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## Sex differences in lung-cancer susceptibility: a smoke screen?

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In this issue of *The Lancet Oncology*, Freedman and colleagues<sup>1</sup> report a large cohort analysis that studies incidence rates of lung cancer stratified by smoking status and sex in the National Institutes of Health (NIH)-AARP cohort of 463 837 individuals followed up from 1995–1996 until the end of 2003. The size of the study and inclusion of individual-level smoking data make this study especially informative. Because patient-level smoking data are absent from the NCI's Surveillance, Epidemiology, and End Results (SEER) and other population-based–cancer registries, analyses of this sort are difficult outside of prospective cohort studies. Although SEER data on lung-cancer incidence have been linked with population-based information on tobacco use,<sup>2</sup> this approach is restricted to broad demographical and geographical subgroup patterns.

The question of whether women and men differ in their susceptibility to tobacco carcinogens has been debated for many years. Initial case–control analyses argued for higher risk in women per pack-year of exposure, but more recent cohort studies dispute this observation.<sup>3</sup> Potential explanations for sex differences in lung-cancer susceptibility to DNA damage by tobacco carcinogens include: involvement of oestrogen in lung carcinogenesis;<sup>4</sup> decreased DNA-repair capacity in women versus men;<sup>5</sup> differences in mutations within oncogenes such as *P53* in women who smoke compared with men who smoke;<sup>6</sup> differential expression of the X-chromosome-linked gastrin-releasing peptide receptor (GRPR), which mediates cellular proliferation in the lung;<sup>7</sup> and increased amounts of the CYP1A1 cytochrome P450 enzyme in women, which might be partially regulated by oestrogen and has been associated with increased DNA adducts.<sup>8</sup>

Data from this cohort analysis suggest that in current smokers, especially those who smoke less than two packs of cigarettes per day, women might be at slightly lower risk of lung cancer than men. There was no difference in lung-cancer risk between men and women who were current heavy smokers; and in former smokers, there was marginally lower risk of lung cancer in women versus men. Therefore, these findings point to a potentially increased susceptibility to tobacco carcinogens in men compared with women—quite the opposite of previous hypotheses.

As the researchers acknowledge, smoking data were collected only at one time point and age of initiation of smoking was not asked, so a complete assessment of pack-years of smoking (true-dose effect) could not be ascertained. Another limitation of this study was that it

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included predominantly (93%) white participants, precluding analyses stratified by ethnic groups, which have been shown to have differential amounts of smoking-associated and nonsmoking-associated lung cancer.<sup>9</sup> Recently, Ou and co-workers<sup>10</sup> from the University of California, Irvine, CA, USA, reported that the percentage of patients with lung cancer who were never-smokers was much higher in Asian and Hispanic people, especially women, than in people classified as black or white. Their data also showed a higher proportion of squamous-cell histology in men compared with women, irrespective of smoking status, as was also noted by Freedman's group. However, the NIH-AARP analysis did not establish that incidence rates of adenocarcinoma and small-cell carcinoma differed by sex, which contrasts with previous findings that showed that women are more likely than men to develop these histological subtypes of lung cancer.<sup>3</sup>

Of particular interest, Freedman and colleagues noted that the incidence rate of lung cancer in never-smokers was significantly higher in women than men, consistent with our recent findings based on four US-based prospective cohort studies.<sup>11</sup> These findings contrast with the finding that men had a higher mortality rate from non-smoking-associated lung cancer than women in the American Cancer Society Cancer Prevention Study cohorts.<sup>12</sup> This discrepancy could be due in part to better survival in women than men with lung cancer. However, all of these analyses were restricted by an absence of information on exposure to second-hand tobacco smoke.

The study by Freedman and co-workers adds to our understanding of sex differences in lung-cancer aetiology by confirming previously reported sex differences in lung-cancer incidence in never-smokers, while also challenging the hypothesis that women who are current smokers are at higher risk of lung cancer than currently smoking men. To capture secular, geographical, ethnic, and other demographical differences in susceptibility to smoking-associated and non-smoking-associated lung cancer, a larger and much more diverse cohort would be needed. Individual-level smoking data will need to be collected by SEER and other population-based cancer registries, and also by general population surveys, for us to truly move forward in our understanding of demographical differences in susceptibility to lung cancer in smokers and non-smokers.

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Risk of lung cancer in women who are heavy smokers is as high as in men

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