Lung Cancer: Targets and Therapy

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REVIEW

Lung cancer in women

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Raúl Barrera-Rodriguez[1]
Jorge Morales-Fuentes[2]

[1]Biochemistry and Environmental Medicine Laboratory, National Institute of Respiratory Disease, [2]Lung Cancer Medical Service, National Institute of Respiratory Disease, Tlalpan, Mexico City, Distrito Federal, Mexico

Both authors contributed equally to this work

Abstract: Recent biological advances in tumor research provide clear evidence that lung cancer in females is different from that in males. These differences appear to have a direct impact on the clinical presentation, histology, and outcomes of lung cancer. Women are more likely to present with lung adenocarcinoma, tend to receive a diagnosis at an earlier age, and are more likely to be diagnosed with localized disease. Women may also be more predisposed to molecular aberrations resulting from the carcinogenic effects of tobacco, but do not appear to be more susceptible than men to developing lung cancer. The gender differences found in female lung cancer make it mandatory that gender stratification is used in clinical trials in order to improve the survival rates of patients with lung cancer.

Keywords: lung cancer, adenocarcinoma, women, genetic susceptibility, genetic differences, tobacco

Introduction

With an estimation of 965,446 new cases per year in men and 386,875 in women, lung cancer continues to be a health problem worldwide.[1] The problem is so serious that it is estimated that about 1.3 million new cases will be diagnosed each year worldwide and 1.17 million will die of the disease.[2] These data are even more alarming when we consider that 58% of these patients will present in the developing countries.[1] In 2009 alone, a diagnosis of lung cancer was made in 4800 men and 3600 women in the Hispanic population, and it is expected that 3100 men and 1900 women have died of lung cancer.[3]

Although historically lung cancer has been more prevalent in men than in women, the proportions of men and women diagnosed with the disease have changed dramatically during the last two decades, with the incidence observed to be decreasing in men but continuing to increase in women in several regions of the world.[1,4] In the European Union, there has been a clear decline in lung cancer mortality in men, ie, 53.3 per 100,000 population in the late 1980s to 44 per 100,000 population in early 2000. The opposite situation is observed for women, in whom lung cancer rates increased from 9.0 to 11.4 cases per 100,000, ie, an increase of 27%. The annual percentage change for women in the European Union was reported to vary from −0.7% in England and Wales, to +4% in France, and to greater than +6% in Spain.[5] In the US, epidemiological records show that the mortality rate in women is 2.7 times higher than that reported in Europe and 3.7 times higher than that reported for central and South America.[1] The ratio for emergence of lung cancer in men and women also varies among the Latin American countries. In Mexico, the ratio is estimated to be 2:1, in Costa Rica is 1.8:1

Correspondence: Raúl Barrera-Rodriguez
Depto Bioquímica y Medicina Ambiental, Instituto Nacional de Enfermedades Respiratorias Clza, Tlalpan 4502, Col Sec XVI, México City, Distrito Federal 14080, México
Tel +52 55 5487 1771
Fax +52 55 5487 1772
Email barrerrarr@hotmail.com

(the same as for white women in the US); while in Cuba and Colombia it is 2.2:1 and 2.0:1, respectively.[6]

In this review, we present data showing clear differences between men and women who develop lung cancer, and how these differences have a direct impact on the treatment and prognosis of the disease.

Clinicopathological differences

Histological differences

It is well known that the histology of lung cancer has varied over the years and is reflected in particular by a decline in the incidence of squamous cell carcinoma but an increased incidence of adenocarcinoma.[7,8] In addition, there are reports showing that the proportion of histological subtypes also differs significantly between men and women with lung cancer.[9] Small cell lung cancer (SCLC) accounts for 17%–34% of lung cancers in women in contrast with 15%–20% in men.[10] Adenocarcinoma has been the most frequently occurring histological subtype of non-small cell lung cancer (NSCLC) since 1960, with the percentage of adenocarcinoma in women higher than in men and averaging from 20% to 60% according to the study series. In addition, the bronchioalveolar carcinoma subtype is 2–4 times more common in women, particularly in female nonsmokers in contrast with male nonsmokers, accounting for 3.6% of all cases. In comparison, the incidence of squamous cell carcinoma is lower in women than in men, accounting for 10%–30% of cases in women and 30%–55% in men.[10,11]

