



# The role of gender in non-small cell lung cancer: a narrative review

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**Abstract:** The role of gender in the development, treatment and prognosis of thoracic malignancies has been underappreciated and understudied. While most research has been grounded in tobacco-related malignancies, the incidence of non-smoking related lung cancer is on the rise and disproportionately affecting women. Recent research studies have unveiled critical differences between men and women with regard to risk factors, timeliness of diagnosis, incongruent screening practices, molecular and genetic mechanisms, as well as response to treatment and survival. These studies also highlight the increasingly recognized need for targeted therapies that account for variations in the response and complications as a function of gender. Similarly, screening recommendations continue to evolve as the role of gender is starting to be elucidated. As women have been underrepresented in clinical trials until recently, the data regarding optimal care and outcomes is still lagging behind. Understanding the underlying similarities and differences between men and women is paramount to providing adequate care and prognostication to patients of either gender. This review provides an overview of the critical role that gender plays in the care of patients with non-small cell lung cancer and other thoracic malignancies, with an emphasis on the need for increased awareness and further research to continue elucidating these disparities.

**Keywords:** Gender; women; lung cancer; esophageal cancer

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## Introduction

### *Does gender matter?*

Over three decades ago, the National Institutes of Health (NIH) established the Office of Research on Women's Health, imposing stringent restrictions on the inclusion of women in research studies on the basis of presumed and unforeseen harm to women of child-bearing age. In 1993,

the NIH Revitalization Act required inclusion of women in their funded trials, but it was not until October 2014 that a formal policy was established requiring a balanced approach to gender analysis in research studies (1). As a result, knowledge regarding gender-differences in oncologic diseases is severely lagging. Numerous studies published since have analyzed the role of gender in development and prognosis for various cancers, however very little attention

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has been focused on thoracic malignancies. Non-small cell lung cancer (NSCLC) continues to be the most common thoracic malignancy and the leading cause of cancer-related deaths in both men and women in the United States and worldwide (2-4). Despite this, NSCLC is being increasingly recognized as a heterogeneous disease in which gender plays a critical, and much bigger, role than previously appreciated in pathogenesis, diagnosis and treatment. The complex interactions between biological factors, hormonal differences, environmental and occupational exposures, are just starting to be identified, and there is an increasing awareness of the importance of gender in thoracic malignancies. This manuscript provides a review on the role that gender plays in the diagnosis, treatment and outcomes of patients with thoracic malignancies, focusing on NSCLC. We present the following article in accordance with the Narrative Review Reporting Checklist (available at: <http://dx.doi.org/10.21037/jtd-20-3128>).

## Materials and methods

An extensive PubMed database research was performed looking specifically at the role of gender and thoracic malignancies. We used the following search terms and their combinations: “thoracic malignancy”, “lung cancer”, “NSCLC”, “esophageal cancer”, “mesothelioma”, “surgery”, “chemotherapy”, “radiotherapy”, “clinical trials”, “gender”, “women” and “sex”. Following the initial search, additional articles retrieved from cited references were included. Only original articles published after the year 2000 were included to provide a more contemporary review of recent knowledge. Conference abstracts, articles without full text or manuscripts not in English were excluded.

## Cancer risk

### *Smoking and non-small cell lung cancer*

The link between tobacco and NSCLC has been clearly established. As a result of cultural and geographical differences in smoking trends, women have been underrepresented in research studies. This has led not only to a paucity of available data for female patients, but, when included, it also overestimates the survival statistics in men who, when analyzed separately, have an overall worse prognosis (5). Women’s survival is higher than men’s, despite being more susceptible to the effects of tobacco (6-9). In the last few decades, the rate of smoking in women

