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The evolving landscape of sex-based differences in lung cancer: a distinct disease in women

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Shareable abstract (@ERSpublications)
Sex-based differences in lung cancer span the care continuum. This suggests lung cancer may increasingly be viewed as a distinct disease in women, with implications for screening and treatment. Lung cancer research should capture these sex-based differences. https://bit.ly/2WfhaB4

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Abstract

In stark contrast to a few decades ago when lung cancer was predominantly a disease of men who smoke, incidence rates of lung cancer in women are now comparable to or higher than those in men and are rising alarmingly in many parts of the world. Women face a unique set of risk factors for lung cancer compared to men. These include exogenous exposures including radon, prior radiation, and fumes from indoor cooking materials such as coal, in addition to endogenous exposures such as oestrogen and distinct genetic polymorphisms. Current screening guidelines only address tobacco use and likely underrepresent lung cancer risk in women. Women were also not well represented in some of the landmark prospective studies that led to the development of current screening guidelines. Women diagnosed with lung cancer have a clear mortality benefit compared to men even when other clinical and demographic characteristics are accounted for. However, there may be sex-based differences in outcomes and side effects of systemic therapy, particularly with chemotherapy and immunotherapy. Ongoing research is needed to better investigate these differences to address the rapidly changing demographics of lung cancer worldwide.

Introduction

The demographic makeup of lung cancer has dramatically shifted over the last few decades. Compared to men, women are more likely to be diagnosed at a younger age and with adenocarcinoma, have a family history of cancer, and lack a smoking history [1, 2]. The pathogenesis of lung cancer in the never-smoker population is not currently well understood. A number of potential exogenous and endogenous risk factors have been proposed. Some risk factors are endogenous and may vary according to biological sex, such as differences in genetic polymorphisms. Other risk factors differ based on gender, such as differences in exogenous exposures including indoor cooking fumes, secondhand smoke and hormone replacement therapy (HRT) [3–5]. Current screening guidelines only capture smoking history and therefore may underestimate risk in women, particularly in underrepresented minorities [3, 6, 7]. While overall lung cancer outcomes are more favourable in women compared to men even when adjusted for age, smoking status and stage, the global rise in incidence of lung cancer in women is alarming and threatens to upend these patterns in the coming decades [8]. This narrative review will examine the evidence regarding sex-based differences in the epidemiology, pathogenesis and outcomes in women compared to men diagnosed with lung cancer. A summary of these differences is displayed in figure 1.