The high rate of adenocarcinomas in nonsmoking women suggests the possible existence of other etiological factors in addition to smoking. Some factors that have been considered include gender-specific genetic alterations, passive smoking, age at onset of nicotine addiction (women begin to smoke at a later age), different nicotine metabolism in women, occupational exposure, diet, and chronic obstructive pulmonary disease.[12]

Differences in response to chemotherapy

Several studies have shown clear differences in survival rates for men and women after a diagnosis of lung cancer.[13–15] According to the Southwest Oncology Group study, the median survival at one and 2 years was significantly higher in women (11 months, 46% and 19%, respectively) than in men (8 months, 35% and 13%) and the risk of death was 14% lower in women than in men (hazards ratio 0.86, 95% confidence interval [CI] 0.75–0.98, $P = 0.02$).[13] The Eastern Cooperative Oncology Group showed that the survival rate in 1594 patients treated with chemotherapy was better in women than in men (9.1 versus 7.4 months).[14] A pooled analysis of five randomized studies including 2349 patients with lung cancer found that women had a higher response rate to platinum-based treatment regimens than men (42% versus 40%, $P = 0.01$), and longer survival than men (median overall survival 9.6 versus 8.6 months, $P = 0.002$), after adjusting for age, stage, performance status, and histology (hazards ratio 0.83, 95% CI 0.74–0.92, $P = 0.0005$). Upon further examination, longer survival in women was only seen in those with adenocarcinoma ($P = 0.006$).[16] Additional data for these differences in survival may be retrieved from the Surveillance, Epidemiology, and End Results database[17] and studies from the Mayo Clinic.[18,19]

Smoking and susceptibility to lung cancer

Smoking is the most important risk factor for development of lung cancer. More than 85% of all patients with lung cancer have a history of smoking, while 20% of smokers develop lung cancer. Interestingly, it has been observed that 10% of men and 20% of women who develop lung cancer are nonsmokers,[20] so it has been suggested that lung cancer in men can be considered a different disease from lung cancer in women.[21]

Several observations have suggested that women may be more susceptible than men to the adverse effects of tobacco carcinogens, whereas they usually have a better prognosis than men.[22] This phenomenon has drawn attention, given that the incidence of lung cancer in women exceeds that expected on the basis of the prevalence of cigarette smoking, raising the question of why this increase has occurred.[23–26]

Risch et al reported an odds ratio (OR) of 27.9 in women with a 40 pack-year history of cigarette smoking compared with nonsmoking women.[27] In contrast, the OR for smoking to nonsmoking men was only 9.6. Zang and Wynder showed an OR for lung cancer which was 1.2–1.7-fold higher in women compared with men across all levels of cigarette use.[28] Similar findings were seen for 156 women and 113 men in the International Early Lung Cancer Action Program, which showed an OR of 1.9 (95% CI 1.5–2.5) for prevalence of lung cancer in women compared with men having a comparable smoking history.[29] Observations made by Thun et al in at least 10 case-control studies showed that women who smoke have a higher relative risk of developing lung cancer than their male counterparts.[30]

However, there are conflicting data on the increased susceptibility to lung cancer in women. Bain et al reported no significant difference in risk of lung cancer between 80,000 men and women who smoked.[31] A smaller study reported an OR

of 19.7 in men with a long smoking history compared with nonsmoking men and an OR of 15.0 in women.[32] In a cohort of nearly 500,000 individuals aged 50–71 years, Freedman et al reported a significant increase in rates of lung cancer for nonsmoking women compared with nonsmoking men, whereas no increased risk was found in current and former female smokers when compared with matched males.[33] However, these data remain controversial.

When attempting to explain some gender susceptibility differences, it has been mentioned that women with lung cancer consistently tend to be younger, have lower smoking histories than men (31 versus 52 pack-years, respectively), are 2–3 times more likely to be nonsmokers, and are more likely to develop adenocarcinoma.[10,24,25] Another point to consider is the physiological differences between men and women, and there may be gender differences with regard to smoke inhalation habits. For example, it has been shown in nonsmokers that the type of breathing, ie, mouth versus nose or deep breathing versus labored breathing may vary between men and women. It is known that lung volume influences the amount of carcinogenic compounds deposited, particularly when there is a low functional residual capacity and during pregnancy. If men inhale more deeply than women and deeper inhalation increases the risk of lung cancer, it is possible that we are underestimating the differences in susceptibility between the genders. Further, it needs to be taken into account that taller people with a larger trachea and larger lungs will have greater deposition of carcinogenic compounds in the ciliated airways than smaller people, who will be more likely to have higher alveolar deposition at the same smoke exposure level. Therefore, the role of body size needs to be considered, because it can explain the increased risk of lung cancer in women who smoke when compared with their male counterparts.

