Gender Differences: Implications for Clinical Trials and Practice

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Lung cancer has been the leading cause of cancer death among men in the United States and throughout the world for years, and since 1988, it has become the number one cause of cancer death among women. More women die annually of lung cancer than of breast, ovarian, and uterine cancers combined. More than 81,000 new cases of lung cancer were diagnosed in American women in 2006.[1] It is estimated that 72,000 women will die of progressive lung cancer, accounting for 26% of all cancer deaths in women.[1]

Lung cancer, rare in women in the early 1900s, has progressively reached epidemic proportion. In the past 30 years, there has been a fourfold increase in lung cancer, referred to as a "contemporary epidemic."[2] The increase in the incidence of lung cancer among women is primarily the result of an increase in their tobacco use. Just as in men, most (85–90%) lung cancers among women are considered to be caused by smoking. Women began smoking in significant numbers in the 1940s, and although overall smoking rates have declined since reaching a peak in the 1970s, the current prevalence of smoking among women is still alarmingly high (22% in 2004).[3]

There is considerable controversy over the relative risk (RR) for lung cancer among women versus men at any given level of tobacco exposure. Several case control studies from the 1990s have argued that women are more susceptible to the carcinogens in cigarette smoke than men. Recently, Henschke and Miettinene evaluated the absolute risk for lung cancer in a high-risk population of women and men older than 40 years and with at least a 10-pack-year tobacco history who underwent baseline computed tomography (CT) screening for lung cancer. After adjusting for age and smoking history, the risk for lung cancer among women versus men was 2.7.[4] However, an analysis of the Nurses' Health Study of more than 60,000 women and the Health Professionals Follow-up Study of more than 25,000 men failed to find an increased lung cancer risk among women.[5] Regardless of sex differences in the RR of lung cancer among smokers, lung cancer seems to be a different disease in women. Moreover, multiple studies suggest that women may be more susceptible than men to the carcinogenic effects of cigarette smoke as a result of genetic, metabolic, and hormonal factors.

GENETIC FACTORS

Tobacco smoke contains more than a hundred diverse mutagens and carcinogens that exert their effects through both gene mutations and formation of DNA adducts. Two classes of enzymes play a crucial role in the metabolism of tobacco-related carcinogens: phase I and II detoxifying enzymes. Whereas phase I enzymes (i.e., cytochrome P450, monooxygenases) activate carcinogens to reactive intermediates, their action is balanced by phase II enzymes, which serve to convert these same reactive intermediates (i.e., reactive oxygen species) into inactive conjugates. Women smokers have an increased expression of the CYP1A1 gene in the lung compared with men smokers, resulting in an increased level of DNA adducts and thus in a decreased ability to detoxify tobacco carcinogens.[6] Increased CYP1A1 enzyme expression may be the result of induction by hormones, notably estrogen. The most common polymorphism in phase II detoxification enzymes is the glutathione S-transferase M1 (GSTM1) null genotype, which is present in 40% to 60% of the general population because of a gene deletion.[7] Although non-expression (null phenotype) does not seem to increase risk by itself, a null phenotype combined with high CYP1A1 expression was shown to increase the risk ratio for lung cancer among women versus men (OR, 6.54 vs 2.36).[8,9] Another area of investigation involves genetic differences in the gastrin-releasing peptide receptor (GRPR) gene that is located on the X chromosome near a cluster of genes that escape X-inactivation. Therefore, women can have two actively transcribed alleles of the GRPR gene, compared with only one in men. Shriver et al. reported that GRPR mRNA is expressed more frequently in women than in men nonsmokers (55% vs 0%), and it is detected at lower levels of tobacco exposure among smokers in women than in men (75% vs 20%).[10] The same group also showed increased expression of the GRPR gene when human airway cells were exposed to estrogen, suggesting that GRPR could also be regulated by the hormone.[10]

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MOLECULAR FACTORS

A tumor suppressor gene that is often mutated in lung cancer is p53 (in 90% of small-cell lung cancers [SCLC] and 40–70% of non-small cell lung cancers [NSCLCs]) with G:C → T:A transversion being the dominant mutation. Kure et al. found a higher frequency of this mutation in the p53 gene and, consequently, a higher average DNA adduct level in the lung tumors of women and men. However, the level of exposure to carcinogens from cigarette smoking was lower among women (mean 23 pack-years) than among men (mean 39 pack-years).[11] Of the Ras family of proto-oncogenes, K-ras is the most frequently affected gene. As in the p53 gene mutation, the formation of DNA adducts secondary to the effects of smoking seems to play a pivotal role. K-ras gene mutations have been found more often in female patients with lung cancer (26%) who were smokers than among male smokers with lung cancer (17%).[12] In most studies, Ras mutations are predominantly associated with adenocarcinoma, and Nelson and colleagues suggest that cigarette smoking induces K-ras mutations and that the resultant clones could be further expanded by a second event possibly involving the growth-promoting effects of hormones (like estrogens) that may be specific for the adenocarcinoma histology.

