Gender differences in lung cancer: Have we really come a long way, baby?

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It has been estimated that 173,770 new lung cancers will be diagnosed in the USA in 2004, and 80,600 (46.3%) will be diagnosed in women. It has also been estimated that 68,510 women will die of lung cancer in 2004, which represents a 4.2% increase from 2001, when lung cancer took the lives of 65,606 women. Lung cancer currently accounts for 12.7% of all cancers diagnosed in the United States and for 28.5% of all cancer deaths.[1] In 1987, lung cancer surpassed breast cancer to become the leading cause of cancer death among women. In fact, lung cancer now kills more women annually than breast, uterine, and ovarian cancers combined. Unfortunately, women have come a long way, but not along a good path. Between 1950 and 1994, female lung cancer mortality increased 500%, from 3% to 22%.[2] In 1965, approximately 30,000 US women died of 10 categories of tobacco-related illnesses, but by 1985 that figure had risen to 106,000.[3] That tobacco-related diseases including lung cancer are an increasingly major health problem for women is undeniable.

Smoking Patterns in Women and Men

The lung cancer epidemic began later among women than among men, in large part because of differences in cigarette smoking patterns. Smoking prevalence among women was 18.1% in 1935, peaked at 33.3% in 1965, and stayed at that level through the late 1970s. Since that time, the rate has declined slowly to its current level of 23.5%.[4] Unfortunately, women are beginning to smoke at a younger age, owing in large part to successful tobacco advertising campaigns directed toward both adolescents and women. The smoking rate among female high school students, for example, increased from 17.9% in 1991 to 23.5% in 1997 and had climbed to 27.7% by 2001.[5] Because of the latency between exposure to tobacco and tobacco smoke carcinogens and the development of lung cancer, the ill effects of tobacco will be with us for many decades.

Lung cancer incidence among men is declining at a faster rate than among women, chiefly because of the decrease in smoking prevalence among men. In the last decade, the incidence of lung cancer among men declined by 2.2% from the previous decade, whereas the incidence of lung cancer among women increased by 0.5% during the same time period. Table 1 illustrates the trends in lung cancer incidence during the last 3 decades.

Lung Cancer Susceptibility

More than 85% of all patients with lung cancer have a cigarette smoking history, yet only 20% of smokers acquire lung cancer. This suggests that factors other than smoking predispose an individual toward development of lung cancer. Factors that have been implicated include sex, genetic alterations, second-hand smoke, occupational exposure (eg, asbestos), diet, chronic obstructive pulmonary disease, and previous tobacco-associated cancer. Lung cancer incidence among women exceeds that expected from smoking prevalence alone, which raises the question of women's increased susceptibility to this disease.[6] Several studies have suggested that women may be more susceptible than men to the ill effects of the carcinogens in tobacco and tobacco smoke.[6-11] Women with lung cancer have been consistently shown to (1) have smoked less on average (31 vs 52 pack-years), (2) be younger, (3) be 2 to 3

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Received for publication May 18, 2004; accepted for publication May 24, 2004.

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J Thorac Cardiovasc Surg 2004;128:346-51

0022-5223/$30.00

doi:10.1016/j.jtcvs.2004.05.025

times more likely to have never smoked, and (4) get adenocarcinoma more often than their male counterparts. Women were also found to have started smoking at a later age, to smoke brands with lower tar content, and to inhale less deeply than men in a study by Zang and Wynder.[8] Despite these findings, women had 1.2- to 1.7-fold higher odds of getting lung cancer than men at every level of exposure to cigarette smoke in that study. Although this finding has been confirmed by others,[9] it has not been corroborated by all studies.[12,13]

TABLE 1. Trends in lung cancer incidence, United States

Decade	Men	Women
1973–1980	+2.2%	+6.3%
1981–1990	−0.2%	+3.4%
1991–1999	−2.2%	+0.5%

Biologic Differences

Reasons offered to help explain these findings include (1) differences in nicotine metabolism, (2) differences in the cytochrome P-450 enzyme system that activates and detoxifies tobacco and tobacco smoke carcinogens, (3) differences in DNA adduct levels and an individual's ability to repair damaged DNA, and (4) hormonal effects. It has been suggested that women have reduced plasma clearance of nicotine and its metabolites and that these products may be the precursors of tobacco-specific carcinogens.[14,15] It has also been hypothesized that an individual's ability to activate and detoxify tobacco and tobacco smoke carcinogens and to repair damaged DNA modulates his or her risk of lung cancer.[16] The schema in Figure 1, adapted from Hecht,[17] has been proposed to help explain the reasons for differences in lung cancer susceptibility.