In Latin American countries, the number of young people who smoke is increasing, along with early-onset tobacco addiction (at approximately 11–17 years of age).[34] The implications of this alarming trend for health is a matter for reflection, and is particularly disturbing in view of the fact that girls and young women are taking up the smoking habit in higher numbers than boys and young men. However, regardless of gender, it is a reality that the duration of exposure to tobacco smoke will increase rates of lung cancer in young people who are at an economically productive age. The economic cost of this for our countries will be high if immediate action is not taken to control tobacco use.

Finally, we have to take into account that there are other risk factors for lung cancer in addition to early onset of smoking, including genetic susceptibility, environmental pollution, occupational exposure to asbestos and radon, and perhaps low consumption of fruit, vegetables, and micronutrients.[35,36]

Difference in lifestyle

Difference in lifestyle might also contribute to the observed gender difference in lung cancer. Of the four components of indoor pollution (combustion products, chemicals, radon, and biologic agents), combustion-generated pollutants, principally those from solid fuel (wood, charcoal, crop residues, dung, coal) and cooking or heating stoves have been the focus of research in developing countries.

A consistent body of evidence, particularly from China, has shown that women exposed to smoke from coal fires in their homes have an elevated risk of lung cancer.[37] Lissowska et al found that cooking or heating with solid fuel increases the risk of lung cancer and suggested that cooking with wood carries a higher risk than does cooking with coal.[38] In a retrospective analysis, Gupta et al reported the highest risk of lung cancer on the basis of a cumulative exposure of more than 45 years in women using coal or wood for cooking or heating (OR 1.43, CI 0.33–6.30).[39] Further, Behera and Balamugesh found the strongest risk factor for development of lung cancer in nonsmoking Indian women to be exposure to cooking fuel (OR 5.33, 95% CI 1.7–16.7).[40] In a population-based case-control study of lung cancer among white women in Los Angeles, Wu et al reported elevated risks for lung cancer in relation to reported heating or cooking with coal burned on a stove or fireplace during childhood and in the teenage years. For adenocarcinoma, the smoking-adjusted OR was 2.3 (95% CI 1.0–5.5) and for squamous cell carcinoma was 1.9 (95% CI 0.5–6.5).[41]

Biological differences

Nicotine and cytochrome P450 enzymes

Nicotine is a major constituent of tobacco and plays a critical role in establishing and maintaining tobacco dependence. In humans, the main metabolic pathway for breakdown of nicotine is through the isoforms of cytochrome P450 *(CYP)2A6* and *CYP2B6*, which catalyze C-oxidation of nicotine via cytosolic aldehyde oxidase to produce cotinine.[42] Differences in nicotine metabolism between men and women and/or different racial groups have been linked to *CYP2A6*.[43–46] It has been reported that *CYP2A6* catalyzes 16-α-hydroxylation of estradiol and has substantial activity in the conversion of estradiol to estrone and several dehydroestradiol metabolites.[47] This pathway is even more likely if we consider that *CYP2A6* expression is induced by estradiol via the estrogen receptor.[48] Therefore, it is

possible to consider a picture in which hormonal overstimulation induces enzymes that metabolize estradiol, including *CYP2A6*, which can play an important role in protecting against the adverse effects of estrogen in tissues responsive to hormones. In addition, overexpression of *CYP2A6* in the presence of tobacco-derived metabolites can launch unexpected molecular events leading to formation of tobacco-derived carcinogens.

DNA adducts

As a part of the metabolism of carcinogenic compounds related to tobacco smoke, the polycyclic aromatic hydrocarbons and nitrosamines exert biologic effects via formation of DNA adducts and other genetic mutations in target tissues, including epithelial cells in the lung.[49,50] The metabolism of polycyclic aromatic hydrocarbons is complex and includes an activation reaction involving *CYP1A1* and *CYP1B1*, known as Phase I detoxification enzymes, and a detoxifying conjugation reaction involving various Phase II enzymes, including glutathione *S*-transferase. When there is an imbalance, cellular protection is lost, and under these conditions, active metabolites may bind DNA, thereby forming DNA adducts which ultimately play an important role in carcinogenesis.

