Small Cell Lung Cancer
Sex and Survival
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Lung cancer is recognized as the most lethal form of cancer in both men and women, now exceeding that of breast cancer in women. In 2003, World Cancer Report1 reported that the annual new cases of lung cancer totaled 904,746 for men and 337,000 for women, of which 80,600 occurred in American women, with a death rate of 13%. There is little doubt that the major cause of this epidemic is tobacco, accounting for approximately 90% of lung cancer cases, including both active and passive smoking. In the 732 cases of Ferguson et al,2 16% were nonsmokers. Sasco et al3 reported an increased risk of 16% to 18% in the workplace and 20% to 30% at home. It has been reported4 that passive smoking accounts for 20% to 30% of cases. Marginal causes are radon exposure, asbestos, and so forth. Grivaux et al5 reported that of 904 women in France with proven primary lung cancer, one third never smoked.

Prior to World War I, lung cancer was comparatively rare and occurred in men 10 times as often as in women. Men were tobacco users of all kinds: pipes, cigars, cigarettes, and chewing, whereas women had not yet adopted this habit. World War II changed American culture in many ways. Among them was the entrance of many women into the workplace, for example, Rosie the Riveter, with accompanying independent incomes and greater personal liberation. Large numbers of women began smoking, particularly cigarettes, seduced by cigarette company ads, appealing to diet (“Reach for a Lucky instead of a sweet”), to health (“Not a cough in a carload”), and to liberation (“You’ve come a long way, baby”). In the 60 years since then, the male-female incidence ratio has changed from 10:1, reaching parity in Connecticut, where the tumor registry survey of 1977 reported that in the 35- to 45-year-old age group, the number of women with lung cancer exceeded that of men.6 In this respect, equality has been reached, perhaps exceeded. Indeed, you have come a long way, baby. Because many young women regard cigarette smoking as “cool,” this is not likely to change. In 2003, the number of new cases of lung cancer among American women was expected to be 337,115. Among American women, 80,600 cases were expected, with 68,000 deaths.

HISTOPATHOLOGY
Oncologists divide lung cancers into small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), because of the tendency of the former to early and widespread metastases and its greater responsiveness to irradiation and chemotherapy. The reliability of the histologic diagnosis of SCLC is high,7 as opposed to the specific diagnosis by biopsy of poorly differentiated NSCLC, which includes squamous cell carcinoma and adenocarcinoma. Lung cancers are derived from the epithelium that lines the primitive bronchial tubules and differentiates into all the types of cells of the bronchi, bronchioles, and alveolar lining cells. This results in heterogeneous histologic expression in lung cancer.8 Nevertheless, classic SCLC differs biologically and clinically from NSCLC in a number of ways. The cells have little cytoplasm, frequent mitoses, an endocrine-like network of small blood vessels, necrosis accompanied by DNA deposits in adjacent vessels, and a lack of host responses.9 Small cell lung cancers show variable neuroendocrine characteristics but so do a group of NSCLCs.10 Small cell lung cancers are more susceptible to chemotherapy, which usually does not result in cure, possibly in part because of their heterogeneity, in which the nonresponsive NSCLC cells continue to grow.9 On the other hand, about 70% of NSCLCs have a mutation in the kinase domain of the epithelial growth factor receptor (EGFR), which may be overexpressed in premalignant lesions as well.10,11 In those NSCLC cases, especially adenocarcinomas with bronchioalveolar differentiation in which this mutation occurs, 10% to 20% show objective responses to tyrosine kinase inhibitors, for example, gefitinib (monoclonal antibodies that bind to EGFR).11,12 This has not been found in SCLC, with the exception of a case report of a 72-year-old Japanese woman, who had a right upper lobe lesion with liver metastases.14 The sputum cytology was read as adenocarcinoma, and she was treated with gefitinib. There was marked regression of her lesions by computed tomography. Biopsy of the lung lesion was read as SCLC. After 5 months, she died of a cerebral hemorrhage without further regression. This may have been a combined SCLC and adenocarcinoma, which expressed functional EGFR.

SUSCEPTIBILITY
Patel et al15 reported that female smokers who smoked the same amount as male smokers were twice as likely to develop lung cancer. In addition, they found that female nonsmokers also were twice as likely to get lung cancer as male smokers, and
that female smokers developed lung cancer at a younger age than male smokers and after fewer years of smoking. Henschke et al. used computed tomography scans to screen more than 2000 smokers who were 40 years or older and who smoked at least 1 pack of cigarettes a day. By 2006, 269 cases of lung cancer had been identified, 113 (42%) men and 156 (58%) women. The women had longer survival as well as increased susceptibility. Passive smoking probably plays a part, especially among nonsmoking women. Other factors that influence susceptibility to SCLC are (1) pack-years of smoking, that is, the greater the exposure, the higher the percentage of SCLC and (2) possibly anatomic location of the tumor. Sahmoun et al. has found that SCLC is more common in the right upper lobe of females (54%) than males. Tobacco carcinogens cause DNA damage, which in the case of NSCLC produces genetic mutations in the EGFR kinase domain. This apparently gives them a growth advantage, possibly through activation of antipoptotic pathways, but gefitinib (Iressa), which inhibits EGFR activity, shows beneficial results in only about 10% of them. This does not pertain to SCLC, in which these mutations have not been found. On the other hand, SCLCs appear to be less able to repair DNA damage, which gives them increased susceptibility.

**CONCLUSIONS**

It has long been recognized that women live longer than men by several years. One has only to look at Miami to confirm this. In a recent Austrian study, males born in 1996 have a life expectancy of 73.93 years; females, 80.19 years, a 6-year survival advantage. This is true for those with many serious conditions such as cardiovascular disease. Speculative theories abound, such as that women take better care of their health problems or that they benefit from the support of female friends. Charles Darwin, in 1859, concluded that the single most important determinant of survival was the incessant struggle among individuals within the species with different degrees of fitness.

Physical fitness cannot explain the difference in SCLC survival. Henschke et al. suggested that estrogens might retard the ability of lung tumors to grow. If that is so, the lung tumor must have existed for many years before the tumor became clinical. At the average age of 60 years, long after menopause, a logical extension would be that women treated with estrogens after menopause would live longer than women with low estrogen levels, because of menoapause or earlier panhysterectomy.

This would not explain why women in general live longer than men. In Darwin's treatise on evolution, women are biologically more fit to survive, despite their increased susceptibility.

**References**

Editorial


