Review Article

Lung cancer in females—sex-based differences from males in epidemiology, biology, and outcomes: a narrative review

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Background and Objective: The role of biological sex is seldom considered in characterizing lung cancer, the deadliest cancer in both the United States and the world. Lung cancer has traditionally been regarded as a male disease; as such, research in female-specific phenomena is frequently conflicting or absent. Currently, disparities in lung cancer incidence are primarily driven by females, especially non-smokers and those of younger age. This narrative review provides insight into sex-specific characteristics of lung cancer, highlighting risk factors, diagnosis patterns, carcinogenesis, and treatment outcomes in females.

Methods: The PubMed database was searched on July 26, 2023 to identify research published between 2013 and 2023 in English. Sixty-three articles were considered relevant, and their full texts and citations were studied to compile information for this narrative review.

Key Content and Findings: Exposure-related risk factors, including personal tobacco use, are thought to impact female lung cancer risk more profoundly. However, studies on occupational exposures are underpowered to conclude risk in females. Data characterizing the effect of endogenous and exogenous hormonal exposures on female lung cancer risk remain two-sided. Screening guidelines are tailored to white males, exacerbating sex and race disparities. The effect of biological sex on carcinogenesis and the immune system response to cancer is not fully understood, though the female immune system clearly reacts more aggressively to lung cancer. In early-stage disease, females have greater survival in the perioperative setting and during follow-up of several years, attributed to favorable histopathology and healthier baseline status. Sex-specific response to systemic treatment continues to be optimized as lack of standardization in randomized trials makes interpreting results difficult when aggregated.

Conclusions: Biological sex plays a critical role in non-small cell lung cancer (NSCLC), though further study is needed to depict the complex web of factors that affect lung cancer risk, development, and outcomes. Female underrepresentation in studies has contributed to this lack of understanding. As these disparities are eliminated, we can move towards more effective treatment for both sexes in this pervasive yet deadly disease.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); female; sex; sex difference

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Introduction

Lung cancer is the leading cause of cancer death both in the United States and worldwide. In the United States, it has been the deadliest cancer for males since the 1950s and exceeded breast cancer as the deadliest for females in 1987 (1). In 2020, lung cancer caused 1,800,000 deaths worldwide, almost double the mortality of colorectal cancer, which is the second most deadly (2,3). Fortunately, lung cancer mortality in the United States has decreased annually since 2000. The Centers for Disease Control and Prevention reports the mortality rate of lung cancer was 55.8 per 100,000 people in 2000 but has now decreased to 33.4 per 100,000 people as of 2019, the most recent year for which reliable data are available (4). Likewise, the incidence of lung cancer has declined from 70.2 to 54.3 per 100,000 people, though the actual number of new lung cancers has generally increased over that period due to a growing population (4). Noticeably fewer new cases were reported in 2020, thought to be tempered by the unprecedented impact of the coronavirus disease 2019 (COVID-19) pandemic on health services and recommended screening practices (4). In recent years, lung cancer incidence has been 27% higher among males compared to females (5), though both incidence and mortality are declining more rapidly in males than females. These trends are generally attributed to differences in gendered smoking patterns (5).

This disease has two broad categories: small cell lung cancer and, conversely, non-small cell lung cancer (NSCLC). NSCLC is overwhelmingly more common with approximately 85% of new cases in the United States. Its incidence peaks at ages 80 to 84 in males compared to 75 to 79 in females (5). NSCLC is further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (6,7). While tobacco use is widely known as the principal risk factor for lung cancer, these histologic varieties differ in "strength of the association" (6) with smoking. Importantly, disparities in lung cancer incidence largely depend on increasing rates of adenocarcinoma driven by young females and never smokers (8) yet understanding of this demographic shift is sorely needed. Consensus on lung cancer risk from non-tobacco exposures, the influence of sex-specific hormones, and the sex-based immune response to carcinogenesis are ill-defined in the literature. This narrative review aims to portray how biological sex affects NSCLC—its development, diagnosis, and treatment outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-744/rc).

Methods

The PubMed literature database of the United States National Library of Medicine was used to identify previously published full-text research articles published in English from 2013 to 2023. All study designs and systematic and narrative reviews were included. A database search was performed on July 26, 2023, written as follows: ((gender[Title]) OR (sex[Title])) AND (lung cancer[Title]). The primary author reviewed the titles and abstracts of the 196 articles delivered. Articles of poor reliability or those that examined especially geographically-specific lung cancer trends were excluded. The authors considered sixty-two publications germane to the themes of this review and their full texts, including references, were studied in detail. Additional articles retrieved from references were included for completeness. The search strategy is summarized in *Table 1* and included articles are identified explicitly in *Table 2*.

Risk factors

Smoking and chronic obstructive pulmonary disease (COPD)

Far and away, the most important risk factor for developing lung cancer is tobacco use. The fact that 85% of lung cancer deaths worldwide can be attributed to smoking (2,9) highlights the preventable nature of most lung cancer diagnoses and reinforces that tobacco smoking is the most influential modifiable risk factor for lung cancer (10). Models developed to project smoking patterns and lung cancer mortality in the United States anticipate that sex disparities in lung cancer rates will dissipate by the mid-2040s and that smoking prevalence will drop to only 7.5% by 2065, though this percentage still corresponds to some 50,000 lung cancer deaths (11).

Differences in gendered smoking habits have contributed to the changing demographics of lung cancer (8). In the 1960s, male cigarette use began to decrease, and the incidence of squamous cell carcinoma accordingly declined. It is thought that changes in cigarette filtration systems, which primarily occurred in the late 1960s and 1970s, allowed smaller particles to travel more distally within the lungs thus contributing to the upward trend of adenocarcinoma (12-14). Indeed, adenocarcinoma surpassed squamous cell carcinoma as the most frequently diagnosed lung cancer in males around 1994 (6). In contrast, women began smoking in higher proportions decades after men, the smoking rate began to decline after that of men, and

Table 1 The search strategy summary

Items	Specification
Date of search	July 26, 2023
Databases and other sources searched	PubMed
Search terms used	((gender[Title]) OR (sex[Title])) AND (lung cancer[Title])
Timeframe	2013 to 2023
Inclusion and exclusion criteria	Only full text articles in English included. Articles that examined geographically-specific lung cancer incidence were excluded
Selection process	K.G. conducted selection independently, and the authors discussed the scientific and clinical value of controversial articles to reach an agreement

Table 2 Articles selected for inclusion (first author, PubMed ID)

Risk factors	Screening and diagnosis	Carcinogenesis	Outcomes	ICI efficacy evaluated in recent meta-analyses
Baiu I, 34277072	Araghi M, 34282033	Caetano MS, 30389925	Al Omari O, 36476451	Conforti F, 31106827
Betansedi CO, 29508431	Pinsky PF, 33545164	Dubois C, 30444717	Baum P, 35220299	Liang J, 36128737
Boice JD, 30614747	Ragavan M, 35022255	Freudenstein D, 32545367	Baum P, 35738973	Madala S, 35400597
Bugge A, 27846762	Ruano-Ravina A, 34858780	Gu T, 25320584	Bugge A, 27846762	Takada K, 35999618
Cheng TD, 29346580	Smeltzer MP, 36208717	Mederos N, 33148544	Conforti F, 31106827	Wang C, 30972745
Fuentes N, 34080912	Tolwin Y, 32532368	Nabi H, 29688493	Conforti F, 34455288	Xue C, 34513654
Hansen MS, 29087432	Warner ET, 31054908	Pérez-Díez I, 33526761	Deng HY, 33899137	
Lin PC, 30225650	Yoshida Y, 26366891	Raskin J, 35884463	Duma N, 31036771	
May L, 37370722		Siegfried JM, 34927202	Huang Y, 35693273	
Mederos N, 33148544		Skjefstad K, 25668612	Isla, D 27885542	
Meza R, 25822850		Stapelfeld C, 28743530	McGuire AL, 35448189	
Pinheiro PS, 36334356		Vavalà T, 34769372	Pinto JA, 29682332	
Ragavan M, 35022255		Xu L, 35577039	Radkiewicz C, 31247015	
Ragavan MV, 32774466			Ragavan M, 35022255	
Siegfried JM, 34927202			Raskin J, 35884463	
Stapelfeld C, 28743530			Sachs E, 33217414	
Stapelfeld C, 31583690			Ten Haaf K, 25312998	
Wijesinghe AI, 37271799			Tong BC, 24726742	
Yu Y, 25064415			Vavalà T, 34769372	
Zeng H, 34112140			Wainer Z, 27625078	
			Wainer Z, 30206043	
			Watanabe K, 29582626	
			Xiao J, 32984005	
			Yoshida Y, 26366891	
			Yu XQ, 35124253	

