Minireview

Role of sex hormones in lung cancer

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Impact statement

Lung cancer is the third most diagnosed cancer in female patients, and the most diagnosed cancer in males. In addition, lung carcinoma ranks as the leading cause of cancer mortality for both men and women worldwide. While tobacco use has been widely associated with its diagnosis in both sexes, epidemiological data indicate that women who do not smoke are more than twice likely than men to develop lung cancer. Hormonal factors, including endogenous and exogenous sex hormones, have been implicated in the disease development, progression, and prognosis. This study provides a summary of the available evidence linking gonadal hormones and lung cancer in women and men. Collectively, the existing literature indicates that tobacco use, as well as hormonal, genetic, environmental, and metabolic factors, contribute to the observed sex and gender differences in lung cancer rates and outcomes, supporting the consideration of sex as a biological variable in lung cancer basic, clinical, and translational research.

Abstract

Lung cancer represents the world's leading cause of cancer deaths. Sex differences in the incidence and mortality rates for various types of lung cancers have been identified, but the biological and endocrine mechanisms implicated in these disparities have not yet been determined. While some cancers such as lung adenocarcinoma are more commonly found among women than men, others like squamous cell carcinoma display the opposite pattern or show no sex differences. Associations of tobacco product use rates, susceptibility to carcinogens, occupational exposures, and indoor and outdoor air pollution have also been linked to differential rates of lung cancer occurrence and mortality between sexes. While roles for sex hormones in other types of cancers affecting women or men have been identified and described, little is known about the influence of sex hormones in lung cancer. One potential mechanism identified to date is the synergism between estrogen and some tobacco compounds, and oncogene mutations, in inducing the expression of metabolic enzymes, leading to enhanced formation of reactive oxygen species and DNA adducts, and subsequent lung carcinogenesis. In this review, we present the literature available regarding sex differences in cancer rates, associations of male and female sex hormones with lung cancer, the influence of exogenous hormone therapy in women, and potential mechanisms mediated by male and female sex hormone receptors in lung carcinogenesis. The influence of biological sex on lung disease has recently been established, thus new research incorporating this variable will shed light on the mechanisms behind the observed disparities in lung cancer rates, and potentially lead to the development of new therapeutics to treat this devastating disease.

Keywords: Lung, cancer, sex differences, sex hormones, carcinogenesis, estrogen receptors

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Introduction

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.[1] In 2020, there were an estimated 2,206,771 new lung cancer cases and 1,796,144 lung cancer deaths around the world, with 235,760 cases and 131,880 deaths only in the United States.[1,2]

The main risk factor associated with lung cancer diagnosis is tobacco use, although secondhand smoke exposure, ionizing radiation, air pollution, and several occupational and chemical exposures have also been linked to lung cancer diagnosis.[3–7] A role of hormonal factors such as exogenous hormone use in adult women (e.g. oral contraceptives and/or hormone replacement therapy), as well as endogenous circulating levels of sex hormones has also been associated with lung cancer development.[8,9] To date,

the mechanisms by which reproductive hormones could contribute to lung cancer development, progression, and/or severity have not been fully elucidated.

Sex and gender differences in lung cancer epidemiology

The available data suggest that both biological (sex) and social (gender) influences can impact lung cancer rates. While the incidence of lung carcinoma in both men and women below the age of 40 is relatively low, it increases with age in most populations.[10] According to the most recent report, with 1,435,943 cases reported in males and 770,828 in females worldwide in 2020, the age standardized rate (i.e. the average of age-specific mortality rates/100,000 persons) for lung cancer incidence is 31.5 in males and 14.6 in females, and the cumulative risk for lung cancer incidence by age 74 (the likelihood that a person will develop lung cancer by age 74) is 3.78% in males and 1.77% in females.[1] In the United States, sex stratified data indicate an estimated 119,100 cases and 69,410 deaths in males, and 116,660 cases and 62,470 deaths in females, as illustrated in Figure 1.[1,2]

While over the past few decades, the overall rates for cancer incidence have decreased in men, they have remained stable in women. On the other hand, all cancer mortality rates have declined in both groups.[11] In the same period, both lung cancer incidence and mortality rates have been reported to display sex differences, with wide variations across countries.[1] The current male to female incidence ratio ranges from 1.2 to 5.6 across nations, but on average, these rates are generally twice as high for men than women.[1] However, variations in this ratio have been reported over time and largely attributed to changes in tobacco use rates.[12,13] Regarding global mortality, with 1,188,679 deaths reported in males and 607,465 in females in 2020, the age-standardized rate is 25.9 in males and 11.2 in females, with a cumulative risk for lung cancer mortality by age 74 of 3.08% in males and 1.34% for females.[1] While about 30% of global lung cancer deaths can be attributed to smoking, sex differences in mortality cannot be fully explained by smoking behavior.[13,14]

