

## Gender Differences in Pulmonary Disease

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### Abstract

Epidemiologic evidence points to gender-based differences in incidence, risk, histology, and pathogenesis of certain lung diseases in women as compared with men. Gender influences not only physiological differences, but also the social, economic, and cultural context in which men and women coexist. Central to these differences is the role of sex hormones, which may contribute to the pathogenesis of disease or serve as protective factors. This paper seeks to review the role of gender in major areas of pulmonary disease and explore the mechanisms that may underlie gender differences in asthma, chronic obstructive pulmonary disease and mycobacterial disease (tuberculosis and *Mycobacterium avium intracellulare* infection), on lung cancer.

**Key Words:** Antiestrogens, asthma, cigarette smoking, COPD, epidemiology, estrogens, lung cancer, mycobacteria, sex hormones, women.

### Introduction

EPIDEMIOLOGIC EVIDENCE points to gender-based differences in the incidence, risk, histology, and pathogenesis of certain lung diseases in women as compared with men. Gender differences in asthma may be related to both cyclical and age-related changes in sex hormones, resulting in an age-related increase in asthma rate in females as compared with males, and to premenstrual asthma (PMA) syndrome, and fluctuations of asthma symptoms during pregnancy. However, the effects of postmenopausal use of hormone replacement therapy (HRT) on asthma are unclear. Gender-related differences in chronic obstructive pulmonary disease (COPD) may include an increased genetic sus-

ceptibility to tobacco smoke in women, which may be responsible for the observed decrease in lung function and increase in rate of hospitalization and mortality for COPD in women as compared with men. Gender differences in mycobacterial disease also exist, with females having increased prevalence of infection and clinical progression of disease as compared with males. In lung cancer, there is an increase in the incidence of both smoking- and nonsmoking-related lung tumors in women and an increased relative risk of lung cancer in women as compared with men. In addition, gender-related differences in the histology, etiologies, clinical presentations, therapy, and molecular oncogenesis of lung cancer exist.

Gender influences not only physiological differences, but also the social, economic, and cultural context in which diseases occur. Perhaps central to these differences is the role of sex hormones, which may contribute to the pathogenesis of disease or serve as protective factors. This paper seeks to review the role of gender in major areas of pulmonary disease and explore the mechanisms that may underlie these differences.

### Gender and Asthma

The importance of asthma as a cause of chronic respiratory disease, whether it begins in

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childhood, adolescence, or adulthood, is reflected in its increasing prevalence, morbidity, and mortality (1). Gender differences in asthma prevalence and severity vary by age and may be attributed to differences in biologic susceptibility due to changes in hormonal milieu with aging, environmental exposures, and health care accessibility (2). Asthma and wheezing are more common in prepubertal boys, and the odds ratio (OR) for asthma for boys between the ages 2 to 5 is 1.8 compared to girls. By age 14, the risk of chronic asthma is 4 times greater for boys and the risk of hospitalization is 3 times greater as compared to girls (2, 3). This difference may be attributed to boys' relatively smaller airway size and caliber as compared to girls at this age (4).

By age twenty there is a reversal of this incidence and a distinct female predominance in asthma: the OR for hospitalization is 2.5 to 3.0 for females as compared to males (2, 5–10). In addition, there is a greater prevalence of atopy in female asthmatics, increased bronchial responsiveness in women, and longer duration of hospitalization and morbidity with age in women (2, 5–10). To some extent, this reversal may be related to smaller relative airway caliber in women vs. men after puberty, but other factors may contribute, including changes in hormonal status occurring naturally with aging, differences in environmental/occupational exposures, and differences in quality of and access to health care, management of asthma, or perception of disease (2, 11).

Asthma severity may vary with short-term reproductive processes, including the menstrual cycle and pregnancy, and major female sex hormones such as progesterone and estrogen may play roles (12–19). As many as 40% of asthmatic females report premenstrual asthma (PMA). In normal menstruating subjects without asthma, lymphocyte  $\beta_2$  adrenoreceptors are upregulated. During the luteal phase, serum progesterone levels decline just before menstruation. In menstruating subjects with asthma, this cyclical upregulation is absent (20, 21). Thus, the cyclical fluctuations in asthma symptoms may be related to the loss of upregulation of the  $\beta_2$  adrenoreceptors and increased airway responsiveness to adenosine monophosphate (20–24). The reduction in premenstrual serum estrogen levels may also play a role, and it has been suggested that exogenous administration of estrogen may improve peak expiratory flow rate (PEFR) and attenuate symptoms (25). In premenopausal female asthmatics unresponsive