Polycyclic aromatic hydrocarbons and nitrosamines are both present in tobacco smoke and exert their effects through both gene mutations and the formation of DNA adducts in target tissues such as the lung.[18,19] It has been shown that women with lung cancer have gene polymorphisms in the cytochrome P-450 enzymes (*CYP1A1*, *CYP1A2*, and *CYP3A4*) that result in an increased level of DNA adducts and thus a decreased ability to detoxify tobacco carcinogens.[20] High levels of DNA adducts are believed to play a role in the initiation of carcinogenesis.[21] Women with the *CYP1A1* mutation had a higher lung cancer risk than men (odds ratio 4.98 vs 1.37). Women with both *CYP1A1* and *GSTM1* mutations had a higher lung cancer risk than men (odds ratio 6.54 vs 2.36). Furthermore, women with lung cancer had higher incidences of both *CYP1A1* and *GSTM1* mutations than did women without lung cancer.[22,23]

It has been found that DNA adduct levels are higher among women with lung cancer than among their male counterparts after adjustment for smoking dose. This suggests that women are exposed to higher levels of tobacco carcinogens than men and may thus have a higher relative risk than men of tobacco-induced lung cancer.[20,22-23] A reduced capacity to repair damaged DNA has also been associated with an increased risk of lung cancer, and women have been found to have a lower capacity than men for DNA repair.[22]

Hormonal Differences

The role of hormones, estrogen in particular, as a risk factor for the development of lung cancer is another area of vigorous investigation. Estrogen is known to be a risk factor for the development of adenocarcinoma of the breast, ovary, and endometrium, and lung adenocarcinoma is known to be more common among women than men. Non–small cell lung cancer lines (both squamous cell and adenocarcinoma) have been found to express estrogen receptors.[24,25] Estrogen may be involved in lung carcinogenesis by activating cell proliferation through an indirect action on lung fibroblasts or by metabolic activation to intermediates that produce DNA adducts and cause oxidative damage.[24]

Further observations that support a role for estrogen in the development of lung adenocarcinoma include the following: (1) Early age (<40 years) at menopause is associated with a decreased risk of lung adenocarcinoma (odds ratio 0.3). (2) Estrogen replacement therapy is associated with an increased risk of lung adenocarcinoma (odds ratio 1.7); however, in that study no adjustment was made for the amount of smoking. (3) A positive interaction of estrogen, smoking, and lung adenocarcinoma has been found (odds ratio 32.4).[26] In addition, Zang and Wynder[8] found that women older than 55 years with lung cancer (particularly adenocarcinoma) were nearly twice as likely as younger women with lung cancer to have never smoked. No similar age-related difference was found among men with lung cancer or among female control subjects.

Genetic Differences

There is a higher frequency of p53 tumor suppressor gene mutations among women with non–small cell lung cancer than among men with non–small cell lung cancer. There is also a higher DNA adduct level in normal lung tissue in women with lung cancer, which supports the contention that p53 mutations might be responsible in part for higher DNA adduct levels.[27] It has been found that the frequency of nucleotide transversions at the p53 locus is higher among female smokers with lung cancer than among either male smokers with lung cancer or female never-smokers with lung cancer.[28,29]

K-*ras* gene mutations have also been found more commonly in female patients with lung cancer (26.2%) who

