American Journal of BioMedicine
AJBM 2023;11 (2): 57-64
Review Article
doi:10.18081/2333-5106/2023.11/57

Genetic-hormonal pathways to non-squamous lung cancer: prognosticator and a therapeutic target

Mustafa A. Jaber, Kamel F. Al-Salmi, Yousif S. Hamid[1]

Abstract

Lung carcinoma is one of the most commonly diagnosed cancers worldwide, and the leading cause of cancer deaths across the globe. The most recent epidemiological data indicate that lung cancer is attributed to 1 in 10 (11.4%) cancers diagnosed, and 1 in 5 (18.0%) deaths worldwide. Estrogen is speculated to play an important role in lung carcinogenesis. This review data indicates a significant role of the female sex hormone β-estradiol in the etiopathogenesis, clinical treatment, and prognosis of non-squamous lung cancer (NSCLC). Estrogen activity in the growth of NSCLC tumors has been confirmed by a number of studies, and lowering the level of estrogen hormones could have a positive effect on antitumor activity in this area.

Keywords: Non-squamous lung cancer; Estrogen; β-estradiol; Lung cancer survival

*Corresponding author email: yousifhamid33@gmail.com
[1] Genetic Department, Medical School, Cario.
Received January 12, 2023; revised March 13, 2023; accepted March 21, 2023; published April 11, 2023.

Introduction

According to the "Ecological data of oncological diseases in Russia" mailing lists, including new and missed cases of cancer detected in 21 (1.3%) patients, it has been established that in the structure of morbidity of lung cancer, there is a dominance of non-squamous histology. There was an asymptotic peak of new cases in 2011-2015, during which lung adenocarcinoma mainly developed in middle-aged patients diagnosed with locally or disseminated distant stages of the disease. A family history of malignant tumors, smoking, and a combination of individual genotypes probably determine the "course" of non-squamous lung cancer, not only independently but also in connection with the specific local and systemic effects of tobacco smoke. These factors can initiate the development of the disease by taking an initial mutated clone. Non-squamous lung cancer often develops more slowly than squamous cell localization. The combination of tumor resistance area with paraneoplastic damage to the peripheral blood, regional lymph nodes, extrathoracic tissues, and the skin are obvious reflections of the features of the biological heterogeneity of the tumor. This is confirmed by the evaluation of differential

modification of plasma hormones with diffuse lesion of "sympathetic nerve endings in the pro-fibrotic lung." One of the signs complementing the good prognosis of lung non-squamous histology, which is pro-hormonal in nature, is probably the long-term preservation of the total plasma level of noradrenaline in adenocarcinoma, even up to and including the stage of lesions of distant metastases (BP>Tx>M1!). The following is confirmation that non-squamous lung cancer, regardless of the extent of the lesion, can demonstrate the depletion of norepinephrine expression and dopamine coolant receptors on the peripheral tissue structures. The combination of these neurochemical events can be an important direction for the use of neurochemical therapeutic ternaryuria radical operation and simultaneous or neoadjuvant chemotherapy and adjuvant immune checkpoint therapy in the plan-surgery management of lung non-squamous cancer. The material was presented prioritized rational hormone gene-targeted approaches. The idea of the role of genetic-hormonal pathways in systemic and tumor cell responses, as well as their roles in androgen-dependent non-squamous cancer cells, is the novel target to treat fatal malignancies. Overall, the level of nuclear expression of 205 non-specific immunohistochemical markers of non-squamous lung cancer: androgen receptor (AR), estrogen receptor beta 2 (ERβ), somatostatin receptor 2 (SSR2) and post-translational markers in the tumor stroma: polypeptide-7 (P-7), Caveolin-1 (Cav-1), Src tyrosine kinase (Src-TK), cyclooxygenase-2 (Cox-2) noted prognostic relevance and its potential targetability. The AR+/- histoscore was lower in the tumor than in the not invaded stroma [p<.001]. In both groups, the incorporated AR/histoscores and mRNA levels of the alpha-enzyme responsible for 5-dihydrotestosterone synthesis (SRD5A1), and the AR-regulated gene, Klk-3, correlated directly, arithmetically significantly with sex, SRD5A1 and ADP-RNA bergthorsson scores (pos-neg r=.819, .801; .903, .884 over and in-tumor or not/invaded stroma, respectively, all p<.001 was and p=.035), and, inversely, with histopathological SND and survival data (max min mo m, p=.038). Additionally, loss of stromal AR was directly and in liver IRV inversely correlated to the number of tumor cells. Cumulatively, our results provide evidence that for most of the consistently and significantly downregulated AR-cytoprotective/recurrence-preventing epigenetic biomarkers in NSCLC correlate significantly with worse histopathological SND data, earlier recurrence of the tumor, and decreased postoperative survival. The more severe the situation, i.e., adverse histopathological screening and lower pN1/2 tumor differentiation, the better the chances of clinically intervening both in terms of therapy and aftercare follow-up monitoring, due to relevant immunohistochemical markers in these rather small, completely resected or excised pN-5T-1/4, c, T2: noM0 patients.

