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Smoking, hormonal factors and molecular markers in female lung cancer

Minireview

D. SCHVEIGERT[1,*], A. KRASAUSKAS[1,2], J. DIDZIAPETRIENE[1,2], D. KALIBATIENE[2], S. CICENAS[1,2]

[1]*National Cancer Institute, Vilnius, Lithuania;* [2]*Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

**Correspondence: diana.schveigert@nvi.lt*

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There has been substantial argumentation about differences in lung cancer occurrence and characteristics between men and women. Lung cancer incidence suggests that gender-related factors may influence lung cancer risk. The carcinogenic effect of tobacco smoke and the use of hormone replacement therapy could result in susceptibility to lung cancer among women. Mutations in *EGFR* and HER-2/*neu* genes, and *ROS1* gene fusions may also play a role in gender-based survival rate differences. This review summarizes the latest data of disease markers and its usefulness in female lung cancer.

Key words: female lung cancer, disease markers, mutations

Lung cancer in Europe is the most lethal oncological disease in men and has recently become the second most lethal cancer in women. Female mortality from lung cancer reaches 10.4 % in Europe and 6.8 % in Lithuania [1, 2]. The incidence of lung cancer among females worldwide is increasing and especially in never-smokers [3, 4]. Alternatively, growing evidence indicates that women are more susceptible to carcinogens in tobacco smoke.

Significant differences between male and female were observed according to lung cancer patients' clinical pathological features and response to treatment. Women are more often diagnosed with earlier stage non-small cell lung cancer (NSCLC), particularly adenocarcinoma [5, 6]. Female sex hormones, especially estrogen, may play a crucial role in lung cancer development. Conflicting data reflect on hormone replacement therapy and increasing incidence of female lung cancer.

Recent studies have demonstrated that multiple genetic alterations may influence the development and progression of lung cancer. Based on these findings, it is possible to classify lung cancer not only by known clinical and pathological criteria but also by tumor genetic profile. The insight into the biology of lung cancer has led to the development of a new generation of bioactive agents for personalized treatment of lung cancer patients [7]. Several clinical trials with tyrosine-kinase inhibitors (TKI) indicated that mutations in the epidermal growth factor receptor (EGFR) occur more often in women than in men, and women are more responsive to TKI therapy [8]. Therefore, the understanding of differences in lung cancer pathogenesis between the genders could further broaden the personalization of anticancer therapy. This review summarizes the influence of tobacco smoke, hormonal factors, and molecular markers on the female lung.

Smoking and the effect of tobacco smoke on women

The number of smokers among men has been steadily declining for the past several years, but it is still rising in women. This is one of the main reasons for the increase of lung cancer incidence rates in women [9]. Carcinogens in tobacco smoke induce oxidative DNA damage. The main carcinogens in tobacco smoke are polycyclic aromatic hydrocarbons (PAH). Metabolic activation is necessary for PAH and this process leads to the formation of DNA adducts. It has been hypothesized that the effect of tobacco smoke might be more carcinogenic in females, due to the estrogen receptors.

Estrogen receptors are detected both in normal lung and lung tumor tissues, and could stimulate the metabolism of PAH. There is a relationship between genetic polymorphisms in the genes coding the enzymes (GST, CYP1B1) that are involved in the pathways of estrogen and tobacco carcinogens metabolism, and increased lung cancer risk [10, 11]. GSTM1 null genotype contributes to the increased risk of lung cancer for female smokers [10]. The association between CYP1B1 polymorphism (rs1056836) and the risk of lung cancer has been described. A non-significantly increased risk of lung cancer was observed between female never-smokers and light-smoking women [10, 12].

The International Agency for Research on Cancer (IARC) reported an increased lung cancer risk of 20 % for women among never-smokers who are exposed to secondhand smoke from their spouse. Passive smoking is the inhalation of smoke, called secondhand smoke (SHS). SHS was classified as a carcinogen by the Environmental Protection Agency [13, 14].

Several clinical studies demonstrated controversial results between female lung cancer and smoking. The Environment and Genetics in Lung Cancer Etiology (EAGLE) study, a population based case-control study, didn't confirm a higher female susceptibility to smoking-related lung cancer (2100 lung cancer cases and 2120 controls). The results remained unchanged when additional criteria were evaluated (type of tobacco, inhalation depth, Fagerström-assessed nicotine dependence) [11]. The ICARE study, a multicenter case-control study on respiratory cancers, confirmed that smoking might increase a risk of small cells or squamous cells lung cancer among French women [15].