ICI, immune checkpoint inhibitor.

smoking cessation continues to take place at a slower pace in women (8). Adenocarcinoma now accounts for more than 50% of lung cancer cases in females compared to approximately 30% 50 years ago (6).

Data disagrees on which is the more important prognostic factor in developing lung cancer—smoking status or smoking intensity. Some studies purport that smoking status trumps intensity as higher pack-years in males compared to females did not affect mortality rates between the two sexes (15). Conversely, when smoking amount was measured as a continuous variable in another study, female smokers had a progressively greater risk of lung cancer as pack-years of use, number of daily cigarettes, and usage duration increased as compared to males (16).

In the past, studies have generally recognized that females are more sensitive to cigarette smoke (14,17-19). Of those diagnosed with COPD or lung cancer, studies show that females generally have 20–25% less pack-years of tobacco use (20). Similarly, with equivalent amounts of smoking history, females are more likely to develop both adenocarcinoma and squamous cell carcinoma compared to males (18). Conversely, a meta-analysis published in 2014 with more than 400,000 individuals from 47 studies found a 1.61 relative risk ratio [95% confidence interval (CI): 1.37–1.89] of developing lung cancer for male to female smokers (21). Thus, debate remains about which sex is more susceptible to the negative effects from smoking.

COPD is also a risk factor for lung cancer. Bronchial hyperresponsiveness, airway obstruction that is often a component of asthma and COPD, is present in 87% of female smokers with mild to moderate COPD *vs.* 63% of male smokers (22). In females, airway obstruction presents earlier and with greater bronchial wall thickening as compared to males (20). Cigarette use is the single most important risk factor in exhibiting bronchial hyperresponsiveness in females. In contrast, atopy and asthma are the foremost risk factors for males. Females are twice as likely as males to develop lung cancer with comparable decreases in forced expiratory volume in one second, even when adjusted for smoking history (22). Mathematical quantification of the effect of cigarette smoke on lung parenchyma using a novel smoking-emphysema index, determined by low-attenuation area volume percentage on three-dimensional computed tomography scan divided by pack-years of smoking, demonstrated a greater volume of emphysematous change in male lungs overall. Nonetheless, females were found to have greater low-attenuation area volume percentage per cigarette smoked (23).

Exposure-related risk factors in females

Exposure to second-hand smoke, more commonly experienced by women, increases the risk of lung cancer. An observational study of non-smokers with lung cancer found 69% of females experienced environmental tobacco smoke exposure, compared to only 17% of males. Interestingly, males in this study reported exposure only at work, while females experienced exposure at home and work (24). Known risk factors such as asbestos and radon have been particularly poorly studied in women, though women spend more time in the home and consequently have greater exposure to indoor pollution including radon and tobacco smoke residues that persist on indoor surfaces, termed thirdhand smoke (14,25). A recent meta-analysis found cooking factors, including fume and coal smoke exposure, conferred the highest lung cancer risk to non-smoking Asian women [odds ratio (OR), 2.15; 95% CI: 1.87–2.47] among pooled risk categories of personal and family history, environmental tobacco exposure, diet, and reproductive factors (26). Female chefs exposed more intensely and for more years to cooking oil fumes, which contain known carcinogens, had a significantly higher risk of lung adenocarcinoma compared to male chefs and those less often exposed to cooking oil fumes due to specific cooking practices (27). Research on occupational cancer epidemiology shows that in male-dominated fields like extractive industry, construction, and agriculture, exposure studies are more likely to have a greater than 3.5 ratio of male to female participants ($P<0.001$), therefore making it difficult to draw conclusions about male *vs.* female occupational exposure risk (28). Differences in lung cancer risk secondary to radiation exposure remain ill-defined, partially because studies have relatively low female participants (29). However, as the incidence of breast cancer in younger females increases, concern over early exposure to radiation is warranted (30).

Hormonally based risk

Many doubts remain about one category of lung cancer patient: the female never-smoker. The label "never smoker" refers to someone who has smoked less than 100 cigarettes in their lifetime (7). Alarmingly, deaths from lung cancer in never smokers would rank as the seventh most common cause of cancer death worldwide (7,10). Female never smokers are more likely to develop lung cancer than their male counterparts (1,8,17), which holds true across ethnicities (31).

The rate of lung cancer diagnosis in never-smoking females is characterized as 14.4 to 20.8 per 100,000 person-years *vs.* 4.8 to 13.7 per 100,000 person-years for males (25).

Within this demographic, the effect of hormonal exposures has been considered a probable contributor (9,32). Of reproductive factors examined including parity, age at first birth, age at menopause, and exogenous hormone use, only bilateral oophorectomy significantly increased lung cancer risk in never smokers [hazard ratio (HR), 1.47; 95% CI: 1.00–2.16] in an observational study of almost 162,000 women from the United States (33). In a study that closely followed over 71,000 never-smoking Chinese females, older age at menopause, longer reproductive period, increased parity, and history of intrauterine device usage significantly decreased lung cancer risk (32). On the whole, though, data regarding lung cancer risk secondary to endogenous estrogen exposure is inconsistent. Additionally, the role of endogenous *vs.* exogenous estrogen exposure is a secondary query that requires further investigation (30). A meta-analysis of sex steroids and female lung cancer risk found that the summative effect of higher levels of both endogenous and exogenous hormone exposure reduced lung cancer risk in females by 10%. This result was consistent in subgroup analysis of both Asian (OR, 0.90; 95% CI: 0.84–0.99) and Western (OR, 0.90; 95% CI: 0.84–0.96) females, though for distinct underlying causes of exposure (34). However, there is evidence suggesting estrogen exposure via hormone replacement therapy may in fact increase lung cancer risk in women (8,30,35,36).

Screening and diagnosis

The National Lung Screening Trial was a large, multicenter, randomized-controlled trial that found a 20% reduction in mortality for heavy smokers screened annually with low-dose computed tomography (LDCT) *vs.* chest X-ray (37). In consideration of these and other results, the United States Preventative Services Task Force currently recommends annual screening with LDCT for adults aged 50 to 80 years with a 20-pack-year tobacco use history who continue to smoke or have quit within the last 15 years (38). Guidelines were expanded in 2021 in part to reach high-risk groups, particularly women and minorities (30,39). Similarly, the National Comprehensive Cancer Network recommends patients aged greater than 50 years with at least 20 years of smoking history to participate in shared decision-making with their healthcare provider regarding lung cancer screening with LDCT (40). Regrettably, screening uptake remains low despite expanded criteria, and many diagnosed with lung cancer do not meet eligibility for screening (39,41).