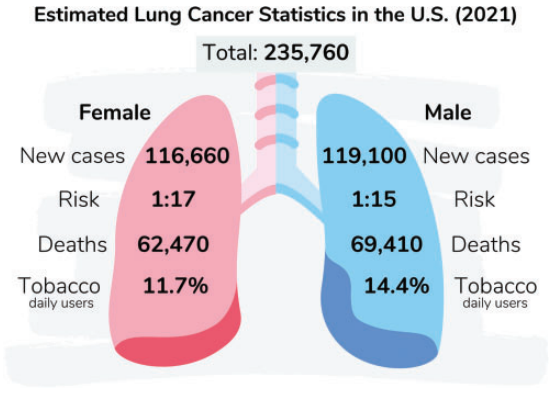

Figure 1. Estimated lung cancer statistics in the U.S. (2021). The estimated rates of lung cancer in the United States for 2021 are: (1) 235,760 new cases, including 119,100 in men and 116,660 in women. (2) The risk to develop lung cancer in one's lifetime is about 1 in 15 for men and 1 in 17 for women. (3) About 69,410 yearly deaths from lung cancer are men, and 62,470 are women. (4) On average, 14.4% and 11.7% of men and women are daily tobacco users, respectively. (A color version of this figure is available in the online journal.)

In men, lung carcinoma represents the most diagnosed cancer type, and ranks as the leading cause of cancer mortality. In women, lung cancer ranks third for incidence and second for mortality.[1] Interestingly, for women, it represents the leading cause of cancer deaths in both highly industrialized countries, and countries with higher rates of outdoor ambient air pollution and household exposure of burning solid fuels for heating or cooking.[15,16] In this regard, the global proportion of cancer deaths attributable to outdoor air pollution exposure ranges from 4.7% to 20.5%, with a global average of 14%.[17]

Tobacco smoke and lung cancer rates in men and women

Tobacco use is the most recognized risk factor for lung cancer. In the United States, smoking can be attributed to approximately 80% of lung cancer fatalities.[2] Similarly, more than 85% of all patients diagnosed with lung cancer are current or former smokers, and it is estimated that about 20% of all smokers will develop lung cancer in their lifetime.[18,19] On the other hand, about 20% of non-smoker women (and 10% of men) develop lung cancer.[3,20] It has been well-recognized that women are more susceptible to the adverse effects of tobacco consumption, although they usually show a better prognosis than men.[21] This sex difference, however, cannot be explained by anatomical differences or smoking history, and it is thought to be associated with a higher susceptibility to tobacco carcinogens in female patients.[22,23]

As indicated above, even with lower tobacco use rates, females who smoke are more likely to develop lung cancer than men. One possible factor contributing to this phenomenon is that female sex hormones like estrogens are able to exacerbate the carcinogenic effects of tobacco (Figure 2).[16] The synergism of estrogen with some of the toxic compounds present in tobacco smoke, vis induction of the enzyme CYP1B1 (responsible for estrogenic metabolism), leads to a heightened formation of reactive oxygen species, which in turn promotes carcinogenesis.[24] Epidemiological and experimental evidence also indicates that these mechanisms are also influenced by exposure to air pollutants and other environmental factors such as secondhand/passive smoke.[25] Moreover, female smokers also display greater levels of PAH (polycyclic aromatic hydrocarbon)-derived DNA adducts, as well as a higher frequency of p53 mutations despite lower levels of exposure to these toxins (Figure 2).[26–28]

The patterns of lung cancer incidence in many countries also reflect trends in gender-specific smoking behaviors.[5,12,29] In the United States, where 20.4 million males and 7.2 million females are current smokers, both lung cancer incidence and death rates among women are on the rise.[30] Interestingly, these rates are declining in men for certain age groups, and increasing in women, reflecting historical patterns of tobacco use in women in some birth cohorts.[31] Globally, there are over 940 million men and 175 million women over the age of 15 who currently smoke.

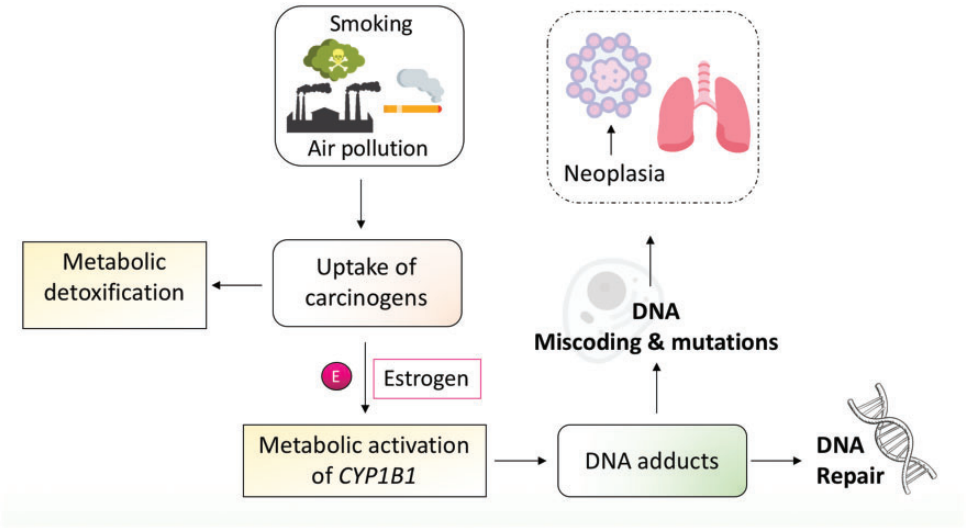

Figure 2. Role of smoking, air pollution, and estrogen in carcinogenesis. Exposure to tobacco smoke and/or environmental toxins leads to the uptake of carcinogens that are metabolized by lung cells. The estrogen metabolizing enzyme CYP1B1 is upregulated by tobacco carcinogens and estrogens, resulting in increased levels of carcinogenic derivatives of estrogen. CYP1B1 also metabolizes polycyclic aromatic hydrocarbons (PAH) resulting in PAH-DNA adduct formation. Unrepaired DNA adducts and inefficient DNA repair can result in DNA miscoding and mutations, leading to uncontrolled cell growth and lung neoplasia. (A color version of this figure is available in the online journal.)