has increased, an epidemic that has likely not yet reached its peak, particularly in developing countries (10). Although the impact of e-cigarettes is not yet fully characterized, studies show that there are gender-specific differences regarding reasons behind initiation and maintenance of smoking (7,11,12). Tobacco companies have also intensified targeted advertising, especially as more women are entering the workforce and becoming financially independent. They emphasize menthol cigarettes, which are associated with higher levels of cotinine (by-product of nicotine), which has been related to higher nicotine exposure and associated with more severe addiction (13). In a recent study utilizing the North American Association of Central Cancer Registries, among 30–50 year old non-Hispanic whites, the female-to-male incidence ratio of tobacco-related lung cancer has increased from 0.88 (95% CI: 0.84–0.92) in 1995–1999 to 1.17 (95% CI: 1.11–1.23) in 2010–2014 (14). This partially explains why the rates of smoking related lung cancer are not decreasing as steeply in women as they are in their male counterparts. The reasons behind smoking also appear to be influenced by gender; for example, fear of weight gain disincentivizes women from quitting, but is not considered as important to men (15). Following smoking cessation, the annual risk reduction is 8% for adenocarcinoma and 17% for squamous-cell carcinoma (16). Since women are more affected by adenocarcinoma, the overall lung cancer risk reduction following smoking cessation is not as pronounced in this group (14,17). However, tobacco use does not explain everything (18). Identifying gender differences beyond tobacco use can guide targeted social interventions, treatment and support programs.

### *Non-smoking risk factors for lung cancer*

Over the last couple of decades, the incidence of lung cancer among non-smokers has been steadily increasing and disproportionately affecting women more than men (14.4 to 20.8 per 100,000 person-years compared to 4.8 to 13.7 per 100,000 person-years respectively) (19). As more female patients are included in research studies, several other important differences between genders have been unveiled among non-smokers (20). For example, hazardous exposures in the environment and workplace can vary by gender. Occupational exposures such as construction-related asbestos significantly increase the risk of mesothelioma and lung cancer in men (21). Industrial pollution, radon gas in mines, and arsenic have synergistic effects with smoking and historically increased risk of lung cancer mostly in men (15).

As these identifiable exposures decreased over the years, the decline in lung cancer in men has been steeper than in women.

Environmental exposures specifically impacting women have been less well-studied. For example, secondary exposures to chemicals present in men's clothing could account for some of the risk. High-temperature cooking (e.g., wok), aerosolization of carcinogens or volatile oils have also been implicated in the development of lung cancer among non-smoking Chinese women (22). The role that hormone replacement therapy plays in NSCLC development and progression remains controversial; a recent secondary analysis of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial found that estrogen is associated with a reduced incidence of NSCLC particularly in female smokers (4). Although outdoor pollution is not expected to differentially affect men *vs.* women, no one has investigated this topic. Another area that has not been investigated is the role of talc, mica, silica and other nanoparticles present in powder that are aerosolized and inhaled primarily by women who use cosmetics. The exposure to residential radon, which is known to be associated with the development of NSCLC, varies based upon the location of one's home and socioeconomic status; since traditionally women have been more likely to be home-makers, their exposure is presumably increased, yet no studies have investigated gender differences (23,24).

### *Gender differences in prognosis of lung cancer*

While female gender imparts a significant and independent risk for the development of most types of lung cancer (20), numerous studies have shown that men actually have lower overall survival and disease-free survival regardless of histology, stage or treatment (25-29). These findings have been consistent for lung cancer as well as malignant pleural mesothelioma. A meta-analysis of pooled hazard ratios of 86,800 patients revealed higher survival for women with non-small-cell lung cancer (NSCLC) in both univariate and multivariate analyses (HR 0.78,  $P < 0.0001$ ) (25), and multiple other reports show female gender to be a predictor of improved survival in multivariate analyses of patients with lung adenocarcinoma (30).

### *Other thoracic malignancies*

Although not the focus of this narrative, gender has also been implicated in other thoracic malignancies.