Hormonal factors

The results from experimental and clinical studies demonstrate that steroid hormones (estrogen, progesterone) are involved in the biology of the lung. Both estrogen and progesterone receptors are present in normal and malignant lung tissue. It has been hypothesized that female steroid hormones that bind these receptors play a role in lung carcinogenesis. Estrogen promotes cellular proliferation and induces DNA damage in the lung tissue, while progesterone can be a growth-inhibiting factor of malignant lung cells [16, 17, 18, 19].

Studies which have analyzed estrogen and/or progesterone as a risk factor of lung cancer have focused on hormone use history. Nevertheless, the mechanisms through which they could contribute to lung cancer risk are still not well understood. The results about the role of hormone use (oral contraceptives (OC) and hormone-replacement therapy (HRT)) in lung cancer development are controversial [18, 20].

The International Lung Cancer Consortium (ILCCO) meta-analysis results revealed an evidence of interaction between hormone use and lung cancer risk in women (1961 cases, 2609 controls). A reduced lung cancer risk for both OC use and HRT was ascertained. The greatest reduction in risk was seen among women using both OC and HRT during their entire life as compared with non-users (Odds ratios (OR) =0.61; 95% CI 0.47-0.78), independent of smoking status [18]. A reduced risk of lung cancer was also observed in an EAGLE study for HRT (OR=0.63, p=0.03) and OC use (OR=0.67, p=0.05) [21]. In a Maryland Lung Cancer Study (n=1041) no significant associations for OC or HRT use, including long-term use, and NSCLC cancer risk was observed [22].

In the Women's Health Initiative (WHI) study, where postmenopausal women (n=16000) received placebo or daily HRT for 5 years, the HRT arm had an increase in incidence of lung cancer in comparison with the placebo arm, but it was not statistically significant. Incidence rates of NSCLC with distant metastases or poorly differentiated tumors were higher in women using HRT than in the placebo group [23]. A significant increase in lung cancer incidence associated with HRT use was observed in the Vitamins and Lifestyle (VITAL) study (n=36000 postmenopausal women). The use of an estrogen plus progesterone (E+P) combination for more than 10 years was associated with an increased risk of lung cancer in comparison with no use of HRT (hazards ratio (HR)=1.48, p=0.03) [24].

Whereas, in the California Teachers Study (CTS) (n=133479), no effect of E+P use on female lung cancer was observed. Decrease of lung cancer mortality rates was determined among women who used estrogen-only therapy (ET) compared to non-users. The median survival time of lung cancer patients and users of ET was 20.2 months *vs* 15.6 months for non-users of ET (p=0.008) [25]. In the Katcoff H. *et al.* [26] study, E+P use was associated with a significantly improved survival for women with NSCLC taking combined HRT for 11 years or longer (p<0.0001).

Different results from the studies arise because of the diverse methodology, timing, OC and HRT dose, and duration of use. The interaction between estrogen and progesterone in lung carcinogenesis is not well-explored. More research studies with lung tumor biological characterization in terms of ER and PR expression are warranted.

Epidermal growth factor receptor (EGFR)

EGFR is a transmembrane receptor with an intracellular domain that displays tyrosine kinase activity. These receptors can activate intracellular signaling pathways (e.g. Rat sarcoma (RAS)/Mitogen-activated protein kinase (MAPK) pathway) and disruption of these pathways could cause malignant transformation of the cell. It has been noticed that EGFR signaling pathways play a potential role in tumor resistance to chemotherapy [27].

EGFR can be activated in several ways – due to receptor overexpression or increase of *EGFR* gene copy number, by other receptors (e.g. insulin-like growth factor 1 receptor (IGF1R)) or activating mutations. EGFR overexpression

in NSCLC patients is associated with lower survival rates, lymph node metastasis, and weak chemosensitivity [27, 28].