Of these, nearly 75% of male and 50% of female daily smokers live in highly developed countries. Gender influences such as societal acceptance of tobacco use and affordability of use for women could contribute to the differential rates of lung cancer observed in these nations. Regarding cessation, women tend to stop smoking at lower rates than men and are motivated to smoke by a desire to avoid weight gain.[32] Maternal tobacco use during pregnancy still occurs in the United States, where 1 in 14 women who gave birth in 2016 reported smoking during pregnancy, despite this behavior being linked to multiple negative health outcomes.[33]

Among non-smokers, females are about 2.5 times more likely to develop lung carcinoma at a younger age than males.[32,34,35] These differences have also been attributed to sex steroids, genetic mutations, molecular pathways involving epidermal growth factors and sex hormone receptor signaling, regulation of gene expression by miRNAs, and differences in environmental chemical exposures, such as air pollutants and secondhand smoke toxins.[36–45]

Sex differences in lung cancer types

About 95% of all lung carcinomas are classified into two main types: (1) non-small cell carcinoma (NSCLC), and (2) small cell carcinoma (SCLC). NSCLC is further classified into two subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (AC).[46,47] This distinction is important in the clinic, not only for staging, but also for treatment and prognosis. Sex differences in both AC and SCC have been reported, with AC found more frequently in females, and SCC being more prevalent in males.[48–50]

Historically, SCC were the most commonly diagnosed lung cancers, accounting for about 50% of all male lung cancers in the 1970s.[51] Over time, the SCC relative rates have decreased and currently account for about 30% of cases. On the other hand, ACs have increased, from representing about 20% of lung cancers in the 1970s, to over 40% of all current cases. The rates for SCLC, on the other hand, have remained constant at about 20%, whereas NSCLC rates have decreased from 10% to $<3\%$. While SCLC, SCC, and NSCLC rates continue to decrease for both sexes, AC rates are increasing in females and remaining relatively constant in males.[51] As indicated earlier, AC is more represented in female than male patients, accounting for more than 50% of female cases in 2010.[52] In contrast, the SCC rates have decreased from 30% to 20% during the same time period. The trends for SCLC and NSCLC are similar between the sexes.[53]

Sex differences in lung cancer treatment

Lung cancer therapy comprises surgery, regular chemotherapy, radiation, and therapy directed against specific tumor genetic and molecular characteristics. Appropriate treatment for lung cancer is based on tumor type and molecular markers, disease staging, and assessing the patient's clinical condition and comorbidities.[54]

NSCLC in the first three stages is routinely treated with a combination of surgery, chemotherapy, radiation therapy, or a combined-modality approach. Immunotherapy may also be part of the management strategy for some unresectable tumors (stage III) and advanced disease, including metastases (stage IV) or recurrence following initial definitive treatment. There are specific targeted therapies for NSCLC patients with mutations in the epidermal growth factor receptor (EGFR) as well as in the B-Raf proto-oncogene (BRAF), those with the echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene, and c-ROS oncogene 1 (ROS1) fusions.[55] The current clinical recommendations suggest testing for EGFR mutations and ALK fusion for all patients with advanced staging to guide patient

selection for therapy with an EGFR or ALK inhibitor, regardless of sex, race, smoking history, or other risk factors.[55] EGFR inhibitors target cancer cells with superior ability and a better safety profile when compared to conventional chemotherapies.[56]

Other approved therapies for metastatic ALK-positive NSCLC tumors include the drugs ceritinib, alectinib, and brigatinib, representing next-generation ALK inhibitors.[57–60] Other therapeutics include ALK/ROS1 tyrosine kinase inhibitors (TKIs).[61,62] The drug crizotinib is an ALK-TKI indicated for ROS1 positive advanced NSCLC tumors.[60] Immunotherapy (e.g. the anti–PD-L1 antibody atezolizumab) is the first-line treatment for patients without driver mutations and a high level of programmed death-ligand 1 (PD-L1) expression. Combinations of chemotherapy and immunotherapy are available for those with lower PD-L1 expression. In patients with metastatic NSCLC, atezolizumab has provided an overall survival benefit.[63,64]

In a clinical trial, Socinski *et al.* found that the combination of atezolizumab to bevacizumab (VEGF-A-targeting monoclonal antibody) plus chemotherapy notably enhanced progression-free survival and overall survival in those with metastatic NSCLC, despite ALK genetic alteration status or EGFR and PD-L1 expression.[65] Overall survival hazard ratios contrasting anti-PD-1/PD-L1 with or without chemotherapy found that anti-PD-1 alone had a considerable effect in men and anti-PD-1/PD-L1 plus chemotherapy had a more significant impact in women. Therefore, these data exhibit the benefit of the addition of chemotherapy to anti-PD-1/PD-L1 in women.[66]