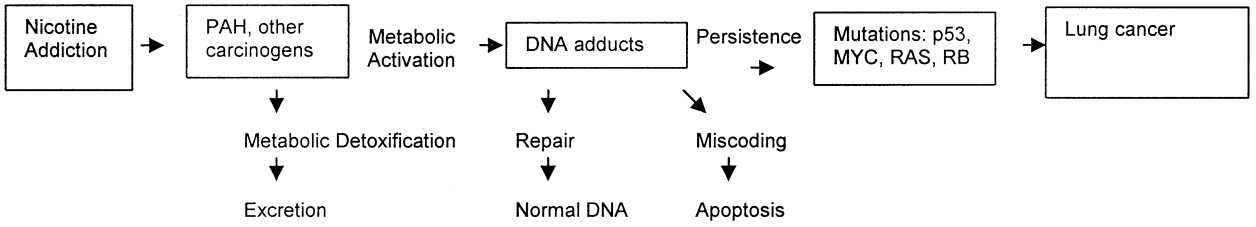

Figure 1. Schema depicting individual differences in response to carcinogens. *PAH,* Polycyclic aromatic hydrocarbons. (Adapted from Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst.* 1999;91:1194-210. Published with permission of Oxford University Press.)

were smokers than among male smokers with lung cancer (17.4%). The presence of K-*ras* mutation has been found to predict a poor prognosis. It has been found mainly in adenocarcinomas of the lung and only in patients with lung cancer who also have a history of smoking.[30] This observation has led Nelson and colleagues[30] to propose that "cigarette smoking induces K-*ras* mutations and the resultant clones are further expanded by a second event that may involve the growth-promoting effects of hormones (like estrogen) that may be specific for the adenocarcinoma histology."

Another area of investigation involves genetic differences in the gastrin-releasing peptide receptor *(GRPR)* gene that is located on the X chromosome. The peptide plays a role in carcinogenesis by stimulating cell proliferation.[31] Shriver and colleagues[32] found that *GRPR* messenger RNA was detected more frequently in female than male nonsmokers (55% vs 0%) and that among smokers *GRPR* messenger RNA was detected at lower levels of tobacco exposure in women than in men (75% vs 20%). The authors concluded that the presence of two copies of the *GRPR* gene in women might play a role in their increased susceptibility to lung cancer. They also considered that *GRPR* expression in the airway, either de novo or as a result of exposure to tobacco, might predispose an individual toward the development of lung cancer.[32]

In summary, complex interactions of tobacco, tobacco smoke carcinogens, and biologic, hormonal, and genetic factors probably explain the differences in lung cancer risk between women and men. The precise nature of these interactions is the focus of ongoing investigations.

Histologic Differences in Lung Cancer Between Men and Women

In recent years, the histologic distribution of lung cancer has changed in both sexes. Four separate studies that used data from large cancer registries have demonstrated an overall decrease in the incidence of squamous cell carcinoma and an increase in the incidence of adenocarcinoma.[33-36] The histologic distribution of lung cancer among women is distinctly different from that among men. Most nonsmokers and never-smokers with lung cancer are female, and adenocarcinoma prevails in these groups.

Like men, most women who acquire lung cancer are current or former smokers. The incidence of squamous cell cancer is lower among women than among men, ranging from 10% to 35% among women versus 30% to 55% among men.[37-40] Small cell carcinoma histologic type accounts for 17% to 34% of lung cancers among women, in contrast to 15% to 20% among men. The percentage of lung adenocarcinomas among women has been higher than that among men since the 1960s and averages between 20% and 60% in reported series.[8-10, 34,37-45] The incidence of adenocarcinoma among women who are nonsmokers is even higher.[38,46] The bronchoalveolar subtype of adenocarcinoma is 2 to 4 times more common among women with lung cancer, particularly women who are nonsmokers, than among men and constitutes 3.6% of the cases in most series.[8,37,47,48]

The increased incidence of adenocarcinoma, as opposed to other histologic types of lung cancer, among women has been attributed to several causes, including biologic factors, such as hormones, enzyme phenotypes, and underlying lung disease, and environmental factors, such as second-hand smoke, to which women are more often exposed.[34,46, 49-52] For example, Adami and colleagues[50] demonstrated a 30% increase in lung cancer among women receiving estrogen replacement therapy. The predominance of adenocarcinoma is particularly striking among nonsmokers, among whom the incidence ranges from 50% to 93%.[38,43,46,51] Among nonsmokers with lung cancer, women outnumber men nearly 3:1 a fact that strongly supports a sex-based difference in the susceptibility toward the development of lung cancer, particularly adenocarcinoma of the lung.