Screening recommendations are largely based on the lung cancer risk of white males, and because females typically develop lung cancer at a younger age and with less smoking exposure, they are less likely to qualify for screening (39). By examining a "natural experiment" in which patients with a suspicious lung nodule were assessed for lung cancer screening eligibility, Smeltzer *et al.* proved that expanding eligibility criteria to include patients with 10 pack-years' tobacco use and patients who quit within the last 25 years would reach a new population comprised of 57% females (P=0.0476), reversing some of the sex disparity in current screening recommendations (39). In a nationwide survey, females were less likely than males to report having discussed lung cancer screening with their healthcare provider regardless of smoking status, though these results did not reach statistical significance, and 32% less likely to have heard of LDCT (OR, 0.68; 95% CI: 0.47–0.99). Over the survey period of 2012–2017, there was no evidence of increased discussion between provider and patient regarding screening recommendations (42). Moreover, a study in Spain found no clinically relevant differences in symptoms at diagnosis between patients of either sex or variable smoking status (43), highlighting that healthcare providers must remain vigilant when determining patients who may benefit from lung cancer screening.

Review of the Surveillance, Epidemiology, and End Results (SEER) database reveals that a greater proportion of males are diagnosed with stage III and IV lung cancer compared to females (75.6% *vs.* 72%, P<0.0001) (44). This finding is replicated in other high-income countries including Australia, Canada, Ireland, Norway, and the United Kingdom (45). Predictably, when SEER data were examined at the county level, the percentage difference in late-stage diagnosis for males and females diminished as the proportion of female smokers increased. This trend remained consistent when examining lung cancers more associated with smoking (squamous and small cell carcinomas), perhaps suggesting that smokers of either sex are less likely to seek medical opinion when faced with symptoms concerning for lung cancer (44).

Carcinogenesis and the resultant immune response

Smoking, sex steroids, and carcinogenesis

Cigarette smoking has been demonstrated to affect the immune system by reducing neutrophil, antigen-presenting

cell, and global T-cell activity (46). On the whole, animal studies generally indicate that when exposed to cigarette smoke and its metabolites, females mount a robust inflammatory response leading to increased oxidative stress in the environment, eventually making cells more susceptible to genetic mutation and malignancy (22). Further, female smokers have higher levels of DNA adducts in peripheral blood mononuclear cells as compared to males (20), and 10–15% less capacity for DNA repair (14,22). Compared to male smokers, female smokers have increased cytochrome P450 (CYP) enzyme expression in their lungs (22). Tobacco smoke itself induces expression of CYP1B1, which then metabolizes estrogen and procarcinogens to their toxic state (47). N-nitrosamines and polycyclic aromatic hydrocarbons, two harmful tobacco-related substances, are primarily catalyzed by CYP to become carcinogenic (22,48). For example, an N-nitrosamine known as nicotine-derived nitrosamine ketone (NNK) is normally broken down via carbonyl reduction; yet without carbonyl reduction, NNK is hydroxylated by CYP and forms DNA adducts. A study which investigated the inhibitory effects of sex hormones on this process showed that progesterone and its synthetic analog were the most powerful inhibitors of safe NNK metabolization (36).

Various studies have attempted to utilize sex steroids, including estrogen receptor-alpha and beta, as a biomarker or determine their prognostic value in lung cancer (9,14,49-52). In order to influence gene expression, estrogen can bind with its receptor and function as a transcription factor or translocate across the cell membrane to induce more immediate events such as ion channel regulation, activation of protein kinase, or formation of second messengers (9,53). Estrogen receptor-beta, which is found more diffusely throughout the body, is highly expressed in bronchial epithelial cells and pneumocytes and contributes to maintenance of extracellular matrix of the lung (9). *KRT16*, an essential gene in estrogen receptor signaling, was found to be significantly overexpressed in the tumor tissue of female non-smoking lung adenocarcinoma patients compared to that of males, and likelihood of death in females with high *KRT16* expression was nearly double compared to males. Bearing in mind these results, estrogen blockade signaling may be an effective option for targeted therapy in non-smoking patients (54). A prospectively enrolled case-case study on hormone receptor expression demonstrated that female sex was associated with lower cytoplasmic estrogen receptor-alpha and nuclear estrogen receptor-beta expression than male sex when adjusted for age, race, and smoking. Additionally, ever-smokers also had lower cytoplasmic estrogen receptor-beta expression. The authors concluded their results supported the "estrogen hypothesis"—that is, estrogens play a role in lung carcinogenesis (17). However, concerns have been raised about the application of these findings, given the study did not consider obesity in its analysis, which is known to modulate estrogen and possibly estrogen receptors (55).

Studies with murine models likewise present conflicting data. Exposure to estradiol resulted in two-fold larger lung tumors, as well as increased angiogenesis and lymphangiogenesis, in immunocompetent female mice compared to male mice. This paradigm persisted in ovariectomized mice, which displayed the least tumor development, while ovariectomized mice treated with estradiol supplementation displayed moderate tumor growth. In contrast, castration of male mice did not affect tumor size, nor did castration with subsequent estradiol supplementation (56). Conversely, another study showed that when estrogen signaling was inhibited via tamoxifen in female mice, *KRAS* mutant lung cancer development was augmented (57). Sex steroids seem to play a role in the relationship between tobacco smoke and carcinogenesis, thus contributing to sex-based differences in lung cancer development, though this relationship remains to be clearly described.

Females have a stronger immune system

It is well known that females have a more robust immune system, which is borne out in higher incidence of autoimmune disease and lower prevalence of infection or cancer compared to males (46,58). Many genes that participate in the regulation of immune response are located on the X chromosome (46,58,59). Females have enhanced function of both innate and adaptive immunity (46,58-62), including higher phagocytic capacity of both neutrophils and macrophages, greater antibody response with elevated basal immunoglobulin levels and B-cell numbers, and increased $CD4^+$ T-cell count, and T-cell proliferation and activation (46,58). Additionally, estrogens alter the milieu of inflammatory cytokines produced by macrophages and neutrophils, which may influence overall less cancer risk seen in females (46).

Immune response differences in adenocarcinoma according to sex

Novel studies reveal baseline differences in male and female immune responses to lung adenocarcinoma that may

contribute to sex disparities in tumor burden and disease outcome (13). Female adenocarcinoma patients tend to have a more robust anti-cancer immune response, specifically a higher proportion of immune infiltrate, than their male counterparts, which may contribute to worse prognosis seen in males (13,63). In fact, lymphocytic infiltration with $CD3^+$ and $CD8^+$ cells has been linked to superior outcomes in multiple tumors (64). In "The Immune Landscape of Cancer", Thorsson *et al.* described a framework for examining "immune signature" in various cancers, which includes six subtypes: wound healing, interferon (INF)-gamma dominant, inflammatory, lymphocyte depleted, immunologically quiet, and transforming growth factor (TGF)-beta dominant (65). In female lung adenocarcinoma, INF-gamma, lymphocytic infiltration, and M1 macrophage enrichment were noted. Evaluation of immune-related gene expression revealed predominance of antigen processing and presentation pathways. In contrast, male tumors trended towards M2 macrophage enrichment (65). Those with wild type-*TP53* tumors and high expression of these immune-related genes demonstrated a statistically significant survival benefit compared to the wild type-*TP53*, low expression group, and mutant *TP53* groups with both high and low expression of these genes, regardless of sex, highlighting the clinical significance of this work (13).

Outcomes

Understanding of lung cancer in females generally concludes favorable prognosis compared to male counterparts. From 1999 to 2019 in the United States, females with lung cancer consistently had decreased age-standardized mortality rates compared to males (66). In fact, when controlling for age, smoking history, stage at diagnosis, and histology, females demonstrate superior survival rates (30,67,68). SEER data reveals that males have significantly worse survival than females across all stages defined in the 8th edition of the tumor, node, metastasis staging system, with the greatest disparity noted in early stage disease at both 1 and 5 years of follow-up (69).