For example, while the incidence of malignant pleural mesothelioma is lower in women, survival is significantly higher, particularly for young women (21,31). Esophageal cancer remains a male-dominant disease and less is known about the role of gender influences on its clinical course (32). Men are six to eight times more likely to develop adenocarcinoma of the esophagus, and slightly more likely to develop squamous cell carcinoma, compared to women (33). Reflux esophagitis is a predisposing risk factor for esophageal cancer, and there appears to be a strong and dose-dependent association with body mass index in women, but not in men; however, it is not clear if this necessarily translates to a higher risk of cancer (34,35). Moreover, gender has been shown in some studies to be an independent prognostic factor in esophageal cancer. Specifically, women have a higher 5- and 10-year survival as well as metastasis-free survival, which is partially attributed to diagnosis at an earlier stage compared to men (36-38). Indeed, esophageal adenocarcinoma is one of the main cancers contributing to the increasing rate of death among men in the United States (39). Overall, the literature regarding thoracic malignancies other than lung cancer is somewhat limited at the time of this review. This is not to say that gender does not play a role, but rather that it has not yet been specifically investigated as a primary predictor of cancer incidence.

## **Screening and diagnosis**

### *Lung cancer*

Although the medical community has become more cognizant of gender differences in thoracic malignancies, the general public's awareness is lagging behind. A population survey of over 2,026 adults in the U.S. revealed that only 6% of responders knew that lung cancer is the primary cause of cancer death in women. Screening for breast and colon cancer have been widely publicized in the media, but lung cancer screening has not yet reached such proportions. Following the 2011 National Lung Cancer Screening Trial (NLST) and the 2018 Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trials, the U.S. Preventive Services Task Force (USPSTF) now recommends annual screening for lung cancer with low-dose chest CT (LDCT) for adults ages 55–80 years with a 30 pack-year smoking history who are current smokers or quit within the past 15 years (40-42). This was just updated in 2020, expanding to 50–80 years of age with 20 pack-year smoking

history (43). The newest version of USPSTF guidelines (pending publication at the time of this manuscript) have lowered the age and smoking exposure requirements to meet screening criteria (44). The change is expected to double the number of eligible individuals, and will hopefully benefit all of those potentially at risk, particularly the younger females with less smoking exposure.

Despite being large, these above studies focus on high-risk populations, whereas non-smokers and women are considered low risk. There are currently no established recommendations for screening non-smoking women despite the disproportionately high incidence of lung cancer among female never-smokers, because it is difficult to justify the added screening effort in the absence of strong data that better define the predisposing risk factors in this population.

Even among patients identified as high risk, it has been a challenge to broadly implement screening. A study analyzing national database registries from 2016 found that only 1.9% of 7.6 million eligible smokers were screened (45). Although smoking intensity is a part of lung cancer screening guidelines, eligibility for screening does not take in to account sex-based differences in lung cancer risk; women tend to start smoking at an older age and smoke less intensively than men (46). Given that in the last decade the rate of diagnosis of lung cancer in non-smokers has doubled (47), and that non-smoking women are disproportionately affected, the current guidelines are already outdated. Furthermore, they do not account for non-tobacco related exposures (aerosolized cooking oils, prior malignancy, emphysema and recurrent pneumonia, second hand smoke), some of which disproportionately affect women more than men (18). Family history of lung cancer is also strongly associated with adenocarcinoma, early age of onset, and female gender, however is not included in the screening guidelines (48). A study based in a NSCLC endemic area of Taiwan looking at 1,075 Asian patients, found that family history of lung cancer and female gender were the two most important predictors of lung cancer (OR 11.2 and OR 2.8 respectively) (49). Overall, there has been a decline in the proportion of patients who meet USPSTF criteria, from 56.8% in 1984–1990 to 43.3% in 2005–2011 ( $P<0.001$ ) (50). Notably, the decline is much more pronounced in women (52.3% to 36.6%,  $P<0.05$ ) compared to men (60.0% to 49.7%,  $P=0.03$ ).

