Are Women More Susceptible to Lung Cancer?

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For most of the past 100 years, lung cancer has generally been thought of as a disease primarily affecting men. In the past several decades, however, the incidence of lung cancer has risen among women in the United States and most other parts of the world. While incidence is still higher among men than among women, the gap has narrowed and lung cancer has become the leading cause of cancer death among American women (1). The rise in rates of lung cancer among females has paralleled the increase in the prevalence of cigarette smoking. Just as in men, the majority (85%–90%) of lung cancers among women are considered to be caused by smoking (2).

The early epidemiologic studies that established cigarette smoking as the major cause of lung cancer almost exclusively involved men (3). When relative risks of lung cancer among female smokers first began to be reported, they tended to be lower than those for men, a finding not unexpected because of women’s lower average levels of cigarette exposure from later age at starting, shorter duration of smoking, and fewer cigarettes smoked per day.

Despite the historic male predominance of lung cancer and the male lead in smoking, the suggestion that females may be as susceptible to or perhaps even more susceptible to lung cancer began to arise in the 1980s. Adenocarcinomas of the lung were noted to occur in greater proportions among women than among men, and reports began to appear of associations between female hormonal and reproductive factors and lung cancer risk, particularly for adenocarcinoma (4–8).

In the 1990s, several case–control studies indicated that relative risks of lung cancer associated with specific amounts and duration of cigarette smoking may actually be higher among women than among men. Risch et al. (9) conducted interviews in Canada with more than 800 lung cancer patients or their next of kin and found higher odds ratios among women for every smoking measure evaluated. A U.S. hospital-based study involving nearly 1900 lung cancer cases likewise found odds ratios to be higher, by about 50% on average, among women than among men for multiple classifications of smoking (10). Biologic rationales emerged to attempt to explain why women might be more susceptible to tobacco or other lung carcinogens. Included were sex differences in the metabolism or detoxification of nicotine and other compounds in tobacco; hormonal interactions, as suggested by the detection of estrogen and progesterone receptors in human lung tumor tissue; and differential proliferative or growth stimulation effects indicated by gastrin-releasing peptide receptor expression markers more common among female than male nonsmokers and smokers (10–11).

In this issue of the Journal, data from Bain et al. (12) show that the incidence of lung cancer among female smokers is about the same as that in male smokers after standardizing for amount smoked. The data are important because they arise from carefully conducted follow-ups since 1986 of large cohorts of female nurses and male health professionals. In total, approximately 1300 lung cancers were observed in current and former smokers in these cohorts; thus, there was a sufficient number of cases for the kind of detailed analyses needed to control for differences in age at start of smoking, age at quitting smoking (among former smokers), and number of cigarettes smoked per day when assessing female–male differences (although even with the large total, the number of cases became sparse in some cross-classifications of these variables). Additional covariates examined included height, body mass index, and dietary fruit and vegetable intake. The key finding was that the ratio of exposure-standardized lung cancer incidence rates for female current smokers to male current smokers was 1.1. The same rate ratio of 1.1 was also found for former smokers. The upper limit of the 95% confidence intervals about these rate ratios was 1.4 for both current and former smokers, in effect ruling out all but a slightly higher risk among women than among men (the lower 95% confidence limit was 0.9). In analyses by histologic type of lung cancer, female smokers did have a significantly higher rate of adenocarcinoma than male smokers, consistent with a priori hypotheses about greater susceptibility. However, interpretation of cell type differences is clouded by the unexpected statistically significantly lower rate of large-cell carcinoma among female smokers than among male smokers.

The combined nurses and health professionals cohort is the third large American cohort in which there has been no measurable excess of lung cancer among female smokers compared with male smokers, once amounts smoked have been controlled. The largest investigation to date has been the American Cancer Society’s Cancer Prevention Study II tracking more than 1 000 000 adults; nearly 3000 lung cancer deaths have been reported, with a statistically significantly lower (by 40%) mortality rate among female smokers than among male smokers (13). More than 1000 lung cancer cases were observed among participants in a randomized intervention trial providing beta-carotene and retinol supplements to a cohort of heavy smokers or asbestos-exposed workers, but no female–male difference was detected (rate ratio = 0.9, with an upper 95% confidence limit of 1.1) (14). Similarly, none of four other cohort studies reviewed by Bain et al. (12) evaluating female–male differences in rates of lung cancer among similarly exposed smokers found a higher rate among women. Hence, with large numbers and consistent

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findings, the clear picture that emerges from the cohort studies is that women do not have higher rates of smoking-induced lung cancer than men.

Why cohort and case–control studies might produce different results regarding female susceptibility to lung cancer is not clear. The findings from the case–control studies have been mixed, and not all studies have shown higher smoking-related risks among females than among males [e.g., a large case–control study in New Jersey did not show sex differences in odds ratios associated with smoking (15)]. Case–control studies typically present only relative risks, i.e., the risk of lung cancer among smokers compared with nonsmokers, whereas cohort studies can assess absolute incidence or mortality rates. If the incidence of lung cancer among female nonsmokers were lower than that among male nonsmokers, the relative risk would be higher among female smokers than among male smokers, even if the incidence of lung cancer among smokers of both sexes were identical. It is noteworthy, however, that Bain et al. (12) reported a 33% higher incidence of lung cancer among nonsmoking female nurses than among nonsmoking male health professionals. Case–control interview studies are also subject to recall bias, a problem not encountered in the cohort setting where exposure data are obtained prior to disease onset. Such bias usually takes the form of increased reporting of exposure by the patients, who may be more intent on trying to recollect prior toxic events, but a bias could also arise if there were underreporting of smoking by controls, especially females, because of societal concerns. Furthermore, interviews with next of kin were often used in the case–control studies because of the high fatality of lung cancer, with the possibility of misclassification for detailed categorization of smoking histories.

Bain et al. (12) suggest that the search for biologic mechanisms for a female–male difference in rates of smoking-induced lung cancer may be misplaced. Indeed, if there are no differences, the research question need not be addressed. However, the possibility remains that some differences in the way females and males are exposed to and/or respond to carcinogenic agents do exist and that exploration of these differences may be of benefit in reducing the toll of lung cancer among both sexes. Such research can be carried on while at the same time reinforcing the public health message that curtailment of smoking among smokers, and prevention of smoking initiation among nonsmokers, particularly adolescents, remain the keys to lung cancer prevention.

REFERENCES