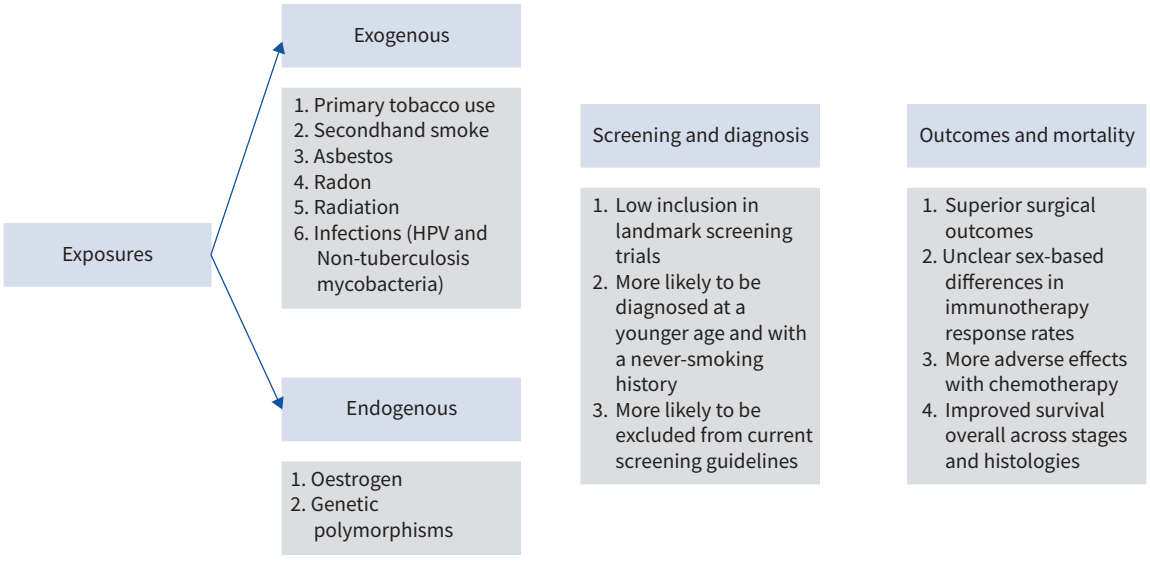

FIGURE 1 Summary of the unique exogenous and endogenous risk factors, screening considerations and outcome differences women with lung cancer face in comparison to men. HPV: human papillomavirus.

Risk factors and epidemiology

Smoking patterns: a delayed rise and an unequal fall

While there has been a notable rise in the incidence of lung cancer in never-smokers, the predominant risk factor for the development of lung cancer worldwide remains tobacco use. Cigarette smoking contributes to about 80% of annual lung cancer deaths in the United States and the majority of men and women diagnosed with lung cancer globally have a history of tobacco use [1]. In many parts of the world, tobacco use has declined as a result of expansive public health campaigns and awareness regarding the link of tobacco to lung cancer. In the US, in tandem with declining smoking rates, incidence of lung cancer has declined from 70.6 to 55.2 cases per 100 000 people over the last two decades [9]. However, the rate of decline for both smoking rates and lung cancer incidence occurred later and has been slower for women compared to men [10]. In the European Union, smoking rates are declining in both sexes [11], but again the pace has been slower for women. In contrast, in many developing nations, smoking rates remain alarmingly high, leading to rising rates of lung cancer incidence, particularly in women [12]. Continued widespread public health awareness campaigns, such as targeted messaging for women, are essential to help curb the rise of tobacco use [3].

Among smokers, men may have a slightly higher increased risk of developing lung cancer than women [12, 13], although it is unclear if the pathogenesis of lung cancer in women who smoke compared to men who smoke is a distinct process. A number of studies have evaluated whether women may be more susceptible to the carcinogens in tobacco smoke. Specifically, prospective cohort studies and multiple meta-analyses have concluded that women do not appear more susceptible than men when adjusting for tobacco exposure [3, 4]. Prescott *et al.* [14] evaluated the risk of lung cancer associated with smoking status and quantification of tobacco use and found that lung cancer incidence rates were higher in men compared to women in those who had ever smoked. Bain *et al.* [15] evaluated patients with a new diagnosis of lung cancer and found no differences between men and women regarding rates of lung cancer incidence once adjusted for smoking patterns. In contrast, however, some studies have shown that there may be some sex-based genomic differences in patients who smoke and develop lung cancer. For example, among women with lung cancer, those with a history of tobacco use have been found to more frequently harbour a tp53 point mutation when compared to those who have never smoked, and this finding does not appear to be consistent in men [2, 16]. Mutations in the glutathione s-transferase Mu 1 gene are also more common in women and have been linked to the development of lung cancer in smokers [17]. Limitations to these studies, however, include uncertain characterisation of tobacco exposure, as certain elements such as depth of inhalation and tar content of cigarettes are not readily or easily measured [15].

Exogenous exposures

Secondhand smoke

Secondhand smoke may be the third most common known risk factor for the development of lung cancer after primary tobacco use and radon. Current studies evaluating this link in women are mixed. One pooled

analysis of 37 studies that aimed to evaluate the impact of secondhand smoke on lung cancer found that women whose spouses smoked had a 24% increased risk of developing lung cancer [18]. A secondary cohort analyses analysed data collected from the UK Million Women Study and evaluated the link between various risk factors and the development of lung cancer among women. The analysis did not identify secondhand smoke as a significant risk factor in lung cancer development among women who had never smoked; however, extent and duration of exposure was not characterised [5]. Quantifying exposure to secondhand smoke at a population level is even more challenging than quantifying tobacco use; thus, major conclusions are difficult to draw even in well-designed prospective or retrospective cohort analyses.