to standard steroid therapy, hormone replacement therapy (HRT) may increase forced expiratory volume in one second ( $FEV_1$ ) (26). Oral contraceptive pills (OCP), both combined estrogen-progestin and unopposed estrogen forms, may reduce dynamic fluctuations in patients with PMA and decrease menses-associated asthma (26). Furthermore, oral contraceptive users are found to have significantly higher total lung capacities when compared with nonusers during the follicular phase of the menstrual cycle and both combined estrogen/progesterone and unopposed estrogen forms of HRT may be associated with higher ( $FEV_1$ ) in elderly postmenopausal females as compared to nonusers (26).

Results of studies addressing the effect of pregnancy on asthma are conflicting; discordant results may be due to differences in methodology and outcomes measured (19). Clinical studies suggest that asthma improves in one-third of pregnant women, worsens in one-third, and is unaffected in the remaining third (18, 19). According to some studies, women with more severe corticosteroid-dependent disease experience more exacerbations, especially during late pregnancy, while other studies suggest that symptoms abate during the third trimester and that 26–40% experience an increase in asthma symptoms post partum (18, 19). Reasons for these clinical observations are thought to be depressed T-cell function and changes in levels of sex hormones, other steroid hormones and pregnancy-related anti-inflammatory factors.

Among studies addressing how changes in hormonal status with aging and the postmenopausal use of HRT affect asthma, conclusions are divided. Use of unopposed estrogen was associated with reduced airway reactivity to histamine challenge in postmenopausal non-smoking women without pulmonary disease. Those taking estrogen showed a lower maximal decrease in  $FEV_1$  after bronchopulmonary challenge compared to nonusers, suggesting that estrogen replacement may have an inhibitory effect on bronchial reactivity (27). For a cohort of 2,353 women over age 65, in the Cardiovascular Heart Study, overall HRT use was significantly associated with lower prevalence of obstruction. However, a different conclusion was reached in the Nurses Health Study, in which postmenopausal women using HRT for ten years or more had twice the age-adjusted risk of developing asthma when compared to postmenopausal women not using HRT (28). Self-report questionnaires in the Copenhagen City

Heart Study showed only a weak association between HRT and self-reported asthma, but found that in premenopausal women, use of oral contraceptive pills was associated with a greater prevalence of asthma (6.2%) as compared to nonusers (4.8%) (29). *In vitro* estrogens are shown to possess anti-inflammatory properties, and in healthy postmenopausal women the administration of estradiol reduces the skin-delayed immune responses and mixed lymphocyte reactions; estradiol and progesterone reduce the oxidative capacity induced by phagocytic stimulus and inhibit neutrophil degranulation; and estrogen and progesterone receptors are overexpressed in the human allergic mucosa and occur mainly on activated eosinophils (17). These observations may suggest the underlying mechanisms for a protective effect of estrogens on respiratory function, while the reasons these hormones may predispose to pulmonary disease are unclear.

#### **Gender and Chronic Obstructive Pulmonary Disease**

In 1997, chronic obstructive pulmonary disease (COPD) was the fourth largest cause of death in the U.S., after cardiovascular disease, cerebral vascular disease, and tumors, and in 2020, COPD is expected to become the third largest cause of death worldwide (30). Risk factors have been thought to include age, male gender, smoking/air pollution, occupational exposures, and lower socioeconomic status (30). COPD is believed to be more prevalent among men than women, due to higher smoking rates in men and their occupational exposures; however, with the increase in smoking among women and their entrance into the workforce, these demographic differences are disappearing. Moreover, there is evidence that women are more susceptible to smoking-related COPD than are men, having increased rate of decline of lung function associated with COPD, and increased COPD-related morbidity and mortality (30–35). Gender bias may also underestimate the rates of COPD in women, as shown in one study (36), in which physician rates of diagnosis of asthma vs. COPD were gender-dependent. In this study, a single hypothetical case presentation consistent with COPD was presented to 192 primary care physicians and assigned either to a female or male patient. If the patient was presented as a female, physicians were more likely to diagnose asthma, and the male patient was more likely to be diagnosed

with COPD (58% vs. 42% of the time). The likelihood of a COPD diagnosis increased significantly and initial differences between the sexes decreased as objective information was provided, but only 22% of the physicians would have requested spirometry after the initial presentation. The authors concluded that in North America, primary-care physicians underdiagnose COPD in women and that spirometry, though underutilized, reduces the risk of underdiagnosis and gender bias (36).