To answer the question of whether never-smoker women benefit from LDCT, a 2018 Korean retrospective study of 4,365 subjects aged 40–79 found that after 9.7-year follow-up 22 (0.5%) of women had lung cancer. Out of these new

diagnoses, 73% were Lung Imaging Reporting and Data System (Lung-RADS) category 4. The authors argued that the risk of lung cancer in never-smoking women was sufficiently low that repeat annual LDCT screening is not necessary for at least 5 years if the initial screen was Lung-RADS 1–3 (51). Similarly, a group from Taiwan applied the NLST criteria to a population 1,763 subjects ages 40–80, 1,029 men and 734 women. Low-dose CT was indicated in 8.4% of these patients using the NLST guidelines, but only one patient would have been diagnosed with lung cancer using these criteria. Among the 1,615 patients who did not meet criteria for screening, the detection rate of lung cancer was 2.6% in women and 0.56% in men. These data illustrate that the National Lung Cancer Screening criteria might not apply to women in the same way as they do to men. A study analyzing CT screening of lung cancer in North America found the prevalence of lung cancer to be significantly higher in women compared to men of similar age and smoking history (odds ratio 1.9, 95% CI: 1.5–2.5) (9). Given that women have higher survival rates compared to men, it raises the question of whether the tumors detected through screening or diagnostic imaging are more indolent in females. Presently, there are more young women than young men diagnosed with lung cancer, particularly among 30–49 years old, a group that, irrespective of smoking status, does not typically meet screening criteria (14). The mean preclinical sojourn (i.e., the preclinical duration in the absence of screening of each stage of cancer) is higher for women (3.35–6 years) than for men (3.09–5.32 years), and most pronounced in adenocarcinoma (52). This study suggests a greater window of opportunity for screening, particularly among patients with adenocarcinoma and women.

In the absence of screening, another potential contributor to delay in diagnosis is lower levels of help-seeking behavior for early symptoms of lung cancer (e.g., cough, hoarseness) among smokers, which differ between the sexes (53). Gender differences have also been observed with respect to referral to care; a study in malignant pleural effusions (including, but not limited, to lung cancer) suggested that women have a lower referral rate for definitive care (54). To minimize delays in diagnosis, screening efforts must be accompanied by efforts to educate the public about early diagnosis methods. In order to direct these tools appropriately, current epidemiologic trends must be studied in conjunction with predictive models for future changes to the population at risk in order to mount a timely response to shifts in incidence and prevalence of lung cancer. This,

in turn, requires a deeper understanding of the cultural and social norms associated with initiation of smoking and other exposures, as well as the stigma associated with a new diagnosis, all of which have been shown in the literature to differ among men and women (15).

### *Other thoracic malignancies*

Early detection of esophageal cancer is associated with improved outcomes. Women tend to be younger at presentation, diagnosed at an earlier stage, possibly due to lower frequencies of cigarette smoking and alcohol consumption compared to men (38). Although screening methods for esophageal cancer exist, they have not demonstrated feasibility or cost effectiveness in prospective studies due to relatively low incidence of this disease (36–39). The lack of a known hereditary link also makes population-wide screening techniques less practical for patients with family history of esophageal cancer. There are well established screening guidelines for esophageal cancer in patients with Barrett's esophagus and/or symptoms of gastroesophageal reflux disease (GERD). However, the adherence to these guidelines is variable, and similar to lung cancer, worse for women compared to men patients (55).

## **Medical therapy**

### *Lung cancer*

One of the critical discoveries in the treatment of lung cancer in the last decade has been the identification of gender-differences in tumor biology and response to therapy. Gender-specific pharmacology, particularly with regard to the role of estrogen receptors, is expected to be part of future chemotherapy regimens for thoracic malignancies. The treatment modalities are anecdotally different between genders. For example, one study of over 200,000 patients using the SEER database from 1975–1999 suggests that men were more likely to receive radiotherapy as a first line treatment, while women more likely to undergo surgery, although this difference alone does not explain the higher survival in women (56). These differences, however, may be attributable to treatment practices that are outdated. Multiple molecular and genetic differences have been identified between men and women and implicated in both susceptibility to lung cancer and treatment response (57). For example, activating mutations in the tyrosine kinase domain of EGFR are more common in