Levels of DNA adducts are often higher in women than in men with lung cancer. This observation suggests that women are exposed to higher levels of carcinogens than men and may have an increased risk of tobacco-induced cancer.[51–53] A Taiwanese report found that levels of DNA adducts induced by polycyclic aromatic hydrocarbons in women with lung cancer were markedly higher than in men, suggesting differences in susceptibility to DNA damage derived from exposure to environmental carcinogens.[54] It is interesting to note again that variations have been observed between men and women with regard to levels of expression of genes encoding enzymes that metabolize carcinogens.[51,53,55] Some reports have shown that expression of *CYP1A1* and *CYP1B1* in lung tissue is significantly higher in smokers than in nonsmokers. However, among smokers, women have 3.9 times higher levels of CYP1A1 than men.[51] Larsen et al reported overexpression of the *CYP1A1*2B* allele in young Caucasian women with NSCLC (OR 4.6, 95% CI 1.7–12.4, $P = 0.003$).[56] Furthermore, Uppstad et al found differences in levels of formation of DNA adducts in adenocarcinoma cell lines derived from women. Further, these cell lines showed higher basal mRNA expression of *CYP1A1* and increased CYP1 enzyme activity on exposure to benzo(α)-pyrene in comparison with those derived from men.[57]

Genetic polymorphisms also have an important role in the detoxification system.[52] Thus, an A→G transition in the promoter region of the *CYP3A4*1B* gene appears to increase the OR in women with SCLC (OR 3.04, $P = 0.06$) more than in men (OR = 1.0, not statistically significant). Further, women who are heavy smokers carrying this genotype were found to have an 8-fold increase in OR for SCLC ($P = 0.005$) compared with homozygous women carrying the *CYP3A5*1* allele.[58,59]

Genetic epidemiological studies have suggested that individuals with *CYP1A1* polymorphism (I462V) carrying a homozygous deletion for glutathione-S-transferase (*GSTM1*) are at increased risk of lung cancer if they are exposed to tobacco smoke.[59] An interesting observation is that women with lung cancer are significantly more likely to have both the *CYP1A1* mutation and the *GSTM1*-null genotype than women without lung cancer. Dresler et al showed that women had a higher OR for developing lung cancer than men if they had polymorphism in *CYP1A1* (OR 4.98 versus 1.37, respectively) and combination with *GST-M1*-null conferred an OR of 6.54 for lung cancer in women compared with men (OR 2.36), independent of age and smoking history.[60] In another case-control study of 136 patients with NSCLC, the results suggested the risk of the *GSTM1*-null genotype is greatest in female smokers.[61] In addition, *CYP1A1*2B* polymorphisms are associated with an increased susceptibility to lung cancer, and this association appears to be greater for squamous cell carcinoma that for adenocarcinoma, especially in Caucasian women without a history of smoking.[62]

Phase III of the ABC transporter system has been identified to be part of the pathway for removal of tobacco carcinogens. *ABCB1* (MDR1) and *ABCC1* (MRP1) are expressed in both normal lung tissue and lung cancer tissue, and mediate the transport and removal of benzo(α)-pyrene and nitrosamines, respectively. Polymorphisms in the genes encoding these transporters appear to have profound implications for the development of lung cancer. A report by Wang et al showed that a common polymorphism in the 3′-UTR region of *ABCB1* and *ABCC1* can not only contribute to the development of lung cancer but also has a strong association with the *rs384* genotypic variant of the *ABCB1* gene and confers a high risk for lung cancer in women (OR 2.57, 95% CI 1.36–4.85), particularly adenocarcinoma (OR 1.42, 95% CI 1.03–1.99).[63]