#### **Gender and Mycobacterial Disease**

Tuberculosis (TB) is a global problem, particularly in developing countries, where it is the third most common cause of morbidity and mortality combined and kills more women than any other infectious disease, including malaria and AIDS (37). TB kills more than one million women per year, and 646 million women and girls are infected globally (37). Epidemiological studies note differences in prevalence of infection, rate of progression, incidence of clinical disease and mortality between men and women. Women have a higher progression rate from infection to disease and a higher case-fatality rate (38, 39). Prevalence studies indicate that males are more likely to exhibit positive skin tuberculin tests and that fewer females are smear-positive on sputum sampling as compared to males (38, 39). Differences in immune responses may account for the differences in signs, symptoms, forms, and outcomes of TB in women as compared with men. In addition, sex and non-sex steroid hormones may play a role in these observed differences, as they may with asthma. Social, economic, and cultural factors may also contribute, since 70% of the world's poor are female, with limited access to health care. Other gender disparities, including delayed diagnosis and differences in attitudes of female vs. male patients and of physicians themselves toward TB, are also recognized as important factors (40–45).

Pulmonary disease due to *Mycobacterium avium intracellulare* (MAI) is no longer a disease limited to elderly men with chronic bronchitis and COPD, inactive or active TB, bronchiectasis, pneumoconiosis, chronic aspiration pneumonia, bronchogenic carcinoma and to those with deficient cellular immunity or who are recovering from immunosuppressive drugs. Post-gastrectomy patients are also at risk for pulmonary MAI infection. Disseminated disease in patients with challenged cellular im-

munity is typified by MAI in patients with AIDS. However, recent series show that 81–94% of patients identified with pulmonary MAI in immunocompetent adults were female, with a mean age range of 60–66 (46–52). “The Lady Windemere’s syndrome” was coined after these observations, to describe a syndrome of chronic cough, weight loss, fatigue, fever/night sweats, and hemoptysis in an immunocompetent, elderly, white female nonsmoker with bronchiectasis and nodular disease on computed tomography of the chest (49). A subtle immune defect, which is either acquired or a genetic allelism (e.g., NRAMP1 and interferon-gammaR1), as well as hormonal differences (e.g., declining estrogen levels) have been implicated as mechanisms that result in this apparent gender predilection (53, 54). There is no apparent gender difference in populations of AIDS patients with MAI (55).

### Gender and Lymphangiomyomatosis

Lymphangiomyomatosis (LAM) is a rare disease occurring exclusively in women. It mainly affects premenopausal women and is characterized by smooth muscle cell proliferation, primarily in the lung and extrapulmonary sites such as lower cervical, thoracic, abdominal and pelvic lymph nodes (56–59). Atypical smooth muscle proliferation and infiltration lead to progressive loss of lung function, resulting in the two most common presenting symptoms of dyspnea and pneumothorax. The pathologic findings in LAM are identical to those in tuberous sclerosis involving the lung. Interestingly, as in tuberous sclerosis, there is an association of LAM with renal angiomyolipoma. While there is no direct evidence that LAM is an inherited disorder, as is tuberous sclerosis, many investigators have suggested that LAM may be closely related to or a *forme fruste* of tuberous sclerosis. Such a relationship remains unclear (56).

The involvement of female sex hormones in the pathogenesis of LAM is suggested by the occurrence of LAM in premenopausal women during their childbearing years and the development of symptoms or increase in the extent of the symptoms during pregnancy. Cases of the disease or progression of the disease following exogenous estrogen administration have been reported, but no association has been found between the use of oral contraceptives and LAM (56). While no specific laboratory abnormalities have been reported in patients with LAM,