Radon

The Environmental Protection Agency estimates that radon is the second most common known exposure to cause lung cancer after tobacco, and considered to be the number one cause among non-smokers. Radon is a known radioactive compound present in natural soil, rock and water [19]. Occupational exposures to radon through mining have been associated with the development of lung cancer in prospective cohort studies. Extrapolation of this data to the residential setting is now well described in a number of case-control studies. One such study conducted in the state of New Jersey in the 1980s specifically evaluated the association between radon exposure and development of lung cancer in women. While the study did not demonstrate a significant difference in lung cancer development between women with a radon exposure and women without an exposure, it did reveal a trend of increasing risk of lung cancer with increasing exposure levels [20]. A pooled analysis incorporating seven case-control studies similarly demonstrated that there was a linear trend in the odds of developing lung cancer with higher radon exposure in the residential setting [21].

Asbestos

Asbestos is a common occupational and environmental hazard and is a known carcinogen. It has a well-known and nearly universal association with the development of mesothelioma, but is also commonly associated with the development of lung cancer. Asbestos was widely used in building, textiles and insulation materials until the late 1900s, and exposures have been described both in occupational and non-occupational settings, with often a long latency period (30 years or more) between exposure and development of cancer [22]. While the occupational risk of lung cancer from asbestos has been described with higher frequency in men, one meta-analysis found that women were at slightly higher risk compared to men of developing lung cancer from a non-occupational exposure to asbestos [23]. There is a paucity of cohort studies evaluating the risk of non-occupational asbestos exposure with the development of lung cancer; thus the severity of this risk, particularly in women, may be underrepresented currently.

Radiation

Prior radiation exposure is a well-described iatrogenic risk factor for the development of second primary lung cancer. Hodgkin's lymphoma and breast cancer have both been associated with the development of second primary lung cancer in patients who underwent radiation therapy [24–26]. Breast cancer in particular is also experiencing a demographic shift with rising incidence rates in younger patients, with increasing concern regarding the long-term side effects of early radiation exposure.

Coal

Indoor cooking fumes are another possible risk factor based on gender roles, where it is predominantly women who are exposed as compared to men. One study in Asia demonstrated that women who cook with coal have five times increased odds of developing lung cancer compared to women who do not [27]. Aside from coal, indoor cooking oils lead to the formation of polycyclic aromatic hydrocarbons (PAHs), which are known carcinogens. Women in developing areas of the world, particularly where indoor ventilation may be minimal, may be at risk for cumulative exposure to PAHs [3, 17, 28].

Infection

Likely risk factors for the pathogenesis of lung cancer may also include infections. The two most common infections studied are human papillomavirus (HPV) and mycobacterial infections (both tuberculosis and non-tuberculosis mycobacterium) [28–30]. These infections, which are more common on the Asian subcontinent, are potentially modifiable risk factors. One study in Taiwan demonstrated that among non-smokers, women were more likely to have HPV-positive lung cancer than men, and more likely to have adenocarcinoma compared to women who were not HPV-positive [31]. There are three additional published case studies specifically evaluating the impact of HPV 16/18 infection on lung cancer in never-smoking women, all of which have demonstrated that women with a history of HPV have increased odds for lung cancer development [32].

Tuberculosis (TB) has also been proposed as an independent risk factor for lung cancer development. Patients with a history of TB had a 1.7-fold increased relative risk of developing lung cancer compared to patients without TB history in one meta-analysis, although it is not clear that this risk is higher in women [33]. This relationship has also been demonstrated in non-tuberculosis mycobacteria, which has been shown to have some prevalence among patients diagnosed with lung cancer, particularly among women [34]. There are no large prospective studies that have replicated these findings, but the risk of chronic scarring to the lung from underlying granulomatous disease may be an important and potentially modifiable risk factor for lung cancer, particularly in the developing world [29].

Endogenous exposures

Genetic mutations

There are some well-described genetic variations between the two sexes in the non-smoking population. Polymorphisms in the cytochrome P450, family 1, subfamily A, polypeptide 1 gene which lead to defects in DNA repair, overexpression of X-linked gastrin releasing peptide receptor and mutations in p53 have all been associated with increased pathogenesis of lung cancer in women. Women are also at increased risk compared to men of developing lung cancer with a driver mutation, particularly epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and Kirsten rat sarcoma mutations (KRAS) [3, 16, 17, 29]. Family history of lung cancer has clearly been demonstrated to be a significant risk factor in the development of lung cancer, but it is unclear if that effect is more pronounced in women [5, 35].