DNA repair systems

Genetic variation in DNA repair genes is suggested to be related to both the risk of lung cancer and sensitivity to platinum-based chemotherapy.[64] However, only a few studies

have examined the relationship between polymorphism in the DNA repair system and the influence of gender, smoking status, and histopathological subtypes in lung cancer. Until now, most of the evidence suggests that women have more altered activity in their DNA repair system compared with men. For example, enzyme excision repair complementing factor 1 (*ERCC1*) is part of the pathway that repairs DNA damage caused by platinum-based therapy, and low *ERCC1* expression correlates with worse survival in patients with advanced lung cancer.[65,66] Among patients with NSCLC treated with platinum combinations, carriers of the *ERCC1 C8092C* polymorphism have significantly better survival than those with *ERCC1 C8092A* and *A8092A* polymorphisms.[67] Holm et al have shown that the *ERCC1 C118T* polymorphism is predictive of survival in men with lung cancer (11.8 months versus 7.9 months, $P = 0.005$) but not in women with the disease.[68] Further, there is evidence that *C118T* or *T118T ERCC1* genotypes in patients could be useful predictors of the outcome of platinum-based chemotherapy, mainly in elderly male smokers with squamous carcinoma.[69] In nonsmoking Chinese women, polymorphisms in the *ERCC1 C118T* or x-ray repair cross-complementing group 1 (*XRCC1*) *Arg-399Gln* genotypes were demonstrated to be unfavorable prognostic factors for lung adenocarcinoma.[70]

Polymorphisms in xeroderma pigmentosum group D (*XPD/ERCC2* [Asp312Asn, Lys751Gln]) have been correlated with clinical outcome in patients with advanced NSCLC treated using platinum-gemcitabine-based chemotherapy. Until now, there have been several conflicting reports on the association between this polymorphism and lung cancer. There is no doubt that ethnic and gender differences influence the results. Thus, subjects carrying the *XPD Gln751Gln* genotype have an increased risk of lung cancer (OR 1.30, 95% CI 1.14–1.49).[70,71] The *XPD Lys751Gln* genotype is a risk factor for developing lung cancer among Caucasian smokers, whereas the *XPD Asp312Asn* genotype is considered to be a risk factor among Asian smokers.[72] Yin et al reported that the *XPD Lys751Gln* genotype is associated with increased risk of lung cancer in nonsmoking Chinese females.[73] No significant correlation was found between *ERCC1 Asn118Asn*, *XPD Lys751Gln*, and *XPD Asp312Asn* polymorphisms and age, performance status, smoking status, gender, histology, or clinical stage in a Caucasian population of NSCLC patients.[74]

The *XPA/ERCC5 G23A* polymorphism (position 23 in the transcript, four nucleotides upstream of the start codon) is associated with an increased risk of squamous cell carcinoma but not adenocarcinoma (OR 1.69, 95% CI 1.00–2.84) in young Asian smokers. The risk association was more evident among younger individuals, males, and those with a family history of cancer.[64] Nevertheless, new studies and meta-analyses have not found a statistically significant association between *XPA G23A* polymorphism and risk of lung cancer.[75] In addition, there is no statistical evidence that *XPG Asp1104His* polymorphism might contribute to the risk of lung cancer.[76] Further studies are needed to understand better the association between *XPA* polymorphism and lung cancer.

Another key enzyme involved in DNA repair is ribonucleotide reductase M1 (RRM1 −37C→A polymorphism), which is also involved in DNA synthesis. Many studies have shown that high levels of RRM1 are associated with resistance to platinum and gemcitabine and with low survival rates.[66] However, at this time, there is no evidence for an association between RRM1 expression and clinical stage, histology, age, gender, or smoking habit; therefore, more research on this enzyme is needed to understand its biological relevance in tumors.[77]

Single nucleotide polymorphisms in cytidine deaminase (*A79C*, *C435T*, and *C435T*) have been correlated with clinical outcome in patients with advanced NSCLC treated using platinum-gemcitabine-based chemotherapy. However, to date, no correlation with age, smoking, gender, or histological type has been found.[78]

XRCC1 plays an important role in the repair of DNA damage and adducts. Genetic polymorphisms in the *XRCC1* gene (*Arg194Trp* and *Arg399Gln*) have been associated with overall survival and response to platinum-based chemotherapy in patients with lung cancer.[79,80] The *XRCC1 Gln*399*Gln* genotype has been associated with an increased risk of lung cancer among Asians (OR 1.34, 95% CI 1.16–1.54) but not among Caucasians.[81] Yin et al found that nonsmoking female patients with lung adenocarcinoma and the *XRCC1 Arg399Arg* genotype had a shorter survival time (9.23 months versus 19.10 months) and higher risk of death (adjusted hazards ratio 2.68, 95% CI 1.79–4.02) than patients with the *XRCC1 Gln*399*Gln* genotype or a combination of both polymorphisms. *ERCC1*, *C118T* or *T118T,* and *XRCC1 Arg-399Gln* might be prognostic factors in nonsmoking women.[70] Finally, a decreased risk of lung cancer in females seem to be associated with polymorphisms of *XRCC3 Thr241Met* (OR 0.37, 95% CI 0.16–0.85).[64]