The frequency of particular mutations within a tumor is known as tumor mutational burden (TMB). After adjusting for age at the time of surgery, lung cancer stage, and smoking history in a population of 335 patients with lung AC, male tumors showed a statistically more significant burden of genetic alterations when compared to female tumors.[67] Additionally, TMB is a more effective marker for predicting response to immunotherapy in female lung cancer patients than males.[68] Finally, in the modern chemotherapy era, women suffering from advanced NSCLC survive longer than their male counterparts, suggesting that female hormone levels may interact with the efficacy of current chemotherapy prescriptions after adjustment for other prognostic factors.[35,69,70]

Regarding SCLC, tumors are very responsive to chemotherapy. Limited stage disease, radiation therapy, and—rarely—surgery may be options as well. Cytotoxic agents such as platinum plus etoposide and topotecan remain standard therapy, neither showing survival benefit over the combination of antitumor antibiotics, microtubule inhibitors, or alkylating agents.[71] Despite recent studies that have increased our understanding of genomic alterations and signaling pathways in SCLC, molecularly targeted therapy agents have shown no improvement in overall survival. The two targeted drugs with early promising results are sunitinib (a multitargeted TKI that inhibits tumor cell proliferation and angiogenesis), and alisertib (an inhibitor of aurora A kinase which regulates cell cycle transit from G2 to cytokinesis). Inhibitors of mTOR, including everolimus, also show good efficacy when combined with paclitaxel.[72,73] Despite the face of well-known sex differences in innate and adaptive immune responses, neither study assessing the efficacy and safety of these antitumor agents reported sex dissimilarities.[68] Future studies should consider sex as a biological variable, as this variable is crucial to assess the clinical response to these novel treatments and improve their efficacy.[68,74]

Molecular basis for sex differences in lung cancer

As indicated earlier, several factors have been attributed to the observed differences in lung cancer clinical outcomes between male and female patients.[75–77] Mutations in oncogenes, transcription factor genes, and other signaling molecules have also been implicated.[78–80] Lung ACs typically present with genetic alterations including mutations in the KRAS (KRAS Proto-Oncogene, GTPase), BRAF, and EGFR genes, and mutations or amplifications of ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2), MET (MET Proto-Oncogene, Receptor Tyrosine Kinase), FGFR1 (Fibroblast Growth Factor Receptor 1), FGFR2, ALK, ROS1, RET (Ret Proto-Oncogene), and NRG1 (Neuregulin1) oncogenes. SCCs, on the other hand, are characterized by mutations in the TP53 (Tumor Protein P53), FGFR1, FGFR2, FGFR3, DDR2 (Discoidin Domain Receptor Tyrosine Kinase 2), PTEN (Phosphatase and Tensin Homolog), and CDKN2A (Cyclin Dependent Kinase Inhibitor 2A), as well as genes involved in the Phosphoinositide 3-kinases (PI3K) pathway.[80]

In cancer, Ras proteins are likely to mutate and remain constitutively active.[81,82] There are three proteins in the Ras family of small GTPases: N-, H-, and K-Ras. Ras proteins are associated with the activation of surface receptors such as RAF1 (Raf-1 Proto-Oncogene, Serine/Threonine Kinase) and BRAF. Interestingly, estrogen activates human RAF1 in SCLC cells, which inhibits growth by arresting the G1 and G2 phases of the cell cycle.[83] However, sex differences in these mechanisms have not been reported so far.

The aforementioned data indicate that RAF1 triggers signal transduction of the cell cycle and can act as a growth suppressor gene in SCLC. On the other hand, RAF1 association with smokers and female sex in NSCLC is well documented. Therefore, the RAF/MEK/MAP pathways may be considered as potential drug candidates for SCLC and other neuroendocrine tumors, with emphasis on sex differences. Several drugs inhibiting Ras, Raf or MEK, including selumetinib, are currently under clinical investigation.[84,85]

Several studies have shown the loss of wild-type KRAS alleles in both human and mouse lung SCC and AC. In addition, chemically induced mouse lung ACs have KRAS gene mutations in 67%–100% of cases. In humans, KRAS gene mutations are in 10%–30% of lung carcinomas, indicating robust connotations with smoking.[86] While KRAS mutations have not been extensively reported in SCLC, Kodaz *et al.* identified 16.2% KRAS mutations in a cohort of 37 SCLC patients, a number much higher than that reported in previous studies for SCLC (1%–3%).[87] On the other hand, EGFR and KRAS mutational analysis in

NSCLC patients showed that KRAS mutation (study frequency 28.1%) was more commonly linked with smokers ($p < 0.001$) and females ($p = 0.01$).[88]

Interestingly, reports have indicated that chemotherapy effects and survival are greater in females than males.[89–91] The downside of these studies is that they included almost exclusively postmenopausal women.[89–91] New studies have reported an interplay between the EGFR and estrogen signaling mechanisms in lung carcinogenesis. Therefore, a treatment combination based on TKIs and anti-estrogen treatment is being assessed.