Compared to males, females are more likely to be diagnosed at earlier stages, be never-smokers, and have adenocarcinoma histology (70,71). The period during which a patient is asymptomatic from disease yet lung cancer is detectable on imaging was found to be 4.48 years for males compared to 6.01 years for females (72). This is indicative of the fact that females are more likely to be diagnosed with adenocarcinoma, characteristically slower-growing, thus offering greater opportunity for early-stage diagnosis. Furthermore, most of the excess death risk in males diagnosed with lung cancer can be attributed to known prognostic factors, including patient characteristics, demographic and lifestyle data, and tumor- and treatment-related factors (73). When adjusting for these predictive factors, Yu *et al.* were able to show reduction in risk of death from HR 1.33 to 1.06 (95% CI: 0.96–1.18; P=0.26), achieving a non-significant difference in death risk between males and females. Approximately 50% of the excess risk of death came from treatment-related factors, specifically receiving surgery, systemic therapy, or radiation within 6 months of diagnosis (73). This review will concentrate on sex-based differences in outcomes of surgery, the favored management of early disease, and contemporary systemic treatments.

Surgery for early-stage lung cancer

The primary treatment of stage I and II lung cancer is surgery with curative intent. Definitive radiation is considered if the patient is not a surgical candidate secondary to comorbidities or problematic tumor location. A previous meta-analysis of patients with inoperable NSCLC treated with radiation found that female gender was the sole demographic factor to confer an overall survival benefit (74). In contrast, a large retrospective study of patients who underwent stereotactic body radiation therapy found that unfavorable histology, increased body mass index, significant comorbidities, and radiation dosing were predictive of local treatment failure, but not sex (75).

Various studies of patients with early-stage NSCLC undergoing resection find superior outcomes for females in both overall and perioperative survival. A retrospective review of 735 NSCLC surgical resection cases from 1995 to 2010 at a single Japanese institution demonstrated that overall survival at 1, 3, and 5 years was significantly better for females. Subgroup analysis further revealed that female sex and adenocarcinoma histology were significant positive prognostic factors only in pathologic stages I and II (n=557). Female survival advantage was lost in late-stage disease; survival curves crossed at around 4 years of follow-up (70). Importantly, length-time bias could have contributed to the improved overall survival seen in females as they were more frequently diagnosed with screening or with incidental imaging (70). Similarly, male sex was found to be an independent negative prognostic factor (HR, 1.54; 95% CI: 1.10–2.16) for mortality at 5-year in an Australian

cohort study performed between 2000 and 2009. As female patients were diagnosed with higher stage disease, their mortality risk increased at a faster pace compared to males. For example, stages III and IV conferred a HR 8.71 for female patients *vs.* 3.66 for male patients compared to the reference group which was comprised of patients diagnosed at Stage IA, meaning their tumors were less than three centimeters (76).

Even in studies with longer follow-up, survival advantage in females persists. A prospective cohort study of stage I and II NSCLC patients conducted in Norway from 2003 to 2013 determined 37.8% survival for females *vs.* 28.2% in males at 10 years of follow-up, though this difference did not reach statistical significance in the relatively small study population (n=692) (15). Females 66 years and older did have a statistically significant greater survival than males at 10 years (28.2% *vs.* 19.5%, P<0.03). By the end of ongoing follow-up, that significance was lost (P=0.06), which was attributed to confounders such as pack-years of smoking, cancer stage, large cell carcinoma histology, and lobectomy (15). A nationwide observational cohort study of 6,536 patients who underwent pulmonary resection for lung cancer in Sweden from 2008 to 2017 found a lower risk of death in females compared to males with increasing absolute survival difference over 10 years of follow-up (77). When the cohort was divided by pathologic stage, histology, and age, except for those younger than 60 years, improved survival for women was maintained regardless of differences in patient characteristics such as comorbidities, frailty, and socioeconomic status. The advantage was conferred in both adenocarcinoma and squamous cell carcinoma, though to a lesser extent with the latter (77). These studies beg the question: why do younger females with early-stage lung cancer have comparatively less survival advantage than their elders?

Regarding perioperative survival, females undergoing lung resection are generally younger and have fewer comorbidities (78,79). A retrospective review of a German discharge registry of almost 39,000 patients undergoing lung resection from 2014 to 2017 compared in-hospital mortality, complications, and comorbidities between the sexes. They found a difference in raw in-hospital mortality: 1.8% for females and 4.1% for males. Regardless of surgical approach, women had significantly fewer post-operative complications, including prolonged ventilation, pneumonia, tracheotomy, empyema, and sepsis. Women were significantly less likely to have hypertension, chronic renal failure, diabetes mellitus, and COPD, which continued to be true after stratifying for open *vs.* minimally invasive surgery. They were also significantly more likely to be referred, compared to males, who were more frequently admitted in an emergent fashion or transferred from another hospital. In multivariable regression, in-hospital mortality advantage for females was maintained—they were 21% less likely to die in hospital following lung resection for cancer (OR, 0.79; 95% CI: 0.66–0.93; P<0.005) (78). An analogous study performed in the United States reviewed more than 34,000 patients from the Society of Thoracic Surgeons General Thoracic Surgery Database undergoing resection for lung cancer between 2002 and 2010 similarly found females to have significantly less coronary artery disease, diabetes, and renal insufficiency. Combined in-hospital and 30-day mortality was found to be 1.5% in females and 3% in males (79).

It is imperative to recognize these studies were performed during years in which video-assisted thoracoscopic surgery (VATS) techniques were being adopted. In the Society of Thoracic Surgeons database, lobectomies via VATS increased by 10.4% between 2004 and 2006 (80). By 2013, surgeons in Japan self-reported performing 68.9% of lobectomies using VATS techniques (81). As this minimally invasive technique was being implemented, it is logical that surgeons may have chosen certain patients, such as those with smaller tumors or better functional status, to undergo a relatively unfamiliar VATS procedure. Years later, the data exists to show that VATS procedures reduce post-operative complications and improve long-term survival (77,82), which may have influenced superior survival outcomes following lung resection seen in females.

Studies have demonstrated sex disparities in surgery for early-stage lung cancer. A review of patients with stage I NSCLC who participated prospectively in the National Lung Screening Trial found that women were "less likely to undergo full resection" despite having surgery as often as men, though this was not statistically significant. The authors posited favorable pathology and patient preference may have influenced these decisions (83). An early comparison of limited resection *vs.* lobectomy for stage IA lung cancer showed that limited resection was performed in females more often (84), though we now have robust evidence that sublobar resection is non-inferior to lobectomy in patients with clinical stage IA peripheral NSCLC tumors less than two centimeters (85,86). What was previously considered a limited resection is now known to be a suitable choice in select patients. Further, propensity-matched patients with stage IA peripheral NSCLC were found to have no difference in the rate of

lymph node metastases between the sexes, suggesting no justification for offering sex-dependent surgical resection (87).

Recurrence after surgical resection

When early-stage tumors are resected with curative intent, molecular testing with next-generation sequencing is not typically performed though up to 70% of these patients will ultimately have cancer recurrence (88). Following surgical resection with frequent surveillance, men more frequently recurred within the first year after surgery while peak recurrence in women occurred over a longer range of duration from 2 to 3 years following surgery (71). A recent propensity-matched cohort controlling for sex and smoking status of early- and late-stage NSCLC patients demonstrated no differences in the frequency of targetable mutations, thus making a case for routine sequencing of resected specimens to optimize systemic therapy for future recurrence, should it be needed (88).