Hormonal differences

Many observations suggest that hormones, especially estrogens, may be involved in lung carcinogenesis by virtue of their

close relationship with activation of cellular proliferation via an indirect action on fibroblasts or via metabolic activation of intermediaries to produce DNA adducts causing damage or oxidative stress.[82]

Some observations include the following: early menopause (<40 years) is associated with a lower risk for cancer,[83] and estrogen replacement therapy raises the OR to 1.7 and is associated with an increased incidence of lung cancer,[84,85] although other studies also suggest a protective effect.[86–88] For example, Ganti et al reported that the survival rate of women with lung cancer and on hormone replacement therapy was significantly lower than the survival of women not treated with exogenous estrogens.[84] In contrast, Schwartz et al determined that the use of postmenopausal hormone therapy was associated with a lower risk of NSCLC expressing the estrogen receptor (ER)-α and ER-β.[89] Thus, differences in the tumorigenic effects of estrogens can be related to the timing of their administration and the presence or not of tumor disease; ER-β expression is associated with a better prognosis, whereas the ER-α expression is associated with a poorer prognosis. This is consistent with the detection of ER-β in 45% of cases in a large series of patients with surgically resected NSCLC, and ER-β overexpression is more common in tumors from nonsmokers (53.5%) than in tumors from smokers (36.6%, $P < 0.004$). Furthermore, among nonsmokers, high expression of ER-β is more frequent in women (58.3%) than in men (40.9%).[90–92] In vitro studies confirm that cell lines from women with NSCLC respond to estrogens and antiestrogens, thus altering gene expression.[93,94] There seems to be a positive correlation between estrogen, smoking, and adenocarcinomas with regard to the development of lung cancer.[84,85] Zang and Wyder found that women over the age of 55 years with adenocarcinoma had twice the probability of not having smoked compared with younger women having lung cancer.[28] These age differences have not been found in men with lung cancer or in women without lung cancer.

Genetic differences

Multiple changes in gene expression could be associated with gender differences in susceptibility to lung cancer. Of the various genetic alterations in lung cancer, abnormalities of the *TP53* gene are among the most frequent. The study of *TP53* has proved to be so important that a database was created in 1994 by the International Agency for Research on Cancer (http://www-p53.iarc.fr) on mutations of this tumor suppressor gene.

The data show that *TP53* mutations are present in at least 50% of NSCLC cases and in more than 70% of SCLC cases.[95] In addition, the frequency of *TP53* mutations is higher in women with NSCLC than in men with the same tumor, which is why it has been suggested that the smoking habit is closely correlated with a high frequency of *TP53*.

Among the most common *TP53* mutations in lung cancer is G:C→T:A transversion, which is a type of mutation rarely seen in other types of cancer. In contrast, G:C→A:T transversion is more common in tumors from nonsmokers and other types of cancer. The prevalence of G:C→T:A transversion is approximately 30% in smokers compared with 10% in nonsmokers, while the prevalence of G:A→A:T transversion is approximately 28% in smokers and 50% in nonsmokers. Analysis by gender shows that *TP53* mutations associated with tobacco are more common in women than in men, which helps to explain why women are more susceptible to the carcinogenic effects of tobacco. In addition, the frequency of G:C→T:A transversion is lower and G:C→A:T transversion is higher in female nonsmokers in comparison with female smokers. This dramatic twist in the *TP53* mutation spectrum among female nonsmokers and female smokers suggests the existence of alternative tumorigenic pathways in the development of lung cancer, the activation of which depends on exposure to tobacco smoke.[96,97] Thus, tumors in female nonsmokers seem to be biologically different from those in male and female smokers. Given that normal lung tissue in women contains a high level of DNA adducts, it has been proposed that *TP53* mutations must be partly responsible for this phenomenon.[98]

On the other hand, with regard to differences in tumor genetics, we have also found alterations in growth factor receptors, including in the epidermal growth factor receptor (EGFR) family (ie, ERBB1/HER1], ERBB2/HER2/neu, and ERBB3/HER3, ERBB4/HER4).

