, while LC mortality rates have decreased among men, they have increased among women. Interestingly, in 2013 LC surpassed breast cancer as the leading cause of cancer death among females in more developed countries (1,2).

It has been suggested that the increase in NSCLC incidence among women can be explained by the increased number of smoker women in developed countries (3). However, this explanation is not entirely satisfactory given that up to 53% of women who develop NSCLC were never-smokers while only 15% of men who develop NSCLC were never-smokers. Moreover, there are studies showing that among women and men with similar tobacco exposure, the onset of LC occurs earlier in women (4,5). This indicates that, in addition to smoking, there are other factors influencing the development of NSCLC in women. Furthermore, the clinical characteristics of female and male patients are very different. For instance, in females: (I) the median age at the time of diagnosis is lower than that of males; (II) there is generally no history of tobacco exposure; (III) the predominant histological subtype is adenocarcinoma; (IV) outcomes are generally better at all diagnosis stages; (V) a positive epidermal growth factor receptor (*EGFR*) mutation status is more common (6,7).

Patients and Methods

Ethics statement

The SEER research data files were downloaded and the data released by the SEER database do not require informed patient consent.

Data collection

SEER*Stat version 8.3.2 was utilized to filtrate and collect the information of representative patients in the research (http://seer.cancer.gov/). Data between the years of 1990-2011 was analyzed, women between the ages 31-50 years old were chosen as representative of the premenopausal group (n=1595) and 51-70-year-old women represented the postmenopausal group (n=7075) as defined by the American College of Obstetricians and Gynecologists. For comparison, men were divided into two categories: younger men (n=2233) aged 31- 50 years and older men (n=10908) aged 51-70 years. Survival rates were analyzed by Kaplan-Meier method and compared by Z-test through SEER*Stat software version 7.0.9.

Statistical analysis

We used SPSS 22.0 software to analyse the information we obtained from the database. The clinical characteristics of the selected patients were compared with the Pearson's $\chi 2$ test. The survival curves were drawn with Kaplan Meier analysis and the curves were compared with log rank test with GraphPad Prism 5.0. Cox regression models were used to identify factors which were significantly associated with overall survival (OS) and lung cancer-specific survival OS, was defined as the time from lung cancer diagnosis to death due to any cause. The 1-year and 2-year survival rate and median survival rate was also calculated. At the meantime, hazard

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ratios (HRs) and 95% confidence interval (95% CI) were also analysed. We defined P-value < 0.05 as statistically significant.

Results

The adenocarcinoma had a significant difference between premenopausal and postmenopausal groups (62% *vs*. 51%) respectively. Furthermore, the survival rate in premenopausal inferior to postmenopausal women in both SCC and BAC *P*<0.05. Premenopausal women more commonly underwent curative surgery, 42%, and 19% of postmenopausal women treated palliative. Additionally, for every stage of disease, 55% of postmenopausal women have radiotherapy.

Figure 1.

Age-adjusted rates of lung cancer in men and women over time (Source: SEER registry data)