Advanced stage and metastatic disease

Significant innovation has led to new therapies for advanced NSCLC in recent decades, and it is thought that over half of patients with advanced NSCLC may have an actionable mutation towards which systemic therapy can be directed. Epidermal growth factor receptor (EGFR)-targeted therapies were introduced in 2003; immune checkpoint inhibitors (ICI) have been Food and Drug Administration (FDA)-approved for treatment of lung cancer since 2015 (89). Currently, the National Comprehensive Cancer Network recommends testing for the several biomarkers in advanced or metastatic disease, including *EGFR*, *KRAS*, *HER2*, *ALK*, *ROS1*, and PD-L1 expression (90). Responses to modern systemic therapies vary greatly between males and females, emphasizing fundamental differences in their respective diseases (68). In comparison, older studies demonstrate that traditional chemotherapy offers marginal benefit (on the order of months) to females over males in certain subgroups (91). In the age of precision medicine, it will become increasingly important to consider biological sex in the lung cancer treatment strategy (92,93).

Targeted therapy

Multiple meta-analyses have been performed to evaluate the efficacy of EGFR inhibitors. There is disagreement on whether EGFR-tyrosine kinase inhibitor (EGFR TKI) confer tangible benefit to females with NSCLC. A meta-analysis of six phase-three trials comparing EGFR-TKI to chemotherapy in patients with identified EGFR mutations, females were shown to have improved progression-free survival (HR, 0.34; 95% CI: 0.28–0.40) compared to males (HR, 0.44; 95% CI: 0.34–0.56), though high heterogeneity was noted in the female group (92). Conversely, in a meta-analysis of 22 studies, Xiao *et al.* found that only in the subgroup analysis comparing EGFR-TKI to placebo did females demonstrate improved overall survival compared to males. There was no improved survival noted when EGFR-TKI was compared to chemotherapy (HR, 1.01; 95% CI: 0.89–1.14; P=0.89) or when only patients with known EGFR mutation were considered (HR, 1.02; 95% CI: 0.78–1.34; P=0.86) (68). As noted in the recent review by Huang *et al.*, it appears that first- and second-generation EGFR-TKI offer longer progression-free survival to females, which may indicate "immediate response to treatment" and inherently does not consider patient characteristics which impact overall survival (93).

ALK and *ROS1* rearrangements also offer opportunity for targeted therapy. They represent a relatively small percentage of NSCLC patients, 3% to 8% of the former and 1% to 2% of the latter, though studies have found these mutations more prevalent in women (94,95). There is no current evidence to identify sex differences in treatment and survival outcomes with ALK and ROS1 inhibitors (59,93).

Immunotherapy

For patients without a known driver mutation, immunotherapy is considered. These drugs block negative regulators PD-1, PD-L1, and CTLA-4 of the immune system. Six meta-analyses generated in our literature search have investigated sex differences in ICI efficacy. Essentially, findings have been inconsistent across these analyses, which are summarized in *Table 3*. Given results of early meta-analyses, Conforti *et al.* hypothesized that females could benefit from treatment other than immunotherapy alone. A subsequent meta-analysis demonstrated that women experienced a large survival benefit with anti-PD-1 or anti-PD-L1 therapy in combination with chemotherapy with a pooled HR of 0.44 compared to the male HR of 0.76 (96). It was thought the addition of chemotherapy enhanced the antigenicity of tumor cells, thus prompting the female immune system to respond more vigorously (96). A follow-up study found that despite having high PD-L1 expression, defined as tumor proportion score ≥50%,

Table 3 Recent meta-analyses examining sex differences in efficacy of ICIs in treating NSCLC

Meta-analysis, year published	Number of patients included [number of studies included]	Number of female participants (%)	Intervention *vs.* control arms, and clarifying comments	Pooled HR (95% CI)	Conclusions
Conforti, 2018 (60)	3,482 [6]	1,167 (33.5)	PD-1 inhibitor or CTLA-4 inhibitor plus chemotherapy *vs.* chemotherapy or chemotherapy plus placebo	Overall survival compared to controls: male: 0.72 (0.61–0.86); female: 0.89 (0.71–1.11)	Advanced or metastatic cancers were studied, of which NSCLC was a subgroup. In the overall study of 20 trials and 11,351 patients, pooled male survival was 0.72 (0.65–0.79) and female survival 0.86 (0.79–0.93) with a significant difference in efficacy between sexes (P=0.0019), demonstrating sex-specific benefit in overall survival with ICI therapy
Conforti, 2019 (96)	2,970[†] [5]	991 (33.4)	PD-1/PD-L1 inhibitor plus chemotherapy *vs.* chemotherapy. When excluding the trial with SCLC patients, a statistically significant overall survival benefit for females compared to males remained	Overall survival: male: 0.76 (0.66–0.87); female: 0.48 (0.35–0.67)	Females with advanced NSCLC derive greater benefit from combination chemoimmunotherapy than males, though both demonstrate improved survival with combination therapy over chemotherapy alone. However, only males demonstrate benefit from anti-PD-1 alone over chemotherapy
	4,923[‡] [8]	1,578 (32.1)		Progression-free survival: male: 0.64 (0.58–0.71); female: 0.56 (0.49–0.65)	
	3,974 [6]	1,335 (33.6)	PD-1/PD-L1 inhibitor plus chemotherapy *vs.* chemotherapy (first-line treatment). Three studies tested PD-1 alone; 3 studies tested PD-1/PD-L1 with chemotherapy	Overall survival for anti-PD-1: male: 0.78 (0.60–1.01); female: 0.97 (0.79–1.19)	
				Overall survival for anti-PD-1/PD-L1 with chemotherapy: male: 0.76 (0.64–0.91); female: 0.44 (0.25–0.76)	
Wang, 2019 (97)	8,023 [12]	2,601 (32.4)	PD-1/PD-L1 inhibitor alone or PD-1 or CTLA-4 inhibitor plus chemotherapy or PD-L1 plus chemoradiotherapy *vs.* chemotherapy or chemoradiotherapy	Overall survival: male: 0.76 (0.71–0.82); female: 0.73 (0.58–0.91)	Males experience more reliable benefit from ICIs than females. However, CTLA-4 inhibitors did not demonstrate survival benefit for either sex
	5,622 [10]	1,934 (34.4)	PD-1 alone, PD-1 plus CTLA-4 inhibitor, PD-1 plus chemotherapy, PD-L1 inhibitor plus chemotherapy or chemoradiotherapy *vs.* chemotherapy or chemoradiotherapy	Progression-free survival: male: 0.67 (0.58–0.77); female: 0.73 (0.56–0.95)	

Table 3 (*continued*)

Table 3 (*continued*)