in women compared to men (20% *vs.* 9%, respectively). Furthermore, EGFR mutations are more common in Asian women and non-smokers (63% of cases in Asian female non-smokers) (58,59). Early studies on Tyrosine kinase inhibitors such as gefitinib and erlotinib, which prevent activation of EGFR, lead to a survival benefit only among women, non-smokers, patients with adenocarcinoma, and Japanese patients (57). More recently, in a double blinded phase 3 trial, the use of Osimertinib in patients with EGFR-positive Stage IIA–Stage IIIB non-small cell lung cancer had a significantly improved disease free survival (60). Another example is the improved clinical response in men with the addition of bevacizumab to carboplatin/paclitaxel therapy (ECOG E4599 study,  $P < 0.0001$ ). The lack of benefit in women may be explained by potential interactions of EGFR inhibitors with bevacizumab (57). The first clinical study to evaluate gender differences in tumor biology is the PIONEER randomized controlled trial in women with advanced NSCLC and ECOG performance status 2 (61). Paclitaxel poliglumex (PPX) as a single agent or in combination with carboplatin was been evaluated in phase II trials and showed no benefit in men, but increased survival in women. The proposed mechanism for this difference is the modulation of efficacy through estrogen receptors. The ongoing phase III trial is investigating the use of PPX as a single agent against paclitaxel in women only.

Beyond differences in response to therapy, gender also plays a role in the incidence of side effects, delays in treatment and doses of chemotherapy. Several trials have noted increased side effects as nausea, vomiting, alopecia, neurosensory toxicity, severe hypertension, constipation, abdominal pain in women compared to men (30). All of this suggests a need for gender-specific pharmacologic treatments. Finally, there are no studies investigating fertility problems in women who develop thoracic malignancies at a young age. As lung cancer is increasingly being diagnosed in younger patients, there are no data available to inform decisions regarding treatment options and fertility.

Radiation therapy has also been associated with differential outcomes based on gender, although the data is more limited than for other treatment modalities. In particular, a prospective study of stereotactic body radiotherapy (SBRT) in NSCLC concluded that women had improved survival than men (80.3% *vs.* 51.3% at 3 years,  $P = 0.008$ ), although the authors could not elucidate if this was due to gender alone or the fact that adenocarcinoma

was more prevalent in women who already have an improved survival compared to their male counterparts (62). In a different study, gender has been identified as an independent predictor of survival in patients treated with SBRT for early stage NSCLC, suggesting that indeed gender may influence outcomes regardless of histology (63).

### *Other thoracic malignancies*

A recent review of clinical trials in esophageal cancer revealed a remarkable lost opportunity for inquiry as 23 out of 30 the studies included did not analyze female and male patients separately; despite this, gender differences in response to chemotherapy and radiation were apparent (64). The study quantifies the tremendous paucity of data regarding sex-specific therapies for esophageal cancer. One such study that did investigate gender differences found that, sex has been shown to be an independent prognostic factor in large cohort study investigating esophageal squamous cell carcinoma who underwent definitive radiotherapy; women had a better survival compared to men, yet the underlying etiology for this remains unknown (65).

## **Surgical care**

### *Lung cancer*

Surgical resection is generally considered the standard of care for the majority of early-stage NSCLC, and used in combination with chemotherapy, radiation, molecularly targeted therapy, and immunotherapy for more advanced disease. Despite this, it has been repeatedly reported that women undergo appropriate surgical intervention for NSCLC at lower rates compared to men (66,67). In a study utilizing the Surveillance, Epidemiology, and End Results Program data, women were found to be 25% less likely to receive timely lung resection as compared to men (68). Women are also more likely to undergo a more limited surgical resection compared to men (69,70). There is certainly a role for limited sublobar resection for stage I NSCLC and for patients with significant comorbidities or limited pulmonary function which make them medically unfit for lobectomy. However, the fact that there is a difference in the type of surgical resection as a function of gender is alarming. Furthermore, women with advanced disease (Stage III/IV) have been shown to have a lower a likelihood to receive referrals to cancer care

(including thoracic Women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall post-operative survival in women, surgeons) compared to their male counterparts (71).