Women with a positive EGFR mutation status have earlier onset of lung cancer when compared to men after tobacco exposure.[20,91,92] Emerging data also indicate a potential bidirectional crosstalk between EGFR and the estrogen receptors (ERα and ERβ), both of which are present in lung cancer cells.[93–97] Immunohistochemical assessment of EGFR and ERα expression in tumor specimens from NSCLC patients after surgery showed the combined overexpression of EGFR and ERα in NSCLC patients is a projection of poor outcome and, thus, represents an important prognostic tool.[98] Drug resistance to EGFR TKIs has also been documented in molecular analysis of tumor samples.[99,100] Yu *et al.* identified the EGFR T790M as the most recurrent pathway of acquired resistance to EGFR-TKI therapy in 63% of patients.[100]

Regarding ERs, Kadota *et al.* also reported that stage I lung AC cells express higher levels of ERα in females (19%) than in males (14%) and that ERα expression associates with smaller tumor size and poor prognostic immune microenvironments.[101] Interestingly, most NSCLC lines express both ERs.[102]

In a population based study, estrogen inhibitors in breast cancer patients reduced the risk for lung cancer in older patients (≥50 years), supporting the hypothesis that antiestrogen therapy can modify lung cancer carcinogenesis in older women.[103] At this time, there are clinical trials for lung cancer patients to receive a combined treatment of anti-hormonal drugs such as EGFR TKI.[104] The results from this combination therapy currently show enhanced antiproliferative effects in up to 90% of NSCLC cells.[104]

Role of sex hormones in lung carcinogenesis

In the past years, there has been an escalated interest in discovering whether sex hormones such as estrogens, androgens and progesterone can promote lung carcinogenesis.[105–107] Epidemiological data suggest that estrogen plays a significant role in lung cancer, as well as in adverse prognosis of female patients with this condition.[108]

Estrogens

Regarding circulating estrogen levels, the elevation of estrogen in women together with the reduction of DNA repair capabilities, cause women more vulnerable to the cancer-causing effect of tobacco.[109–112] Stabile *et al.* showed that estrogen signaling is involved in both the lung mesenchyme and the epithelium.[106] The research team further revealed that estrogen could potentially trigger lung cancer via (1) direct or (2) indirect actions, on pre/neoplastic cells and lung fibroblasts, respectively.[106] Meireles *et al.* reported that tobacco smoke can also induce phase-I cytochrome P450 enzymes such as CYP1B1, which can metabolize endogenous estrogens to potentially carcinogenic catechol and quinine forms.[113] Additionally, estrogen can act as direct or indirect carcinogen, by either altering cell proliferation or regulating cell growth factors. Both ERs are expressed in normal and cancerous lung tissue, and regulate lung development, inflammation, and cancer.[47,114–116]

There are several isoforms of the ER receptor (ERα, ERβ, mERs). Of these, ERβ is highly expressed in almost 90% of NSCLC human tumor samples and cell lines derived from both females and males, whereas ERα is commonly low in lung cancer cells.[108] Both ERs can activate carcinogenesis-associated signaling via genomic or non-genomic pathways, although ERβ appears to play a predominant role (Figure 3).[117] A study analyzing histological material from 104 patients (68% men and 32% women) with NSCLC (9% NSCLC, 37% AC, 54% SCC) between 1989 and 1992 indicated that females with ERβ-negative lung cancer had a small reduction in mortality than those with ERβ-positive tumors. On the other hand, a significant decline in mortality rates was observed in males with ERβ positive lung tumors when compared to males with ERβ negative ones, indicating that ERβ could be used as a tool for the prognosis of NSCLC in males.[118] Interestingly, most immune cells that enter the lung express both ERs (ERα and Erβ). Via the genomic pathway, ERβ can displace to the nucleus to modulate transcription. In the non-genomic pathway, ERβ migrates to the cell membrane to regulate ion channels, protein kinases, and secondary messengers (Figure 3).

Researchers have shown that estrogen induces propagation of NSCLC cells and tumor growth.[106] Anti-estrogen treatment strategies can decrease tumor size, growth, and cell proliferation which may contribute to improved patient outcomes.[119,120] Moreover, cell proliferation and tumor growth are in part due to initiation of the non-genomic mechanism via mitogen-activated protein kinases (MAPK), serine/threonine protein kinase B (or AKT), and cyclic adenosine monophosphate (cAMP) signaling pathways, as well as phosphorylation of the extracellular signal-regulated kinase (ERK) and EGFR.[91] Interestingly, mitochondrial ERβ can modulate apoptosis by physically sequestering the B-cell lymphoma 2 (Bcl-2) associated agonist of cell death (Bad) and prevent its interaction with Bcl-2 and B-cell lymphoma-extra-large (Bcl-XL) proteins in lung cancer cells, suggesting an anti-apoptotic role for estrogens.[121–123]

A topic that needs further discussion is the effect of estrogens in angiogenesis. Angiogenesis is key in cancer development and metastases since NSCLC is a highly vascularized tumor and its progression depends primarily on vascular supply.[124] It has been shown that estrogen triggers tumor angiogenesis through activation of the vascular endothelial growth factor (VEGF), which causes an increase in proliferation of vascular endothelial cells.[125] Estrogen also promotes the production of the vascular endothelial growth factor A (VEGFA), an essential ligand for the