Mutations that affect these receptors alter the tyrosine kinase domains, resulting in their constitutive activation in the absence of ligand, and subsequent cell proliferation and resistance to apoptosis.[99] These multiple effects are initiated by activation of three major pathways, ie, the AKT pathway leading to survival via inhibition of apoptosis, activation of the RAS mitogen-activated protein kinase pathway leading to increased proliferation, and STAT signaling which has effects on many other cell functions.

Preclinical and clinical studies suggest that *EGFR* mutations are one of the first events in the development of lung cancer, and more than 80% of these mutations are found in exons 18–21 of the kinase domain of the *EGFR* gene (the ATP-binding cleft), and all lead to increased tyrosine kinase activity. Several different inframe deletions are found in exon

19 (*E746-A750*, *L747-T751 insS*, and *L747-P753 insS*), collectively referred to as *del*19 mutations, which account for 32% of all mutations.[100] A substitution mutation in exon 21 (termed *L858R* or *L961Q*) is the most frequently reported mutation, accounting for 38% of all mutations. In addition, a mutation leading to a T*790*M substitution at codon 790 in exon 20 has been shown to confer resistance to EGFR tyrosine kinase inhibitors. *EGFR* mutations are the first specific genetic mutation associated with adenocarcinoma histology, never having smoked, East Asian ethnicity, and female gender.[101–103]

Among East Asian patients with NSCLC, *EGFR* mutations are even more common in females (33.3%–72.0% versus 9.3%–53% in males) and never-smokers (25.6%–71% versus 12.8%–42% in smokers) than those in the general population.[104] Mutation rates in patients of other ethnic origin are much lower than those in East Asian patients. In an analysis of DNA from NSCLCs in patients in the US, Australia, Japan, and Taiwan (including 361 patients from East Asia), mutation rates were 30% among patients of East Asian origin, but only 8% among those of other ethnicities.[105] In an Italian study, the mutation rate was 4.5% among all NSCLCs and 10% in adenocarcinomas.[106]

The greater response to EGFR tyrosine kinase inhibitors by East Asian patients is probably due to the greater prevalence of *EGFR* mutations in East Asian populations (19%–61%) than in other ethnic populations (5%–10%).[107]

Although the combination of polymorphisms, mutations, and amplifications targeting the same allele may have a role in increasing the susceptibility to lung cancer, the molecular interactions of EGFR are more complex; for example, Matsuo et al observed a significant association between estrogen exposure, NSCLC, and *EGFR* mutations in a case-control study.[108] Thus, the effectiveness of tyrosine kinase inhibitors in a subgroup of patients with lung cancer reflects the homogeneous nature of these tumors, and this strengthens the argument for tumor reclassification to define the treatment options better.

HER2 mutations or amplifications have been identified in patients with lung adenocarcinoma. However, the frequency is less than 5% for mutations and 5%–10% for amplifications. There seems to be a similar association between *HER2* mutations (inserts in the exon 20) and *EGFR* mutations in female nonsmokers of Asian origin.[109] *HER3* mutations have not been reported in patients with lung cancer, but mutations in the kinase domain of *HER4* have been reported in 2%–3% of Asian patients, predominantly in male smokers.[110]

The *K-RAS* oncogene is another of the most commonly mutated oncogenes in lung cancer and is part of the EGFR signaling pathway.[111] Most mutations in *K-RAS* occur in smokers, with 80%–90% occurring in codon 12 and G→T transversion. *K-RAS* mutations have not been found in SCLC. In lung adenocarcinoma, the *K-RAS* protein is mainly overexpressed, but the frequency of genetic alterations is greater in female smokers with lung cancer (26.2%) than in male smokers (17.4%), with an OR of 3.3.[112] It has been found that adenocarcinomas in patients with *K-RAS* mutations and a history of smoking fail to benefit from adjuvant chemotherapy, and that the disease does not respond to EGFR inhibitors.[113] There is also published evidence showing a higher frequency of "nonclassical" *K-RAS* mutations in women.[114] However, these data need further validation and the role of these mutations in prognosis and therapy is still not accurately defined.