estrogen and progesterone receptors have been found in proliferating LAM cells and not in normal smooth muscle cells in the lungs of LAM patients, thus suggesting that sex hormones may play a role in the pathogenesis of LAM (56–58). The occurrence of disease in premenopausal women, reports of worsening with exogenous estrogen, and the presence of estrogen and progesterone receptors in LAM cells provided a rationale for hormonal manipulation as therapy. Currently, patients with LAM are being treated with oophorectomy/radioablation of the ovaries, progesterone, tamoxifen, luteinizing-hormone-releasing agonists, and other antiestrogens (56, 59–61), although the efficacy of these treatments has not been proven. In addition to hormonal involvement, tumor-suppressor genes found in tuberous sclerosis may be involved, given the similarities of disease phenotypes between LAM and tuberous sclerosis (56). Patients with end-stage LAM who underwent bilateral lung transplant have had recurrence of disease in the male donor lungs, suggesting the theory that a circulating factor or mitogen may be involved (56). Whether this mitogen is a sex hormone or the product of imbalances in tumor-suppressor genes is unknown, but given current epidemiological evidence, the pathway to LAM appears to be gender-associated.

An interesting empirical observation is that HMB-45 immunostains lung tissue in a significant number of cases of LAM. HMB-45 is a mouse monoclonal antibody against proteins produced by melanoma cells. The reason for this association is unknown (personal communication, Dr. Joan Gil, November 26, 2002).

### Gender and Lung Cancer

#### Gender Influences on the Epidemiology of Lung Cancer

Worldwide, lung cancer is the most frequent cancer, accounting for 12% of all new cancer diagnoses in both sexes combined (62). Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program suggest a projection of 164,100 new cases in the U.S. in the year 2000, 89,500 males and 74,600 females, with 89,300 new deaths for men and 67,600 for women (63). Since 1950, lung cancer rates have increased by 500% in women, and from 1960–1980 lung cancer death rate ratios in smokers as compared to nonsmokers rose from 12 to 22 in men (1.8-fold

increase), and from 3 to 11 in women (3.6-fold increase) (64, 65). In 1986, lung cancer surpassed breast cancer as the leading cause of female cancer-related deaths. Currently, 21% of the American female population smoke, and for the same level of smoking, the relative risk of non-small-cell lung cancer is 1.7 to 2.9 compared to men (66, 67). Women may also have a higher OR than men for small-cell lung cancer (68–70).

### **Gender Differences in Lung Cancer Histology**

In addition to the above data, the histology of lung cancer indicates gender differences. In the 1980s, adenocarcinoma surpassed squamous cell as the major type of lung cancer (71). SEER data from 1973–1994 reported that the relative risk for women for adenocarcinoma of the lung increased from 1.5 to 8.1, and that for men it increased from 4.6 to 19.0 (72). Between 1973 and 1992, patients younger than 50 presented with more cases of advanced disease, and although there were no significant differences with regard to overall survival, time to progression, or role of smoking status, a surprisingly higher percentage of younger patients were female (45%). Moreover, 26% of these have never been smokers, suggesting that factors other than smoking may contribute to the pathology of lung adenocarcinoma in women (73, 74). Women appear more likely to present with adenocarcinoma. Studies on tumor progression in 3,312 registered Japanese lung cancer patients between 1977 and 1996 showed that only 3.9% of the women were smokers and that 73.6% had adenocarcinoma. Of the 2,369 men, 95% were smokers and only 42% had adenocarcinoma histologically. The odds ratio for advanced disease and the hazard ratio for survival were higher for women with adenocarcinoma than for those with other types of lung cancer, and closely correlated with smoking history. This association was not observed in women with non-adenocarcinoma histological subtypes and was weaker in men, suggesting that the various effects of smoking on lung cancer development depend on gender and histological type of tumor (75).

### **Etiologies and Factors in Lung Cancer**

Factors linked to lung cancer in women include those with environmental, social, and behavioral bases. Environmental factors include:

smoking, radon, arsenic, asbestos, chromium, nickel, silica, coal/cooking oils, air pollution, and petrochemicals. Many social/behavioral factors are recognized. As compared to men who have quit smoking, women are observed to have worse relapse rates; this may be a result of physiological differences such as gender-related responses to nicotine, sensation of satiety/withdrawal, heart rate and muscle tension perception, as well as differences in perception of weight loss control, lower expectations of ability to quit, and higher rates of depression (76). On the other hand, women do appear to be more likely to ask for cessation assistance (76). Specific risk factors for smoking in teenage girls are linked to lower educational goals/socioeconomic status, in which there are no plans for higher education or college degree; the level of parent education; high school dropout status; and single parenthood girls (77).