Sex-Based Differences in Prognosis and Outcome

A retrospective study by Ferguson and associates[53] of 478 men and 294 women with lung cancer demonstrated that the vast majority of patients are seen with advanced disease. Compared with men, however, a higher percentage of women were first seen with stage I disease (16.3% vs 9.4%), whereas fewer had stage III disease (35.4% vs 44.4%). Equal percentages of men and women were first seen with

stage II (4.4% vs 5.2%) and stage IV (43.9% vs 41%) disease. A larger database analysis has suggested that stage I disease may be more equally distributed between men and women, but the fact remains that the majority of both men and women still are first seen with stage III or stage IV disease.[37]

Several studies, including an analysis of 1521 patients treated for small cell lung cancer in several Cancer and Leukemia Group B trials, have demonstrated that stage for stage, women exhibit better survival than do men.[54-57] These studies also found that women tended to be seen with later stage disease, regardless of age, performance status, and whether they were enrolled in clinical trials.[55] In the Southwest Oncology Group Study 8269 of limited stage small cell lung cancer, female sex was found to be a strong favorable independent predictor of survival in the univariate analysis. Five-year survival rates for women were 37%, compared with 19% for men. However, female sex was not found to be a significant predictor of survival in the multivariate analysis.[58]

Several studies have shown improved survival for women treated for lung cancer.[38,59-62] The 5-year survival is 15.6% for women, compared with 12.4% for men.[61] It is of interest that a recent study by Minami and colleagues[38] demonstrated that complete surgical resection was possible in women less often than in men because of increased incidence of malignant pleural effusion and T4 disease (19.9% vs 14.4%). In cases of surgically resectable disease, however, survival after complete resection, especially for women older than 60 years, was markedly improved relative to their male counterparts. Much of the increase in survival is likely attributable to an increased life expectancy of women relative to men in this age group. When complete resection, greater life expectancy, and better performance status were all taken into consideration, women were found to have a 2-fold increased chance of long-term survival.[63] In advanced non–small cell lung cancer a significant benefit was also seen, whereby the 2-year survival rate was more than doubled from 11% in men to 27% in women.[64] Improved survival for women in every stage was shown in a retrospective cohort study of 104 men and women.[65] Women lived an average of 12 months longer than men, even though equal numbers of stage I disease were present in both groups and more stage IV disease was present among the women. Overall, nearly all clinical studies performed that have focused on survival in women with lung cancer have found the female sex to be at least a positive or neutral prognostic factor. The dichotomy of lung cancer in women, as predominantly stage I or disseminated stage IV disease, has resulted in the appearance of equal survivals of men and women overall when in fact survival is improved among women when adjusted for the clinical stage of disease. This improved survival according to clinical stage was demonstrated in a small cohort study by Ouellette and associates[65] as well as a large population-based study from Poland[37] that analyzed more than 20,000 cases of lung cancer, of which nearly 3000 cases were in women. In this study,[37] female sex was a positive prognostic variable in both univariate and multivariate analyses, behind clinical stage and performance status in terms of importance and clinical impact. That the survival benefit of female sex remains even when these other prognostic factors are taken into account suggests that the evaluation of disease-free survival and hormonal status will be important parameters to include in future sex-based clinical studies.

Conclusion

Evidence is accumulating to support the notion that the risk of development of lung cancer is different among women than among men. Women may be more susceptible to the ill effects of carcinogens in tobacco and tobacco smoke as a result of hormonal, genetic, and metabolic differences between the sexes. The preponderance of adenocarcinoma among women compared with men, and among women who are nonsmokers as well as younger women, argues in favor of a hormonal influence in this subtype of lung cancer. Future research efforts will continue to investigate and corroborate the findings outlined in this editorial and it is hoped will lead to a better understanding of lung cancer in both women and men.

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