Meta-analysis, year published	Number of patients included [number of studies included]	Number of female participants (%)	Intervention *vs.* control arms, and clarifying comments	Pooled HR (95% CI)	Conclusions
Xue, 2021 (98)	12,037 [19]	3,751 (31.2)	PD-1, PD-L1, CTLA-4 inhibitor, or CTLA-4 plus PD-1 inhibitor together or PD-1, PD-L1, CTLA-4 inhibitor plus chemotherapy *vs.* chemotherapy or chemotherapy plus placebo	Overall survival: male: 0.73 (0.67–0.79); female: 0.73 (0.61–0.85)	Both males and females benefit from treatment with ICI over chemotherapy. There is no significant difference in overall survival (P=0.97) and progression-free survival (P=0.43) between the sexes
	6,940 [14]	2,088 (30.1)	PD-1, PD-L1, or CTLA-4 plus PD-1 inhibitor together or PD-1 or PD-L1 inhibitor plus chemotherapy *vs.* chemotherapy or chemotherapy plus placebo	Progression-free survival: male: 0.62 (0.55–0.70); female: 0.68 (0.55–0.81)	
Liang, 2022 (99)	10,155 [16]	3,370 (33.2)	PD-1/PD-L1 or CTLA-4 inhibitor alone, in combination, or with chemotherapy *vs.* chemotherapy or placebo. Six studies tested ICI plus chemotherapy *vs.* chemotherapy, 9 studies compared ICI *vs.* chemotherapy, and 1 study reviewed ICI *vs.* placebo	Overall survival: male: 0.76 (0.71–0.81); female: 0.74 (0.63–0.87)	In general, females benefitted more from combination chemoimmunotherapy, while males benefitted more from ICIs alone. However, in squamous cell carcinoma, only males demonstrated a statistically significant benefit from ICI therapy, either with or without chemotherapy
Madala, 2022 (100)	9,270 [12]	3,144 (33.9)	PD-1/PD-L1 inhibitor alone or combined with chemotherapy *vs.* chemotherapy, placebo, or their combination	Overall survival: male: 0.74 (0.66–0.83); female: 0.72 (0.63–0.82)	No statistical difference was found in overall survival (P=0.709) and progression-free survival (P=0.372) between the sexes
	6,193 [11]	2,059 (33.2)		Progression-free survival: male: 0.63 (0.53–0.75); female: 0.72 (0.58–0.88)	
Takada, 2022 (101)	5,280 [8]	1,554 (29.4)	PD-1/PD-L1 or CTLA-4 inhibitor, or PD-1 plus CTLA-4 inhibitor in combination, or PD-L1 + VEGF inhibitor in combination plus chemotherapy *vs.* chemotherapy, placebo plus chemotherapy, or VEGF inhibitor plus chemotherapy	Overall survival: male: 0.80 (0.72–0.87); female: 0.69 (0.54–0.89)	During first-line treatment, patients with advanced NSCLC demonstrated both improved overall survival and progression-free survival when treated with combined chemoimmunotherapy rather than chemotherapy alone, though this favors females to a greater degree
	3,701 [6]	1,184 (32.0)	PD-1/PD-L1 inhibitor or PD-1 plus CTLA-4 inhibitor in combination, or PD-L1 + VEGF inhibitor in combination plus chemotherapy *vs.* chemotherapy, placebo plus chemotherapy, or VEGF inhibitor, placebo, and chemotherapy	Progression-free survival: male: 0.60 (0.55–0.66); female: 0.56 (0.44–0.70)	

†, 13.6% of patients with SCLC; ‡, 8.2% of patients with SCLC. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; VEGF, vascular endothelial growth factor.

females did not derive statistically significant benefit from ICI monotherapy (61). In their review on gender differences in immunotherapy outcomes, Vavalà *et al.* appropriately highlights that heterogeneity within randomized-controlled trials, lack of subgroup data, and relatively short follow-up allow only conjecture, but not durable conclusions, to be drawn from these analyses (46). As plainly demonstrated in *Table 3*, the heterogeneity of the intervention and control arms offers an avenue for bias introduction in these investigations.

Another important factor for consideration is the risk that comes ICI treatment. Females treated with anti-PD-1 therapy were more likely to experience immune-related adverse events (48% *vs.* 31%, P<0.008), notably pneumonitis and endocrinopathies, in a retrospective review of NSCLC patients. They were also more were likely than males to discontinue the offending agent secondary to side effects (17% *vs.* 7%, P<0.04). Multivariable analysis examining patient and tumor factors found that only sex was associated with an increased risk of these adverse events. Interestingly, females who experienced immune-related adverse events more frequently demonstrated radiographic response when evaluated several weeks following initiation of ICI therapy (78% *vs.* 23%, P<0.0001) and had longer progression-free survival (10 *vs.* 3.3 months, P<0.0006) compared to females with no adverse events. This distinction was not statistically significant in males. Ultimately though, there was no association between immune-related adverse events and overall survival in the NSCLC cohort (102).

The limitations of this narrative review must be acknowledged. A single database was used to collect relevant literature, and articles were selected based on relevancy as determined by the authors' expertise. Our review is not an exhaustive examination of all data published on this topic.

Conclusions

Increasing lung cancer incidence in non-smokers and young females begs demands greater understanding of sex-based drivers of the disease. Environmental exposure studies, especially those which examine risk factors present in the home, are lacking, the effect of sex hormones on carcinogenesis in the lung is not well understood, and females continue to be underrepresented in clinical trials for lung cancer treatment. Randomized controlled trials with uniform control arms are necessary to truly optimize treatment regimens with new systemic therapies. Practically-speaking, clinicians must recognize that current screening guidelines do not reflect the changing demographics seen in new lung cancer diagnoses. Further investigation into the sex-specific differences in lung cancer will not only increase the proportion of patients diagnosed in its early stages, but also generate sex-based treatment modalities.

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Footnote

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References

1. Ridge CA, McErlean AM, Ginsberg MS. Epidemiology of

lung cancer. Semin Intervent Radiol 2013;30:93-8.
2. World Health Organization. Lung cancer. 2023. Accessed July 25, 2023. Available online: https://www.who.int/news-room/fact-sheets/detail/lung-cancer
3. World Health Organization. Cancer. 2022. Accessed July 25 2023. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer
4. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. 2023. Accessed January 5, 2024. Available online: https://www.cdc.gov/cancer/dataviz
5. Cancer Facts & Figures 2023. Atlanta: American Cancer Society, Inc.; 2022. Accessed January 9, 2024. Available online: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf
6. Meza R, Meernik C, Jeon J, et al. Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010. PLoS One 2015;10:e0121323.
7. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 2011;32:605-44.
8. Ragavan MV, Patel MI. Understanding sex disparities in lung cancer incidence: are women more at risk? Lung Cancer Manag 2020;9:LMT34.
9. Hsu LH, Chu NM, Kao SH. Estrogen, Estrogen Receptor and Lung Cancer. Int J Mol Sci 2017;18:1713.
10. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med 2020;41:1-24.
11. Jeon J, Holford TR, Levy DT, et al. Smoking and Lung Cancer Mortality in the United States From 2015 to 2065: A Comparative Modeling Approach. Ann Intern Med 2018;169:684-93.
12. Song MA, Benowitz NL, Berman M, et al. Cigarette Filter Ventilation and its Relationship to Increasing Rates of Lung Adenocarcinoma. J Natl Cancer Inst 2017;109:djx075.
13. Freudenstein D, Litchfield C, Caramia F, et al. TP53 Status, Patient Sex, and the Immune Response as Determinants of Lung Cancer Patient Survival. Cancers (Basel) 2020;12:1535.
14. Mederos N, Friedlaender A, Peters S, et al. Gender-specific aspects of epidemiology, molecular genetics and outcome: lung cancer. ESMO Open 2020;5:e000796.
15. Bugge A, Kongerud J, Brunborg C, et al. Gender-specific survival after surgical resection for early stage non-small cell lung cancer. Acta Oncol 2017;56:448-54.
16. Hansen MS, Licaj I, Braaten T, et al. Sex Differences in Risk of Smoking-Associated Lung Cancer: Results From a Cohort of 600,000 Norwegians. Am J Epidemiol 2018;187:971-81.
17. Cheng TD, Darke AK, Redman MW, et al. Smoking, Sex, and Non-Small Cell Lung Cancer: Steroid Hormone Receptors in Tumor Tissue (S0424). J Natl Cancer Inst 2018;110:734-42.
18. Stapelfeld C, Dammann C, Maser E. Sex-specificity in lung cancer risk. Int J Cancer 2020;146:2376-82.
19. Fuentes N, Silva Rodriguez M, Silveyra P. Role of sex hormones in lung cancer. Exp Biol Med (Maywood) 2021;246:2098-110.
20. Siegfried JM. Sex and Gender Differences in Lung Cancer and Chronic Obstructive Lung Disease. Endocrinology 2022;163:bqab254.
21. Yu Y, Liu H, Zheng S, et al. Gender susceptibility for cigarette smoking-attributable lung cancer: a systematic review and meta-analysis. Lung Cancer 2014;85:351-60.
22. Ben-Zaken Cohen S, Paré PD, Man SF, et al. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. Am J Respir Crit Care Med 2007;176:113-20.
23. Wijesinghe AI, Kobayashi N, Kitazawa S, et al. Sex-specific emphysematous changes evaluated by a three-dimensional computed tomography volumetric analysis among patients with smoking histories who underwent resection for lung cancer. Surg Today 2024;54:113-21.
24. Clément-Duchêne C, Vignaud JM, Stoufflet A, et al. Characteristics of never smoker lung cancer including environmental and occupational risk factors. Lung Cancer 2010;67:144-50.
25. Baiu I, Titan AL, Martin LW, et al. The role of gender in non-small cell lung cancer: a narrative review. J Thorac Dis 2021;13:3816-26.
26. Huang J, Yue N, Shi N, et al. Influencing factors of lung cancer in nonsmoking women: systematic review and meta-analysis. J Public Health (Oxf) 2022;44:259-68.
27. Lin PC, Peng CY, Pan CH, et al. Gender differences and lung cancer risk in occupational chefs: analyzing more than 350,000 chefs in Taiwan, 1984-2011. Int Arch Occup Environ Health 2019;92:101-9.
28. Betansedi CO, Vaca Vasquez P, Counil E. A comprehensive approach of the gender bias in occupational cancer