Risk factors for malignancy were reported as part of a study of 1,000 volunteers aged 60 and older with a minimum of 10 pack/year smoking history enrolled in early lung cancer screening by low-dose computed tomography; 46% of those enrolled were women. Nineteen out of the 29 tumors occurred in women, with a prevalence of 4.1 vs. 1.8% in men. Only two significant predictors of the probability of malignancy were reported in this pilot study: nodule size and female gender (78). The increase in the number of teenage girls smoking provides another population at growing risk and a source of increasing incidence in lung cancer in women over time.

### **Gender Differences in Clinical Observations in Lung Cancer**

There may be gender-associated differences in presentation, therapy, and prognosis of non-small-cell lung cancer (NSCLC). A retrospective study of 208 cases of NSCLC showed that men present with pain, hemoptysis, and cough, while women present with pain, cough and dyspnea. There were no differences in stage of presentation, therapy, or survival advantage (79). In similar studies, women tended to be younger, more asymptomatic and non-to-light smokers, had more adenocarcinoma vs. squamous histology and stage 1 presentation, and tended to have a small survival advantage (80–82). No significant differences in therapy or operative mortality were noted; however, bronchoscopies were done in 90% of men vs. 80% of women and contributed to the preoperative diagnosis in

69% of men vs. 49% of women, while fine-needle aspiration with fluoroscopy was done in 17% women vs. 7% in men. Women had fewer (22% vs. 32%) pneumonectomies than did men (82).

### Gender and Oncogenesis in Lung Cancer

While smoking is a major risk factor for lung cancer, only 10% of heavy smokers will get lung cancer and 10% of all cases of lung cancer are found in nonsmokers (83, 84). Early familial aggregation studies have shown evidence of genetic influence (76). Lung cancer itself represents the interaction between exposure to environmental mutagens and the genetic susceptibility to molecular alterations. These molecular alterations are thought to occur in stepwise fashion over several years, resulting in lung cancer in a small group of susceptible individuals in whom the initiating insult (e.g., cigarette smoke) causes multiple molecular alterations via different pathways (85). Genetic susceptibility or predisposed risk may arise because of differences in levels of enzymes such as glutathione S-transferase and the activity of cytochrome p450 pathways which may alter detoxification of carcinogens and carcinogenic metabolites. These metabolites may directly interact with and bind to DNA, resulting in DNA adduct formation. There is evidence that women are more susceptible to tobacco-associated DNA adduct formation. DNA adducts in peripheral blood leukocytes and normal lung tissues of patients with lung cancer are higher in females for all levels of smoking compared to men, and levels of adducts have correlated with cancer risk (85–87).

If there is failure in DNA repair, persistence of mutations and accumulation of mutations may ultimately lead to lung cancer. Other pathways that may be affected by mutations that result in alterations in the normal cell growth cycle which favor cellular proliferation over normal cellular senescence or apoptosis (88). While the prevalence of smoking and the increase in smoking trends among women may account for part of the increased incidence of lung cancer in women, a growing number of molecular studies also suggest that women smokers and nonsmokers are more susceptible to lung cancer than are their male counterparts.

### Gender and Oncogenic Mutations

Glutathione-S-transferase M1 (GSTM1), thought to be a cancer susceptibility marker, catalyzes the metabolic detoxification of poly-

cyclic aromatic hydrocarbons (PAHs) styrene and ethylene oxides in cigarette smoke. Its associated gene is absent in 40–50% of the U.S. population, and this homozygous deletion can lead to an increased incidence of PAH adducts and mutagenicity. The OR for lung cancer is 3 in female smokers vs. 1.4 in male smokers (89). Among never-smoking females exposed to environmental tobacco smoke (ETS), those who developed lung cancer were more likely to be deficient in GSTM1 activity, with an OR of 2.6 as compared to those without ETS exposure (90). These data support the theory of increased genetic susceptibility of women to the effects of tobacco carcinogens as compared to men, and that polymorphisms play a role in the pathogenesis of lung cancer in passive-smoking exposures in women.