Oestrogen

The impact of oestrogen on lung cancer has been a topic of ongoing study. One retrospective study utilising the Surveillance, Epidemiology, and End Results data demonstrated that premenopausal women diagnosed with lung cancer tended to present with more extensive disease and were more likely to develop adenocarcinoma compared to postmenopausal women [36]. The oestrogen receptor is known to be overexpressed in many lung cancers, but there is no clear consensus on the impact of oestrogen and hormone replacement therapy on the development of lung cancer in women [5, 17, 28]. Greiser *et al.* [37] analysed the associations between ever-use of hormonal therapy and risk of lung cancer in a meta-analysis; ever-use was associated with a 27% decrease in lung cancer risk irrespective of smoking history. However, in a subgroup analysis of patients who developed adenocarcinoma, there was an increased association with ever-use of HRT. Larger, prospective studies on the role of both endogenous and exogenous oestrogen are needed to help more definitively characterise the link between hormones and lung cancer development.

Screening and diagnosis

Many randomised controlled trials evaluated the impact of screening for lung cancer with low-density computed tomography (LDCT) on mortality. The largest prospective study was the National Lung Screening Study (NLST) conducted in the United States with 55 000 participants. Women comprised 40% of those enrolled on the trial. The results of the NLST led to the publication of the United States Preventative Services Task Force (USPSTF) category B recommendation in 2013 that all men and women between the ages of 55–80 with at least a 30 pack-year smoking history undergo annual screening for lung cancer with a low-dose computed tomography (CT) scan [38]. The second largest trial that evaluated the impact of LDCT on outcomes was the NELSON study, which also enrolled patients with a significant smoking history and was conducted in the Netherlands and Belgium [39]. Women comprised only 16% of trial enrollees and were not included in the main outcome analysis. Canada and the European Union have adopted similar guidelines based on the NLST and NELSON data and their own smaller randomised controlled trials that effectively mirror the NLST study in enrolling high-risk patients with a significant smoking history. Even in Asia, where there is a higher percentage of never-smokers who develop lung cancer, there are a few expert consensus guidelines that largely mirror the recommendations borne out of the NLST and apply only to patients with a significant smoking history [40]. There are no worldwide consensus guidelines on lung cancer screening, nor are there any nationally sponsored programmes to promote lung cancer screening. Of note, no current guidelines incorporate additional risk factors for lung cancer besides smoking history, and there are no sex-specific differences in guidelines to date.

Between 2010 and 2015, the National Cancer Institute reported that only 5.9% of all patients eligible per the USPSTF guidelines underwent an LDCT [41], although there is wide variation by state [42, 43]. Women were slightly more likely to undergo screening than men (6.3 *versus* 5.6%), but on the contrary, women eligible for lung cancer screening are also less likely to discuss LDCT with their providers [44], despite consistently being more likely to confer a mortality benefit from these screening modalities. In the German LUSI trial, which enrolled 4052 participants, women who underwent screening with an LDCT had a statistically significant reduction in mortality (hazard ratio (HR) 0.31, p=0.04), whereas men did not (HR 0.94, p=0.81) [45]. A similar effect was demonstrated in a subgroup analysis of the NLST, where

women screened by CT had lower lung cancer related risk of mortality (HR 0.73) compared to men (HR 0.92, p=0.08) [38]. In the NELSON trial, women who underwent interval LDCT screening had a non-statistically significant reduction in lung cancer related mortality at 10 years (HR 0.67), whereas there were no differences in lung cancer related mortality among men who underwent regular CT screening (HR 1.01), although the trial was not powered to detect differences in mortality [39]. The radiographic features and operability of identified nodules may vary between men and women. In a retrospective analysis of the NLST data, women with ground glass nodules had a higher risk of developing lung cancer compared to men [46]. Given that women are more likely to be diagnosed with adenocarcinoma, which is typically slow growing, it is possible that an optimal screening interval in women may be more frequently than annually, although there is currently insufficient evidence to support this.