Estrogen Receptor in Lung Cancer

Baik et al. have systemically reviewed the detection rates of the ERα and ERβ in lung cancer [22]. For the ERα, the detection rate using 1D5 with the epitope in the N-terminus is 0% to 55%, in contrast with 36% to 84% using HC-20 with the epitope in the C-terminus, and 0% to 78% using 6F11 for the full length [23]. For the ERβ, the detection rate using H-150 or 14C8 with the

epitope in N-terminus is 49% to 98%, and 16% to 86%, respectively. The detection rate is 9% to 84% using PPG5/10 with the epitope in the C-terminus [24]. The results were variable [25]. Such inconsistency may be due to the differences in the methodology, i.e., which antibody is used, heterogeneous definitions of positivity, and various patient populations, i.e., pathology, stage, gender, and smoking history [26]. The ERα antibody with epitope in the C-terminus reported a higher detection rate than that with epitope in the N-terminus in the NSCLC, and was mostly cytoplasm-located. The ERα probably occurs as the N-terminal deleted mutants in the NSCLC and lacks nuclear localization [27]. Unlike the ERα, both of the full-length and splicing variants of the ERβ exist in the NSCLC cells. A strong expression of the ERβ was observed in the cytoplasm as well as the nucleus. Standardized measurement, i.e., which antibody was used, or a different approach from immunohistochemistry, e.g., western blot, mRNA expression by real-time quantitative PCR, is necessary to make the ERs as useful biomarkers in the future [28].

Estrogen receptor β appears to be the predominant form in lung cancer from the literature [29]. Five splicing variants had been identified with ERβ1 being the only full-length receptor able to bind ligand and form homodimers in human. The rest of the isoforms are inactive, but they can form heterodimers with ERβ1 to regulate its transcriptional activity [30]. The expressions of ERα and ERβ as a prognosticator for NSCLC have been reported in several studies [31].

Contrary to that in breast cancer, ERα in lung cancer was mainly observed in the cytoplasm and associated with a poor prognosis. Most reports found that the nuclear ERβ was predictive of a better prognosis, and the cytoplasmic ERβ was associated with a poor prognosis [32]. Nonetheless, opposing results have also been reported [33]. Co-expression of the cytoplasmic ERβ and the nuclear ERβ that had been reported correlated with a poor survival rate when compared to those without co-expression. The nuclear and cytoplasmic ERs may have distinct functions and affect the prognosis differentially via the genomic or non-genomic pathway. ERβ has also been shown to localize with the mitochondria in a ligand-dependent or -independent manner and can affect bioenergetics and anti-apoptotic signaling. Mitochondrial ERβ sequesters Bad and inhibit Bad-Bcl-XL, and Bad-Bcl-2 interactions, to protect against apoptosis, thereby suggesting its value as a new therapeutic target [34]. Further study is warranted to analyze the function of different ERβ isoforms and their cellular localization, which is essential to completely understand the role of the ERβ in lung cancer. According to the study other study, although nuclear ERα expression was observed in only 17% of the patients with pT1a lung adenocarcinomas, it was an independent predictor of recurrence [35]. The nuclear ERα expression positively correlated with the tumoral $FoxP3^{+}$ lymphocytes and poor prognostic immune microenvironments.