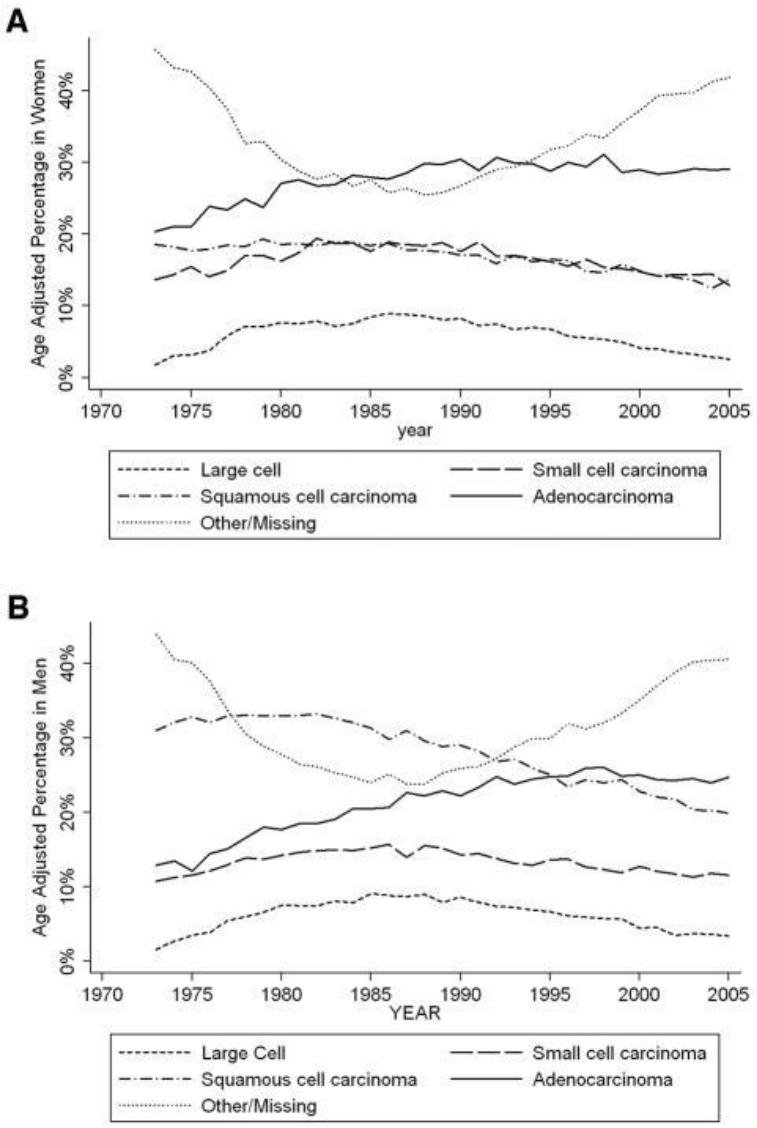

Figure 2.

Age-adjusted percentages of common histological subtypes in women. Age-adjusted percentages of common histological subtypes in men.

Discussion

A large and growing body of literature has accumulated highlighting the important role that estrogen and ERs have on the development and progression of LC. In particular, tumoral ER-β and aromatase expression have emerged not only as important prognostic factors associated with poor survival in NSCLC patients, but also as actionable molecular targets for the treatment of this malignancy. Anti-estrogenic drugs have been successfully used for the treatment of breast cancer; consequently, the information that is already available on these drugs (such as pharmacodynamics, pharmacokinetics, bioavailability, toxicities and dosing protocols alone or in combination with chemo/radiotherapy regimens) makes them ideal candidates to be

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repurposed for the treatment of LC patients. Despite the recent advancements on all fronts of thoracic oncology, the prognosis for patients with LC remains dismal. Indeed, only a small percentage of NSCLC patients are candidates to receive targeted therapies or immune checkpoint inhibitors, which offer a survival advantage. Antiestrogen therapy could be an additional therapeutic strategy that could result in better response rates in premenopausal women but also in male patients with ER^+ and ARO^+ lung tumors. Admittedly, there are still many areas of research on the role of estrogen and ERs that need to be explored in the context of lung carcinogenesis in order to identify the best combination of possible treatments. In particular, it is crucial that the exact molecular mechanisms by which estrogen and its receptors promote the development and progression of LC are elucidated. Finally, in the age of personalized medicine, it is essential that subsequent studies consider that there may be differences in the clinicopathological features, therapy response and survival of NSCLC patients that could be attributed to sex, and to the expression of hormonal markers. Nonetheless, there are several ongoing clinical trials evaluating the tolerability and efficacy of anti-estrogenic drugs alone or in combination with other standard of care agents for the treatment of NSCLC patients. The preliminary, updated data from some of these studies is encouraging and suggest that certain combinations do afford enhanced antitumor activity but confirmation of these findings is still awaited.

Conclusion

A large and growing body of literature has accumulated highlighting the important role that estrogen and ERs have on the development and progression of LC. In particular, tumoral ER-β and aromatase expression have emerged not only as important prognostic factors associated with poor survival in NSCLC patients, but also as actionable molecular targets for the treatment of this malignancy. The results suggest varying estrogen effects between the histology sub-types of NSCLC and support clinical strategies need to block the ER pathway for the treatment of NSCLC.

Competing interests

The authors declare that they have no competing interests.

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