The lack of guidelines and risk assessments for light or never smokers predisposes women with lung cancer in particular to be missed with current screening recommendations. Between 50 and 80% of women diagnosed with lung cancer have been demonstrated to not meet the screening criteria outlined by the USPSTF and other national agencies, a consistent metric worldwide given the high rates of light or never smokers in women diagnosed with lung cancer [7, 47, 48]. In addition, on average, women are diagnosed at younger ages than men, and the incidence of lung cancer in younger patients across sexes is rising [1, 2]. As current guidelines do not adequately identify particular high-risk groups, specifically women and under-represented minorities, the USPSTF published modified guidelines in 2021, liberalising the pack year history to 20 and the lower age limit to 50 years [6]. While the percentage of both men and women eligible for screening will increase with expanded eligibility criteria [49], a rising proportion of the population will continue to be excluded from the screening criteria given the rapidly and constantly changing demographics and epidemiology of lung cancer worldwide. In particular, young women who are still of childbearing age are at increasing risk of being left out of screening guidelines; however, reassuringly, the development of lung cancer during pregnancy is quite rare [50].

Younger patients who are screened for lung cancer could stand to benefit from years of additional life with earlier detection and cure [6]. However, in this population in particular, cumulative radiation exposure also contributes to a lifetime risk of developing lung cancer. One study estimated that this risk in women after three LDCTs amounts to about 1.5 cases of lung cancer alone per 1000 exposed [51]. In addition to the risk of ongoing radiation exposure, the benefits of lung cancer screening must be weighed against the risks of detecting a false positive, which can lead to unnecessary invasive interventions, psychological stress and an increased cost burden to the system.

Outcomes

Lung cancer has now surpassed breast cancer as the number one cancer-related cause of death worldwide in both women and men [11, 35]. In the United States, although mortality from lung cancer has declined steadily over the last two decades due to earlier detection and significant treatment advances such as targeted agents and immunotherapy [3], the mortality of lung cancer in women has still increased five-fold overall since 1950 [52] and is declining at a slower rate than it is in men [29]. In some areas of the world, such as Brazil, mortality from lung cancer is still on the rise in women whereas it is declining in men [11]. Despite these variations in mortality trends, women have been shown consistently over time to have overall improved survival rates compared to men when tobacco exposure, stage at diagnosis, age and treatment modality are accounted for [12, 17, 53–58].

Early stage

Women are likely to be diagnosed with lung cancer at an earlier stage than men [8, 59]. Sex-based differences in outcomes of surgical resection have also been widely reported. Tong *et al.* [54] demonstrated that in a large national database of thoracic surgery patients who underwent surgical resection for lung cancer between 2002 and 2010, women had a lower 30-day mortality (1.5 *versus* 3.0%, p<0.001) and a statistically significantly lower rate of nearly all recorded post-operative complications; however, the women were younger and generally had superior baseline health compared to their male counterparts. In a retrospective study in Finland, women who had a resection for early-stage lung cancer experienced superior survival rates at 5, 10 and 14 years compared to men, in addition to lower morbidity, 30-day mortality and complications rates [60]. Similar results were shown in a retrospective study in Norway, where male sex was a risk factor that conferred a 27% increase in overall mortality following surgical resection for early-stage lung cancer [61].

Stereotactic body radiation therapy (SBRT) is another potentially curative option for early-stage lung cancer that is deemed to not be operable either because of the anatomic location of the tumour or, more commonly, because the patient's underlying comorbidities confer an excessive risk of morbidity and

mortality with surgery. While not extensively studied, there appear to be no major differences in receipt of SBRT *versus* surgery between men and women with early-stage non-small cell lung cancer (NSCLC) [62, 63]. Sex-specific survival data for patients receiving definitive SBRT with curative intent is limited. The largest retrospective study evaluated outcomes in patients over the age of 70 undergoing SBRT for early-stage lung cancer compared to patients who were observed without treatment. Men treated with SBRT did not have an improved survival benefit compared to those who underwent observation, but women treated with SBRT did have slightly improved survival rates compared to women who underwent observation [64].