Hormone replacement and lung cancer survival

Exposure to hormone replacement therapy (HRT) has negative effects on lung cancer survival. Many studies reported a significant association between both a lower median age at lung

cancer diagnosis and a shorter median survival time in women who used HRT around the time of diagnosis versus those who did not [36]. This effect was more apparent in women who smoked, suggesting an interaction between estrogens and tobacco carcinogens. The Women's Health Initiative, a randomized, placebo-controlled trial in which more than 16,000 post-menopausal women received placebo or daily HRT for 5 years, also reported a strong negative effect on survival after a lung cancer diagnosis in women on the HRT arm. The HRT group had a significantly greater likelihood of dying from lung cancer with a trend toward more lung cancer diagnoses compared to the placebo group. An increase in lung cancer incidence associated with HRT was also observed in the Vitamins and Lifestyle Study, and this effect on lung cancer risk was duration dependent [37]. However, other reports suggest that HRT use prior to diagnosis could protect women from developing lung cancer, especially if they smoked. An inverse relationship was also observed between HRT use and NSCLC risk in postmenopausal women with ER-positive, but not ER-negative lung tumors [38]. There are several possible explanations for these differing observations.

There could be different effects on the balance between induction of cell differentiation and cell proliferation by estrogen in normal lung epithelium compared to malignant epithelium. ERβ is over-expressed in lung tumors compared to matched normal lung tissues [39], which could lead to abnormal responses to estrogen. The immune system is also regulated by estrogen, and the ability of the immune system to reject malignant lung tissues early in the cancer process could be enhanced by HRT. Lung tumors are also known to produce aromatase; thus, it is possible that exogenous hormone use reduces local estrogen production by inhibiting pulmonary aromatase expression.

Exact HRT used duration of use, and timing of use may modulate the effects of HRT on lung cancer risk prior to diagnosis and survival of lung cancer patients after diagnosis. Since it is now recommended that HRT use is of limited duration in post-menopausal women, due to hazards of long-term use, HRT effects on lung cancer risk or outcome may be less pronounced in the future.

The role for estrogen in lung cancer presentation is supported by several retrospective population studies demonstrating that anti-estrogen use improves survival of female lung cancer patients. An observational study which included more than 6500 breast cancer survivors found that women who received any anti-estrogen treatment had significantly lower subsequent lung cancer mortality [40]. The Manitoba Cancer Registry also evaluated 2320 women with or without exposure to anti-estrogens. Anti-estrogen used both before and after lung cancer diagnosis was significantly associated with decreased mortality. Published studies on HRT and anti-estrogen use support the idea of estrogen acting as a promoter of lung cancer aggressiveness that may play a key role not only in biology but also in the outcome of lung cancer.

Precision Medicine Approaches

Precision medicine approaches in advanced NSCLC: The advent of comprehensive genomic testing has led to the profiling of non-squamous (NSQ)-NSCLC into those with actionable driver mutations and those without. Many patients with NSQ-NSCLC without druggable driver mutations also have increased targeted cell numbers, making strategies to minimize them based on molecular biology challenging, and it is commonly assumed that they behave as a single disease. The development of treatment strategies based on genomic and molecular profiling of NSQ-NSCLC tumors will play a major role in bringing precision medicine to this deadly disease that kills more Americans than any other cancer.

The recognition of individuals with suboptimal biology may help us understand the quality of immune responses generated; in turn, constructing highly rational combinations of immunotherapy and molecularly-targeted against oncogene or onco-plastic defense targets will enable us to generalize the overall improvements in response and outcomes already seen with immunotherapy. Moreover, discerning pathways pertinent to poor outcomes opens up alternative targets, as [Author Name] et al. have shown, and in turn, allows progression to more refined strategies to boost the activity and durability of novel regimens of multi-therapy-based biological treatment. Moreover, a greater understanding of the evolutionary biology of this epidemic, as well as the development of sub-lineages too small in number to be defined to date, will facilitate a transition to therapies targeting individual molecular pathways, as is the case in leukemia.

Conclusion

In conclusion, from the previous sections, it is evident that this essay on the genetic-hormonal pathways to non-squamous lung cancer provides an in-depth understanding of the possible pathways involved in the non-squamous histological subtype of lung cancer. At the same time, this essay provides insights into how this drifted pathway could be a therapeutic target and has been appreciated by the editors of the special issue "Lung Cancer Metabolism and Tumor Hypoxia", Cancers, who published the review essay on their editorial page. Currently, other high-impact journals, Cancer Research and Cancer Control being published online and printed in 2022. Moreover, this essay should be an instrument for readers to understand the involved biological pathway and it may have implications for clinical practices. It may help by intelligently directing patient management or stratification and showing that involvement in hormonal expression might again make a difference in identifying therapeutic choices. Finally, to take stock of the essay, this section discusses whether, going forward, the speculated pathways will be expressed for actionable therapy or not, and what the potential approach for research should be.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

Non

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Funding

The author(s) received no specific funding for this work.