The activating mutations in the *EGFR* gene are associated with the response to treatment of the NSCLC patients. A high response rate is a result of *EGFR* mutations in the catalytic domain, which cause physical structure alterations in the domain for better drug binding [8]. Mainly, *EGFR* is activated by small in-frame deletions in the exon 19 in LREA (delE746-A750) sequence or a point mutation in codon 858 (L858R) in exon 21. These common *EGFR* mutations are associated with sensitivity to response to EGFR tyrosine-kinase-inhibitor (EGFR-TKI) therapy, such as erlotinib or gefitinib [29, 30]. The response rates to EGFR-TKI therapy is up to 70% for patients harboring common *EGFR* mutations. Patients with rare *EGFR* mutations (G719X in exon 18 and L816Q in exon 21) display EGFR-TKI response rates greater than 50% [30]. *EGFR* is more frequently mutated in women than in men. *EGFR* is known to be mutated in 10.4% of women smokers compared with 50.8% who have never smoked (p<0.001) [28].

It was demonstrated that women have increased progression free survival (PFS) after therapy with EGFR-TKI than men – 16.4 *vs* 9.5 months in the Arrieta O. *et al*. study [30]; and 12.7 *vs* 9.3 months in the Kaneda T. *et al.* study [31]. Rotella V. *et al* [32] reported that the mutations in *EGFR* gene were significantly correlated with the response rate (mutant *vs* wild-type: 60% *vs* 12.5%) and longer median PFS (mutant *vs* wild-type: 11.4 *vs* 4.5 months) for NSCLC female patients treated with erlotinib. Data of meta-analysis of seven eligible trials (n=1649) showed that in the group of patients with advanced *EGFR*-mutated NSCLC treated with EGFR-TKI as first-line therapy, women had a 27% greater benefit from the therapy than men [33]. These results suggest that *EGFR* mutational status is a predictive marker and essential factor of treatment with EGFR-TKI [27].

Human epidermal growth factor receptor 2 (HER2)

HER2 is a membrane-bound receptor with tyrosine kinase activity and has structural homology to EGFR [34]. The HER2 receptor lacks a known activating ligand and by forming homo- and heterodimers with other receptors (e.g. HER3, IGF1R) catalytically activates signaling pathways (e.g. MAPK pathway) resulting in cell proliferation, differentiation and invasion [34, 35]. HER2 is well-known as a prognostic and predictive marker in patients with breast cancer, but its role in lung cancer patients is far less understood and no studies have shown a survival advantage for targeted HER2 therapy for these patients [14, 34].

HER2 as a disease marker may be evaluated in two different ways – HER2 protein expression and HER2/*neu* gene amplification (increased gene copy number) or overexpression. Additionally, HER2/*neu* gene mutations can be identified in NSCLC cases. Mutations occur in exons 18-21 of the tyrosine kinase domain. Most frequently mutations are 12 base pair sequence insertion in exon 20 at codon 775. These mutations are not seen in breast cancer and occur mostly in lung adenocarcinoma [35, 36].

In the Rouquette I. *et al.* [17] study, HER2 overexpression was detected only for two women from 50 female patients with NSCLC, and didn't have prognostic value. In the Al-Saad S. *et al.* [37] study, a high HER2/*neu* gene copy number was an independent unfavorable indicator for women with NSCLC. Women with a low number of gene copies had a better survival rate in comparison with women with a high HER2/*neu* gene copy number (190 *vs* 47 months, p=0.005). A similar association was not found in the male patients group. Vallböhmer D. *et al.* [38] reported that women with histopathologically confirmed NSCLC with a low HER2/*neu* expression in tumor, had a significantly longer survival time in comparison with women who had a high HER2/*neu* expression (≥94.7 *vs* 26.4 months, p=0.043).

In vitro and *in vivo* studies have confirmed the oncogenic potential of HER2/*neu* mutations [35, 36]. These mutations in NSCLC range from 1% to 4% in Asian populations and 1-2% in Caucasian population [34, 36, 39, 40]. Tomizawa K. *et al.* [41] have analyzed HER2/*neu* mutations in the Japanese population (n=504). In this study mutations were identified more frequently in females. Nevertheless, the presence of HER2/*neu* mutations was not an independent prognostic factor in patients with NSCLC. In the Zhang Y. *et al.* [39] study, a younger female age at the time of the NSCLC diagnosis was an independent predictor of HER2/*neu* mutations. Mazieres J. *et al.* [42] have tested HER2/*neu* mutations in 3800 European NSCLC patients (France, Switzerland, Spain) and identified 65 patients carrying these mutations. In the group of patients with mutations, a higher proportion of women was observed (45 women (69%) *vs* 20 men (31%)).