*K-ras* is the proto-oncogene in which most mutations occur in smokers, with 80–90% occurring in codon 12 and G to T transversions. Wang et al. (91) studied *K-ras* mutations in 84 Taiwanese women, predominantly nonsmokers with resected stage I adenocarcinomas for *K-ras* mutations, and found that only 6% had mutations, with 4 out of 5 occurring in codon 12 or 13. All mutations found in males occurred in smokers, suggesting a difference in lung cancer pathogenesis between men and women in this population of patients. Nelson et al. (92) examined the role of gender in smoking and survival as they related to *K-ras* mutations in patients with adenocarcinoma of the lung. *K-ras* mutation was associated with adenocarcinoma of the lung only in smokers and was more likely to be found in women than in men, with an OR of 3.3, suggesting an increased female susceptibility to this mutation and to the effects of smoking. However, decreased survival was only noted for stage I tumors. These two studies of different populations appear to support an overall increase in *K-ras* in smoking women, which may be caused by an increased susceptibility to the effects of tobacco smoke in women. The studies also suggest that the pathogenesis of adenocarcinoma in nonsmoking men and women may occur by different pathways.

p53 is a tumor-suppressor gene in which mutations occur in guanine/cytidine base pairs in regions between exons 4 and 9. Hotspots include codons 157–158, 179, 245–249, 273, and 282. Kure et al. report an increase in p53 mutations in females vs. males with NSCLC (93), while another study reports that the frequency of p53 mutations is similar for smoking men and women, but the mutations are different

(94). In the latter study, *K-ras* mutations in smoking women were increased in women with lung cancer, but were identical to those occurring in men. Tseng et al. (95) examined p53 in 37 females and 28 males with small-cell lung cancer and noted fewer mutations in p53 in women vs. men. None of the females had more than one mutation, whereas four of the males had more than one. The most common mutations in women were adenosine to guanine in 27%, 17% guanine to thymidine and 12% guanine to adenosine, suggesting that pathways in small-cell lung cancer in women may not involve p53 as frequently as they do in men.

### Gender and Trophic Influences in Lung Cancer

Gastrin-releasing peptide receptor (GRPR) is a bombesin-like peptide and autocrine growth factor gene located on xp22.3-p21. It can cause growth stimulation in lung cancers and is mediated through a family of G-protein-coupled bombesin receptors such as GRPR, neuromedin B receptor, and bombesin receptor subtype 3. It escapes inactivation in females and may be activated earlier in females in response to tobacco exposure. The presence of two expressed copies of the gene may be a factor in women's increased susceptibility to lung cancer. Increased expression of the receptor in females for all levels of smoking has been reported, with increased expression of GRPR mRNA found in lung tissue and cultured cells from 40 males and 38 females, suggesting either gene duplication or increased transcription. Expression was highest in female nonsmokers and short-term smokers in women vs. men (96).

A hormonal factor, i.e., estrogen, is postulated as a reason for increased susceptibility to lung cancer in women. Animal studies show increased incidence of pulmonary neoplasms in animals receiving estrogen (97). Women receiving exogenous estrogen replacement therapy have increased risk of adenocarcinoma of the lung as compared to patients with early menopause, and this risk is additive with smoking (98). Estrogen-dependent cancer models such as those of the breast and the endometrium have been well studied. With the finding of the estrogen receptor alpha and beta in both normal and lung tumor tissues by immunohistochemistry, affinity binding, and reverse transcription polymerase chain reaction (RT-PCR), it now seems that estrogen may play a role in the pathogenesis of lung cancer and that it may ac-

count for the increased incidence in women. However, the role of estrogen in lung cancer still remains unclear (99). Estrogen may play a biological role in lung cancer growth stimulation in cancers expressing the receptors. With the discovery of the estrogen receptor (ER) beta and multiple functional isoforms, and since studies suggest important functional differences between ER alpha and beta, it is possible that different receptor types or forms of the estrogen receptor may play different roles in the pathogenesis of lung cancer. This possibility provides a rationale for novel therapies for certain lung cancers with antiestrogens (99). Tamoxifen induces apoptosis and blocks estrogen-induced cellular proliferation of lung tumor cell lines *in vitro*. Clinical studies involving phase II trials of tamoxifen as adjuvant therapy in advanced NSCLC showed acceptable toxicity and favorable response rate and survival times in patients who received conventional therapy and tamoxifen (100–103).

### Conclusion

Epidemiologic and molecular evidence points to women's susceptibility to lung cancer, and gender differences in pulmonary diseases not generally restricted to or typical of women. These physiological differences may provide important clues to the prevention, diagnosis, and treatment of pulmonary disease in women, but differences in social, economic and cultural contexts in which both men and women exist must also be considered when addressing both women's and men's health issues.

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