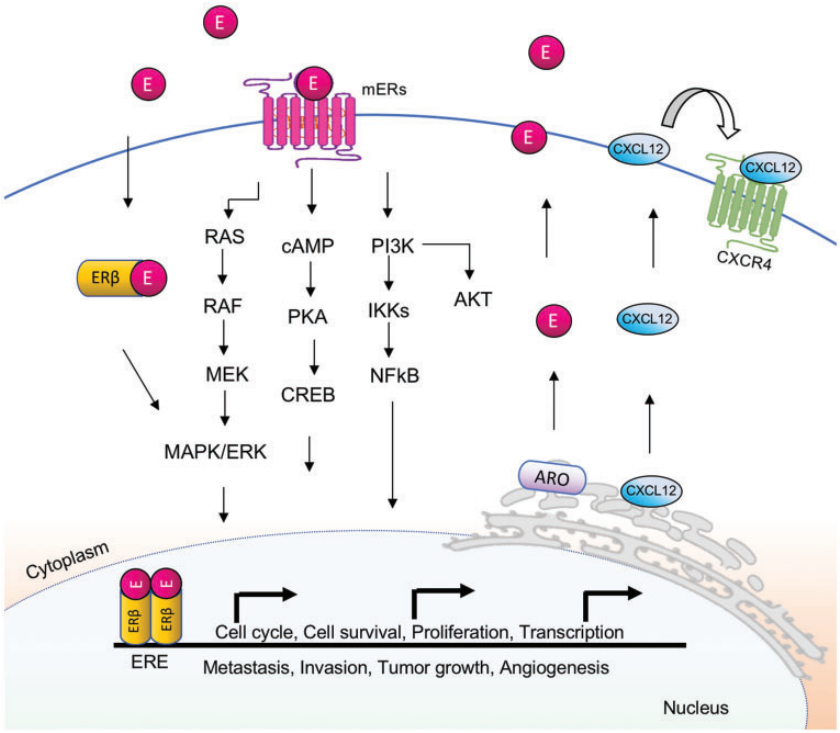

Figure 3. Estrogen/estrogen receptor signaling in lung carcinogenesis. Estrogen receptor β is expressed in cytoplasm, nucleus, mitochondria, and plasma membrane of lung cancer cells. ERβ activates the MAPK, cAMP, and AKT signaling mechanisms via the non-canonical (or non-genomic) pathway. Briefly, the E2/ER complexes translocate to the nucleus where they bind to estrogen response elements (ERE) to induce gene expression. Some of the genes regulated by ER and involved in lung cancer can promote apoptosis, metastasis, mitochondrial biogenesis, proliferation aromatase (ARO) mechanism, cell cycle progression (CXCL2), and angiogenesis (VEGF). (A color version of this figure is available in the online journal.)
AKT: AKT serine/threonine kinase 1; cAMP: cellular levels of cyclic AMP; CREB: cAMP-response element binding protein; CXCL2: C-X-C chemokine ligand 2; CXCR4: C-X-C chemokine receptor type 4; E: estrogen; ERβ: estrogen receptor β; ERE: estrogen response elements; IKKs: IκB kinase; MAPK: mitogen-activated protein kinases; MEK: mitogen-activated protein kinase kinase; mERs: membrane estrogen receptors; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphoinositide-3 kinase; PKA: protein kinase A; RAF: serine/threonine (S/T) kinase; RAS: guanine triphosphatase.

vascular endothelial growth factor receptor-2 (VEGFR-2) expressed in endothelial cells. Remarkably, VEGFA is downstream of EGFR, which is estrogen dependent. Therefore, the combination of fulvestrant and vandetanib, inhibitors of EGFR and ER, respectively, decreased cell proliferation and angiogenesis in NSCLC.[125] In addition, recent studies have shown high expression levels of cytoplasmic and nuclear membrane bound estrogen receptors (mERs or GPER) in NSCLC specimens, and blocking these receptors stops estrogen-induced cell proliferation.[126]

Progesterone

Regarding progesterone, another ovarian hormone involved in cell proliferation and lung disease,[40,127] emerging evidence has revealed an active role in lung carcinogenesis. Studies have revealed that progesterone receptors (PRs) are present commonly in non-tumor lung tissues compared with cancer tissue.[129] PRs are localized mostly in both the nucleus and extranuclear areas of the lung.[128,129] While researchers have shown that PR expression in tumor-surrounding stromal cells is connected with enhanced survival for both men and women,[130,131] it was also revealed that PR expression in tumor epithelial cells is an autonomous, non-favorable predictor for disease-specific survival in women, suggesting that PR expression may be a potential marker for NSCLC.[130] Other studies have proposed that increase in VEGF production and proliferation of endothelial cells are due to a combination of both estrogen and progesterone in NSCLC (Figure 4).[128]

Progesterone has also been confirmed to be produced locally in NSCLC surrounding tissues. Expression of progesterone-synthesizing enzymes such as the cholesterol side-chain cleavage enzyme (P450scc), the steroidogenic acute regulatory protein (StAR), and the 3β-hydroxysteroid dehydrogenase (3βHSD) correlates with concentrations of progesterone and PR expression in lung cancer.[131] Further investigation is needed to better understand the multifaceted interaction between these enzymes, progesterone levels and regulatory mechanisms, and lung cancer.