HORMONAL FACTORS

The role of hormones, particularly estrogen, as a risk factor for the development of lung cancer among women is another area of vigorous investigation because the most obvious biological differences between men and women are hormonal. Estrogens contribute to differentiation and maturation in the normal lung and stimulate growth and progression of lung tumors. These biological effects are mediated by estrogen receptors with ERβ expressed at a higher level in lung cancer, as demonstrated by Stabile et al.[13] A 17-fold increase in cellular proliferation after β-estradiol treatment was observed in lung cancer-derived cell lines, as opposed to only a 3.8-fold increase in normal lung fibroblasts. Based on these data and on preclinical data showing an inverse cross-talk between the EGFR and ER pathways, at ASCO 2005, Traynor et al. presented the preliminary results of a combination treatment with fulvestrant, a drug able to block estradiol-stimulated tumor growth in NSCLC cell lines, and gefitinib, an EGFR tyrosine kinase inhibitor in postmenopausal women with advanced NSCLC. The combination was well tolerated with disease activity. Correlative studies showed no relation between the amount of ERα, ERβ, or EGFR expression in the tumor and response to treatment.[14] Conflicting data exist about hormone replacement therapy (HRT) in women. Using case-control data, Taioli and Wynder showed that early menopause is associated with a decreased risk of adenocarcinoma in women, whereas the use of HRT and its interaction with smoking leads to an increased risk of lung cancer (ORs, 1.7 and 32.4 in non-smokers and smokers, respectively).[15] Some data suggest that HRT may actually exert a protective effect, with the risk of lung cancer decreasing with length of use. A study from MD Anderson reported that tobacco and estrogen interact in women who currently smoke, whereas HRT seems to have more than a protective effect for never or former smokers.[16] All these studies are limited by the lack of information on the exact dose and duration of HRT use in each patient. Further research on this topic is needed and should include a detailed gynecological history and use of all forms of hormone therapy to obtain a better understanding of the role of estrogens and progestins in the pathogenesis of lung cancer.

CLINICAL IMPLICATIONS

Multiple population-based studies of patients presenting with all stages of lung cancer have demonstrated that the female sex is an independent predictor of survival in multivariate analyses. By the mid-1970s, Edmonson et al. had already reported that women with chemotherapy-treated adenocarcinoma or with inoperable SCLC survived longer than men.[17] A Polish population-based study of 20,561 patients in the cancer registry from 1995 to 1998 showed men to have a 1.15 RR of death ($p = 0.001$).[18] In this series, female patients were younger (age <50 years, 23.3% vs 12%; $p < 0.001$) and more likely to have adenocarcinoma (21.6% vs 9.6%; $p < 0.001$) and SCLC (26.6% vs 19.9%; $p < 0.001$). More women than men were non-smokers (18.8% vs 2.4%; $p < 0.001$). A retrospective review of 7,553 patients treated for NSCLC between 1974 and 1998 at a single institution found an overall median survival of 12.4 months for women and 10.3 months for men ($p < 0.001$).[19] The survival advantage was present at all stages. In addition to retrospective population-based studies, prospective cohort studies also found female sex to be an independent predictor of survival. Visbal et al.'s study of patients with NSCLC treated at a single institution from 1997 to 2000 found male sex to be an independent predictor of poor prognosis, with an RR of death of 1.2.[20] In addition, tumor grade was also found to be an independent predictor of prognosis, a sort of surrogate for underlying genetic differences, which are ultimately responsible for differences in outcome between men and women.

NSCLC: EARLY-STAGE DISEASE

In localized NSCLC (i.e., stage I or II), women experience superior survival after either surgical resection or radiation as single modalities. Minami et al. evaluated the results of 1242 consecutive operative interventions for lung cancer and observed that even if complete resection was achieved less often in women than in men (79.6% vs 85.2%), women who underwent a complete resection, especially women older than 60 years, survived longer (5- and 10-year survival rates were 69% and 51%, respectively) than their male counterparts.[21] Female sex has also been associated with superior outcome in patients treated with radiotherapy. A better outcome for women than for men (11.4 vs 9.9 months, respectively) was observed when more than 1900 patients, treated in nine Radiation Therapy Oncology Group trials between 1983 and 1994 with thoracic radiation with or without chemotherapy (cisplatin-based), were reviewed by Werner-Wasik et al.[22] Interestingly, the preliminary results of an analysis of 91 patients (21 female) with curatively resected NSCLC demonstrated that several prognostic markers seemed to be sex-specific.[23] High levels of ERCC1, Her2, and

RXR predicted better survival among women but not men. In men, low cyclooxygenase-2 expression and high ornithine decarboxylase expression predicted better survival, but they were not predictive in women. This study is limited by its small numbers and requires validation. However, it serves to further emphasize the potential importance of sex in analyzing outcomes as well as potential predictive and prognostic markers.