The differences in the likelihood of the recommendation of surgical resection to surgical candidates based on gender has been shown to be at least partly related to physician bias (67). In a survey of over 100 cardiothoracic trainees and attending surgeons, estimation of complication risk was independently associated with the gender of the physician and the patient, thereby influencing the likelihood of recommending an operation for reasons unrelated to age, indication, and/or comorbidities of the patient (67). The dearth of research in gender-differences in surgery for thoracic malignancies represents an unmet need (72).

Of the women who do undergo surgical resection for lung cancer, only a handful of studies have investigated differences in perioperative and postoperative outcomes between men and women. An STS General Thoracic Database study demonstrated that women had lower in-hospital and 30-day mortality (O.R. 0.56, 95% CI: 0.44–0.71;  $P < 0.001$ ) (70). Women had significantly lower rates of postoperative cardiovascular and pulmonary complications and overall post-operative survival in women, however it is important to note that men did have a higher pathological stage (70). Others have shown that women had shorter lengths of stay post-operatively (73). The specific reasons for these differences have not been studied, but hormonal, inflammatory, and additional immunologic factors, and societal influences may play a role.

Female gender has been associated with increased pain and narcotic use after various procedures, however less clearly for lung cancer operations. In a study investigating 1,164 patients (601 of which were female), no difference was seen in perioperative pain levels between men and women who underwent minimally invasive surgery (74). A smaller study investigating 157 patients who underwent resection via a major thoracotomy (62 of which were female) reported that women had significantly greater pain in the perioperative setting as well as following discharge (75). With these mixed findings, additional research is needed to identify if different approaches to postoperative pain management for men compared to women is warranted.

There have also been mixed findings for data regarding the risk for postoperative readmissions for women versus men. A single institution study found that women had significantly more unplanned readmissions within 30 days

of discharge after having lung cancer resection (67% vs. 36%,  $P=0.038$ ), despite having a similar amount of ED admissions within the first 30 days of discharge (12% vs. 10%,  $P=0.531$ ), indicating there are differences not only in treatment planning, but also in the short-term postoperative period (76). This may in part be due to the fact that women and men have different postoperative symptom experiences (76-78). However, other large database studies have demonstrated men were more likely to be readmitted than women after being discharged from the index operation (4.9% versus 3.8%,  $P<0.001$ ) (79). Although the data is unclear as to which gender is more likely to be readmitted, efforts to optimize readiness for discharge, provide education about expectations post-discharge, resources for questions and concerns, can help prevent unplanned readmissions following thoracic oncological resections for both genders.

### Clinical trials and health research

Prospective clinical trials are the standard for evaluating clinical interventions and advancing medicine. It has been reported that the majority (84%) of participants in NCI-sponsored surgical oncology trials are women (80). However, this statistic is a gross overestimate as a result of the enormous number of women included in surgical oncology studies for breast cancer such as the NSABP B-32, ACOSOG Z10, and Z11 trials. In stark contrast, women are significantly underrepresented in lung cancer trials (80).

Substantial knowledge gaps remain because of a continued lack of inclusion of women especially those who are in childbearing age or pregnant despite recent research policy changes expanding inclusion criteria. Given the known molecular, hormonal, and immunologic differences between men and women, which may lead to different response to specific pharmacological agents, gender must be evaluated further in clinical trials. Examples include differential effect of EGFR-specific tyrosine kinase inhibitors favoring women and in anti-PD1 checkpoint inhibitors, favoring men (26).

Several recent studies have focused specifically on women and gender differences in lung and esophageal cancer (26,81). Another evaluated 354 female patients with mesothelioma to identify female specific disease trends (82). There is a great need for similar studies for all thoracic malignancies to drive hypothesis development for important prospective clinical trials.

### Summary

Gender plays a critical role in thoracic malignancies, not only in terms of risk factors, but also for diagnosis, treatment and outcomes. As oncologic care is advancing toward individualized approaches to patient care and personalized pharmacotherapy, the need for further research is more urgent than ever given the unexplained and increasing incidence of cancer in non-smokers and women. Furthermore, as gender-based differences are slowly starting to be elucidated, there is a dire need for advocacy and increased awareness for screening and early detection of thoracic malignancies, which are continuing to be the primary cause of death from cancer in both men and women.

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