Androgens

Due to the multiple studies indicating the sex hormones play a role in lung carcinogenesis in female non-smokers, most of the discussion about sex hormones and lung cancer has been centered around estrogens and progesterone. However, the role of male sex hormones in lung cancer has also been reported and studied. In this regard, the androgen receptor (AR), which is expressed mostly in pneumocytes and lung epithelium of male patients, is known to be an active player in lung cancer pathogenesis

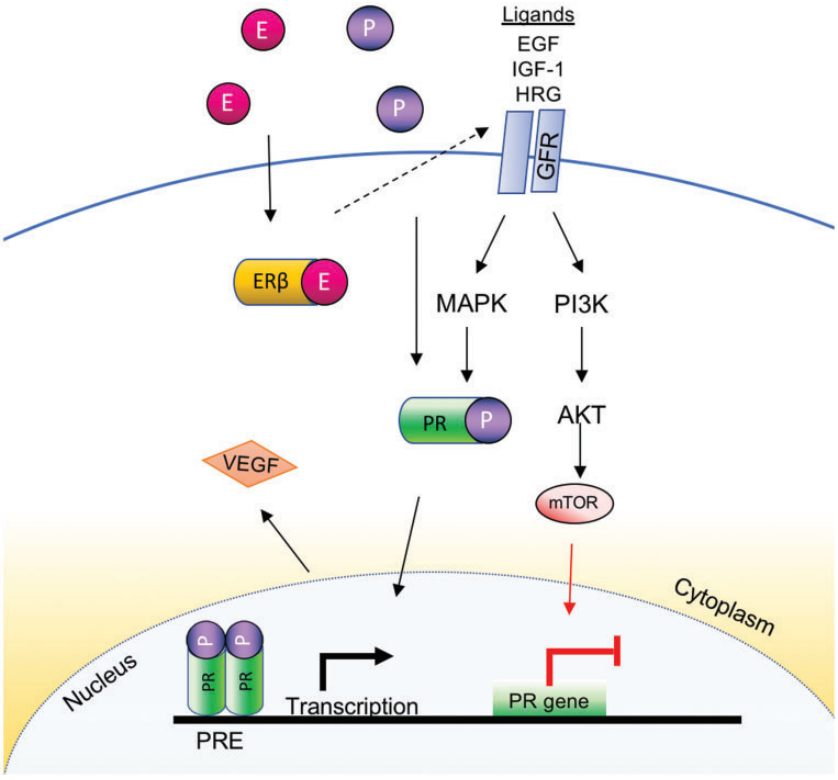

Figure 4. Progesterone/progesterone receptor signaling in lung cancer. The growth factor receptor signaling is stimulated by its ligands (e.g. EGF, IFG-1, HRG), resulting in the activation of MAPK-related pathways and the subsequent stimulation of both (1) the ligand independent receptor activation and (2) the AKT/mTOR pathway, which increases and suppresses PR expression, respectively. In addition, estrogen and progesterone promote VEGF in lung cancer. (A color version of this figure is available in the online journal.)
AKT: AKT Serine/Threonine Kinase 1; E: estrogen; EGF: epidermal growth factor; ERβ: estrogen receptor β; GFR: growth factor receptor; HRG: histidine rich glycoprotein; IGF-1: insulin-like growth factor 1; MAPK: mitogen-activated protein kinases; mTOR: mechanistic target of rapamycin; P: progesterone; PI3K: phosphoinositide-3 kinase; PR: progesterone receptor; PRE: progesterone response elements; VEGF: vascular endothelial growth factor.

(Figure 5).[132–134] A study using NSCLC cell lines showed that AR inhibition decreases cyclin D1 expression and cell proliferation.[135] Interestingly, researchers created a male inducible AR-KO mice and analyzed tumor formation in the tobacco carcinogens.[136] AR-KO mice reduced tobacco carcinogen-induced tumor size when compared to control suggesting that AR has a central role in the development and progression of lung cancer. Another research group discovered that androgens promote M2 macrophage polarization, which enhances tumor growth and suppresses antitumor immune responses.[137,138] More recently, it was reported that NSCLC tumor growth was triggered in part by miR-224-5p, which inhibits AR and regulates the epithelial–mesenchymal transition.[139] Overall, more research needs to be done to unveil the cellular and molecular mechanisms of androgens in lung cancer (Figure 5).

Hormone replacement therapy and lung cancer in women

Hormone replacement therapy (HRT) is a common treatment used in postmenopausal women. Due to the effects of female sex hormones on lung cancer tumors discussed above, there are several controversies in the relationship between the HRT and lung cancer.[109,110,140] The Women's Health Initiative trial concluded that treatment with both estrogen and progestin in postmenopausal women did not increase lung cancer incidence.[141] However, HRT was found to increase lung cancer mortality, predominantly, deaths from non-small-cell lung cancer.[141,142] These results have led to extensive research on the association of Hormone Therapy (HT) and lung cancer prevalence and outcome.

HRT consists of estrogen alone (estrogen-only HRT), used in women who have undergone hysterectomy, or estrogen combined with a progestogen (combined HRT) for women who need a progestin to avert endometrial hyperplasia. Taioli *et al.* observed a 1.7-fold increased risk of lung AC with the use of estrogen replacement therapy, and an even higher risk (OR = 32.4) among women who smoke and receive this type of HRT.[143] In addition, Liu *et al.* found that induced menopausal women with a history of HRT had a significantly higher risk of lung cancer compared to naturally menopausal women, with a relative risk of 2.40.[144] Other observational studies suggest that estrogen may be related to the cause and outcome of lung cancer, but there has been inconsistency in their findings.[142,145–155] We have summarized the most recent studies and their main findings in Table 1. Discussions about risks and benefits considering combined HT are needed for those with a higher risk of developing lung cancer.