NSCLC: LOCALLY ADVANCED AND METASTATIC DISEASE

Studies in locally advanced disease evaluating differential outcomes between the sexes are few; however, some reports have shown that women fare better than men when treated with radiation therapy with or without chemotherapy. Several large databases consisting exclusively of patients with advanced NSCLC also found female sex to be an independent predictor of survival. Albain et al. reviewed the 2531 patients enrolled in 13 SWOG trials of therapeutic interventions in advanced NSCLC conducted between 1974 and 1987 and found female sex to be a strong independently favorable factor for survival with a risk ratio of 0.77.[24] The median survival ratio for women versus men was 5.7 versus 4.8, with 1-year survival rates of 19% versus 14% ($p \leq 0.01$ for survival comparisons within each category). Identical results were reported by the European Lung Cancer Working Party (ELCWP) in a review of 1052 patients with locally advanced or metastatic NSCLC treated with cisplatinum-based chemotherapy from 1980 to 1991.[25] Female sex was one of the eight variables significantly associated with superior survival. In second-line therapy, female sex has also shown to be predictive of improved outcomes. In several studies, epidermal growth factor receptor tyrosine kinase inhibitors, such as gefitinib and erlotinib, had better efficacy in women. Two large phase II trials of gefitinib monotherapy, the IRESSA Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 studies, evaluated the agent in pretreated NSCLC.[26,27] Retrospective subset analysis demonstrated that female sex, adenocarcinoma (in particular, bronchiolalveolar histology), and non-smoking status were predictors of response.[27,28] Response rates to epidermal growth factor receptor inhibitors have been associated with mutations in the tyrosine kinase domain of the epidermal growth factor receptor. The improved prognosis observed for women may be secondary to differences in frequency of the underlying activating mutations: 20% in women versus 9% in men.[29,30] Caution should be taken in the interpretation of these results because neither trial was randomized, and the factors analyzed were retrospectively selected. Similar results have been obtained with erlotinib, a chemically similar agent recently approved for second- and third-line therapy of advanced NSCLC.

SCLC

Studies of SCLC also show a superior outcome for women. The NCI-Navy Medical Oncology Branch analyzed the results of four consecutive prospective trials and found that women had superior survival compared with men, with the most pronounced advantage for patients surviving longer than 2.5 years, which implies that the chance of cure is higher among women than men.[31] A total of 2580 patients enrolled in 10 SWOG SCLC trials including both limited disease and extensive-stage disease were analyzed for prognostic indicators.[32] In the six SWOG LD trials, female sex predicted the best outcome with a median survival of 24.4 months among women versus 17.7 months among men. However, in the SWOG ED trials, there was a non-significant trend toward superior survival in women. A retrospective review of outcomes and toxicities of four trials of SCLC was performed by the National Cancer Institute of Canada.[33] At multivariate analysis, women were found to have increased toxicity with chemotherapy, and significantly increased treatment delays (2 or more weeks; $p = 0.022$) were also observed. Despite the delays, women had an increased overall response rate (80.3% for women vs 66.9% for men; $p = 0.0001$) and median survival (1.31 years for women and 0.91 for men; $p = 0.0001$).

Improved survival of women with lung cancer (NSCLC and SCLC) needs to be correctly evaluated in the light of sex migration. From 1990 to 2003, an increase in the number of new cases of lung cancer among women was reflected in the proportion of women participants in clinical trials. In the same period, a stable number of men were diagnosed as having lung cancer. Sex migration can certainly confuse even carefully designed clinical trials, suggesting that future trials may benefit from stratification by sex.

CONCLUSIONS

Approximately 85% to 90% of lung cancer cases can be ascribed to smoking. It is clear that the most effective form of intervention aimed at stopping the lung cancer epidemic in both women and men is to reduce smoking rates to zero. In this context, further support should be given to campaigns of smoking prevention in youngsters (especially girls). Until now, early detection of lung cancer, even among former-smoking women, has only been performed in two prospective studies of lung cancer screening. There are very clear differences in the biology, natural history, and response to therapy between men and women with this disease, and emerging literature provides a biological basis for these differences. However, because most of the literature on this topic is retrospective, prospective evaluations of these differences, particularly as they apply to clinical practice, are required. No definitive statement can be made about the outcome of treatment for lung cancer among women compared with men. For current clinical practice, there is no area in which sex enters into the equation in patient management. Even if the value of the epidermal growth factor receptor tyrosine kinase inhibitors (gefitinib, erlotinib) is clearly most pronounced among never-smoking women, this approach will need to be confirmed by prospective clinical trials. Sex-based clinical trials taking sex-associated differences into account are warranted to provide new options for patient treatment and to affect clinical practice.

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