epidemiology: A systematic review of lung cancer studies (2003-2014). Am J Ind Med 2018;61:372-82.
29. Boice JD Jr, Ellis ED, Golden AP, et al. Sex-specific lung cancer risk among radiation workers in the million-person study and patients TB-Fluoroscopy. Int J Radiat Biol 2022;98:769-80.
30. Ragavan M, Patel MI. The evolving landscape of sex-based differences in lung cancer: a distinct disease in women. Eur Respir Rev 2022;31:210100.
31. Pinheiro PS, Callahan KE, Medina HN, et al. Lung cancer in never smokers: Distinct population-based patterns by age, sex, and race/ethnicity. Lung Cancer 2022;174:50-6.
32. Weiss JM, Lacey JV Jr, Shu XO, et al. Menstrual and reproductive factors in association with lung cancer in female lifetime nonsmokers. Am J Epidemiol 2008;168:1319-25.
33. Schwartz AG, Ray RM, Cote ML, et al. Hormone Use, Reproductive History, and Risk of Lung Cancer: The Women's Health Initiative Studies. J Thorac Oncol 2015;10:1004-13.
34. Zeng H, Yang Z, Li J, et al. Associations between female lung cancer risk and sex steroid hormones: a systematic review and meta-analysis of the worldwide epidemiological evidence on endogenous and exogenous sex steroid hormones. BMC Cancer 2021;21:690.
35. May L, Shows K, Nana-Sinkam P, et al. Sex Differences in Lung Cancer. Cancers (Basel) 2023;15:3111.
36. Stapelfeld C, Neumann KT, Maser E. Different inhibitory potential of sex hormones on NNK detoxification in vitro: A possible explanation for gender-specific lung cancer risk. Cancer Lett 2017;405:120-6.
37. National Lung Screening Trial Research Team; Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
38. U.S. Preventative Services Task Force. Lung Cancer: Screening. 2021. Accessed 8/4 2023. Available online: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening
39. Smeltzer MP, Liao W, Faris NR, et al. Potential Impact of Criteria Modifications on Race and Sex Disparities in Eligibility for Lung Cancer Screening. J Thorac Oncol 2023;18:158-68.
40. National Comprehensive Cancer Network. Lung Cancer Screening. In: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines. 2023. Accessed August 4, 2023. Available online: https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
41. Pinsky PF, Lau YK, Doubeni CA. Potential Disparities by Sex and Race or Ethnicity in Lung Cancer Screening Eligibility Rates. Chest 2021;160:341-50.
42. Warner ET, Lathan CS. Race and sex differences in patient provider communication and awareness of lung cancer screening in the health information National Trends Survey, 2013-2017. Prev Med 2019;124:84-90.
43. Ruano-Ravina A, Provencio M, Calvo de Juan V, et al. Are there differences by sex in lung cancer characteristics at diagnosis? -a nationwide study. Transl Lung Cancer Res 2021;10:3902-11.
44. Tolwin Y, Gillis R, Peled N. Gender and lung cancer-SEER-based analysis. Ann Epidemiol 2020;46:14-9.
45. Araghi M, Fidler-Benaoudia M, Arnold M, et al. International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SURVMARK-2 Study. Thorax 2022;77:378-90.
46. Vavalà T, Catino A, Pizzutilo P, et al. Gender Differences and Immunotherapy Outcome in Advanced Lung Cancer. Int J Mol Sci 2021;22:11942.
47. Peng J, Xu X, Mace BE, et al. Estrogen metabolism within the lung and its modulation by tobacco smoke. Carcinogenesis 2013;34:909-15.
48. Li Y, Hecht SS. Metabolic Activation and DNA Interactions of Carcinogenic N-Nitrosamines to Which Humans Are Commonly Exposed. Int J Mol Sci 2022;23:4559.
49. Skjefstad K, Richardsen E, Donnem T, et al. The prognostic role of progesterone receptor expression in non-small cell lung cancer patients: Gender-related impacts and correlation with disease-specific survival. Steroids 2015;98:29-36.
50. Gu T, Wen Z, Xu S, et al. Decreased levels of circulating sex hormones as a biomarker of lung cancer in male patients with solitary pulmonary nodules. Afr Health Sci 2014;14:356-63.
51. Ishibashi H, Suzuki T, Suzuki S, et al. Progesterone receptor in non-small cell lung cancer--a potent prognostic factor and possible target for endocrine therapy. Cancer Res 2005;65:6450-8.
52. Stabile LP, Dacic S, Land SR, et al. Combined analysis of estrogen receptor beta-1 and progesterone receptor expression identifies lung cancer patients with poor outcome. Clin Cancer Res 2011;17:154-64.
53. Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Adv Protein Chem Struct Biol 2019;116:135-70.
54. Xu L, Wang L, Cheng M. Identification of genes and pathways associated with sex in Non-smoking lung cancer