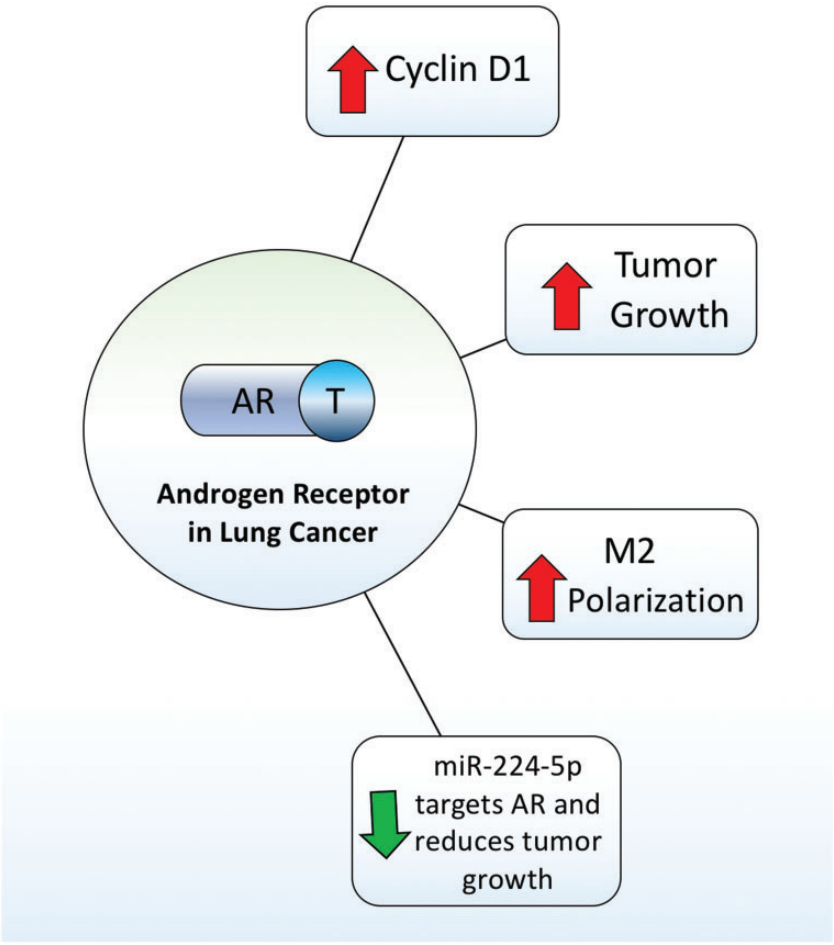

Figure 5. Androgens in lung cancer. Androgen receptor signaling induces cyclin D1 expression, tumor growth, and macrophage M2 polarization. There is also evidence that miR-224-5p negatively targets AR causing a decrease in tumor incidence and growth. (A color version of this figure is available in the online journal.) AR: androgen receptor; M2: Macrophage M2 polarization; T: testosterone.

Table 1. Recent clinical studies assessing the role of hormone replacement therapy in lung cancer.

Study	Study type	Sample size	Conclusions
Brinton et al., 2012[150]	Retrospective cohort study	118,008	No evidence that either estrogen therapy-only or estrogen + progestin therapy use is associated with lung cancer risk.
Katcoff et al., 2014[148]	Cross-sectional study	485	Hormone replacement therapy is associated with improved survival.
Clague et al., 2014[149]	Cross-sectional study	727	Lung cancer mortality decreased in women who used only estrogen replacement. No association was observed for estrogen + progestin therapy use.
Ganti et al. 2016[152]	Retrospective cohort study	498	Overall survival was significantly higher in patients with no hormone replacement therapy compared with patients who received it.
Chao et al., 2019[153]	Retrospective cohort study	968,440	Use of hormone replacement therapy is associated with a decreased risk of lung cancer in women.
Titan et al., 2019[154]	Randomized control trial	75,587	Hormone replacement therapy has a protective effect on lung cancer development among women.
Jeon et al., 2020[155]	Cross-sectional study	4,775,398	No statistically significant association was found between reproductive factors and the risk of lung cancer in postmenopausal women.
Abdel-Rahman, 2020[151]	Randomized control trial	77,911	Prior exposure to hormone replacement therapy is protective against lung cancer development. Similarly, prior exposure to hormone replacement therapy seems to be protective against death from lung cancer.

Conclusions

The studies summarized in this minireview indicate that there is accruing evidence to support the concept that there are sex differences in the risk of development of lung cancer. The available data support the hypothesis that women are more disposed to the effects of carcinogens in tobacco and tobacco smoke due to hormonal, genetic, and metabolic differences compared to men. Thus, the significance of sex and hormone status as separate contributing factors shall be considered in prognosis and therapeutic management of lung cancers.

AUTHORS' CONTRIBUTIONS

MSR, NF, and PS conceptualized the review. MSR, NF, and PS reviewed the literature and extracted the data. MSR, NF, and PS wrote and revised the manuscript.

DECLARATION OF CONFLICTING INTERESTS

All authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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