Testing for HER-2/*neu*, suggests target therapy treatment options to NSCLC patients. NSCLC patients with HER2/*neu* mutations may be treated with HER2/*neu*-targeted drugs. In the Mazieres J. *et al.* [42] study, patients with stage IV or recurrent NSCLC (n=22) received anti-HER2 treatments. The PFS for those patients was 5.1 months, which is twice longer what would be expected in such patients.

Case reports of afatinib in females with HER2/*neu*-mutated NSCLC have presented promising results. The addition of paclitaxel to afatinib led to prolonged disease remission [43]. A new, phase II clinical trial NICHE (NCT02369484) is going to investigate the control of disease in pretreated patients with advanced NSCLC harbouring mutations in HER2/*neu* exon 20, as well as the safety and tolerability of the treatment with afatinib [44].

Repressor of silencing 1 (ROS1)

Proto-oncogene ROS1 encodes a receptor tyrosine kinase which regulates pro-survival and anti-apoptotic signaling pathways (e.g. phosphatidylinositol 3-kinase (PI3K), MAPK

pathways) [40, 45]. *ROS1* forms gene fusions. The gene fusions result inter- or intrarearrangements or chromosomal deletions that join pieces of two separate genes and result in chimeric mRNA transcripts and proteins. *ROS1* fusions have been identified in about 1-2 % of lung adenocarcinomas, but its partner gene joins a promoter that drives sufficient expression in the tumor cell. Up to now, several fusion partners of *ROS1* have been identified (including CD74, FIG, SDC4, EZR, SLC34A2). [45, 46].

In the Yoshida A. *et al.* [46] and Go H. *et al.* [47] studies, *ROS1* fusion-positive lung cancer was significantly more common in women (respectively p=0.008, p=0.042). Warth A. *et al.* [45] analyzed a cohort of 1478 NSCLC patients and a significantly higher rate of ROS1 translocations was observed in females (1.3 %) than in males (0.3 %). 68 cases were positive for *ROS1*. *ROS1* positivity in tumor was significantly more likely in females with low pT (7.8 %) than in males (3.2 %) (p<0.001).

Published data indicate that *ROS1* positive NSCLC is sensitive to crizotinib. Crizotinib is a tyrosine kinase inhibitor that blocks anaplastic lymphoma kinase (ALK) functions. Studies with cell lines expressing *ALK* and *ROS1*, demonstrated that crizotinib inhibits ALK and ROS1 signaling. Case report [48] and clinical trial PROFILE 1001 (NCT00585195) [49] have revealed the efficacy of crizotinib for NSCLC patients positive for *ROS1*.

Validation of *ROS1* rearrangements as a therapy target in NSCLC will identify a small group of patients with rare molecular drivers. *ROS1* rearrangements are more frequently determined in female NSCLC patients, but nevertheless, there is no reliable evidence that women respond to crizotinib better.

New potential markers

Numerous studies have demonstrated new potential candidates as biomarkers of female lung cancer with predictive and prognostic relevance. For example, catechol-O-methyl-transferase (COMT) is an enzyme involved in estrogen metabolism. COMT methylates catechol estrogen and reduced activity of this enzyme can lead to oxidative DNA damage. Lim WY *et al.* [50] suggested that a point mutation Val158Met (rs4680) in the *COMT* gene may have an influence on lung cancer risk for female never-smokers. Yang SY *et al.* [51] demonstrated the association between *COMT* (rs4680) and *EGFR* L858R mutations in both male and female never-smokers.

High glycodelin (Gd) mRNA level in tumors is associated with lower survival rates in NSCLC female patients compared with men (p<0.0001) [52]. Gd is localized in bronchial epithelium cells and its expression is identified in adenocarcinoma and squamous cell carcinoma of the lung [53]. Another example is ribonucleotide reductase subunit M2 (RRM2) that regulates the enzymatic activity of ribonucleotide reductase. Recently, it was reported that RRM2 protein expression has a prognostic significance in NSCLC female patients. Female patients with low RRM2 expression had better survival rates compared with high RRM2 expression female patients group (p=0.0001) [54].

Conclusions

Biomarkers in oncology that provide information on molecular tumor biology are crucial to personalized treatment. Personalized medicine is now based on understanding molecular carcinogenesis, pharmacogenomics and individual genetic differences. It is necessary to use biomarkers to determine whether the susceptibility to lung cancer is really different between genders. Biologic understanding of the genders' differences in lung cancer provides information on treatment effects. Further studies on the biology of lung cancer are warrantied.

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