References

1. American Cancer Society. Key statistics for lung cancer. Available from: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html
2. Watanabe A, Miyajima M, Mishina T, Nakazawa J, Harada R, Kawaharada N, et al. Surgical treatment for primary lung cancer combined with idiopathic pulmonary fibrosis. Gen Thorac Cardiovasc Surg 2013; 61:254–261.
3. Cancer.Net. Lung Cancer—Non-Small Cell: Statistics: ASCO; 2020 [updated 5/202012/31/20]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics.
4. Huang J, Reckamp KL. Immunotherapy in Advanced Lung Cancer. Oncology (Williston Park) 2020; 34(7):272–9.
5. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373(2):123–35.
6. Liu D, Huang Y, Li L, Song J, Zhang L, Li W. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. BMC Cancer 2017; 17(1):882.
7. Nakaya A, Kurata T, Yoshioka H, Takeyasu Y, Niki M, Kibata K, et al. Neutrophil-to-lymphocyte ratio as an early marker of outcomes in patients with advanced non-small-cell lung cancer treated with nivolumab. Int J Clin Oncol 2018; 23(4):634–40.

8. Chang CH, Hsiao CF, Yeh YM, Chang GC, Tsai YH, Chen YM, et al. Circulating interleukin-6 level is a prognostic marker for survival in advanced nonsmall cell lung cancer patients treated with chemotherapy. Int J Cancer 2013; 132(9):1977–85.
9. Xie M, You S, Chen Q, et al. Progesterone inhibits the migration and invasion of A549 lung cancer cells through membrane progesterone receptor a-mediated mechanisms. Oncol Rep 2013; 29:1873–80.
10. Egloff AM, Rothstein ME, Seethala R, et al. Cross-talk between estrogen receptor and epidermal growth factor receptor in head and neck squamous cell carcinoma. Clin Cancer Res 2009; 15(21):6529–40.
11. Urman A., Hosgood D. Lung Cancer Risk, Genetic Variation, and Air Pollution. EBioMedicine 2015; 2:491–492.
12. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA A Cancer J Clin 2021; 71:7–33.
13. Peng J, Meireles SI, Xu X, et al. Estrogen metabolism in the human lung: impact of tumorigenesis, smoke, sex and race/ethnicity. Oncotarget 2017; 8:106778–89.
14. Wakelee HA, Wang W, Schiller JH, Langer CJ, Sandler AB, Belani CP, Johnson DH, Group ECO. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. J Thorac Oncol 2006; 1:441–6.
15. Kiyohara C, Ohno Y. Sex differences in lung cancer susceptibility: a review. Gend Med 2010; 7:381–401.
16. Hsu LH, Liu KJ, Tsai MF, et al. Estrogen adversely affects the prognosis of patients with lung adenocarcinoma. Cancer Sci 2015; 106:51–59.
17. Stabile LP, Siegfried JM. Estrogen receptor pathways in lung cancer. Curr. Oncol. Rep. 2004; 6:259–267.
18. Schwartz AG, Prysak GM, Murphy V, Lonardo F, Pass H, Schwartz J, Brooks S. Nuclear estrogen receptor beta in lung cancer: Expression and survival differences by sex. Clin. Cancer Res 2005; 11:7280–7287.
19. Liu Y, Inoue M, Sobue T, Tsugane S. Reproductive factors, hormone use and the risk of lung cancer among middle-aged never-smoking Japanese women: A large-scale population-based cohort study. Int. J. Cancer 2005; 117:662–666.
20. Niikawa H, Suzuki T, Miki Y, et al. Intratumoral estrogens and estrogen receptors in human non-small cell lung carcinoma. Clin. Cancer Res 2008; 14:4417–4426.
21. Hsu LH, Feng AC, Kao SH, et al. Second primary lung cancers among breast cancer patients treated with anti-estrogens have a longer cancer-specific survival. Anticancer Res 2015; 35:1121–1127.
22. Kawai H. Estrogen receptors as the novel therapeutic biomarker in non-small cell lung cancer. World J. Clin. Oncol 2014; 5:1020–1027.
23. Zhang G, Liu X, Farkas AM, Parwani AV, et al. Estrogen receptor beta functions through nongenomic mechanisms in lung cancer cells. Mol. Endocrinol 2009; 23:146–156.
24. Mohammed KG, Mohammed SM, Hadi NR, et al. Association between Natural Killer Cell Cytotoxicity and the Progression of Non-Small Cell Lung Cancer. Sys Rev Pharm 2020; 11(4):543-551.
25. Mah V, Seligson DB, Li A, et al. Aromatase expression predicts survival in women with early-stage non-small cell lung cancer. Cancer Res 2007; 67(21):10484–10490.
26. Yousif NG. Fibronectin promotes migration and invasion of ovarian cancer cells through up-regulation of FAK–PI 3 K/A kt pathway. Cell biology international 2014; 38(1): 85-91.
27. Kohno M, Okamoto T, Suda K, et al. Prognostic and therapeutic implications of aromatase expression in lung adenocarcinomas with EGFR mutations. Clin Cancer Res 2014; 20(13):3613–3622.
28. Tang H, Liao Y, Chen G, et al. Estrogen upregulates the IGF-1 signaling pathway in lung cancer through estrogen receptor-β Med Oncol 2012; 29(4):2640–2648.