Advanced stage

Similarly, women with advanced stage cancer have improved survival rates compared to men. This survival benefit persists when histology, stage at diagnosis, smoking history and age are taken into account [8, 55]. Wheatley-Price *et al.* [65] conducted a pooled analysis in 2010 of five randomised trials of platinum-based chemotherapy in advanced NSCLC and found that women had a higher response rate (42% *versus* 40%) and a longer overall survival (OS) (9.6 *versus* 8.6 months). More recently, there has been interested in identifying sex-based differences in response rates to immunotherapy in NSCLC, and results of such studies have been mixed. In one pooled analysis of five of the landmark immunotherapy trials in NSCLC, monotherapy with anti-PD1 inhibitors significantly improved progression-free survival (PFS) when compared with chemotherapy in men enrolled on the trials, but there was no PFS difference between the two groups found in women [66]. However, in another pooled analysis of eight trials in NSCLC evaluating the impact of chemotherapy plus immunotherapy *versus* chemotherapy alone, women had a slight survival advantage when receiving combined chemotherapy and immunotherapy compared to men [67]. There are also sex-based differences in the development of side effects of systemic therapy. Women have been demonstrated to be more likely to experience side effects from chemotherapy, and there are evolving data to suggest that women receiving immunotherapy may be at higher risk of immune-related adverse events [68, 69]. Duma *et al.* [70] found in a retrospective study of patients diagnosed with NSCLC and melanoma that women were more likely to develop immune-related adverse events compared to men and, interestingly, that this risk was higher in premenopausal women. Sex-based differences in response to immunotherapy may also be explained by biological differences in the tumour immune microenvironment. For example, there has been increasing evidence that the gut microbiome, which may differ significantly between men and women based on both environmental and endogenous factors, plays a role in immunotherapy response rates [71]. The higher predisposition of women to develop autoimmune conditions has also been linked to differences in the gut microbiome [72]; it is not yet clear whether sex-based differences in the microbiome directly translate to differences in immunotherapy response rates.

In more recent landmark studies, there have been no significant differences in outcomes between women and men. Women have been shown to have higher response rates to first-generation EGFR inhibitors [66]. In the landmark FLAURA trial, which demonstrated superior PFS and OS of osimertinib compared to first-generation EGFR tyrosine kinase inhibitors, women tended towards having improved survival (HR for progression 0.40 *versus* 0.58 in men), but this difference was not statistically significant [73]. Similarly, in the landmark study showing the superiority of alectinib over crizotinib in overall survival for patients harbouring an ALK mutation, women tended towards having improved survival compared to men, but this difference was not statistically significant (HR for disease progression 0.39 *versus* 0.61 in men) [74].

Small-cell lung cancer (SCLC) is less extensively studied, particularly as it is uncommon in women, but there are some limited data to suggest that women have improved outcomes at both limited and extensive stages compared to men. In one pooled analysis of 10 trials conducted through the Southwestern Oncology Group of 2580 patients with SCLC, among patients with limited stage disease, women had improved survival compared to men (24.4 months *versus* 17.7 months). However, this same analysis did not find sex-based differences in survival among women with extensive stage disease and was conducted over two decades ago [75]. A more recent retrospective study conducted by Duma *et al.* found that women have an improved median OS in both limited stage SCLC (15.2 *versus* 12.7 months) and extensive stage SCLC (6.4 *versus* 5.7 months), although the latter benefit was modest [76].

Conclusions

The pathogenesis, screening, diagnosis, outcomes and treatment side effects for women diagnosed with lung cancer have unique and distinct features compared to men but are currently not fully understood. These sex-based differences suggest that lung cancer may be increasingly considered a distinct disease in women. These differences are increasingly important for cancer researchers and clinicians to understand, as the incidence of lung cancer continues to rise globally in younger, never-smoker patients, a demographic group that far favours women compared to men. Current screening guidelines, which unfortunately have

had similarly low uptake in men and women in the United States and have not been adopted on a global scale, reflect the epidemiologic patterns of lung cancer from nearly half a century ago and are expected to miss more than half of all women diagnosed with lung cancer worldwide. While women have improved mortality compared to men across lung cancer types and stages, the changing demographic patterns of lung cancer globally threaten to shift this paradigm over the coming decades. Population-level studies on the unique exposures faced by women, expansion of screening guidelines to incorporate risks other than tobacco, and ongoing emphasis of enrolment of women and reporting of sex-based differences in pivotal clinical trials will help address existing sex-based disparities in lung cancer.

Provenance: Commissioned article, peer reviewed.

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