There are also genetic alterations in the gastrin-releasing peptide receptor (*GRPR*). In normal tissues, *GRPR* stimulates proliferation and growth of bronchial epithelial cells and has been implicated in regulating development of the human lung.[115] Activation of *GRPR* also stimulates cell proliferation, and acts as a growth factor in the pathogenesis of many types of cancer, including lung cancer. Shriver et al reported that *GRPR* mRNA expression was 55% in female nonsmokers but none was detected in male nonsmokers, and that 75% of females who were short-term smokers (1–25 pack-years) had *GRPR* mRNA expression compared with 20% of male short-term smokers.[115] It is believed that the presence of two copies of the *GRPR* gene in women can play an important role in increasing the susceptibility to lung cancer. In addition, *GRPR* expression increases in airways cells exposed to estrogens, suggesting that the *GRPR* gene could also be regulated by this hormone.

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase *(EML4-ALK)* fusion represents a novel target in a subset of NSCLCs. In these tumors, the presence of *EML4-ALK* fusion and EGFR mutations are mutually exclusive. The reported incidence of *EML4-ALK* in adenocarcinoma is 5%–7%, but is higher in younger patients, light smokers, never-smokers, and male subjects from Western populations.[116]

Gender differences associated with lung cancer have also been described for *B-RAF* mutations.[117] In patients with NSCLC, *V600E B-RAF* mutations are more common in women and are associated with aggressive tumor histology and a poor prognosis.[118]

Viral association

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the world, occurring at some point in up to 75% of sexually active women. Although the presence of oncogenic HPV in lung tumor tissue has been reported in several studies, the causal association between HPV and lung cancer needs to be substantiated with evidence. An argument supporting a causative role of HPV in tumorigenesis of lung tissue is that HPV DNA is indeed integrated into the host genome, which is the initial key step in tumor initiation.[119] Furthermore, *E6* and *E7* viral oncoproteins are in fact found to be expressed in lung tumors, downregulating tumor suppressor genes such as *TP53*.[120]

Although a few studies have reported an absence of HPV in nonsmokers with lung cancer, this may reflect technical variations in experimental conditions, such as specificity of the primers and probes used, disparity in study subjects, and above all, the overall prevalence of HPV in the study population.

A Taiwanese study reported that female nonsmokers with lung cancer had a particularly high prevalence of infection with the HPV-16 and HPV-18 oncogenic variants. Moreover, female nonsmokers are more prone to HPV positivity than their male counterparts.[55,121] Also, compared with male smokers, female nonsmokers are at a higher risk of having HPV in their lung tumor tissue.[122] The reason for this gender-based difference in prevalence has yet to be unidentified. In addition, Yousem et al confirmed the presence of positivity for HPV serotypes 6/11, 16/18, and 31/33/35 in bronchial squamous metaplasia but not in adenocarcinoma or SCLC.[123] In the Japanese population, serotypes 6, 11, 16, and 18 have been detected in well differentiated squamous cell carcinoma tissue and adenocarcinoma cells adjacent to squamous cell carcinoma in the lung.[124]

We do not know the mechanism of HPV-induced carcinogenesis in the lung, but in cervical carcinoma, the increased expression of E6 and E7 viral oncogenes is induced by aromatase, which is involved in the biosynthesis of estrogen.[125] In lung tissue, this enzyme catalyses local production of estrogens from androgens. This enhanced local production of estrogen triggers a nongenomic mechanism for estrogen action, which rapidly activates EGFR. Thus, probable ER-EGFR crosstalk could occur in the lung tissue, consequently favoring persistence of HPV and malignant transformation in lung tissue. This picture could explain the increased vulnerability of females who have never smoked to develop HPV-induced lung cancer as well as the histological affinity of HPV for NSCLC.[126]

Conclusion

Despite several studies suggesting that female gender may be a positive prognostic factor in NSCLC, much more research is needed to show a clinically relevant difference between men and women. Future research will probably need to contemplate not only the contribution of patient gender, but also other important variables, such as smoking history, histology of the tumor, and some genetic characteristics of susceptibility or resistance to chemotherapy. Better understanding of these variables will be important in the planning and interpretation of future trials in lung cancer. The gender differences shown in this paper point to a need for reassessment of the existing knowledge about conventional treatments for lung cancer. Advances in our knowledge about the lung cancer biology will allow us to propose new classifications that may be reflected in better treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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