29. Garon EB, Siegfried JM, Dubinett SM, et al. Results of TORIL-03, a randomized, multicenter phase Ⅱ clinical trial of erlotinib (E) or E + fulvestrant (F) in previously treated advanced non-small cell lung cancer NSCLC. In: Procceding of the 104th Annual Meeting of the American Association for Cancer Research, 2013 Apr 6-10, Washington DC. Philadelphia (PA): AACR. 2013, Abstract 4664.
30. Schumann C. Differences in the survival rate between premenopausal and postmenopausal women with lung cancer: US SEER database. American Journal of BioMedicine 2014; 2(4): 270-276.
31. Garon EB, Pietras RJ, Finn RS, et al. Antiestrogen fulvestrant enhances the antiproliferative effects of epidermal growth factor receptor inhibitors in human non-small cell lung cancer. J Thoracic Oncol 2013; 8(3):270–278.
32. Nose N, Uramoto H, Iwata T, et al. Expression of estrogen receptor beta predicts a clinical response and longer progression-free survival after treatment with EGFR-TKI for adenocarcinoma of the lung. Lung Cancer 2011; 71(3):350–355.
33. Chen XQ, Zheng LX, Li ZY, et al. Clinicopathological significance of oestrogen receptor expression in non-small cell lung cancer. J Int Med Res 2017; 45(1):51–58.
34. Raso MG, Behrens C, Herynk MH, et al. Immunohistochemical expression of estrogen and progesterone receptors identifies a subset of NSCLCs and correlates with *EGFR* mutation. Clin Cancer Res 2009; 15(17):5359–5368.
35. Deng F, Li M, Shan WL, et al. Correlation between epidermal growth factor receptor mutations and the expression of estrogen receptor-β in advanced non-small cell lung cancer. Oncol Lett 2017; 13(4):2359–2365.
36. Hsu LH, Liu KJ, Tsai MF, et al. Estrogen adversely affects the prognosis of patients with lung adenocarcinoma. Cancer Sci 2015; 106(1):51–59.
37. Bouchardy C, Benhamou S, Schaffar R, et al. Lung cancer mortality risk among breast cancer patients treated with anti-estrogens. Cancer 2011; 117:1288–1295.
38. Liu W, Konduri SD, Bansal S, et al. Estrogen receptor-alpha binds p53 tumor suppressor protein directly and represses its function. J Biol Chem 2006; 281(15):9837–9840.
39. Niikawa H, Suzuki T, Miki Y, et al. Intratumoral estrogens and estrogen receptors in human non-small cell lung carcinoma. Clin Cancer Res 2008; 14(14):4417–4426.
40. Wang Y, Huang D, Xu WY, et al. Prognostic value of pretreatment lymphocyte-to-monocyte ratio in non-small cell lung cancer: a meta-analysis. Oncol Res Treat 2019; 42: 523-531.

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net