population. Gene 2022;831:146566.
55. Nabi H, Provencher L, Diorio C. RE: Smoking, Sex, and Non-Small Cell Lung Cancer: Steroid Hormone Receptors in Tumor Tissue (S0424). J Natl Cancer Inst 2018;110:1422-3.
56. Dubois C, Rocks N, Blacher S, et al. Lymph/angiogenesis contributes to sex differences in lung cancer through oestrogen receptor alpha signalling. Endocr Relat Cancer 2019;26:201-16.
57. Caetano MS, Hassane M, Van HT, et al. Sex specific function of epithelial STAT3 signaling in pathogenesis of K-ras mutant lung cancer. Nat Commun 2018;9:4589.
58. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626-38.
59. Raskin J, Snoeckx A, Janssens A, et al. New Implications of Patients' Sex in Today's Lung Cancer Management. Cancers (Basel) 2022;14:3399.
60. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018;19:737-46.
61. Conforti F, Pala L, Pagan E, et al. Sex-based differences in response to anti-PD-1 or PD-L1 treatment in patients with non-small-cell lung cancer expressing high PD-L1 levels. A systematic review and meta-analysis of randomized clinical trials. ESMO Open 2021;6:100251.
62. Pérez-Díez I, Hidalgo MR, Malmierca-Merlo P, et al. Functional Signatures in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Sex-Based Differences in Transcriptomic Studies. Cancers (Basel) 2021;13:143.
63. Han J, Yang Y, Li X, et al. Pan-cancer analysis reveals sex-specific signatures in the tumor microenvironment. Mol Oncol 2022;16:2153-73.
64. Behrens C, Rocha P, Parra ER, et al. Female Gender Predicts Augmented Immune Infiltration in Lung Adenocarcinoma. Clin Lung Cancer 2021;22:e415-24.
65. Thorsson V, Gibbs DL, Brown SD, et al. The Immune Landscape of Cancer. Immunity 2018;48:812-830.e14.
66. Al Omari O, Jani C, Ahmed A, et al. Lung Cancer Mortality in the United States between 1999 and 2019: An Observational Analysis of Disparities by Sex and Race. Ann Am Thorac Soc 2023;20:612-6.
67. Radkiewicz C, Dickman PW, Johansson ALV, et al. Sex and survival in non-small cell lung cancer: A nationwide cohort study. PLoS One 2019;14:e0219206.
68. Xiao J, Zhou L, He B, et al. Impact of Sex and Smoking on the Efficacy of EGFR-TKIs in Terms of Overall Survival in Non-small-Cell Lung Cancer: A Meta-Analysis. Front Oncol 2020;10:1531.
69. Wainer Z, Wright GM, Gough K, et al. Sex-Dependent Staging in Non-Small-Cell Lung Cancer; Analysis of the Effect of Sex Differences in the Eighth Edition of the Tumor, Node, Metastases Staging System. Clin Lung Cancer 2018;19:e933-44.
70. Yoshida Y, Murayama T, Sato Y, et al. Gender Differences in Long-Term Survival after Surgery for Non-Small Cell Lung Cancer. Thorac Cardiovasc Surg 2016;64:507-14.
71. Watanabe K, Sakamaki K, Nishii T, et al. Gender Differences in the Recurrence Timing of Patients Undergoing Resection for Non-Small Cell Lung Cancer. Asian Pac J Cancer Prev 2018;19:719-24.
72. Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev 2015;24:154-61.
73. Yu XQ, Yap ML, Cheng ES, et al. Evaluating Prognostic Factors for Sex Differences in Lung Cancer Survival: Findings From a Large Australian Cohort. J Thorac Oncol 2022;17:688-99.
74. Siddiqui F, Bae K, Langer CJ, et al. The influence of gender, race, and marital status on survival in lung cancer patients: analysis of Radiation Therapy Oncology Group trials. J Thorac Oncol 2010;5:631-9.
75. Woody NM, Stephans KL, Andrews M, et al. A Histologic Basis for the Efficacy of SBRT to the lung. J Thorac Oncol 2017;12:510-9.
76. Wainer Z, Wright GM, Gough K, et al. Impact of sex on prognostic host factors in surgical patients with lung cancer. ANZ J Surg 2017;87:1015-20.
77. Sachs E, Sartipy U, Jackson V. Sex and Survival After Surgery for Lung Cancer: A Swedish Nationwide Cohort. Chest 2021;159:2029-39.
78. Baum P, Eichhorn ME, Diers J, et al. Population-Based Analysis of Sex-Dependent Risk Factors for Mortality in Thoracic Surgery for Lung Cancer. Respiration 2022;101:624-31.
79. Tong BC, Kosinski AS, Burfeind WR Jr, et al. Sex differences in early outcomes after lung cancer resection: analysis of the Society of Thoracic Surgeons General Thoracic Database. J Thorac Cardiovasc Surg 2014;148:13-8.
80. Boffa DJ, Allen MS, Grab JD, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247-54.
81. Mun M, Ichinose J, Matsuura Y, et al. Video-assisted

thoracoscopic surgery lobectomy via confronting upside-down monitor setting. J Vis Surg 2017;3:129.
82. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. J Thorac Cardiovasc Surg 2009;138:419-25.
83. Balekian AA, Wisnivesky JP, Gould MK. Surgical Disparities Among Patients With Stage I Lung Cancer in the National Lung Screening Trial. Chest 2019;155:44-52.
84. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg 2010;251:550-4.
85. Altorki N, Wang X, Kozono D, et al. Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer. N Engl J Med 2023;388:489-98.
86. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;399:1607-17.
87. Deng HY, Liu C, Qiu XM, et al. Assessing Differences in Lymph Node Metastasis Based Upon Sex in Early Non-Small Cell Lung Cancer. World J Surg 2021;45:2610-8.
88. McGuire AL, McConechy MK, Melosky BL, et al. The Clinically Actionable Molecular Profile of Early versus Late-Stage Non-Small Cell Lung Cancer, an Individual Age and Sex Propensity-Matched Pair Analysis. Curr Oncol 2022;29:2630-43.
89. Baum P, Winter H, Eichhorn ME, et al. Trends in age- and sex-specific lung cancer mortality in Europe and Northern America: Analysis of vital registration data from the WHO Mortality Database between 2000 and 2017. Eur J Cancer 2022;171:269-79.
90. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. In: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). 2023. Accessed September 7, 2023. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
91. Tsai LL, Chu NQ, Blessing WA, et al. Lung Cancer in Women. Ann Thorac Surg 2022;114:1965-73.
92. Pinto JA, Vallejos CS, Raez LE, et al. Gender and outcomes in non-small cell lung cancer: an old prognostic variable comes back for targeted therapy and immunotherapy? ESMO Open 2018;3:e000344.
93. Huang Y, Cho HJ, Stranger BE, et al. Sex dimorphism in response to targeted therapy and immunotherapy in non-small cell lung cancer patients: a narrative review. Transl Lung Cancer Res 2022;11:920-34.
94. Isla D, Majem M, Viñolas N, et al. A consensus statement on the gender perspective in lung cancer. Clin Transl Oncol 2017;19:527-35.
95. Remon J, Pignataro D, Novello S, et al. Current treatment and future challenges in ROS1- and ALK-rearranged advanced non-small cell lung cancer. Cancer Treat Rev 2021;95:102178.
96. Conforti F, Pala L, Bagnardi V, et al. Sex-Based Heterogeneity in Response to Lung Cancer Immunotherapy: A Systematic Review and Meta-Analysis. J Natl Cancer Inst 2019;111:772-81.
97. Wang C, Qiao W, Jiang Y, et al. Effect of sex on the efficacy of patients receiving immune checkpoint inhibitors in advanced non-small cell lung cancer. Cancer Med 2019;8:4023-31.
98. Xue C, Zheng S, Dong H, et al. Association Between Efficacy of Immune Checkpoint Inhibitors and Sex: An Updated Meta-Analysis on 21 Trials and 12,675 Non-Small Cell Lung Cancer Patients. Front Oncol 2021;11:627016.
99. Liang J, Hong J, Tang X, et al. Sex difference in response to non-small cell lung cancer immunotherapy: an updated meta-analysis. Ann Med 2022;54:2606-16.
100. Madala S, Rasul R, Singla K, et al. Gender Differences and Their Effects on Survival Outcomes in Lung Cancer Patients Treated With PD-1/PD-L1 Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Clin Oncol (R Coll Radiol) 2022;34:799-809.
101. Takada K, Shimokawa M, Mizuki F, et al. Association between sex and outcomes in patients with non-small-cell lung cancer receiving combination chemoimmunotherapy as a first-line therapy: a systematic review and meta-analysis of randomized clinical trials. Eur J Med Res 2022;27:157.
102. Duma N, Abdel-Ghani A, Yadav S, et al. Sex Differences in Tolerability to Anti-Programmed Cell Death Protein 1 Therapy in Patients with Metastatic Melanoma and Non-Small Cell Lung Cancer: Are We All Equal? Oncologist 2019;24:e1148-55.

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